VNIVERSITAT DE VALÈNCIA

FACULTAD DE MEDICINA Y ODONTOLOGIA
DEPARTAMENTO DE MEDICINA

OPTIMIZACIÓN Y CUANTIFICACIÓN DE LOS PARÁMETROS DE ESTIMULACIÓN EN LA ESTIMULACIÓN CEREBRAL PROFUNDA DEL NÚCLEO SUBTALÁMICO EN LA ENFERMEDAD DE PARKINSON

OPTIMIZATION AND QUANTIFICATION OF STIMULATION PARAMETERS IN SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE

TESIS DOCTORAL INTERNACIONAL

Presentada por
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Dirigida por
Dra. Patricia Limousin
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Valencia, Marzo 2014

I, Patricia Limousin, Professor in Clinical Neurology at the Institute of Neurology, University College of London,

CERTIFY:

That Miss Irene Martinez-Torres has performed a training in Movement Disorders and Movement Disorders Surgery from October 2006 to October 2008 in the Unit of Functional Neurosurgery, Sobell Department, Institute of Neurology of London under my supervision. During this period she undertook part of her research that led to the writing of her thesis Project, entitled: "Optimization and quantification of stimulation parameters in subthalamic nucleus deep brain stimulation for Parkinson's Disease"

Upon review of the work, I authorize its presentation to obtain the PhD degree.

For this purpose, I sign the present certificate in London, on 5th of March, 2014

Sincerely,

Patricia Limousin MD, PhD
Professor in Clinical Neurology
Honorary Consultant

D. Juan J. Vílchez Padilla, Profesor Titular del Departamento de Medicina de la Universidad de Valencia,

CERTIFICA :

Que **Dña. Irene Martínez Torres**, Licenciada en Medicina y Cirugía por la Universidad de Valencia, ha realizado bajo mi dirección el trabajo titulado **"Optimización y cuantificación de los parámetros de estimulación en la Estimulación Cerebral Profunda del Núcleo Subtalámico en la Enfermedad de Parkinson",** para obtener el grado de Doctora en Medicina.

Revisado el trabajo, autorizo su presentación para optar al grado de Doctora en Medicina.

Y para que así conste y surta los efectos oportunos, firmo el presente certificado en Valencia, a 10 de Marzo de 2014.

Dr. Juan J Vílchez Padilla
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A Luis y Silvia

“No, no em puc aturar

I mirar la vida

des del finestral”

De *Irene*, canción de Lluis Llach

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Durante mi último año de residencia, me planteaba la difícil decisión de cómo continuar mi formación académica y como neuróloga. La inmersión durante este último año en la consulta de Enfermedad de Parkinson y Trastornos del Movimiento del Hospital La Fe fue clave para tomar esta decisión. Finalmente decidí, y creo que muy acertadamente, realizar una estancia en la Unidad de Neurocirugía Funcional de Queen Square, un centro con una amplia experiencia en Enfermedad de Parkinson y Estimulación Cerebral Profunda. La idea inicial era realizar un año de formación, sin embargo, cuando fui a entrevistarme con la Dra. Patricia Limousin, ésta me sugirió y apoyó para que la misma fuera de dos años. Esto supuso un nuevo planteamiento, fundamentalmente, en mi vida personal. Por eso, a la persona a la que estoy más agradecida durante todo este periodo de investigación en Londres y posteriormente en Valencia es a mi pareja, Luis, que supo entender mis aspiraciones y me brindó todo su apoyo para desarrollarlas.

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ABBREVIATIONS

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A	Adjustment session
AL	Ansa Lenticularis
DBS	Deep brain stimulation
DRS	Dyskinesia rating scale
GPe	Globus pallidus externus
GPi	Globus pallidus internus
IC	Internal capsule
LEDD	Levodopa equivalent daily dose
LFP	Local Field Potentials
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PMd	Dorsal premotor cortex
PPN	Pedunculopontine nucleus
Pre-DBS	before DBS
Off M	Off medication condition
Off S	Off stimulation condition
On M	On medication condition
On S	On stimulation condition
RN	Red nucleus
SE	Standard error
SD	Standard deviation
SMA	Supplementary motor area
SN	Substantia nigra
SNc	Substantia nigra pars compacta

SNr	Substantia nigra pars reticulata
SP	Stimulation parameters
STN	Subthalamic nucleus
TEED	Total electrical energy delivered
UPDRS	Unified Parkinson's disease Rating Scale
V	Visit

I. INTRODUCTION

1. THE BASAL GANGLIA

The basal ganglia are a group of nuclei located in the diencephalon and mesencephalon. The classical concept of the basal ganglia as involved in motor control has been largely modified during the last decades on the basis of the extensive research carried out. These nuclei are involved not only in motor behaviours but also in cognition and emotion. They are intimately related with cortical areas and thalamus as well as with other brainstem nuclei. Cortical information is processed by the basal ganglia in well differentiated parallel loops and each of these loops project back to the cortical area of origin. Although there is some segregation, cortical information from different areas is also integrated throughout the basal ganglia circuits for the selection of appropriate behaviours in relation with the environment, learning and rewards.

Basal ganglia dysfunction is involved in a wide range of diseases. Traditionally basal ganglia disorders have been classified in hypokinetic and hyperkinetic disorders. Hypokinetic disorders, such as Parkinson's disease (PD), are characterized by slowness of movements, loss of movements, rigidity and tremor. In contrast, hyperkinetic disorders (chorea, ballism, dystonia) are distinguished by an excess of movements. Although disorders of the basal ganglia were classified on the basis of the "amount" of movement, impairment of cognition and behaviour are also common features of some of these diseases. The basal ganglia have also been related with neuropsychiatric disorders such as Tourette syndrome and, obsessive-compulsive disorder supporting their role in emotional functions.

The resurgence of functional neurosurgery and in particular the development of deep brain stimulation for certain of these conditions has allowed to confirm in

humans some of the data found in animal studies and it has contributed to our understanding of neuronal activity in pathological and physiological conditions.

ANATOMY OF THE BASAL GANGLIA

The basal ganglia comprise four major nuclei: the striatum (caudate nucleus and putamen), the globus pallidus (GP, internal and external segment), the subthalamic nucleus (STN), and the substantia nigra (SN, pars compacta and pars reticulata) (figure 1). The striatum is the main input structure. It receives massive afferents from the entire cerebral cortex as well as from the thalamus and to a lesser degree from the dorsal raphe nucleus and the amygdala. The output nuclei are the internal segment of the globus pallidus (GPi) and the pars reticulata of the substantia nigra (SNr). Gamma-amino-butyric acid (GABA), which is considered the main neurotransmitter of the basal ganglia, is used by the striatum to project directly or indirectly - via the external segment of the GP (GPe) and the STN - to the output nuclei, which in turn project to the thalamus.

The globus pallidus is divided into the internal and external segment (GPi and GPe) by the internal medullary lamina. Although GPi and GPe share similar morphology and a common neurotransmitter, GABA, they are functionally distinct. The GPi is one of the output nuclei of the basal ganglia whereas the GPe could be considered as a modulator nucleus of the activity of the basal ganglia. Similarly the SN consists of two major sub-nuclei, the pars compacta (SNc) and the SNr. These two parts share similar inputs from other basal ganglia nuclei and have mostly different outputs and are neurochemically distinct. The SNr uses GABA as neurotransmitter whereas the SNc uses

dopamine. The STN uses glutamate as neurotransmitter and can be considered as both modulator and input structure.

Cortical information is processed in a segregated topographical manner that is maintained along the whole axis of the basal ganglia. Three main territories can be identified within the nuclei: sensorimotor, associative and limbic (Alexander et al., 1986; Alexander and Crutcher, 1990). Within the sensorimotor territory it is also possible to identify a body map (somatotopy), analogous to the cortical homunculus, and the information for the different body parts is also processed in parallel. Although there is a high degree of segregation of cortical information, convergence also exists within the basal ganglia.

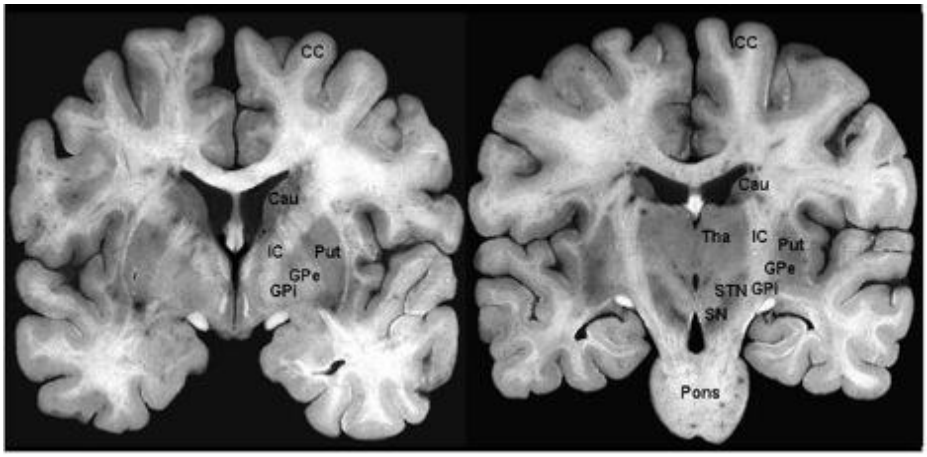

Figure 1. Brain slices in the coronal plane showing the basal ganglia nuclei. Abbreviations: Cau: caudate nucleus; CC: cerebral cortex; GPe: Globus pallidus externus; GPi: Globus palllidus internus; IC: Internal capsule; Put: putamen; SN: Substantia nigra; STN: subthalamic nucleus; Tha: Thalamus (From Martinez-Torres I et al., 2008)

The input nucleus of the Basal Ganglia: The striatum

The striatum is the major input structure of the basal ganglia and comprises the caudate, putamen and accumbens (ventral striatum) nuclei. The striatum receives glutamatergic afferent from all cortical areas. These corticostriatal projections are topographically organized and project to three distinct regions of the striatum: the sensorimotor, the associative and limbic striatum (Alexander et al., 1986; Parent and Hazrati, 1995a; Middleton and Strick, 2000). The sensorimotor territory in the dorsolateral putamen and caudate receives projections from primary motor cortex, somatosensory cortex, premotor cortex, supplementary motor area, and cingulate motor area. A study revealed that the sensorimotor striatum also received axon collaterals from corticofugal axons that descend toward the brainstem (Parent and Parent, 2006). Electrophysiological studies have shown that neurons located in the sensorimotor striatum respond to passive and active movements of the limbs and a well-defined somatotopic organization has been described, with the leg being dorsal and the trunk, arm and head more ventral (Crutcher and DeLong, 1984; Flaherty and Graybel, 1991; Miyachi et al., 2006). The associative territory comprises large part of the putamen rostral to the anterior commissure and most of the head, body and tail of the caudate nucleus. It receives projections from associative cortices in frontal, parietal and temporal lobes (Alexander et al., 1986). The limbic striatal territory is located in the ventral part of the caudate and putamen, the nucleus accumbens and portions of the olfactory tubercle. It receives projections form the limbic and paralimbic cortex, the amygdala and hippocampus.

The striatum receives dopaminergic afferents from the SNc. Other sources of dopaminergic inputs come from the retrorubral region (A8) and the ventrotegmental area (VTA). Dopaminergic nigral neurons make synaptic contacts with necks of the dendrites spines, but only in those spines that also receive cortical input. Such synaptic organization allows dopamine to modulate the excitatory effect of corticostriatal projections.

The striatum receives major thalamic glutamatergic afferents from the centromedian/parafascicular (CM-Pf) complex of the thalamus (Sadikot et al., 1992). The CM nucleus projects mainly to the putamen (sensorimotor striatum) and receives afferents from the motor cortex and GPi. The Pf nucleus projects to the caudate nucleus (associative striatum) and the pallidum and its afferents come from the premotor cortex. The ventromedial part of the Pf nucleus also projects to the limbic striatum.

The inputs from the STN are glutamatergic and are also segregated in the three main domains. Suthalamostriatal projections are scarce and exert an *en passant* excitatory effect over striatal neurons (Parent and Hazrati, 1995a).

Other inputs to the striatum are: serotoninergic projections from the midline raphe nuclei and noradrenergic from the locus ceruleus. More recently serotoninergic projection has gained increasing attention because serotoninergic axons have been suggested to underlie graft-induced dyskinesias and by extension levodopa-induced dyskinesias in Parkinson's disease (Carta et al., 2010).

The striatum contains two different types of neurons: projection neurons and interneurons. Projection neurons, also called medium spiny neurons, are GABAergic neurons (Smith et al., 1987) which project mainly to GPe, GPi or

SNr where they inhibit the neurons within these target structures (Chevalier and Deniau, 1990). Spiny neurons can be divided into two subgroups according to their neurochemical features: spiny neurons containing enkephalin and expressing predominantly D2 subtype of dopamine receptors that project to the GPe (indirect pathway) and, spiny neurons containing substance P (SP) and dynorphin, and expressing mainly D1 subtype receptors that project to the SNr and the GPi (direct pathway) (Bertran-Gonzalez et al., 2010). Efferent projections to the pallidum are mainly from the putamen and convey sensorimotor information. Those to the SNr originate mainly in the caudate nucleus and convey information from the associative cortex.

In addition to spiny medium neurons, the striatum also contains local-circuit neurons (interneurons) with different neurochemical profiles.

Control nuclei of the Basal Ganglia: Globus pallidus external segment and subthalamic nucleus

Globus pallidus external segment

The GPe receives massive GABAergic afferents from the striatum and glutamatergic afferents from the STN. Both, striatum and STN send convergent fibers to pallidal neurons suggesting that cortical information received by these two structures could be integrated at the level of single pallidal neurons (Hazrati and Parent, 1993). Other inputs to the GPe come from the cerebral cortex, intralaminar thalamic nuclei (CM/Pf), GPi, SNc, raphe and pedunculopontine nucleus (PPN).

The majority of the projections of the GPe end at the STN (indirect pathway), GPi/SNr, and striatum. Reciprocal loops exist between the GPe-striatum and

the GPe-STN. The GPe has been classically seen as an indirect link between the striatum and the output nuclei of the basal ganglia. However, the existence of a massive inhibitory projection from the GPe to the GPi/SNr, places the GPe in an essential position to directly control the output stations of the basal ganglia (Parent and Hazrati, 1995b).

Subthalamic nucleus

The STN can be considered as an input and control nucleus of the basal ganglia. It receives massive projections from the primary motor cortex, supplementary motor area, and premotor cortex that terminate in the sensorimotor STN. These cortico-subthalamic projections constitute the fastest pathway by which cortical information reach the basal ganglia and is known as the hyperdirect pathway (Hazrati and Parent, 1993; Nambu et al., 2002). Other important input to the STN comes from the GPe with which it forms a reciprocal loop and constitutes the indirect pathway from the striatum to the output nuclei. The STN also receives projections from the intralaminar thalamic nuclei (Lanciego et al., 2004; Lanciego et al., 2008) keeping a topographical organization where the CM nucleus projects to the sensorimotor STN and the Pf nucleus innervates its associative and limbic territories. It is also worth noting that the STN receives sparse dopaminergic projection from the SNc (Rommelfanger and Wichmann, 2010).

The dorsolateral part of the STN is the largest portion of the nucleus and corresponds to the sensorimotor territory. Neurons in this area change their discharge rate during movements. A representation of the body map has also been delineated: the leg is dorsal, the face ventral and the arm is in-between. Associative cortical areas and frontal eye fields project to the ventromedial part

of the STN (associative territory). The medial tip of the STN is connected with limbic structures and is considered the limbic territory.

The major efferent projections from the STN project to both segments of the globus pallidus in a topographic arrangement. These projections form parallel bands in the GPe and GPi. Part of the subthalamo-nigral projections that reach the SNr are involved, together with the caudatonigral projections, in the control of saccadic eye movements. Some of the axons of subthalamonigral neurons located in the ventromedial part of the STN ascend and synapse the neurons in the SNc, comprising one of the mechanism for the control of dopamine release. STN also sends scant projections to the striatum with a topographic organization and to the PPN and ventral tegmental area (Parent and Hazrati, 1995b; Hamani et al., 2004).

The output nuclei of the basal ganglia: globus pallidus internal segment and the substantia nigra pars reticulata

The output nuclei of the basal ganglia are the GPi and the SNr. Both structures have similar connections and differ in their functions and topographical organization. They receive cortical information processed by the striatum, both, directly and indirectly, through the GPe and STN. GPi receives more prominent projections from the striatal sensorimotor territory, while SNr receives projections mainly from the associative striatum. Both nuclei consist of inhibitory GABAergic neurons with a high rate of discharge that fire tonically to inhibit their targets.

Globus pallidus internal segment

The GPi receives inputs from the striatum (direct pathway), STN (indirect pathway) and GPe. Other inputs come from the intralaminar thalamic nuclei, the dorsal raphe nucleus, the PPN, and from the SNc.

The sensorimotor area of the GPi is localized in the ventral two-third of the GPi, displaying a somatotopic arrangement: with the leg being dorsal, the head ventral and the arm in-between. The associative territory is localized in the dorsal one-third of the GPi and the limbic in the medial tip. Afferents from the GPe and STN project onto the same neurons in the GPi. Reciprocal connections exist between GPi and GPe.

Neurons in the GPi are GABAergic and fire spontaneously at high frequencies without pauses which entails a tonic inhibition of thalamic target. The pattern of arborization of pallidal neurons is different within each target. They project to the ventral anterior (VA, pars principalis) and ventral lateral (VL, pars oralis) thalamic nuclei onto the thalamocortical neurons and thalamic interneurons, suggesting that they exert a double inhibition onto the thalamic projection neurons, one directly and other by inhibiting the excitation that the interneurons exert on them. Pallidothalamic projections to the VA/VL give off collaterals to the CM nucleus in primates, which in turn projects back to the striatum forming an ancillary subcortical loop (Striatum-GPi-CM-striatum) that conveys sensorimotor information. The existence of a similar parallel loop involving the Pf nucleus has been proposed to convey associative type information.

Other output structures receiving projections from the GPi are the habenula, which is involved in limbic functions, and the PPN (Parent and Hazrati, 1995a).

Substantia nigra pars reticulata

The SNr receives afferents from the striatum, GPe and STN. Striatonigral, pallidonigral, and subthalamonigral inputs are topographically organized and converge onto the same SNr output neurons. SNr neurons and nigral afferents are topographically organized following a laminar arrangement in an onion-like manner. The lateral half of the SNr processes information coming from sensory and motor cortical areas. The medial part of the SNr is innervated by striatal subterritories related to prefrontal and limbic cortical areas (Deniau et al., 2007). SNr efferents, keep topographical subdivisions, are GABAergic, inhibitory and project to the VA and VL thalamic nuclei, mesopontine tegmentum, SNc, superior colliculus and pedunculopontine nucleus (Parent and Hazrati, 1995a).

2. INTRINSIC CIRCUITS OF THE BASAL GANGLIA

The striatum receives massive cortical input, which is then processed and projected through the other basal ganglia structures. The arrangement of the striatal output is classically divided into the direct and indirect pathway (Albin et al., 1989; DeLong, 1990). In the direct pathway, the striatal spiny neurons (D1 receptor/SP/Dynorphin) project monosynaptically onto the GPi/SNr which project to the thalamus, facilitating thalamocortical projections and cortical initiated movements. In the indirect pathway, spiny neurons (D2 receptor/ENK) project onto the GPi and SNr via the GPe, and STN. The direct and indirect pathways are considered to produce opposing effects on the thalamic targets of the basal ganglia outflow, to respectively facilitate or suppress cortically initiated activity. Activation of the direct pathway inhibits GPi/SNr tonic activity, inducing a pause of neuronal firing – and therefore disinhibition of thalamic nuclei –

which is associated with the occurrence of an action. In contrast, the net effect of the indirect pathway is increased inhibition of the thalamic targets and consequently reduced thalamic input to cortical areas (figure 2). Recent studies in the rat using optogenetics have provided strong support for the classical model (Kravitz et al., 2010).

The basal ganglia nuclei also participate in several subsidiary circuits: 1) the CM/Pf thalamic nuclei-striatum-GPi-CM/Pf which is probably a positive feedback loop leading to increase striatal neuronal activity; 2) CM/Pf-STN-GPi-CM/Pf circuit, which is probably a negative loop leading to reduced neuronal activity; 3) STN-GPe-STN circuit, which is an excitatory-inhibitory loop with autostabilizing characteristics and; 4) the STN-GPe/GPi dual projections. Another important connection is the direct cortical projection to the STN, which may be important in synchronizing oscillatory activity in the cortex, STN and pallidum (Nambu et al., 2000) (figure 3).

The direct and indirect pathway model has become widely accepted and provides a framework for understanding basal ganglia diseases such as Parkinson's disease, chorea and dystonia. According to this model in Parkinson's disease, loss of striatal dopamine leads to underactivity of the direct and overactivity of the indirect pathways, resulting therefore in overactivity of STN and GPi, which results in excessive inhibition of thalamocortical projections. Per contrast, in hyperkinetic disorders, such as dystonia and chorea, the basal ganglia output is reduced leading to a disinhibition of the thalamocortical projections and development of involuntary movements (DeLong and Wichmann, 2007). However, the direct and indirect pathway

model, while providing a conceptual framework has major limitations. It is best illustrated in the paradox that GPi lesions are beneficial for both Parkinson's disease and dystonia (Marsden and Obeso, 1994a). This led Marsden and Obeso (1994a) to propose a major refinement of the model, namely that the pattern rather than the rate of activity within basal ganglia structures carries the information signal for both normal and disease states.

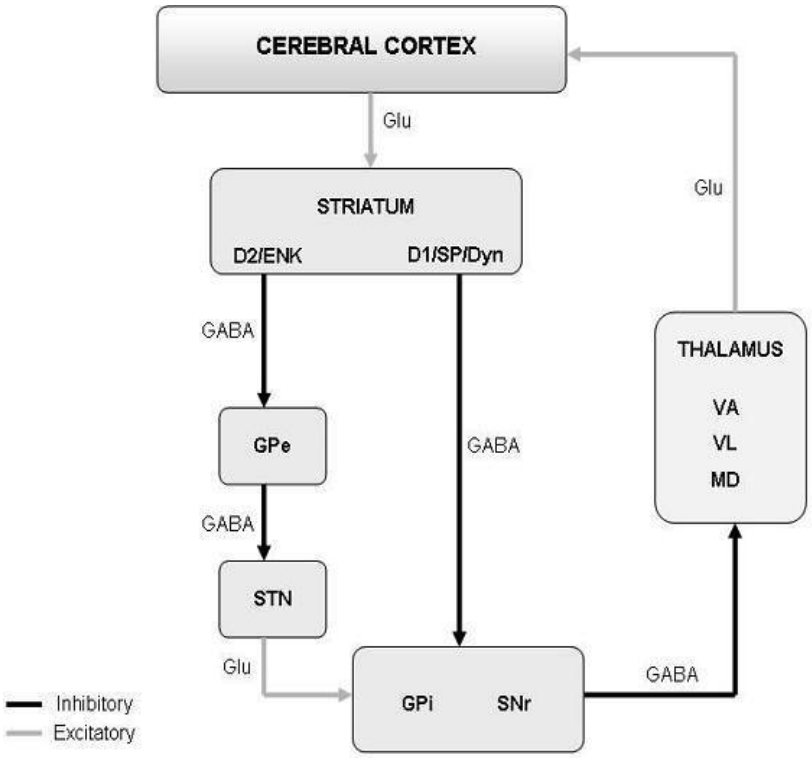

Figure 2. Schematic representation of the direct and indirect pathway between the striatum and the GPi/SNr. Abbreviations: D1: D1 subtype of dopaminergic receptor; D2: D2 subtype of dopaminergic receptor; Dyn: dynorphin; ENK: encephalin; GABA: gamma amino butyric acid; Glu: glutamate; GPe: globus pallidus externus; GPi: globus pallidus internus; MD: mediodorsal thalamic nucleus; SNr: substantia nigra pars reticulate; STN: subthalamic nucleus; VA: ventral anterior thalamic nucleus; VL: ventral lateral thalamic nucleus (From Martinez-Torres et al., 2008)

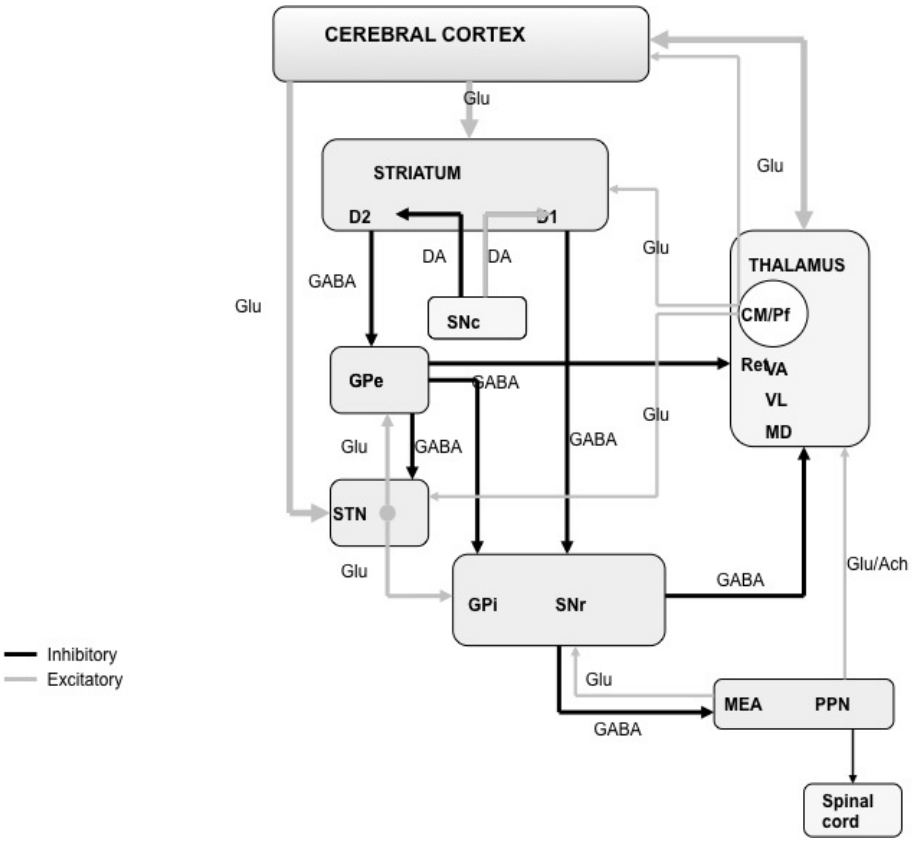

Figure 3. Schematic representation of the organization of the basal ganglia-thalamocortical circuits. Abbreviations: Ach: acetylcholine; CM/Pf: centromedian and parafascicular thalamic nuclei; D1: D1 subtype of dopaminergic receptor; D2: D2 subtype of dopaminergic receptor; DA: dopamine; Dyn: dynorphine; ENK: encephalin; GABA: gamma amino butyric acid; Glu: glutamate; GPe: globus pallidus externus; GPi: globus pallidus internus; MD: mediodorsal thalamic nucleus; MEA: midbrain extrapyramidal area; PPN: pedunculopontine nucleus. (From Martinez-Torres et al., 2008).

3. BASAL GANGLIA-THALAMOCORTICAL CIRCUITS

Traditionally the basal ganglia were seen as structures that funnelled the information originating in distinct cortical areas and then projected back to the primary motor cortex. In 1986 Alexander et al. on the basis of the anatomical and physiological findings accumulated described the existence of five circuits

between cortical areas and the basal ganglia: the motor circuit, the oculomotor circuit, two prefrontal circuits (the dorsolateral prefrontal circuit and the lateral orbitofrontal circuit) and the limbic circuit (figure 4). The designation of the circuits was made according to its cortical area of origin and termination. The segregated organization of these loops has been given further support by studies using retrogradely transported virus particles. Two additional circuitries were later described (Middleton and Strick, 1996; Clower et al., 2001), as well as an open loop between the primary motor cortex and the ventral putamen, which may allow interaction between the limbic and motor systems (Kelly and Strick, 2004). All circuits share similar characteristics, they originated in specific cortical areas, pass through separated portions of the basal ganglia and thalamus and end in the cortical area of origin. Within each circuit the information is processed following the direct and indirect pathways that link the striatum with the output nuclei. However this last organization is less clear in the limbic circuit.

The circuits maintain a clear topographical organization of inputs and outputs. The segregation is such that further channels within circuits can be found. For example, in the motor circuit, which is the best studied, the information from different cortical areas (somatosensory, motor and premotor cortices) is processed in parallel. These channels within the motor circuit are subdivided in somatotopic subchannels representing each body part (Romanelli et al., 2005). Furthermore, neurons in the putamen that represent a single body part respond to different characteristics of the movement: some respond to preparation of the movement, others are movement related and, others are specific to the direction of the movement.

Despite the high level of segregation convergence also exits. This idea is support by the comparison of the large number of corticostriatal versus the much smaller number of striatal and pallidal output neurons. Anatomical and electrophysiological studies have demonstrated that convergence of information occurs within distinct territories of the same nuclei and at the level of single cells.

This classical view of functional organization of basal ganglia as a loop has been recently modified. It is now known that the basal ganglia have several loops, where cortical and subcortical projections interact with internal re-entry loops. This complex network is designed for selecting and inhibiting simultaneously occurring events and signals. Although feedback loops between basal ganglia and several subcortical regions were not well considered in the initial model, they have been extensively studied during the last years (Redgrave et al., 2011; Smith et al., 2011). There is as well increasing evidence for direct anatomical interactions between cerebellar and basal ganglia circuitries (Bostan et al., 2010). These connections may become of relevance in the future to explain aspects of tremor and dystonia.

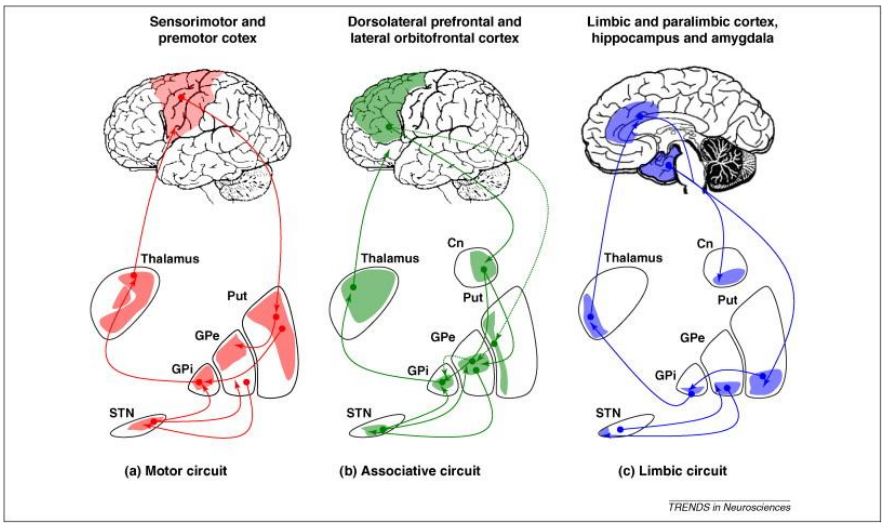

Figure 4. Schematic diagram illustrating the main cortico-basal ganglia-thalamocortical circuits within human brain. This figure shows a pseudo-anatomical arrangement of the motor, associative and limbic pathways. **(a)** Motor circuit. Neurons from the sensorimotor cortex project to the posterolateral putamen (Put). From the putamen there are two main projections topographically organised onto the posterolateral region of the target nuclei: (i) the direct circuit to the GPi and (ii) the indirect circuit connecting the posterior putamen to the globus pallidus pars externa (GPe), the STN and the GPi. The GPi is the primary output nucleus of the basal ganglia to the cortex via the ventrolateral thalamus. **(b)** Associative circuit. This circuit originates in the dorsolateral prefrontal and lateral orbitofrontal cortices, which project to the caudate nucleus (Cn) and anteromedial portion of the putamen. From the striatum (Cn + Put) it projects to the dorsomedial region of the GPi and anteromedial parts of the GPe and STN to converge onto the GPi and back to the cortex via the ventral anterior nuclei of the thalamus. **(c)** Limbic circuit. This loop starts in the hippocampus, amygdala and paralimbic and limbic cortices and projects to the ventral striatum (ventral portion of the caudate and putamen, including NAcc). The ventral striatum projects to the limbic portion of the GPe and medioventral STN and ventral GPi and to the cortex via the mediodorsal nucleus of the thalamus. (From Krack et al., 2010 – modified from Obeso et al., 2008-).

4. FUNCTION AND PHYSIOLOGY OF THE BASAL GANGLIA

Research in recent years has challenged the traditional view of basal ganglia as only involved in control of movement. Anatomical studies have demonstrated the connection between basal ganglia and cortical areas concerned with cognition. The activity of the neurons within the basal ganglia nuclei is more related to cognitive or sensory tasks than to motor function. Finally, some lesions in the basal ganglia produce cognitive and sensory disturbance, sparing the motor function.

Motor function

Despite the recent interest in non-motor function of the basal ganglia, most of the research has focused in motor aspects of basal ganglia physiology.

Microelectrode studies in primates have allowed us to describe the neuronal activity within the basal ganglia nuclei. Neuronal activity is defined by: firing rate, pattern of discharge and the degree of synchronization and frequency of oscillation of neuronal populations. Variation in these parameters can influence the function of the basal ganglia in normal and pathological conditions. The firing rates of neurons vary by nuclei. At rest striatal neurons show a low frequency rate, GPi and SNr neurons show a high rate and tonic discharging pattern. In the GPe two types of activity have been recognized: neurons with a pausing and slightly lower discharge rate than GPi neurons, and other neurons with very low spontaneous rate with occasional high frequency bursts. STN neurons fire tonically at medium frequencies (20-30 Hz). Thus, at rest basal ganglia nuclei neurons discharge tonically, independent and mainly in a non-oscillatory way.

These studies have demonstrated the existence of neurons within the basal ganglia nuclei that change their firing rate (increase or decrease) in relation to movement. A clear somatotopic organization within the sensorimotor territory of the nuclei has been delineated. Pallidal neurons respond selectively to single joint and direction of movement (Brotchie et al., 1991a). Some studies have also found specificity related with some parameters of the movement such as amplitude and velocity (Crutcher and DeLong, 1984). The majority of pallidal neurons increase their firing rates in response to movement thus leading to an inhibition of thalamocortical projections and only a small number of cells decrease in firing rate. On the basis of these finding Mink (1996) proposed the center-surround model, where the primary role of the basal ganglia is to focus selection of desired movement and to inhibit competing movements. In this model the direct pathway constitute the excitatory center and the indirect pathway is proposed to provide the inhibitory surround suppressing competing motor programs. Electrophysiological studies have also revealed that neuronal activity of the basal ganglia structures occurs relatively late to be involved in execution or planning of movements. Initiation of movement is most likely to occur at cortical levels.

Neurons in oculomotor circuit do not change their discharge in respond to all saccades, but appear to be activated in respond to attractive targets in the environment or to remembered points in visual space. This suggests that basal ganglia will respond most likely to facilitate movement in particular circumstances or contexts than to operate in a particular type of movement. In this line, Brotchie et al. (1991b) demonstrate that GP appears to be more involved in movements that are predictable and well practiced. They found that

pallidal neurons discharge in a phasic way during a sequential movement task. They suggested that phasic discharge may be the “internal cue” to switch from one movement to another, particularly when the second movement is predictable and automatic (after learning). Further studies have also pointed the participation of the GPi in sequential movements (Mushiake and Strick, 1995). Other regions of the striatum different to the motor territory respond to environmental cues in preparation of the movement.

Further studies have demonstrated that distinct parts of the striatum respond to visual stimuli (tail of caudate and ventral putamen), to visual stimuli of emotional significance (ventral striatum) or, environmental events that are cues for behavioral responses (head of caudate). The dopaminergic nigrostriatal neurons also show responses that are context dependent, particularly they respond in relation to reward or predicted reward after learning (for review see Marsden and Obeso, 1994a).

More recently, studies have emphasized the role of neuronal oscillations and synchrony in pathological conditions such as Parkinson’s disease. However oscillatory activity, although weak, also exists in the physiological state. According to the frequency, oscillatory activity can be divided in different bands. Oscillations in the 8-30 Hz are the best documented in human striatum, GPi and STN. This band is subdivided into 8-13 Hz and 14-30 Hz bands. Oscillations in the latter range are known as beta band. Suppression in the beta band is seen prior to voluntary movements in normal conditions. An augmentation of the power in this band occurs when a pre-prepared movement requires cancellation. Beta activity in the cortex behaves in a similar manner that in the basal ganglia. These findings suggest that beta band oscillatory activity may

play a role in the normal function of the basal ganglia and that their attenuation may be necessary for generation of motor behaviours (Brown and Williams, 2005).

Alterations in the degree of oscillations and pattern of discharge are seen in pathological conditions. Parkinson's disease is associated with an abnormal increase in discharge rate, a greater tendency of neurons to discharge in burst and an increase in oscillatory and synchronized activity. The direct connection between the cortex and the STN as well as the basal ganglia and thalamus may serve to predispose the circuit to synchronize oscillatory activity.

Cognitive and behaviour functions

On the basis of anatomical observation is apparent that cortical areas such as dorsolateral prefrontal cortex, the lateral orbitofrontal cortex and the anterior cingulate/medial orbitofrontal cortices are connected with the basal ganglia. These frontal regions are involved in planning, working memory, rule-based learning attention, and other aspects of higher executive function. More recently a new output from the basal ganglia to the area TE (visual area) of inferotemporal cortex has been identified. This cortical area participates in higher-order visual functions and in visual working memory.

The role of basal ganglia in cognition and behaviour is supported by electrophysiological, functional imaging and clinical studies (for review see Middleton and Strick, 2000).

Electrophysiological studies in monkeys have stressed that the majority of the neurons of the output nuclei do not respond to movement. These neurons are located within regions of the GPi and SNr that project to prefrontal cortices. Recordings of single neurons in trained primates showed neurons in the SNr

that change their activity during the cue and delay periods of the tasks but not during the movement period. Other studies have revealed that the responses of striatal neurons depend strongly on the reward contingencies of the task. Inactivation of the caudate and anterior striatum of primates leads to deficits in learning sequences. Moreover some studies have shown that certain outputs from the GPi participate in tasks involving the use of working memory. A study in primates demonstrated that the inactivation of the GPe using a GABA antagonist induced stereotyped behaviours when performed in the limbic part of the GPe and, attention deficit and/or hyperactivity when performed in the associative territory of the GPe (Grabli et al., 2004).

Functional imaging studies have demonstrated the activation of caudate nucleus during learning of new sequences (Jueptner et al., 1997) and the participation of GPi in planning and spatial working memory (Owen et al., 1998).

Clinical studies support the role of the basal ganglia in cognition. Lesions or diseases involving the striatum in humans (Parkinson's disease, Huntington disease) as well as of the output nuclei are correlated with cognitive impairment. In Parkinson's disease, which is characterized by a reduction in the dopaminergic nigrostriatal inputs, deficits in attentional set shifting, working memory, planning and problem solving can be identified. Bilateral lesions of the SNr produce deficits in working memory, visual hallucinations and other neurological symptoms. Lesions in the pallidum can also produce cognitive deficits, particularly in implicit learning, compulsive behaviours and "psychic" akinesia.

Overall there is growing evidence that alterations of the basal ganglia occur with neuropsychiatric disorders, such as depression, obsessive-compulsive disorder,

Tourette's syndrome, autism, and attention deficit disorder. DBS of different nuclei of the basal ganglia are currently being used or explored to treat some of these disorders with encouraging results.

5. PHARMACOLOGY OF THE BASAL GANGLIA

Four main neurotransmitters act in the basal ganglia: glutamate, GABA, dopamine and acetylcholine (Ach). Cortical and thalamic inputs to the striatum are glutamatergic as well as thalamocortical projections. With the exception of the STN that also uses glutamate, the rest of the basal ganglia nuclei use GABA as neurotransmitter. Dopamine has an important modulatory effect on the striatum and the levels of dopamine are crucial to determine the output activity of the basal ganglia. The role played by acetylcholine is far from being ancillary and it might influence striatal output by neuromodulating corticostriatal glutamatergic projections. All the basal ganglia nuclei also receive serotoninergic input from the rostral raphe nuclei in the midbrain and upper pons. The major target for the serotoninergic projections is the medium spiny neurons. Animal studies suggest that serotonin may exert a tonic inhibitory effect on striatal glutamatergic input and on stimulated dopamine release.

Glutamate

Glutamate is an excitatory neurotransmitter employed by corticostriatal, thalamostriatal and, thalamocortical projections. It is also the neurotransmitter employed by the STN; therefore glutamate is not only the major driving input to the basal ganglia but also participates in the intrinsic basal ganglia circuits. Glutamate transmission is modulated by dopamine, acetylcholine, GABA and nitric oxide. Glutamate has been recently related with the pathogenesis of PD.

Studies in rats have demonstrated an increase of concentration and release of glutamate from corticostriatal terminals in the striatum following nigrostriatal denervation. Accordingly, studies using glutamate receptor antagonists have shown that they can promote motor behaviours and intensify the effect of Levodopa (Lindefors and Ungerstedt, 1990; Blanchet et al., 1997).

GABA (Gamma amino butyric acid)

GABA is an inhibitory neurotransmitter used by all the basal ganglia nuclei with the exception of the STN. It is used by the medium spiny neurons to project to the other basal ganglia nuclei. At the same time the activity of medium spiny neurons is also regulated by GABAergic inputs from striatal interneurons. Moreover GABA is the neurotransmitter used by the output nuclei to project outside the basal ganglia. GPi/SNr neurons fire tonically at rest suppressing thalamocortical projections. Among all the cortical inputs that basal ganglia receive, they select the desired and appropriate input by suppressing the competing and unwanted programs (Hikosaka, 2007).

Dopamine

Dopaminergic system innervates all basal ganglia nuclei and probably exerts powerful modulatory control of the basal ganglia intrinsic circuits. It arises from three main groups of neurons designated as areas, A8 (retrorubral area, RRA), A9 (SNc) and, A10 (VTA). According to connectivity and morphological features midbrain neurons are divided in a ventral and dorsal tier. The dorsal tier includes the dorsal SNc and VTA, and the RRA. Neurons in the dorsal tier are calbindin-positive and innervate the ventral striatum and limbic and cortical areas, as well as the dorsal striatum. The ventral tier is located in the ventral part of the SN and VTA and project to the striatum. Cells in the ventral tier are

calbindin-negative and can be divided in a densocellular part and columns of dopaminergic neurons that penetrate deeply into the SNr. This last group seems to be the first to degenerate in PD.

The dopaminergic system is separated into three different projection systems: the nigrostriatal, mesolimbic and mesocortical system. Although the projections of these systems are clearly separated, their neurons of origin in the SN and VTA intermingle.

The nigrostriatal system arises from the SNc, VTA and RRA and project to the sensorimotor striatum. The mesolimbic and mesocortical systems originate in the VTA and in the dorsal tier of the SN and RRA. Mesolimbic system projects onto the limbic striatum, the amygdala and hippocampus, and mesocortical system projects onto prefrontal and associative cortices (Smith and Kieval, 2000).

There are five types of dopamine receptors that can be classified in two main groups, D1-like and D2-like. D1-like receptors include D1 and D5 receptors and stimulate adenylyl cyclase. D2-like receptors include D2, D3, and D4 receptors and inhibit adenylyl cyclase. They are heterogeneously distributed along the striatum and other basal ganglia nuclei.

The nigrostriatal dopaminergic projections are characterized by their convergence with cortical terminals on individual dendritic spine of the spiny neurons, which suggests that one of the main functions of dopamine is to regulate corticostriatal projections. Dopamine also modulates striatal efferents by facilitating the direct pathway via D1 receptors and inhibiting the indirect pathway via D2 receptors. Therefore the net effect of dopamine in basal ganglia is the facilitation of thalamocortical projections. Activation of dopamine

receptors influences neuroplasticity at corticostriatal synapses. Dopamine seems to be necessary not only for maintaining and modulating neuroplasticity but also for inducing it (long-term potentiation and long-term depression). Dopamine also induces plasticity exerted by other neurotransmitters (acetylcholine, nitric oxide, endogenous cannabinoids) (Calabresi et al., 2007).

The action of dopamine is more widespread; Dopaminergic neurons innervate the GP and the STN and probably regulate intrinsic circuits of the basal ganglia. Interestingly, dopaminergic neurons regulate not only the dopaminergic neurons themselves but also the release of GABA within the SNr and therefore the output projections of the basal ganglia.

The mesolimbic system is involved in reward. Dopamine neurons are activated by rewards and reward-predicting stimuli. Aversive stimuli however produce slower dopamine responses that consist predominantly on depression (Schultz, 2007). The striatum, frontal cortex, and amygdala also process specific reward information but do not participate in the prediction of reward.

Acetylcholine

The cholinergic system is of crucial importance in determining the final output from the striatum to other basal ganglia nuclei. Despite only around 1-2% of the striatal neurons are cholinergic interneurons, the striatum contains the highest concentration of all the cholinergic markers in the brain. Other source of acetylcholine to the striatum comes from the PPN. Cholinergic neurons receive glutamatergic and dopaminergic inputs from the cortex and the SNc, respectively. Although they are sparse, their dendritic trees arborize profusely projecting to the spiny neurons. The fact that cortical glutamatergic and striatal cholinergic inputs converge at the level of striatal projection neurons supports

the idea that Ach influences striatal function by modulating the corticostriatal glutamatergic transmission (Pakhotin and Bracci, 2007; Calabresi et al., 2000). Striatal cholinergic neurons act over two main subtypes of muscarinic receptors that have opposing effects: M1 receptors, which activate spiny neurons and M2 receptors with an inhibitory effect. The overall effect of the Ach in the striatum might be the long-term potentiation of the glutamate activation of striatal projection neurons.

The classical view that balance between dopamine and Ach is necessary for the normal motor control and that the imbalance of both systems is responsible for parkinsonian motor symptoms has been recently modified and the current evidence is that the main adaptive response to loss of striatal dopaminergic afferents is, in fact, the hyperactivity of corticostriatal glutamatergic neurotransmission. The benefits observed in PD with anticholinergic drugs might be explained by interaction with glutamate-mediated transmission. There is also evidence that striatal cholinergic neurons participate in reward-related learning although this process seems to be dopamine dependent.

This chapter has been adapted from Martinez-Torres I, Tisch S, Limousin P. The Basal Ganglia. In: Conn M. Eds. Neuroscience in Medicine 3rd edition. 2008; 401-414

2. PATHOPHYSIOLOGY OF THE BASAL GANGLIA IN PARKINSON'S DISEASE

2.1 THE BASAL GANGLIA IN PARKINSON'S DISEASE

The classical model of organization of the basal ganglia into a direct and indirect pathway has been used to explain the phenomenology observed in PD. Dopamine depletion produced an imbalance between the direct and indirect striatal output pathways. The loss of dopaminergic input to the striatum removes inhibition from the D2 receptor-mediated GABA/enkephalin indirect pathway to GPe, increasing the GABAergic inhibitory tone on the GPe-STN pathway. This pathway, which is also inhibitory, becomes underactive, and this results in increased burst firing of glutamatergic STN-GPi/SNr pathway, activating the GABAergic output of GPi and SNr towards the thalamus and brainstem. Dopamine depletion on the direct D1-mediated GABA/substance P/dynorphine pathway leads as well to decrease inhibitory tone on GPi/SNr. The final consequence of both processed is the increased activity of GPi/SNr neurons and therefore an increased inhibition of thalamocortical projections (Figure 1) (Obeso et al., 2000). Therefore, depletion of dopamine predicts an overinhibition of the GPe, disinhibition of the STN and increased excitation (indirect pathway) and reduction of inhibition (direct pathway) of GPi/SNr neurons. The result is an excessive activation of basal ganglia output neurons and excessive inhibition of motor circuitry, which leads to parkinsonian state.

The classical model for levodopa-induced dyskinesias (LID) proposed the opposite of events that occur in the parkinsonian state. Excessive dopaminergic stimulation of the striatum would in turn lead to a decreased basal ganglia

output to the motor thalamus by an increase of inhibition of the indirect pathway and reduced excitatory input to the direct pathway (figure 1). Several studies in animals and patients confirm the imbalance between direct and indirect pathways in parkinsonian and dyskinetic state (table 1).

However, this model has turned out to be far too simplistic to explain the amount of biochemical and electrophysiological data known nowadays and there are some observations that cannot be explained by this model. The most prevailing apparent paradox of experimental and clinical findings has been that although reduction of GPi neuronal firing rates is associated with choreic dyskinesias, lesions or blockade of the GPi is not (Marsden and Obeso, 1994b). According to the model, one would expect that the more GPi activity is decreased, the more severe dyskinesias should be. In contradiction to this expectation, dyskinesias are only not worsening by GPi lesions but they are largely improved after pallidotomy of DBS of the GPi. More recently, Dybdal and colleagues (Dybdal et al., 2013) reported that chemical blockade of the SNr in monkeys does in fact induce choreiform dyskinesias, which is exactly the expected consequence of reducing basal ganglia output. Nevertheless, this finding needs to be further confirmed.

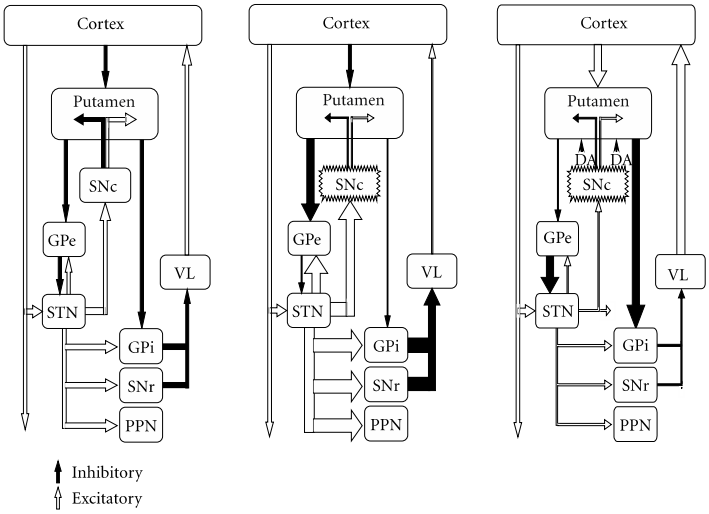

Figure 1 Classic model of BG in normal, parkinsonian and dyskinetic conditions. Black arrows indicate inhibitory projections and white arrows represent excitatory projections. The thickness of the arrows indicates the degree of activation of each projection. Note that the striatum communicates with output neurons in the globus pallidus pars intema (GPi) and substantia nigra pars reticularis (SNr) through a direct pathway, and with synaptic connections in the globus pallidus pars externa (GPe) and the subthalamic nucleus (STN) through an indirect pathway. Dopamine is thought to inhibit neuronal activity in the indirect pathway and to excite neurons in the direct pathway. In the parkinsonian state, dopamine depletion leads to disinhibition of dopamine D2-receptor-bearing striatal neurons in the indirect pathway leading to increased inhibition of the GPe, and disinhibition of the STN. The resulting overactivity in STN neurons leads to excess excitation of neurons in the GPi/SNr and overinhibition of thalamo-cortical and brainstem motor centres resulting in parkinsonism. Dyskinesia induced by L-dopa is characterized by reduced activity in the STN. The classical model proposes that this is due to dopamine-induced overinhibition of striato-GPe neurons, resulting in excess inhibition of the STN and reduced activation of GPi/SNr. The net result is reduced inhibition of thalamo-cortical neurons with excess drive of cortical motor areas resulting in dyskinesia. Abbreviations: DA, dopamine; PPN:

pedunculopontine nuclei; SNc, substantia nigra pars compacta; VL, ventralis lateralis (Adapted from Guridi et al., 2012).

Table 1. Observations supporting the classical model

- In MPTP-treated monkeys, an increase in STN and GPi/SNr activity has been demonstrated using 2-deoxyglucose uptake as a marker of synaptic afferent activity (Mitchell et al., 1989), *in situ* hybridization of cytochrome oxidase subunit I mRNA as a measure of mitochondrial activity (Vila et al., 1997), glutamic acid decarboxylase (GAD) mRNA as a measure of GABA activity (Herrero et al., 1996) and neurophysiological studies measuring the mean neuronal firing rate in single-cell recordings (Filion and Tremblay, 1991).
- Lesions or high frequency stimulation of the STN in MPTP-treated monkeys and patients with PD improves parkinsonian features and reduces hyperactivity in the GPi/SNr (Wichmann et al., 1994; Guridi et al., 1996; Limousin et al., 1998).

Abbreviations: GPi: Globus pallidus pars interna internus; MPTP: 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine; SNr: substantia nigra pars reticulate; STN: subthalamic nucleus (Adapted from Obeso et al., 2000).

Considering the limitations of the classical model, Obeso and colleagues (2004) proposed a new scheme for the model. The new model incorporates dopaminergic projections to other basal ganglia nuclei rather than striatum and the importance of internal loops such as the STN-GPe-GPi loop. This model proposes that in the presymptomatic phase dopamine depletion would affect mainly projections to STN rather than striatal innervation, rendering the STN hyperactive. Therefore the GPe would be overstimulated by the STN and functionally operative. In turn this would lead to an increased inhibition of GPi, which may partially compensate for the augmented excitation from the STN and reduced inhibition on the direct pathway. With progression of nigrostriatal degeneration both striatopallidal projections are altered and parkinsonian symptoms become evident. There is an increased inhibition of the GPe from the striatum, which becomes hypoactive and is no longer compensated by STN

hyperactivity, resulting in overactivity of GPi output and abnormal inhibition of motor areas (figure 3).

Additionally, glutamate corticostriatal system has become more and more involved in PD pathophysiology. In PD and animal models, striatal dopaminergic denervation alters glutamatergic synapses in medium spiny neurons, affecting their capacity to function normally and to modulate basal ganglia output. This hypothesis is supported by the fact that cortical stimulation in animal PD models reverses akinesia and reduced firing rate of GPi and STN (Drouot et al., 2004).

Despite the complexity derived from cellular and electrophysiological studies in BG functioning, the hypothesis of the classical model has been fully supported using transgenic animals and optogenetics (Kravitz et al., 2010). In this study, direct stimulation of the indirect pathway promoted movement arrest while activation of the direct pathway was prokinetic and ameliorated parkinsonian signs in a mouse model of PD.

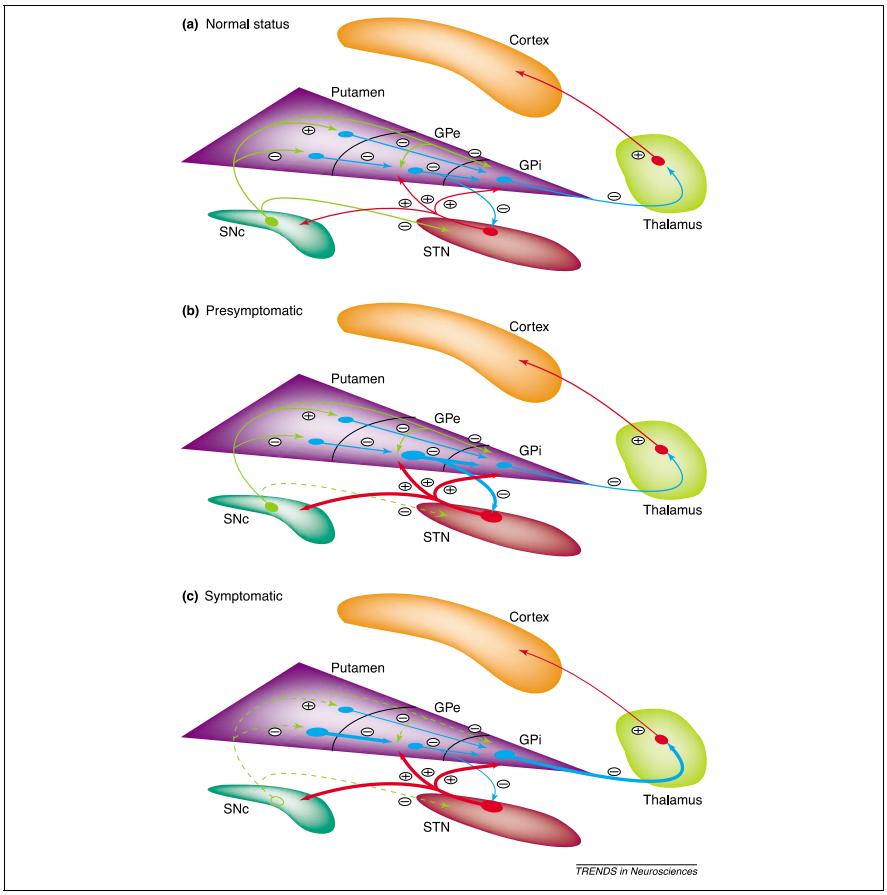

Figure 3 Modification of basal ganglia circuitry in different stages of Parkinson's disease. (a) Main basal ganglia connections in the normal state. Green arrows correspond to the dopaminergic nigrostriatal and extrastriatal projection. Blue and red arrows indicate inhibitory GABAergic efferents and excitatory glutamatergic efferents, respectively. Thickness of the arrows indicates relative functional activity. Abbreviations: GPe, globus pallidus pars externa; GPi, globus pallidus pars interna; SNc, substantia nigra pars compacta; STN, subthalamic nucleus. (b) Proposed basal ganglia modifications induced by dopamine depletion in the presymptomatic stage of Parkinson's disease. Loss of dopaminergic projections leads to hyperactivity of the STN before the onset of functional changes in the putamen. GPi output is maintained at this stage through increased inhibition from the GPe, which is excited by the

STN. (c) Further dopamine loss in the putamen reaches a level that cannot be compensated for by intra- striatal mechanisms. This decreases inhibition of the 'direct' putamen–GPi projection and excessive inhibition of the GPe, which becomes hypoactive. The latter leads to further hyperactivity of the STN and GPi, accounting for the onset of parkinsonian motor features. (From Obeso et al., 2004).

2.2 OSCILLATORY ACTIVITY OF THE BASAL GANGLIA

Due to the limitations of the classical model, over the past decade attention has switched from considerations of discharge rate to characterisation of synchronised activity within the BG network. There is increased evidence of a variety of oscillatory phenomena in the BG and in associated regions of the thalamus and cortex. Most of these studies have been performed in rodents and primates and significant advances have been done from implanted DBS electrodes in PD patients. It now appears that exaggerated synchronisation of neural activity plays an important role in pathological conditions. Although less well established, oscillatory activity is also present in normal conditions and might be important for normal motor processing (Gatev et al., 2006).

There are two principal modes of synchronised activity within the human subthalamo-pallidal-thalamo cortical circuit: < 30 Hz and > 60 Hz. Local field potential activity in the 8-30 Hz range is the best characterized. Because its association with pathological conditions it has been further subdivided into two bands: 8-13 and 14-30 Hz. The later range is named as "beta band" and it is particularly prominent in parkinsonian states on withdrawal of dopaminergic treatment in both the STN and GPi.

Oscillatory activity is modulated by movement as well as by the level of dopaminergic activity; beta band is associated with maintenance of posture and inhibition of new movements; a strong beta band in the STN and GPi is found in the akinetic state and it is suppressed prior to and during movement as well as following dopaminergic treatment. On the contrary, activity at frequencies above 60 Hz is found in parkinsonian patients during levodopa treatment and, these oscillations are enhanced by voluntary movement (Brown, 2003). These findings suggest that beta band activity would be antikinetic while activity above 60 Hz would be mostly prokinetic. On the other hand oscillatory activity at low frequencies (below 10 Hz) have been linked to dystonia and levodopa induced dyskinesias in PD patients (Silberstein et al., 2003; Alonso-Frech et al., 2006).

PATHOLOGICAL OSCILLATORY ACTIVITY IN BASAL GANGLIA-THALAMOCORTICAL CIRCUITRY IN PARKINSON'S DISEASE

Loss of dopaminergic innervation is known to induce abnormalities in neuronal firing rate in the BG and connected regions of the thalamus and cortex. (Rommelfanger and Wichmann, 2010). Considering the mass of evidence in conflict with the classical animal model, it now seems more clear that neuronal discharge pattern, more than firing rate alone, plays a central role in the genesis of parkinsonian signs. Increased burst neuronal discharge and abnormal synchronization in the neurons of the GPi, GPe, STN, thalamus and motor cortices - in animal models and/or PD patients – have been reported (Rubin et al., 2012; Brown, 2003). Burst discharges are often described as "oscillatory" and, indeed both may represent two aspects of one underlying phenomenon (Rivlin-Etzion et al., 2008). Oscillatory activity has been documented in the

STN, GPi, GPe and tonically active striatal interneurons in animal models and PD patients (Rubin et al., 2012). There is also evidence for increased synchrony in the neurons of the BG nuclei in PD (Hammond et al., 2007). Excessive synchronization is lower with systemic dopamine receptor agonist treatment, suggesting that segregation of neuronal activity is, at least in part, maintained by dopamine presence. Synchronous firing – closely linked to oscillatory discharges – is found across the BG nuclei (Hammond et al., 2007). Oscillatory and synchrony recorded at the level of single neurons has been shown to be coherent with concomitant recorded beta-band LFP oscillations (Kuhn et al., 2005). Synchronized oscillatory activity in the BG is closely linked to oscillations in cortex in Parkinsonism, suggesting the existence of large-scale oscillatory synchronization of the entire basal ganglia-thalamocortical circuitry. Global engagement of basal ganglia-thalamocortical circuitry in synchronized oscillations may severely disrupt information processing at all levels of the circuitry and contribute to akinesia. However, the mechanism by which dopamine loss promotes synchrony and the anatomical location at which this occurs is still uncertain. As commented above, dopamine input is not only lost in the striatum but also in other BG nuclei and BG-related structures (thalamus and cortex), which may therefore suffered changes in their neuronal activity (Rommelfanger and Wichmann, 2010). There is experimental evidence that oscillatory patterns can arise and perpetuate in the GPe-STN loop (Holgado et al., 2010). Other mechanism proposed is oscillations driven to the STN by cortico-subthalamic inputs and propagated to related nuclei (Magill et al., 2004).

LFP recording from DBS implanted electrodes in GPi and STN of PD patients after an overnight withdrawal of antiparkinsonian medication have shown power spectra to predominate in the 8 to 30 Hz range - beta band – (Brown et al., 2001; Levy et al., 2002). Levodopa reduces beta synchrony and this reduction is correlated with improvement in rigidity and bradykinesia (Kühn et al., 2006). In contrast to these studies, several animal studies have found that oscillatory activity appears only after the emergence of parkinsonism and, therefore, cannot be fully responsible for it (Leblois et al., 2007). Motor impact of BG oscillations at various frequencies can be tested through the implanted DBS electrodes. Motor impairments can be induced with stimulation at beta band frequencies (Moro et al., 2002; Timmermann et al., 2004; Chen et al., 2007; Eusebio et al., 2009) while high frequency stimulation (above 100 Hz) is widely used because its antikinetic effects (Moro et al., 2002). Indeed, several studies corroborate a reduction of beta LFP power in the STN after STN high frequency stimulation Bronte-Stewart et al., 2009; Kühn et al., 2008; Meissner et al., 2005) although this was not replicated in another study (Foffani et al., 2006).

3. SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE

Overview of Parkinson's disease treatment

Because most of the major motor symptoms of PD are related to striatal dopaminergic deficit, the first line of treatment is dopaminergic medication. Levodopa continues to be the most powerful dopaminergic agent. Unfortunately up to 75% of patients develop motor complications (motor fluctuations and dyskinesias) after 5 years of treatment (Quinn et al., 1987). The next most powerful dopaminergic drugs after levodopa are the dopamine agonists: bromocriptine, pergolide, lisuride, piribedil, ropinirole, pramipexole, rotigotine, cabergoline, apomorphine. They may differ in their affinity for dopamine receptor subtypes and in their effectiveness. The majority of them are effective orally, while others have to be administered subcutaneously (apomorphine) or trandermically (rotigotine). They can be used as monotherapy or in combination with levodopa. They are less powerful than levodopa but they are less likely to induce dyskinesias (Schrag et al., 1998). However, adverse effects are more common with dopamine agonist than with levodopa. Other drugs aim to reduce levodopa metabolism. Catechol-O-methyltransferase (COMT) inhibitors - tolcapone and entacapone – extend the plasma half-life of levodopa and prolong the duration of action of each dose of levodopa. Therefore they have been proved to be useful treating the wearing off phenomenon. Monoamine oxidase (MAO) inhibitors type B – selegiline and rasagiline - offer mildly symptomatic benefit. A possible neuroprotective effect has been shown with rasagiline (Olanow et al., 2009). Other non-dopaminergic agents are also useful to treat some motor symptoms. Anticholinergic drugs, although less effective

than dopaminergic drugs, may be especially useful for alleviating tremor. Amantadine, which has both dopaminergic and antiglutamatergic properties, reduces choreic dyskinesias induced by levodopa (Del Dotto et al., 2001). Other agents, such as adenosine A2A antagonist have shown conflicting effects.

In the lack of any neuroprotective treatment, onset of PD treatment should be delayed until symptoms become troublesome to the patient. Older patients are usually started on levodopa due to the risk of side effects related to dopamine agonists. In younger patients (less than 60 years of age) treatment is started with dopamine agonist in order to postpone levodopa induced motor complications. However, as the disease progresses levodopa has to be added to the treatment. Motor fluctuations in an early stage can be improved by adding COMT inhibitors, MAO inhibitors and decreasing the interval of levodopa doses. Peak of dose dyskinesias may benefit by adding amantadine and also fractioning the dose of levodopa. However, when motor fluctuations and dyskinesias aggravate, oral treatment may be insufficient controlling the symptoms. At this stage, surgical therapies, such deep brain stimulation, or continuous infusion of dopaminergic agents – subcutaneous apomorphine or intrayeyunal levodopa/carbidopa – provide additional benefit.

Deep brain stimulation for Parkinson's Disease

Deep brain stimulation (DBS) can provide additional help for selected patients whose symptoms are not controlled sufficiently by medication. DBS has progressively replaced brain lesioning, such as thalamotomies and pallidotomies, over the last 20 years. After a few earlier reports on the use of DBS (Sem-Jacobsen, 1965; Bechtereva et al., 1972), the first target in the modern era of DBS was the ventro-intermediate nucleus (Vim) of the thalamus

in 1985 (Benabid, 1987). Thalamic DBS was initially performed contralateral to thalamotomies to try to reduce the morbidity of bilateral ablative procedures, particularly on speech and balance. In view of its efficacy on tremor, adaptability, and low morbidity, thalamic DBS was progressively performed bilaterally and the positive effect on tremor was confirmed (Benabid et al., 1991). Thalamic DBS provided limited effect on other symptoms, however, such as limb bradykinesia or rigidity and no favourable effects on gait and balance.

The limits to the effectiveness of thalamic DBS prompted the application of this procedure to new targets, the internal part of the globus pallidus (GPi) and the subthalamic nucleus (STN), in parallel in 1993 (Limousin et al., 1995; Siegfried and Lippitz, 1994). The application of DBS to GPi was based on the noted similarities of the effects of a lesion and high-frequency stimulation to the thalamus and the knowledge on the effect of pallidotomies (Laitinen et al., 1992). The application to the STN was based on basic research work on the STN in 1-methyl1-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys; the animals displayed and excess of activity in the STN and improvement of parkinsonian symptoms with lesion or high-frequency stimulation of the STN (Bergman et al., 1990; Aziz et al., 1992; Benazzouz et al., 1991). STN has progressively become the preferred target for DBS in PD, because it has been found to have a positive effect on a wide range of symptoms (Limousin et al., 1998). Furthermore, STN DBS has been shown to be superior to best medical treatment (Williams et al., 2010; Weaver et al., 2009; Deuschl et al., 2006) and it is a cost-effective procedure (Valldeoriola et al., 2007; Fraix et al., 2006; Meissner et al., 2005; Weaver et al., 2012a; Dams et al., 2013). Literature suggests a greater impact of STN DBS on parkinsonian symptoms; however

three randomized controlled trials comparing the effect of both STN and GPi DBS found similar effectiveness for both targets but lower risk for cognitive and neuropsychiatric problems favouring the GPi (Anderson et al., 2005; Follet et al., 2010; Weaver et al., 2012b). More recently, another randomized trial found similar effectiveness for STN and GPi and similar frequency of cognitive and psychiatric side effects. Nevertheless, STN DBS was associated with larger improvements in the off-medication phase and levodopa equivalent daily dose reduction, suggesting that STN should be the preferred target (Odekerken et al., 2013).

STN DBS has the advantages of reduction of dopaminergic medication and needs lower stimulation parameters than GPi DBS leading to a longer battery life. Nevertheless it has been found to be associated with greater risk of cognitive and neuropsychiatric problems compared to GPi DBS

Long term STN DBS outcome has shown a progressive decline over time. Axial symptoms such as freezing, postural stability, and speech deteriorate both off and on-medication. However at 5 and 8 years STN DBS still provides a 55% and 39% improvement on off-medication scores, respectively (Krack et al., 2003; Fasano et al., 2010). Nevertheless, benefit on dyskinesia and antiparkinsonian medication remains steady over time.

Preoperative response to levodopa predicts good STN DBS outcome in the short term (Welter et al., 2002). In the long term STN DBS outcome is mainly limited by deterioration on axial symptoms. Main predictors for long-term deterioration of postural stability are worse scores on postural stability pre-DBS both off and on-medication and higher doses of dopaminergic medication pre-DBS (Fasano et al., 2010).

4. STIMULATION PARAMETERS IN SUBTHALAMIC NUCLEUS DEEP BRAIN STIMULATION: STRATEGIES FOR SELECTION OF APPROPIATE STIMULATION PARAMETERS

STN DBS is a clinically effective treatment for selected patients with PD. Although high-frequency (HF) DBS mimics the effects of ablation, its mechanism of action is unclear. Presently there are few guidelines to inform selection of stimulation parameters (SP), and programming of stimulation is essentially an empirical process, with associated difficulties of time and expenses. Along with accurately placed electrodes, successful DBS depends on properly set stimulation parameters. Rationally selected stimulation parameters may increase the range between clinical effects and side effects, use less power, and required less time-intensive programming. The parameters that can be controlled are: electrode polarity (electrode's geometry), voltage, pulse width duration and frequency (figure 1).

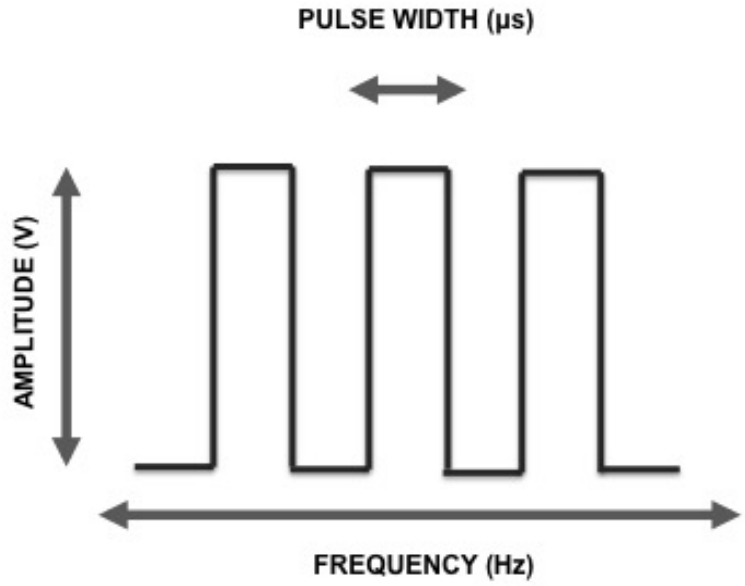

Figure 1. Stimulation parameters for deep brain stimulation

4.1 ELECTRODE GEOMETRY

The DBS electrode used in STN DBS (model 3389, Medtronic Neurological Division, Minneapolis, Minnesota, USA) has four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a centre to centre separation of 2 mm. Contact 0 is the lowermost and contact 3 is the uppermost. Electrode geometries include monopolar and bipolar stimulation. In each configuration there is a cathode or negative electric potential (sink of current), and an anode, or positive electric potential (source of current). The neuroestimulator can only be set as an anode, and if so, no electrode's contact can be set as an anode. Current flows from the anode to the cathode, depolarizing the neuronal elements nearest the cathode and hyperpolarizing neuronal elements nearest the anode. In monopolar stimulation one (single monopolar) o more contacts (double, triple monopolar) of the electrode are

selected to be the cathode and the neurostimulator is set as the anode. In these cases the anode and cathode are relatively distant from each other leading to a broad extracellular electric potential distribution. In bipolar stimulation one or more electrode's contact are set as the cathode and one as the anode, and the current is more focus than in monopolar configuration. Monopolar stimulation is generally the first option for current delivery. Double monopolar is reserved when a single electrode's contact is insufficient to produce an optimal effect. Bipolar stimulation may be preferred if a narrower current to reduce side effects is desired (figure 2) (Volkmann et al., 2002; Deuschl et al., 2006).

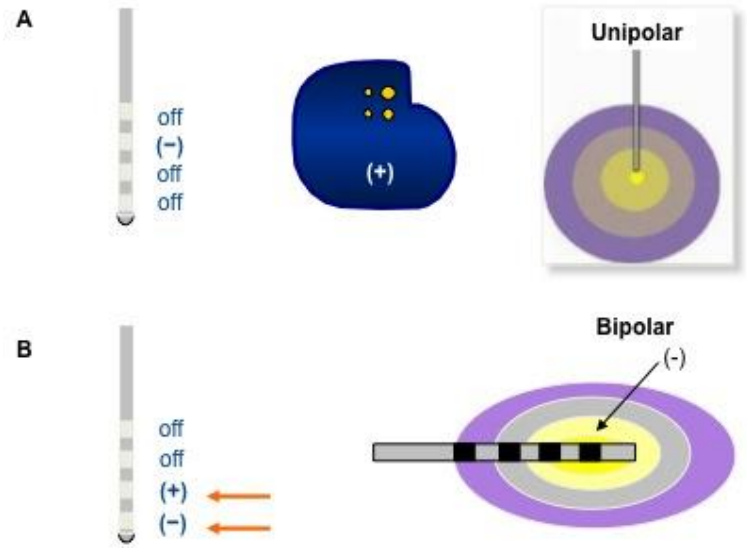

Figure 2. Electrode's geometry configuration and current field generation. A) Unipolar or monopolar stimulation and B) Bipolar stimulation. In monopolar configuration radial current diffusion covers an approximate spherical field around the electrode and lower stimulation intensity is required than with bipolar to achieve equivalent clinical benefit. With bipolar stimulation current field is narrower and more focussed with maximal effect near the cathode; higher

stimulation intensity is required than with monopolar stimulation (Modified from IMPACT-MD: DBS Programming and Troubleshooting, Medtronic).

4.2 STIMULATION PARAMETERS

Stimulation parameters that can be adjusted are voltage, pulse width and frequency. While voltage and pulse width can be set independently for each channel (right or left electrode), frequency has to be set at the same range for both. Mean STN DBS stimulation parameters are 3 volts (V), 82 microseconds (μs), and 152 Herts (Hz) (Obeso et al., 2001). The optimal combinations of the stimulation parameters would best reduce symptoms, minimize side effects and power consumption.

AMPLITUDE

The stimulus amplitude required to activate neural elements depends on the spatial relationship between the electrode and the nerve fibres. As the distance between the active contact and the neural element is increased, the stimulus amplitude required to stimulate neural elements increases non-linearly. Voltage is a crucial factor for ameliorating parkinsonian symptoms (tremor, rigidity and bradykinesia). Nevertheless, DBS studies have shown that the clinical benefits saturate above a certain voltage. Tremor, bradykinesia and rigidity improved between 2 and 3 volts (V) and do not continue to improve beyond 3 V (Moro et al., 2002). Besides higher voltage is associated with adverse effects.

FREQUENCY

DBS has been found to be effective for reduction of rigidity, tremor and bradykinesia at frequencies above 50 Hz (Limousin et al., 1995) with a

maximum benefit at 185 Hz but larger stimulation amplitudes are required at low frequencies. A significant improvement on symptoms occurs increasing frequency from 50 to 130 or 185 Hz, whereas no significant improvement is found for increments from 130 to 185 Hz (Moro et al., 2002). A positive effect on freezing episodes has been found with stimulation at 60 Hz (Moreau et al., 2008; Xie et al., 2012). Frequency of 5 Hz significantly worsens bradykinesia and frequencies around 30 Hz can induce postural tremor (Moro et al., 2002). Rigidity improves above 33 Hz and continues improving up to 185 Hz. Bradykinesia and tremor do not improve with frequencies below 50 Hz regardless the voltage used (Moro et al., 2002). This shows that frequency is along with voltage a critical parameter for DBS.

PULSE WIDTH

Pulse widths used in STN DBS are usually of 60 or 90 μs. Short pulse widths increase the therapeutic window (range from clinical benefit and appearance of adverse effects). However, as pulse width is decreased the stimulus intensity to elicit a clinical improvement on parkinsonian symptoms increases (Rizzone et al., 2001). Improvement on parkinsonian symptoms are seen with higher pulse widths but the effect is not as clear as for voltage or frequency. Bradykinesia improves at pulse widths of 60 μs while rigidity experience a progressive improvement as pulse width is increased. Variation of pulse width does not affect tremor (Moro et al., 2002). This favours the use of narrowest pulse widths (60 μs), a setting that has a beneficial impact on energy consumption.

4.3 CURRENT CHALLENGES FOR STIMULATION PARAMETERS SELECTION

Current challenges for selection of optimal stimulation parameters include a large number of degrees of freedom, electrode geometries combinations, the unknown effects of stimulation, the complexity of the responses and the variability and uncertainty in electrode positioning.

Electrode geometry results in 65 possible electrode configurations and there are nearly 13 000 combinations of pulse width, frequency and voltage within the recommended charge density (Kuncel and Grill, 2004).

The complexity of symptoms responses also contributes to the difficulty of selecting the appropriate stimulation parameters. The impact of stimulation on rigidity, tremor and bradykinesia is usually seen within minutes, although reaching a maximal effect may take longer (from hours to days) (Krack et al., 2002; Volkmann et al., 2002; Temperli et al., 2003). Programming is further complicated by the residual effect of stimulation as symptoms may take hours to return completely once the stimulation is switched off (Temperli et al., 2003). This has probably a major impact when programming involves a change in the stimulated contact and therefore of the stimulation area.

Since the mechanism of action of DBS is not well known, there is no way to select stimulation parameters bases on its physiological action. General guidelines are available to help clinicians selecting the appropriate parameters (Krack et al., 2002; Volkmann et al., 2002); however, these algorithms are vague and based on the acute effect of the stimulation and do not warrant a long-term sustained benefit. Furthermore, placebo effect is well known to occur in Parkinson's disease and it is present on STN DBS programming as well,

especially for bradykinesia (Mercado et al., 2006). One of the aims of this study is to investigate whether the acute and chronic effect of stimulation parameters differ and if the acute effect can consistently predict a sustained benefit.

5. SUBTHALAMIC AREA AND OPTIMAL STIMULATION SITE IN STN DBS FOR PARKINSON'S DISEASE

5.1 THE SUBTHALAMIC AREA: SUBTHALAMIC NUCLEUS AND SURROUNDING STRUCTURES

The subthalamic nucleus is a complex, biconvex lens-shape structure surrounded by dense bundles of myelinated fibres. Its dimensions are approximately 9x7x4 mm (length x height x breadth). STN is bordered on its anterior and lateral sides by fibres of the internal capsule, while posteromedially limits with the prelemniscal radiation and red nucleus. The dorsal border of the STN is with the Forel's Field H2 (lenticular fasciculus) anteriorly, and field H1 (thalamic fasciculus) posteriorly (Gross et al., 2006). Dorsomedially to the STN lays the rostral zona incerta and posterior to the STN the caudal zona incerta (Plaha et al., 2006). Ventral limits of the STN are the cerebral peduncle and the substantia nigra ventromedially (Gross et al., 2006). Pallidolfugal fibres crossing the internal capsule pass over the dorsal and medial surfaces of the STN (figure 1).

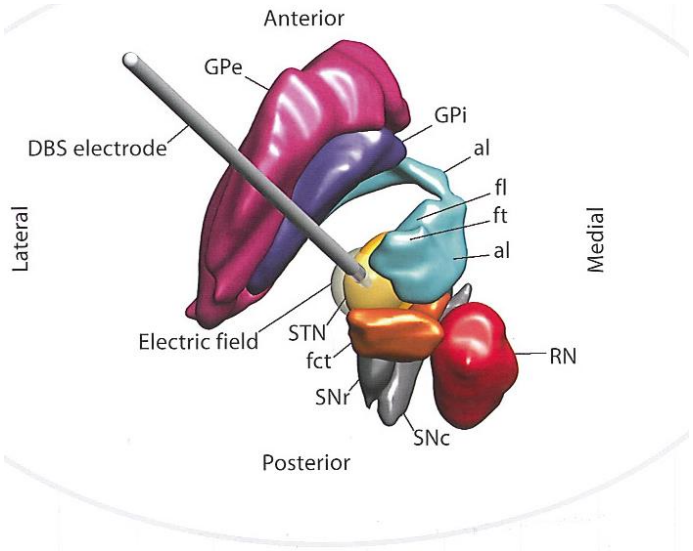

Figure 1. Superior view of a three-dimensional atlas model of the subthalamic area. Subthalamic nucleus (STN), Red Nucleus (RN), fasciculus cerebellothalamicus (fct), ansa lenticularis (al), fasciculus lenticularis (fl), fasciculus thalamicus (ft), substantia nigra pars reticulata (SNr), substantia nigra pars compacta (SNc), internal segment of the globus pallidus (GPi), and external segment of the globus pallidus (GPe). A DBS electrode is placed in the posterodorsal area of the STN (From Aström et al., 2010).

5.2 OPTIMAL STIMULATION SITE FOR STN DBS IN PARKINSON'S DISEASE

Since the introduction of STN DBS as a surgical treatment for Parkinson's disease, several studies have reported significant benefits on PD motor symptoms both in the short and long term (Limousin et al., 1998; Krack et al., 2003; Fasano et al., 2010). High frequency stimulation mimics some effects induced by lesions in the same target (Aziz et al., 1992). However, despite the similitude, the mechanism of action of DBS is poorly understood. Subthalamic nucleus is the most commonly used target for PD. Nevertheless there is substantial debate regarding the optimal anatomical stimulation site within the

subthalamic area. The areas most frequently proposed are the dorsolateral segment of the STN (known to be its sensorimotor territory) (figure 2), and the region dorsally adjacent to it, in the region of pallidofugal fibres and rostral zona incerta (table 1). Some groups had found that although stimulation of both areas are equally effective, active contacts located in the fibres tracks require less stimulation power (Voges et al., 2002; Hamel et al., 2003). Yet other groups have proposed other areas, such as caudal zona incerta (Plaha et al., 2006) and prelemniscal radiation (Velasco et al., 2001).

Even though the mechanism of action of DBS remains controversial it is well known that stimulation does not only affect cell bodies but also fibre tracks “en passant” along the stimulation area. Since excitability of axons is greater than that of the soma, modulation of subthalamic projections is very likely to occur (Hamel et al., 2003). Taking into account that electrical stimulation driven through the surface of each contact of the quadripolar electrode is capable to affect a tissue area of 2-3 mm (Ranck, 1975) and, given the small size of the STN and its close relationship with surrounding fibres; stimulation through contacts located at both dorsolateral segment of the STN or just dorsal to it would most likely affect both regions.

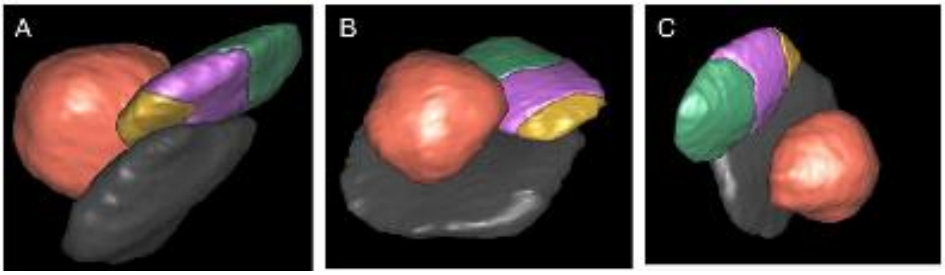

Figure 2. The three functional territories of the subthalamic nucleus. The sensorimotor territory is in green, the associative territory in purple, and the limbic territory in yellow. Anterior view (A), lateral view (B) and superior view (C) with the red nucleus (in orange) and substantia nigra (in grey) (From Yelnik et al., 2007).

Table 1. Optimal stimulation sites proposed for STN DBS in PD

Stimulation sites	References
Dorsolateral STN	Lanotte et al., 2002 Saint-Cyr et al., 2002 Yelnik et al., 2003 Hamel et al., 2003 Zonenshayn et al., 2004
Dorsolateral border zone	Lanotte et al., 2002 Saint-Cyr et al., 2002 Voges et al., 2002 Hamel et al., 2003 Herzog et al., 2004 Godinho et al., 2006
Caudal ZI	Kitagawa et al., 2005 Plaha et al., 2006
Prelemniscal radiation	Velasco et al., 2001

Active contact of the DBS electrode for chronic stimulation is selected on based of its clinical efficacy. Therefore its position reflects the optimal anatomical site as its efficacy is systematically compared with that of the other contacts. Most of the studies reported above have used this approach to define the optimal stimulation site. With current guidelines for stimulation programming, selection of the optimal contact is performed based on the acute effect and usually without objective quantification of symptoms. Furthermore it is assumed that stimulation parameters and stimulated contact remained stable after the first year after surgery. However Moro and co-workers demonstrated substantial improvement with reprogramming in otherwise STN DBS chronic stable patients (Moro et al., 2006). In the subgroup of patients that experienced improvement in motor symptoms, active contact change in 68% of the electrodes. A previous study performed at our institution (N=22, restropective data from time to surgery until six months after) (Odenkerken et al., 2005 unpublished) showed that active contact moved to a more dorsal, posterior and, right position in some patients while in others, remained unchanged. Therefore as stimulation site may change over time, probably reflecting suboptimal selection of the active contact in previous programming sessions; its seems rational to asses the optimal stimulation site taking into account previous changes in the stimulation parameters with objective quantification of symptoms. This is one of the points that this study tried to address. Evolution of the stimulation site was studied throughout three consecutive adjustment sessions, evaluating both acute and chronic effect. Final electrode position would represent the optimal stimulation site. Site of stimulation was determined by visualizing electrode's artefact on postoperative MRI. Electrode's contacts

coordinates were transposed onto preoperative MRI and site of stimulation was defined based on anatomical criteria. This certainly represents a more accurate approach than to transpose coordinates onto stereotactic brain atlases given the interindividual variability (Ashkan et al., 2007). However one limitation of this method is to define the rostro-caudal axis, as MRI slices used in this study had 2 mm thickness. Furthermore, we investigated the relation of the number of electrode's contacts considered to be optimally located with clinical outcome, types of adjustment required and efficiency of stimulation.

5.3 THE VALUE OF MAGNETIC RESONANCE IMAGING FOR SELECTION OF THE OPTIMAL THERAPEUTIC CONTACT

As previously stated, the best electrode's contact is selected based on its clinical efficacy (the best contact will be the most effective at lowest voltage and highest threshold for side effects). Selection of the optimal stimulation parameters requires well-trained neurologists and collaboration from patient. Several difficulties are encountered when programming stimulation parameters. First stimulation parameters should be programmed in the condition off medication in order to be able to test the effect of the stimulation on parkinsonian symptoms. Even when dopaminergic medication is withdrawn for 12 hours patients may not be in a complete off-state and therefore off-symptoms become difficult to assess. In addition, withdrawal of dopaminergic medication may cause discomfort and may difficult transfer of patients to clinic. Besides it is a time consuming procedure and frequently the response from stimulating each contact serially at several-minute intervals can be confounded by the carry over effects of the previously stimulated contact. Adequate patient

cooperation, which can be easily affected by patient's motivation, is essential. This renders the outcome of DBS programming highly dependent on the neurologist capability and patient state and cooperation.

A more rational and objective approach for selection of the active contact may be to select the contact based on its anatomical location. Although most favourable site of stimulation remains controversial it is quite likely that dorsolateral segment of STN or the area just rostral to it may represent the optimal stimulation site. Given the dimensions of the 3389 Medtronic DBS electrode used for STN DBS (7.5 mm length with four platinum/iridium contacts of 1.5 mm each separated by 0.5 mm gaps) and surgical targeting methods, at least one or two contacts will lay within the STN (one in the sensorimotor part of the STN) and one in the rostral area above it. Therefore, selection process for active contact could be limited to two contacts. This approach may simplify current strategies of stimulation parameters selection and would be in benefit of the patients and health system costs. In this direction we explored the concordance of active contact and best MRI contact. Best MRI contact was defined as the one to be located within the STN (central or superior segment) or just rostral to the superior segment. A good concordance would support the hypothesis that active contact can be selected based on its anatomical location.

6. SUBTHALAMIC NUCLEUS LOCAL FIELD POTENTIALS RECORDINGS IN STN DBS IN PARKINSON'S DISEASE

Therapeutic efficacy in STN DBS is limited by difficulties in consistently and correctly targeting the STN. Misplaced electrodes might result in poor outcome of STN DBS and side effects. Besides direct targeting on MR images, microelectrode recordings are often performed to verify localization of the functional sensorimotor STN during surgery (Gross et al., 2006). However, this technique prolongs surgery time and has been associated with increased risk of intraoperative haemorrhage (Binder et al., 2005). In addition, microelectrodes must be withdrawn prior to introduction of the DBS electrode, which may introduce further errors, especially in the rostro-caudal plane. Local field potentials (LFP), which translated the activity of aggregate activity of neuronal populations, can be easy and quickly recorded from the DBS macroelectrode. Although a clear connection between LFP beta activity and symptoms of PD still remains uncertain (Kühn et al., 2009), oscillatory activity in this frequency range can be considered a hallmark of parkinsonian STN, in particular of its dorsolateral part (Kühn et al., 2005; Zaidel et al., 2010). Pathological oscillations are suppressed by volitional movement (Amirnovin et al., 2004; Zaidel et al., 2010), dopaminergic treatment (Brown et al., 2001; Levy et al., 2002; Priori et al., 2004; Weinberger et al., 2006) and STN DBS in some studies, but not others (Foffani et al 2006; Wingeier et al., 2006; Kühn et al., 2008; Rossi et al., 2008; Bronte-Stewart et al., 2009). Moreover, the degree of suppression of the beta oscillations by antiparkinsonian treatment correlates with improvement of the parkinsonian symptoms, bradykinesia and rigidity, although not tremor (Kühn et al., 2006; Kühn et al., 2009). Dorsolateral STN is considered the

sensorimotor part of the STN (Kühn et al., 2005; Weinberger et al., 2006) and implantation of electrodes within this area seems to provide optimal benefits (Herzog et al., 2004; Godinho et al., 2006; Maks et al., 2010). Therefore it seems plausible to suggest that beta oscillatory activity would mark the sensorimotor territory of the STN and that stimulation within this area would provide a favourable outcome on STN DBS. In this line, Chen and coworkers (2006) found that power in the beta band recorded from the DBS electrode intraoperatively showed excellent correlation with the clinical improvement occurring immediately after the implantation of the DBS electrode (stun effect) and with its accurate location within the STN as judged by postoperative stereotactic MRI.

One of the hypotheses of this thesis derived from this work and postulate that the presence of a peak in the beta activity along the trajectory of the DBS will predict a good outcome of STN DBS and optimal stimulation site would correspond to the level of maximum intraoperative beta activity recorded. Hence, coincidence of the level for chronic stimulation and the beta activity level would provide further support for the clinical relevance of the beta oscillatory region within the STN.

II. OBJECTIVES

OBJECTIVES

The aim of this research is to evaluate means to optimise the selection of the stimulation parameters in patients with Parkinson's disease treated with STN DBS. For this purpose several studies were performed pursuing the following objectives:

Study 1: Longitudinal assessment of the impact of consecutive sessions for adjustment of stimulation parameters of STN DBS in PD patients: evaluation of the acute and chronic effects of stimulation parameters

1. To evaluate the acute and sustained effect of adjustment of stimulation parameters on motor symptoms
2. To evaluate the acute and sustained effect on motor symptoms of the different types of adjustment of stimulation parameters.
3. To identify which factors involved in the programming of the stimulation parameters will be predictive of the best clinical outcome in reprogramming STN DBS.

Study 2: Clinical outcome of STN DBS with reprogramming in PD

1. To assess whether intensive programming of stimulation can lead to additional benefits in STN DBS for PD.

Study 3: Analysis of the anatomical stimulation site in STN DBS for PD

1. To study the evolution of the stimulation site throughout consecutive programming sessions in STN DBS
2. To study the optimal stimulation site in STN DBS after intensive programming of stimulation parameters in STN DBS
3. To evaluate whether anatomical information can help in the selection of the therapeutic contact.

Study 4: Analysis of type of adjustment "change in contact"

1. To study the behaviour of the type of adjustment "change in contact" throughout consecutive adjustment sessions

Study 5: The value of the intraoperative LFP recordings in DBS targeting of the STN and optimization of stimulation parameters

1. To evaluate the role of LFP recordings in predicting stimulation parameters in STN DBS for PD

III. METHODS

1. GENERAL METHODOLOGY

PATIENTS

Patients with Parkinson's Disease (PD) treated with subthalamic nucleus (STN) deep brain stimulation (DBS) for at least 6 (for the local field potential study) or 12 months (for the remaining studies) were recruited from the Unit of Functional Neurosurgery, Sobell Department, National Hospital for Neurology and Neurosurgery, University College of London. All patients had surgery at the National Hospital for Neurology and Neurosurgery but two who were operated elsewhere. Follow up visits took place at the Unit of Functional Neurosurgery and were part of the routine evaluation of implanted patients.

SURGICAL PROCEDURE

Implantation of bilateral STN DBS electrodes (Model 3389 DBS lead, Medtronic®, Minneapolis) was performed sequentially in the same operative session under local anaesthesia after overnight withdrawal of antiparkinsonian medication. All patients received bilateral STN DBS stimulation.

Pre-operative stereotactic MRI and target planning

Fast acquisition T2 weighted axial and coronal stereotactic MRI scans (1.5 Tesla) using Leksell Coordinate Frame Model G (Elekta Instrument AB, Stockholm, Sweden) were performed with contiguous slices of 2 mm. This visualized the STN and especially its medial border (Hariz et al., 2003). The anatomical target point within the center of STN visualized at the MRI was selected at a level or 1 mm in front of the anterior border of the red nuclei on the axial image showing the largest diameter of the red nucleus (Bejjani et al., 2000). Contact 1 was intended to reach this point. A double oblique trajectory to

the target was calculated on coronal images during planning to avoid sulci and ventricular system as this has been shown to reduce complications and improve targeting accuracy (Elias et al., 2009; Zrinzo et al., 2009). In addition, the trajectory was modified to maximise the number of quadripolar electrode contacts within the three-dimensional structure of the nucleus. Calculations of Cartesian coordinates of the target point were achieved both manually on enlarged MRI film copies and on Framelink software (Medtronic, Minneapolis). This is performed to ensure that optimal target selection is reviewed in detail for every patient and the possibility of human error or miscalculation is minimised.

Surgical procedure and intra-operative assessments

Impedance monitoring was performed while introducing a 1.5 mm blunt-tip radiofrequency (RF) electrode to the target (Leksell RF electrodes, Elekta, Stockholm). After withdrawal of the RF electrode, a quadripolar DBS electrode (Model 3389 DBS lead, Medtronic®, Minneapolis) was soft-passed down the same track. The DBS electrode was advanced in steps of 2 mm from 4 or 6 mm above to 4 mm below the intended target point.

At each descending step, wrist rigidity and finger tapping contralateral to the brain side were assessed and scored using the corresponding items of the motor part of the Unified Parkinson's Disease Rating Scale. The intraoperative stun-effect (lesion like effect) was determined by a sustained reduction of rigidity and/or bradykinesia and/or onset of dyskinesias.

Local field potentials recordings

Local Field Potentials (LFP) recordings were made in every 2 mm steps with the patient awake, eyes open and at rest. Detailed description of LFP recording methodology is described later in this chapter.

Intraoperative macrostimulatio

Intra-operative high-frequency test stimulation for therapeutic effect and to rule out side effects (dysarthria, oculomotor deviation, sensory or capsular responses) was performed monopolarly at each electrode's contact after LFP recordings. Frequency was set at 130 Hz, pulse width at 60 microseconds and voltage was progressively increased from 0 to 3.0 volts.

Once the optimum target point for stimulation was identified, the electrode was advanced in 1-3 mm, in order for the contacts to "encompass" the optimal target point before it was fixed in the position with the Medtronic burr hole cap or the Stimloc system (Medtronic®, Minneapolis).

Postoperative MRI

Immediate post-operative stereotactic MRI (in the same manner as preoperatively: contiguous slices of 2 mm thickness but less number of slices) with the Leksell Frame still on the head of the patient was completed. This allowed us to confirm the correct position of the DBS electrode.

For safety reasons the specific absorption rate was kept below 0.4 W/Kg.

Implantation of the neurostimulator

The neurostimulator (Kinetra, Medtronic®, Minneapolis) was implanted under general anaesthesia, either the same day or few days later according to theatre

availability. Patients stayed in the ward about 10 days after battery implantation to allow the initial adjustment of medications and stimulation parameters (SP).

CLINICAL SCALES USED THROUGHTOUT THE STUDY

Clinical evaluations were based on the Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease (Defer et al., 1999). The following scales were used throughout the study:

- Unified Parkinson's Disease Rating Scale (UPDRS) from part 1 to 4 (UPDRS I, II, III, IV)
- Dyskinesia Rating scale (DRS)

UPDRS

The UPDRS is the most widely used scale for measuring symptoms and signs of patients with PD in clinical practice (Siderowf et al., 2002). The UPDRS consists of 42 items in four sections assessing (I) mentation and mood (4 items), (II) activities of daily living based on historical information (13 items), (III) motor function based on clinical examination (14 items) and (IV) complications in patients on dopaminergic therapy based on historical information (11 items).

UPDRS II

Historical information regarding activities of the daily living were taken considering the on-medication and off-medication states (items 5 to 17).

UPDRS III (motor part)

Each of the 14 items of the motor part (III) is given a rate between 0 – no abnormality and 4 – severe abnormality. Some of the items (symptoms) are rated for the different body parts, for example tremor at rest (item 20) is rated for the head and neck, right and left upper and lower limbs respectively. As a consequence, the maximum score (all items rated as severe) is 108. Maximum points for the different parkinsonian symptoms are as follows: speech (4), facial expression (4), tremor (28), rigidity (20), akinesia (32), axial symptoms and gait (20). High internal consistency (Martinez-Martin et al, 1994), inter-rater reliability (Richards et al, 1994) and test-retest reliability (Siderowf et al., 2002) have been shown for the part III UPDRS.

UPDRS III hemibody scores

Hemibody scores were calculated from the UPDRS III subscores for upper and lower limb tremor (items 20 and 21; range 0-12), upper and lower limb rigidity (item 22; range 0-8), upper and lower limbs bradykineisia (items 23-26; range 0-16): finger tapping (item 23), hand movements (item 24), arm movements (item 25) and leg movements (items 26). Maximum score for hemibody scores (all items rate as severe – 4 -) is 36.

UPDRS III axial scores

Axial scores were calculated from the UPDRS III subscores for arise from chair, gait and postural stability (items 27, 29, 30; range 0-12).

UPDRS IV

Motor fluctuations and dyskinesia were assessed using UPDRS IV. This part of the scale was subdivided in: 1) UPDRS IV dyskinesia comprising items 32, 33 and 34 (duration, disability and pain) and; 2) UPDRS IV off time comprising item 39 (offs duration).

Dyskinesia Rating scale (DRS)

Dyskinesias were rated in the on-medication/on-stimulation condition. For quantification, the patient was sitting in a chair and observed at rest. Then the patient was asked to perform the tests in the UPDRS motor part (speaking, hand grips, finger taps, pronation/supination, leg ability, standing, walking). DRS is a five-graded scale (0=non observed; 1= mild, no interference with voluntary motor acts involved in the rated task; 2= moderate, there is interference with voluntary motor acts involved in the rated task but it can be completed; 3= severe, there is intense interference with voluntary motor acts involved in the rated task, and completion is greatly limited; 4= extreme, no completion of the voluntary motor acts involved in the rated task is possible). The following anatomic regions are rated: 1= face (including jaws, lips, tongue, and other components of the face); 2= neck, involving complete head nods, and rotations and tilts; 3= trunk, including abdomen, back, and hips; 4= right upper limb (includes shoulder, upper and lower arm and hand); 5= left upper limb; 6= right lower limb (includes overshooting of the legs when walking, rotations and foot movements); 7= left lower limb. Each of this body part is rated from 0 to 4. Maximum rating is 28. Hemibody and axial subscores were as well classified as follows:

- Dyskinesia hemibody scores: total rating for upper and lower limbs for the same hemibody (maximum score 8).
- Dyskinesia axial scores: total rating for face, neck and trunk (maximum score 12).

STATISTICAL ANALYSIS

Statistical analysis was performed on SPSS version 17 for Windows (SPSS, Chicago, IL) in collaboration with a statistician (Mr. Juan Luis Gómez, St Halley Statistics). Specific statistical methodology is described later on in this chapter

2. STUDY DESIGN

This work is design as prospective longitudinal assessments and comprises five different studies:

1. Longitudinal assessment of the impact of consecutive adjustment sessions of stimulation parameters in STN DBS in PD: evaluation of the acute and chronic effects of stimulation parameters
2. Clinical outcome of STN DBS with reprogramming
3. Optimal stimulation site in STN DBS for PD
4. Study of type of adjustment “change in contact”
5. The value of the LFP recordings in STN DBS intraoperative targeting and optimization of stimulation parameters

2.1 LONGITUDINAL ASSESSMENT OF THE IMPACT OF CONSECUTIVE SESSIONS FOR ADJUSTMENT OF STIMULATION PARAMETERS OF STN DBS IN PD PATIENTS: EVALUATION OF THE ACUTE AND CHRONIC EFFECTS OF STIMULATION PARAMETERS

CLINICAL ASSESSMENTS

Patients with DBS therapy duration for at least 12 months were included in this part of the study. Evaluations took placed at the time of enrolment (visit 1) and, 1 (visit 2), 3 (visit 3) and 6 (visit 4) months later. Patients attended the visits after an overnight withdrawal of dopaminergic medication (off-medication/on-stimulation condition). At each visit, patients were assessed before and after adjustment of stimulation parameters with UPDRS III scale in the off-medication/on-stimulation condition. Later, patients took their morning doses of dopaminergic medication and UPDRS III and dyskinesia rating scale were used

for evaluation when the patient was considered to have achieved the most functional benefits from drugs (on-medication/on-stimulation condition).

Once clinical evaluations were concluded, UPDRS part I, II and IV were recorded.

At visit 1, patients were assessed as well in the off-medication/off-stimulation condition (for practical purposes this took place after around 15 minutes of having switched the stimulation off).

ADJUSTMENT SESSIONS

At each visit patients were assessed before and after adjustment of stimulation parameter. Adjustment sessions comprised a total of three different time points with clinical evaluations performed in the off-medication/on-stimulation condition:

- Baseline evaluation: corresponds to time point prior to adjustment of the stimulation
- Acute evaluation: performed immediately after adjustment of stimulation parameters
- Chronic evaluation: performed at the following visit before adjustment of stimulation. This time point corresponds as well to baseline evaluation of the following adjustment sessions.

The study included a total of three adjustment sessions (Adjustment 1 (A1), A2 and A3).

As an example, for A1, baseline evaluation was performed at visit 1 before adjustment of the stimulation; acute evaluation was performed at visit 1 immediately after adjusting the stimulation parameters; and chronic evaluation

of A1 was performed at visit 2 (before adjustment of SP) and was at the same time the baseline evaluation of A2 (before adjusting the SP at V2) (figure 2.1). The time from acute and chronic evaluation varied for the different adjustments. For A1 it was of 1 month, for A2 two months (3 months from enrolment) and for A3 3 months (6 months from enrolment).

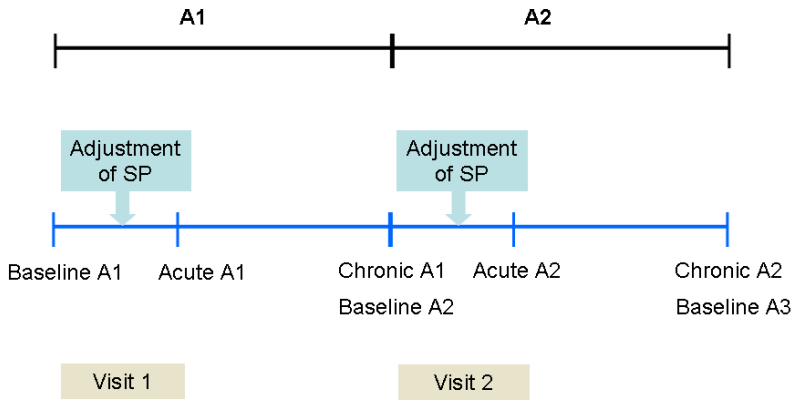

Figure 2.1 Adjustment sessions' time points for A1 and A2. Abbreviations: A1: adjustment 1; A2: adjustment 2; A3: adjustment 3; SP: stimulation parameters. Figure shows the different time points of the adjustment sessions A1 and A2. Baseline time point corresponds to clinical evaluation before any adjustment of stimulation parameters were performed at that visit. Acute time point corresponds to clinical evaluations performed immediately after adjustment of stimulation parameters. For chronic time point, evaluations were performed at the following visit. This time point is at the same time the baseline time point of the following adjustment session.

Minimal clinical important changes in UPDRS III

Minimal clinical important changes in UPDRS III correspond to 2.5 points as estimated by Shulman (2010). We used this cut off value in order to define improvement, deterioration or no clinical changes for the different effects of the

adjustment. For this purpose, raw differences between UPDRS III scores were recalculated into qualitative variables. UPDRS III hemibody scores cut off value was estimated from total UPDRS III cut off value and set as 0.825.

Adjustment of stimulation parameters (SP)

Each electrode's contact was screened to assess both therapeutic efficacy and unwanted side effects. Monopolar stimulation with increasing voltage was used with a note made of effectiveness at stepwise intervals (improvement on rigidity and/or bradykinesia and/or tremor and gait). A pulse width of 60 microseconds and frequency of 130 Hz was used. The contact with the greatest efficacy at the lowest voltage and a wider window for side effects was chosen for each hemibody. Each hemibody was assessed independently. A poor stimulation efficacy on symptoms prompted exploration of wider pulse widths and higher frequencies. In case of persistent side effects bipolar electrode's configuration was used. At the following visit, if the benefit obtained immediately after the previous adjustment was maintained or even a further improvement was detected (chronic UPDRS III- acute UPDRS III ≤ 2.5), no rescreening of the SP was performed. If the acute benefit of an adjustment was not maintained or deterioration was detected, SP were rescreened (figure 2.2). The physician performing clinical evaluations and the patient remained blinded to the adjustment of the SP. Clinical evaluations were performed by the same neurologist all throughout the study. A neurologist with a wide expertise in DBS adjusted stimulation parameters.

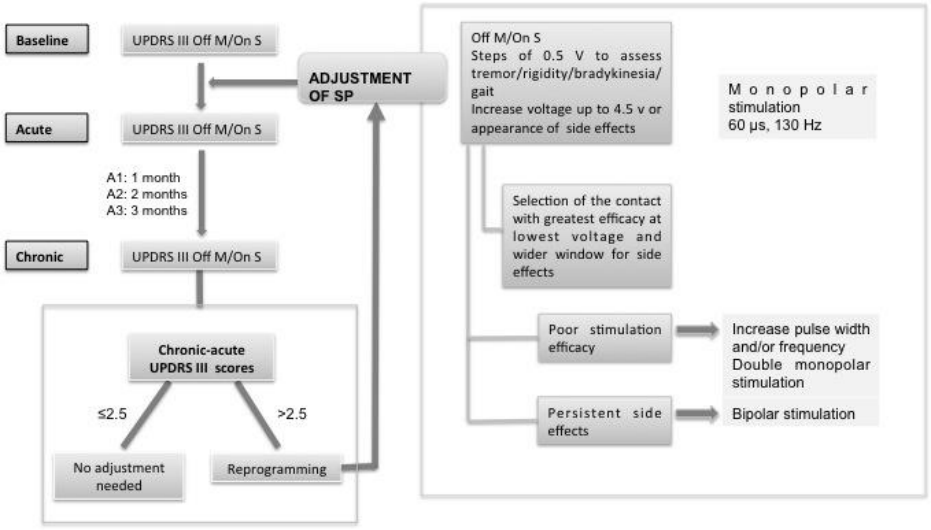

Figure 2.2. Time points evaluations for each adjustment sessions and adjustment of stimulation parameters algorithm. Abbreviations: A1: adjustment 1; A2: adjustment 2; A3: adjustment 3; Off M: Off medication; On S: On stimulation; SP: stimulation parameters; UPDRS: Unified Parkinson's Disease Rating Scale

Type of adjustments of stimulation parameters

The different possibilities of adjustment of SP were resumed in four groups:

- "No changes": parameters are screened but finally no changes of SP are performed.
- "Change in voltage": consisted in changing the voltage of the stimulation keeping the same stimulated contact. Pulse width and frequency could also be modified. Voltage, pulse width and frequency could be increased or decreased.
- "Change in contact": when the stimulated contact was changed, including change in electrode configuration (monopolar, double

monopolar or bipolar). Voltage, pulse width and frequency could also be modified (increased or decreased).

- "No adjustment needed": this type of adjustment was applied when no rescreening of SP was necessary as the benefit of the acute effect of the adjustment was maintained or a further improvement was observed in the chronic effect. In these cases no acute effect of the adjustment was measured.

Types of adjustment were considered by DBS electrodes and, therefore for a single patient two different type of adjustment could occur during the same visit (one for each DBS electrode or brain side). The impact of each type of adjustment was measure by changes in the UPDRS III contralateral hemibody scores. Each patient's hemibody side was analysed independently.

Stimulation Parameters

Electrode's configuration

Medtronic 3389 DBS electrodes were used in all patients. Electrode geometries include monopolar and bipolar configurations. In each configuration there is a cathode, or negative electric potential (sink of current), and an anode, or positive electric potential (source of current). In monopolar configuration the pulse generator is set as an anode and at least one contact of the electrode as a cathode. Two or more contacts can be set as cathodes if desired (double, triple monopolar). In bipolar configuration, two or more contacts of the electrode are activated, one as anode and one or more as cathodes.

Stimulation parameters

Besides electrode's configuration, stimulation parameters that can be programmed are: voltage, pulse width and frequency. The neurostimulator used

in all patients was the dual channel Kinetra (Medtronic Inc., Minneapolis, MN) that provides a finite range of voltage (0-9.50 V), pulse width (60 to 450 μsec) and frequency (3 to 250 Hz). While voltage and pulse width can be set independently for each channel, frequency has to be set at the same range for both channels.

Total electrical energy delivered (TEED) was calculated using the following equation (Koss et al., 2005):

$$TEED = \frac{Voltage^2 \times Frequency \times Pulse\ Width}{Impedance} (1\ second)$$

As Kinetra neurostimulator impedance measure accuracy is poor, for TEED calculation impedance was assumed to be of 1 kΩ (Moreau et al., 2008).

Medication

Patients received a combination of different antiparkinsonian medications drugs depending on individual needs. This included: levodopa/carbidopa, levodopa/benserazide, dopamine agonists (pergolide, cabergoline, pramipexole ropinirole, rotigotine, apomorphine), COMT inhibitors (entacapone) MAO inhibitors (rasagiline or selegiline), amantadine. Antiparkinsonian medications, number of doses and dosage of each drug were recorded at each visit. Total dopaminergic dosage was recalculated into Levodopa Equivalent Daily Dose (LEDD) on basis of the following correspondences: 100 mg standard Levodopa = 130 mg of controlled-released Levodopa = 10 mg bromocriptine = 1mg pergolide = 1 mg lisuride = 1.5 mg pramipexole = 6 mg ropinirole = 2.25 mg cabergoline = 10 mg apomorphine (Reichmann et al., 2003; Thobois, 2006). Medications were modified when required.

ADDITIONAL VISITS

Additional visits between the study fixed visits were available if the patient suffered deterioration. In those visits patients were assessed in the same manner as in regular visits. To allow statistical analysis these patients were excluded from the analysis of the impact of adjustment of SP on clinical scores. We were aware that this decision might have introduced a selection bias. However, this approach allowed us to carry on with the analysis of repeated measures of ANOVA that was consider to be the most appropriate.

STATISTICAL ANALYSIS

All variables were checked for normality with Kolmogorov-Smirnoff test or Shaphiro-Wilks test when $n<15$. When normality assumption was satisfied parametric tests were used for the analysis. Otherwise non-parametric tests were performed.

Impact of adjustment session on clinical scores

General lineal model (GLM) of repeated measures of ANOVA with within-subjects variable (time point of adjustment: baseline, acute or chronic) was used to analyse the impact of adjustment of stimulation parameters on clinical scores. The significance level was set at 0.05. When assumption of sphericity could not be satisfied (Mauchly's test $p<0.05$) a multivariate test, Pillai's trace, was used. Pairwise comparisons were performed using Bonferroni correction.

To assess the impact of the type of adjustment on UPDRS III hemibody scores a GLM of repeated measures of ANOVA with within-subjects variable (time point of adjustment: baseline, acute or chronic) and between-subjects variable type of adjustment (no change, change in voltage, change in contact, no

adjustment needed) was used. When assumption of sphericity could not be satisfied (Mauchly's test $p<0.05$) a multivariate test, Pillai's trace, was used. Pairwise comparisons were performed using Bonferroni correction for within-subjects test. For between-subject test, homogeneity of variances was required for the analysis (Levene test, $p>0.05$). Pairwise comparisons using Bonferroni correction were used to assess differences between types of adjustment. For variables not following a normal distribution Friedman test was used.

Predictive factors for global improvement at each adjustment session

The effect of certain factors on global outcome of total and hemibody UPDRS III scores at each adjustment session was analysed using multivariate regression (backwards-stepwise method). Global outcome for each adjustment session was defined as the difference between chronic and baseline time points. Variables with multicollinearity problems were excluded. Regression model was checked for independence of the residuals (Durbin-Watson statistic), collinearity, normality and homoscedasticity of the residuals.

For analysis of total body UPDRS III scores, type of adjustment was reclassified taking into account the type of adjustment performed at both DBS electrodes:

- No change in any of the DBS electrodes
- Change in voltage in at least one of the DBS electrodes and no change in contact
- Change in contact in at least one of the DBS electrodes

2.2 CLINICAL OUTCOME OF STN DBS WITH REPROGRAMMING

IMPACT OF SUCESSIVE ADJUSTMENT SESSIONS ON CLINICAL OUTCOME

Same patients as in the previous study were included (PD with STN DBS for at least 12 months). Final UPDRS III scores were compared to scores at baseline. Baseline time point of the study was defined as baseline scores at A1. Final time point corresponds to chronic time point of A3. All scores were performed off-medication/on-stimulation. Patients were included regardless the need of additional visits between adjustment sessions.

To analyse the impact of this type of adjustment on final outcome after three consecutive adjustment sessions, patients (by hemibody sides) were grouped according to the following classification “Adjustment of stimulation parameters throughout the study”:

- “No changes” of stimulation parameters (includes no changes and no adjustment needed) along the study
- “One or more change in voltage” but no changes of stimulated contact during the study
- “One change of stimulated contact” during the study
- “Two or three changes of the stimulated contact”

Repeated measures analysis (ANOVA) with main factor TIME (2 levels: baseline and final time point) and between-subjects factor “adjustment of stimulation parameters throughout the study” was performed.

PREDICTIVE FACTOR FOR IMPROVEMENT

Final outcome variable was defined as the differences between chronic time point of A3 and baseline scores of the study (baseline time point of A1).

Final outcome variable = chronic scores of A3 - baseline scores of A1

A minimal clinical important difference was established on 2.5 points for total UPDRS III based on the study by Shulman (2010). Final outcome variable was recodified into a qualitative variable where differences equal or below -2.5 points were defined as improvement and equal or above +2.5 points as deterioration. Values in between were considered as stable scores. For logistic regression analysis the variable was dichotomized into improvement or no improvement (includes stable and deterioration). For hemibody scores cut-off value was calculated at 0.825 points. Final outcome variable was recodified into a qualitative variable. Differences equal or below -0.825 points were defined as improvement and equal or above +0.825 as deterioration. Global outcome variable for each adjustment session was categorized into improvement (differences equal or below -0.825) and deterioration (equal or above 0.825). The probability for global improvement was study using logistic regression analysis (stepwise method or user-controlled backward stepwise method) for both, total and hemibody UPDRS III scores. Model was checked for Hosmer test, normality of the residuals and Nagelkerke coefficient.

2.3 OPTIMAL STIMULATION SITE IN STN DBS FOR PARKINSON'S DISEASE

ANALYSIS OF THE ANATOMICAL POSITION OF THE DBS ELECTRODE AND ACTIVE CONTACTS OF THE DBS ELECTRODE

PD patients treated with STN DBS for at least 12 months were included in this study. Pre and postoperative stereotactic MRI were examined. Post-operative stereotactic MRI data and Framelink software (Medtronic) were used to localize the position of the contacts. Coordinates of DBS electrode contacts were calculated from the centre of the electrode artefact on post-operative MRI. The software allows reconstruction of the imaging data in multiple planes, including trajectory views along the centre of the electrode contacts. The centre of each electrode contact was calculated by superimposing a template of the quadripolar electrode. To avoid artefact from the electrode the coordinates of each contact were transposed onto the pre-operative MRI. Two neurosurgeons blinded to the clinical outcome and stimulation parameters independently assessed and agreed on the anatomical position of each electrode's contacts in relation to the visualized STN on the axial and coronal MRI planes. The visualized STN was divided into five segments: superior (A), anterior-medial (B), central (C), postero-lateral (D) and inferior (E) (figure 2.3). The centre of each contact was localized in relation to the closest STN segment and classified as being inside, superior, medial, inferior or lateral to that segment. A contact located within 1 mm from the STN was considered to be adjacent to the corresponding STN segment. Final anatomical position for each DBS electrode's contact was defined by the anatomical localization around the STN and its surrounding structures and the STN segment.

The **optimal stimulation area** was considered to be the central, superior, posterolateral segment of the STN or the area adjacent to the superior border of the STN (located less than 1 mm from the border of the nucleus).

Position of the DBS electrode was classified into two groups

- Group I electrode's position (Group Ie, good location), when at least one the four contacts of the electrode was within the defined optimal area.
- Group II electrode's position (Group IIe), when none of the contacts was within the defined optimal area.

Active/stimulated contact position was as well resumed into two groups:

- Group I contact's position (Group Ic, good location) the active contact is within the defined optimal area
- Group II contact's position (Group IIc) consisted of those active contacts not fulfilling the above criteria.

Differences between group I and II for electrode's position (group Ie, group IIe) and active contact position (group Ic, group IIc) were examined using univariate analysis. Dependent variables were: DBS efficacy, TEED and voltage, type of adjustment throughout the study and, LEDD. Analysis was performed on total and hemibody scores.

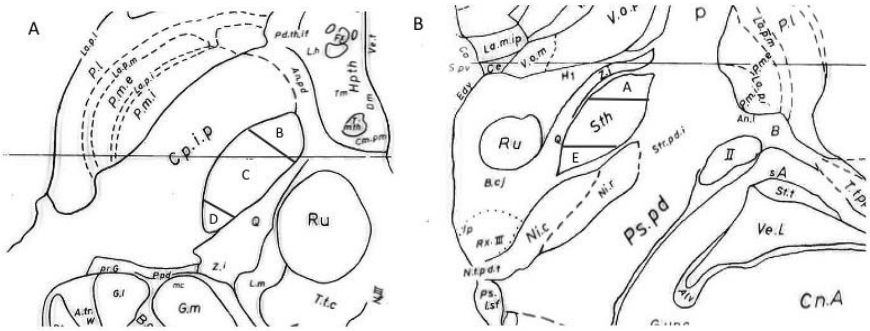

Figure 2.3 Division of STN into different segments viewed on plates from Schalthenbrand atlas. A) Axial view adapted from plate 55, *H.v 4.5:* antero-medial (B), central (C), postero-lateral (D) segments of the STN. B) Coronal view adapted from plate 27, *f.p 3.0*: Superior (A) and inferior (E) segments of the STN.

THE VALUE POSTOPERATIVE IMAGING IN THE SELECTION OF THE OPTIMAL THERAPEUTIC CONTACT

One neurosurgeon blinded to the stimulation parameters and clinical outcome determined on MRI which contact had the best location in the STN. If no contact was found to lie within the nucleus proper, the best contact was considered that being closest to the STN or its superior tip. Contacts were classified in two groups based on concordance between clinical/MRI contact: “no concordance” and “concordance”. Anatomical position of the active contact, clinical and stimulation parameters variables and type of adjustment during the study were compared between both groups using univariate analysis.

2.4. STUDY OF TYPE OF ADJUSTMENT “CHANGE IN CONTACT”

In this part of the study a description of those hemibody sides that underwent “change in the stimulated contact” at any time during the study was carried out. Due to a progressive reduction of the sample mainly descriptive

statistics were used. Non-parametric tests were applied when appropriated. Clinical and anatomical description of the position of the active contact was provided.

2.5 THE VALUE OF THE INTRAOPERATIVE LOCAL FIELD POTENTIAL (LFP) RECORDINGS IN DBS TARGETING OF THE STN AND OPTIMIZATION OF STIMULATION PARAMETERS

Patients with STN DBS for at least 6 months and in whom LFP data was available were included in this study. Implantation of bilateral DBS electrodes was performed as previously described.

LFP RECORDINGS

Recordings were made from every 2 mm steps in the electrode descent while patients were awake, with eyes open and at rest. Each depth was recorded for 60-65 s. STN LFPs were recorded bipolarly from the four adjacent contacts of each DBS electrode (contact pairs 01, 12, 23). Signals were amplified, pass band filtered between 1 and 80 Hz and sampled at 184 Hz in 23 patients, 500 Hz in two patients and 1600 Hz in three patients (Biopotential Analyser Diana, St Petersburg, Russia) or pass band filtered between 1 and 80 Hz and sampled at 1024 Hz in three patients (Porti Amplifier; TMSI International, Enschede, The Netherlands). The optimum sampling rate was 184 Hz, as higher rates do not afford any advantage given that the pass band of interest was under 35 Hz. Purpose written software saved the original time series on a portable PC and displayed online the evolving patterns of beta band power from contact pairs 01, 12, 23 as the DBS electrode was advanced (figure 2.4). Thereafter, LFP were interpolated to a sampling rate of 184 Hz, where

necessary, and examined offline in Spike2 software (Cambridge Electronics Design, Cambridge, UK). Spectra of LFP power were estimated in Spike2 using the discrete Fourier transform. Spectral resolution was 0.72 Hz. Analysis excluded periods of recording while the electrode was moved.

A beta frequency band peak in the power spectra was operationally defined as a local maximum between 11 and 35 Hz in which the mean power over the five contiguous frequency bins centred on the peak frequency exceed 180% of the mean power over the five contiguous bins of lower and higher frequency. Recordings from contact 01 at all depths were considered and the depth with the highest peak power over the frequency band of interest was used to define the centre frequency of the peak. The mean (absolute rather than relative) power over the five frequency bins centred on this peak was then estimated for each recording depth of the electrode. Five bins were chosen to allow for any minor change in peak frequency between depths. A discrete peak between 11 and 35 Hz in power spectra of contact 01 was identified in all but two sides. A step change in peak beta power was operationally defined as at least a 100% increase in mean beta power at contact 01 between successive depths as the electrode was advanced in 2 mm steps or, where the maximum peak lay at the most superficial depth tested (four sides), there was at least a 100% drop in mean beta power at contact 01 when it was advanced a further 2 mm. For example, if the mean power of the peak doubled when the electrode was moved from 4 mm to 2 mm above the anatomical target point, then the step change and site of the local beta generator were considered to be at 2 mm. The beta generator was defined as the local electrical source of beta activity, acknowledging that this may be driven by input from elsewhere. If there was

more than on step change in the beta power between depths, then only the step involving the highest mean beta power was considered. For example if the mean power of the peak doubled when the electrode was moved from 4 mm to 2 mm above the anatomical target point, but then doubled again when the electrode was moved from 2 mm to 0 mm, then the step change and site of the local beta generator were considered to be at 0 mm, the depth with the highest peak mean power. We elected to focus on peak power, rather than on LFP power across the beta band, as previously used (Chen et al., 2006) as this afforded a better signal to noise ratio and given the recent emphasis on spectral peaks rather that broad band power changes in correlation between LFP power and clinical state (Kühn et al., 2009). Absolute and not relative or normalised power was analysed. The beta generator depth was described with reference to the surgical target point.

CLINICAL ASSESSMENTS OF EFFICACY OF CHRONIC DBS

A Neurologist blinded to the intraoperative recordings performed postoperatively clinical assessments and programming of the stimulation parameters. Stimulation parameters and UPDRS motor scores were determined a minimum of 6 months after surgery. Stimulation parameters were selected as previously described.

ELECTRODE'S CONTACT ANATOMICAL POSITION

The contact from each electrode with the best anatomical position was determined and classified into one of two groups (Goup Ic and Group IIc). In group Ic, the contact was inside or adjacent to the most superior part of the STN. Group IIc essentially consisted of the contact that was closest to the superior part of the STN in those electrodes not fulfilling the above criteria. The

depth of the contact of each electrode used for chronic stimulation was also described with reference to the surgical target point (the same reference as used for the depth of the beta generator). In case of bipolar stimulation, stimulation depth was assumed to lie midway between the respective contacts.

STATISTICAL ANALYSIS

Correlations were performed using Spearman's rho so as to accommodate the non-parametric distribution of our data and to avoid any spurious correlations due to outlying values, although this has the disadvantage that correlation coefficients cannot be used to estimate the proportion of the variance of one signal linearly predicted by another.

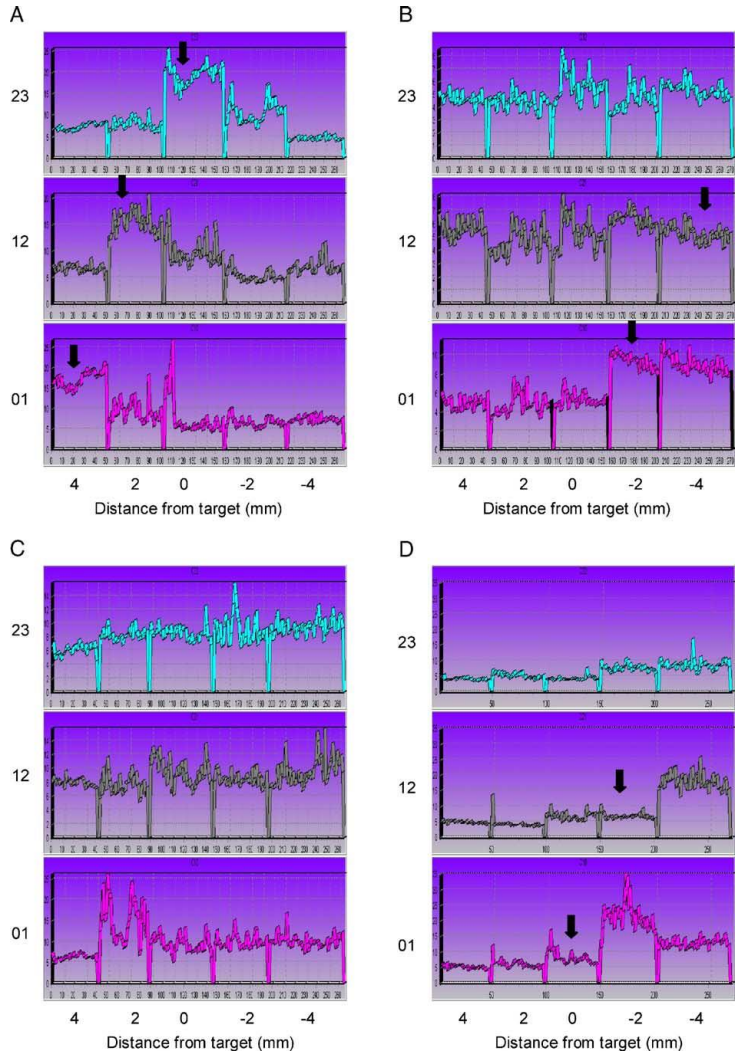

Figure 2.4 On-line displays of spectral change in LFP as DBS electrode descends through the target, obtained intra-operatively. The intended target at 0 mm was the center of the SNT. DBS electrodes were introduced in 2 mm steps from (+) 4 mm above target to (-) 4 mm below. Recordings were made for 60 seconds after each step. The *x*-axes are the distance of contact 0 along the electrode trajectory with respect to the intended target. The depth at which the intra-operative stun effect was obtained is shown by vertical black arrows. The highest level of beta activity is seen in contact 01 first and then recorded in more rostral contact pairs after further descent (A and D). Power is in arbitrary units and its range is independently optimized for each channel by

the software. The depth of contact pair 01 with maximal power in the 13-35 Hz band corresponded to (A, B) or was adjacent to (D) the depth of the intra-operative stun effect, except in panel C where a step in power was recorded at contact pair 01 without an accompanying stun effect (From Chen et al., 2006).

IV. RESULTS

1. LONGITUDINAL ASSESSMENT OF THE IMPACT OF CONSECUTIVE SESSIONS FOR ADJUSTMENT OF STIMULATION PARAMETERS OF STN DBS IN PD PATIENTS: EVALUATION OF THE ACUTE AND CHRONIC EFFECTS OF STIMULATION PARAMETERS

The present study sought to carefully assess the acute and long-term impact of the adjustment of the stimulation parameters of STN DBS in patients with Parkinson's disease.

1.1 DESCRIPTION OF THE STUDY POPULATION

Thirty-one consecutive PD patients (19 male) treated with STN DBS for at least one year were enrolled in the study. All but two patients underwent surgery at the National Hospital for Neurology and Neurosurgery (London, United Kingdom). Mean age was 56.35±6.8 years (range 41-66), age at onset of PD was 44.26±6.1 years-old (range 32-61), duration of PD at time of surgery was 12.39 ± 5.3 years (range 5-24), duration of DBS therapy was 29.94 months (range 12-86) and age at DBS was 56.35 years-old (42-66).

To determine the benefit obtained with STN DBS, preoperative UPDRS III motor scores were compared to postoperative scores (baseline of the study, which corresponds to the first evaluation at visit 1). Preoperative data was available only for 20 patients.

At the baseline of the study, STN DBS provided an improvement on UPDRS III scores of 49.53% (off medication/on stimulation at baseline of the study *vs* off medication pre-DBS) and an improvement of 44.63% when compared to the off medication/off stimulation condition, both at baseline of the study. On

medication UPDRS III scores deteriorated after DBS (from 8.95±6.1 to 12.85±5.6, p=0.01, two-tailed paired t-test) (figure 1.1). UPDRS III score and subscores are shown at table 1.1 and figure 1.1 and 1.2.

Table 1.1 UPDRS III total, axial and hemibody scores pre-DBS and at baseline of the study

UPDRS III SCORES	n	Mean (SD)	Range
UPDRS III off M pre-DBS	20	46.45 (17.31)	18-78
UPDRS III on M pre-DBS	20	8.95 (6.16)	0-20
UPDRS III off M/on S at baseline	31	27.16 (14.33)	11-79
UPDRS III off M/off S at baseline	28	49.14 (18.35)	26-88
UPDRS III on M/on S at baseline	31	14.52 (8.37)	3-40
UPDRS III axial off M/on S at baseline	31	2.65 (2.48)	0-10
UPDRS III axial off M/off S at baseline	28	4.50 (2.51)	2-12
UPDRS III axial on M/on S at baseline	31	1.26 (1.61)	0-8
UPDRS III hemibody off M/on S at baseline	62	8.03 (5.03)	0-29
UPDRS III hemibody off M/off S at baseline	56	16.11 (7.18)	3-31
UPDRS III hemibody on M/on S at baseline	62	3.95 (2.90)	0-13

Abbreviations off M: off Medication; off S: off stimulation; on M: on Medication; on S: on stimulation; pre-DBS: before deep brain stimulation; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

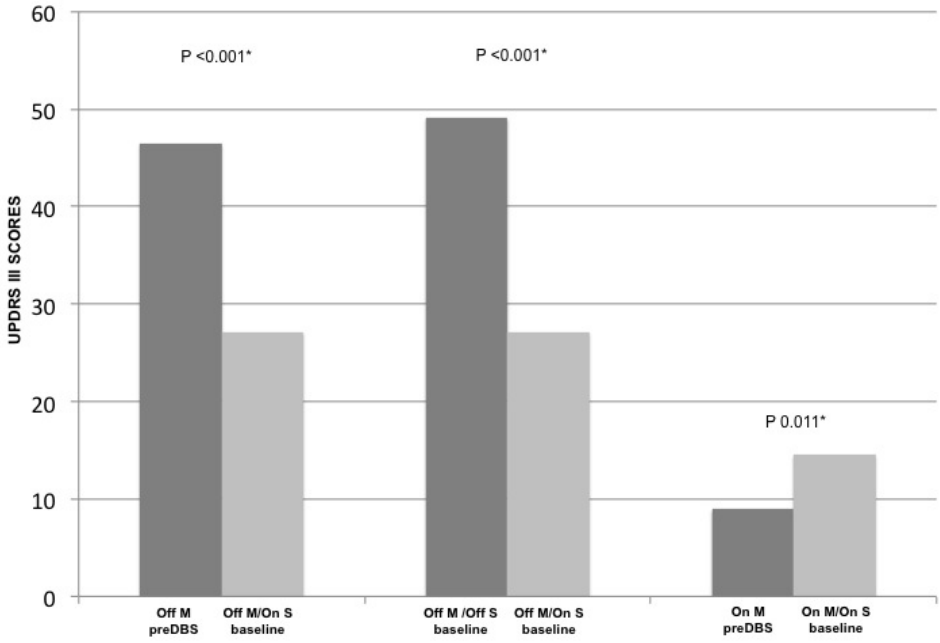

Figure 1.1 UPDRS III scores before DBS and at baseline of the study (off M/on S, off M/off S and on M/on S)

Abbreviations off M: off Medication; off S: off stimulation; on M: on Medication; on S: on stimulation. Dark grey columns correspond to UPDRS III off M preDBS, UPDRS III Off M/off S and UPDRS III On M pre DBS respectively. Ligth grey columns correspond to OffM/On S, Off M/OnS and On M/On S at baseline.

* two-tailed t-test

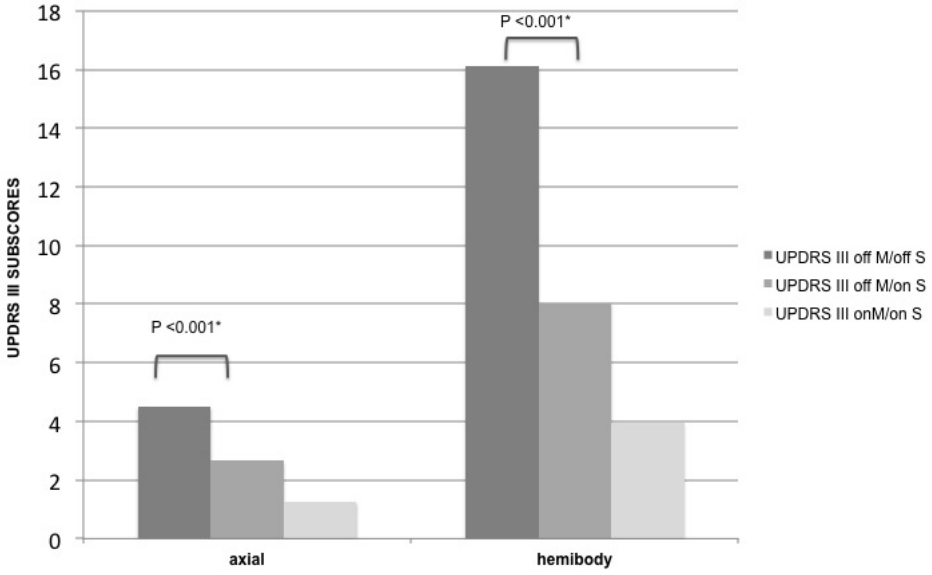

Figure 1.2 UPDRS III subscores (axial and hemibody) at baseline of the study (off M/off S, off M/on S and on M/on S)

Abbreviations off M: off Medication; off S: off stimulation; on M: on Medication; on S: on stimulation.

* two-tailed t-test

Patients attended a total of four visits. As described in the methodology section, three adjustment sessions were performed and named as adjustment 1 (A1), adjustment 2 (A2) and adjustment 3 (A3). Mean time between baseline assessment and chronic effect was 38.29 days (SD 16.536, range 17-99), 70.77 days (SD 25.426, range 25-164) and 87.46 days (SD 23.930, range 47-170) for A1, A2 and A3, respectively.

At the final time point of the study, 5 patients withdrew. All patients completed the A1 and A2 time points. A3 time points were completed by 28 patients (baseline and acute time point) and by 26 for the chronic time point. Reasons for discontinuation were: the development of a cardiac condition that prevented

the patient attending the planned visits (1), and personal decision to discontinue the assessments (4). Six patients required additional visits because of deterioration in parkinsonian symptoms (2 at A1, 1 at A2 and 3 at A3).

1.2 EVALUATION OF ACUTE AND CHRONIC EFFECTS OF STIMULATION PARAMETERS DURING THREE CONSECUTIVE ADJUSTMENT SESSIONS

This part of the study will focus on the impact of each adjustment session (acute and chronic effect) on UPDRS III total, hemibody and axial scores. The impact of the new stimulation setting was assessed in the clinical condition off-medication/on-stimulation. Changes in stimulation parameters were classified in four different groups:

TYPE OF ADJUSTMENT OF STIMULATION PARAMETERS	
No changes	Stimulation parameters are tested for clinical effect but no changes are performed
Change in voltage	Change of stimulation voltage that could also include variations on pulse width and/or frequency
Change in contact	Change of the stimulated electrode's contact. Variations on voltage, pulse width and/or frequency were also possible
No adjustment needed	After A1, some patients did not require further evaluation of the stimulation parameters as a clinically stable benefit was achieved in the previous adjustment session. Clinical acute assessments were not performed for this group

Therapeutic outcome was quantified using contralateral motor scores (referred in the text as UPDRS III hemibody scores) rather than total UPDRS III scores. This is because each DBS electrode programme is independent. This necessarily excludes axial scores, which result from the combined effect of stimulation of both brain sides.

Patients requiring additional adjustment sessions were excluded from this part of the study and will be discussed separately.

Stimulation parameters at each time point of the study are provided in appendix I.

Statistical considerations

Statistical comparisons were made using parametric or non-parametric tests where appropriate, and after checking assumptions of normality (Shapiro-Wilk test; $p < 0.05$ to reject) and homogeneity of variance (Levene test, $p < 0.05$ to reject). Pillai's Trace multivariate test was used when sphericity could not be assumed. With normality assumption repeated measures ANOVA with the time point of the adjustment (baseline, acute, chronic) as the main factor was used to compare baseline, acute and chronic scores of adjustment sessions. To assess the interaction of the type of adjustment, this variable was included in the model as a between-subjects factor. A Bonferroni correction was applied for *post hoc* pairwise comparisons. For variables not following a normal distribution (Shapiro-Wilk test), non-parametric Friedman´s test was used and *post-hoc* analysis with Wilcoxon signed-rank test was conducted with a Bonferroni correction applied, resulting in a significance level set at $p>0.016$ (three samples).

OVERVIEW OF THE IMPACT OF ADJUSTMENT SESSIONS ON MOTOR SCORES

Thirty-one patients completed all A1 time points. Two patients required an additional visit between A1 and A2 and were therefore excluded. Analysis

was performed on the data of twenty-nine patients (58 hemibody sides). Thirty patients completed all A2 time points. One patient required an additional visit between A2 and A3 and was therefore excluded from this part of the study. Data was therefore available for 29 patients (58 hemibody sides). Twenty-six patients completed all A3 time points. Three patients required an additional visit before the chronic time point of A3 and were therefore excluded. Analysis was performed on the data of twenty-three patients (46 hemibody sides).

The impact of the adjustment session was similar for UPDRS III total and hemibody scores. A statistically significant acute benefit was found in A1, A2 and A3; however, the acute improvement was only maintained at A3. Thus, a positive global effect of the adjustment was only seen in the last adjustment session. The impact on axial scores was more variable. A1 produced a significant acute benefit followed by deterioration. A2 did not have any impact on axial subscores and A3 produced an acute and additional chronic benefit.

For total UPDRS III scores and analysis see tables 1.2 and 1.3 and figure 1.3.

For hemibody and axial subscores and analysis see tables 1.4 to 1.10.

IMPACT OF TYPE OF ADJUSTMENT ON HEMIBODY MOTOR SCORES

The interaction of the variable “type of adjustment” was statistically significant in all of the adjustment sessions (A1 $p=0.013$, A2 $p=0.008$ and A3 $p<0.001$; Pillai’s Trace).

Type of adjustment “no change” did not have an impact on UPDRS III hemibody scores in either acute or chronic time points at A1 and A2. At A3, a chronic and global improvement was observed.

Type of adjustment “change in voltage” did not vary UPDRS III hemibody scores at A1 and A2. At A3, an acute sustained improvement was found.

Type of adjustment “change in contact” was the adjustment producing greater variations on UPDRS III hemibody scores. At A1, it produced an acute improvement followed by deterioration. At A2 and A3, the acute benefit was maintained over time, leading to a global improvement in both programming sessions.

“No adjustment needed” condition did not produce variations on motor scores, as expected.

The behaviour of UPDRS III hemibody scores at each adjustment session is displayed in figures 1.4 to 1.6 and for each type of adjustment in figure 1.7

No differences were found for UPDRS III hemibody scores among the different types of adjustment (F=1.366, p=0.264) at A1. At A2, hemibody sides in the group of “no adjustment needed” had significantly lower scores (F=4.309, p=0.009; “no change” (p=0.033), “change in contact” (p=0.043) and “change in voltage” (p=0.056). At A3, hemibody sides included in the group “no adjustment needed” had lower UPDRS III hemibody scores compared with “change in contact” (F=4.984, P=0.005, mean difference 5.62 points, p=0.004).

Table 1.2 UPDRS III scores at different time points of A1, A2 and A3

	A1			A2			A3		
UPDRS III	**BL**	**A**	**C**	**BL**	**A**	**C**	**BL**	**A**	**C**
N	29	29	29	29	29	29	23	23	23
Mean	28.00	22.41	26.59	25.55	23.31	26.03	26.22	24.17	22.39
SD	14.41	9.59	12.13	12.53	10.96	12.48	13.06	10.64	8.91
Range	11-79	7-48	10-50	9-50	9-49	7-66	7-66	7-52	7-45
Pillai’s trace	< 0.001			< 0.001			< 0.027		

Abbreviations: A1, A2, A3 adjustment 1, 2 and 3; A: acute time point; BL: baseline; C: chronic time point; SD standard deviation.

Table 1.3 Differences of UPDRS III scores for A1, A2 and A3

	A1		A2		A3	
UPDRS III differences	Mean difference	p	Mean difference	p	Mean difference	p
BL-A	5.59	<0.001	2.24	0.002	2.04	0.035
A-C	-4.17	0.011	-2.72	0.032	1.78	0.325
BL-C	1.41	1.000	-0.45	1.000	3.83	0.036

Abbreviations: A: Acute scores; A1, A2, A3 adjustment 1, 2 and 3; BL: baseline scores; C: Chronic scores; P: p value. A minus sign indicates deterioration on UPDRS III scores. P values adjusted according to Bonferroni correction. Acute effect: baseline-acute scores; chronic effect: acute-chronic scores; general effect: baseline-chronic scores.

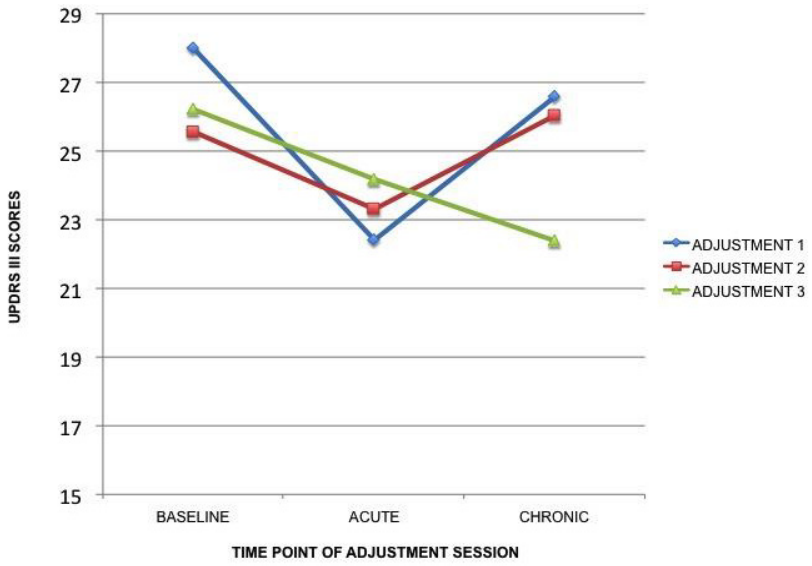

Figure 1.3. UPDRD III scores along the different time points of A1, A2 and A3 (baseline, acute and chronic). Mean values of UPDRS III scores are represented by rhombus, squares and triangles for A1, A2 and A3, respectively.

Table 1.4. UPDRS III hemibody scores at the different time points of A1 (baseline, acute and chronic) by type of adjustment

A1		Total	No Change	Change Voltage	Change Contact
BASELINE	**n**	58	11	19	28
	Mean	8.22	7.46	6.90	9.43
	SD	5.13	3.27	4.33	6.00
	Range	0-29	3-14	0-17	3-29
ACUTE	**n**	58	11	19	28
	Mean	6.29	6.64	5.84	6.46
	SD	3.66	3.01	3,91	3.82
	Range	0-18	3-13	0-16	0-18
CHRONIC	**n**	58	11	19	28
	Mean	7.69	7.55	5.95	8.93
	SD	5.00	2.98	4.70	5.58
	Range	0-21	1-12	0-19	2-21

Abbreviations: SD standard deviation. Baseline: evaluation before adjustment of the stimulation parameters (SP); acute time point: evaluation immediately after adjustment of the SP; chronic time point: chronic evaluation after adjustment of SP (for A1: 1 month).

Table 1.5. Mean differences of UPDRS III hemibody scores at the different time points of A1 by type of adjustment

UPDRS III hemibody differences	Total Mean (p value)	No change Mean (p value)	Change in voltage Mean (p value)	Change in contact Mean (p value)
Baseline-acute				
Mean	1.61	0.82	1.05	2.96
P value	(<0.001)	(1.000)	(0.317)	(<0.001)
Acute-chronic				
Mean	-1.16	-0.91	-0.11	-2.46
P value	(0.024)	(0.947)	(1.000)	(<0.001)
Baseline-chronic				
Mean	0.45	-0.09	0.95	0.50
P value	(1.000)	(1.000)	(0.949)	(1.000)

A minus sign means deterioration. For each column, the first value represents the mean difference in UPDRS III hemibody scores and the p value is shown in brackets. P values were corrected according to Bonferroni adjustment.

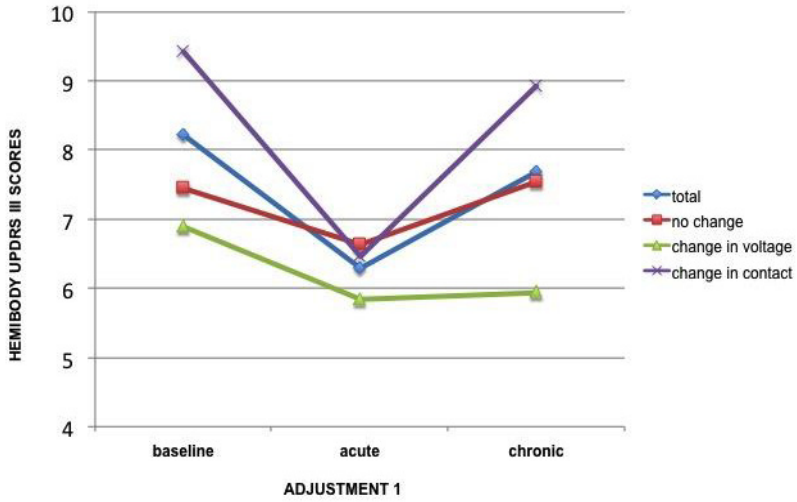

Figure 1.4. UPDRS III hemibody scores along A1 time points grouped by type of adjustment. Rhombus, square, triangle and cross represent mean values of UPDRS III hemibody scores at each time point of the adjustment session. Blue line indicates total scores, red line shows no change, green line denotes change in voltage, and purple line shows change in contact.

Table 1.6. UPDRS III axial scores at A1, A2 and A3

	A1*		A2§		A3**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Baseline	2.83	2.47	2.76	1.50	2.43	2.02
Acute	2.10	1.93	2.31	1.44	2.22	1.78
Chronic	2.83	1.42	2.55	1.86	1.91	1.73

Abbreviations: A: adjustment session; SD standard deviation.

*A1 [p=0.003, Friedman test; pairwise comparisons: baseline vs. acute (p=0.003), acute vs. chronic (p=0.018), baseline vs. chronic (p=0.527)].

§A2 (p=0.093, Friedman test)

**A3 [p=0.010, Friedman test); pairwise comparisons: baseline vs. acute (p=0.059), acute vs. chronic (p=0.083), baseline vs. chronic (p=0.013)].

Table 1.7. UPDRS III hemibody scores at the different time points of A2 (baseline, acute and chronic) by type of adjustment

A2		Total	No change	Change voltage	Change contact	NAN
BASELINE	**n**	58	19	13	8	18
	Mean	7.38	8.11	8.43	11.11	4.00
	SD	5.06	5.09	4.27	5.07	2.54
	Range	0-21	1-21	3-19	5-21	0-11
ACUTE	**n**	58	19	13	8	18
	Mean	6.72	7.84	7.71	8.22	NA
	SD	4.27	4.66	3.80	4.47	NA
	Range	0-19	1-19	4-16	4-18	NA
CHRONIC	**n**	58	19	13	8	18
	Mean	7.83	9.21	9.23	8.25	5.17
	SD	4.93	6.08	4.17	5.37	2.64
	Range	2-27	2-27	2-19	4-19	2-11

Abbreviations: NA: not applied; NAN: no adjustment needed. Baseline: evaluation before adjustment of the stimulation parameters (SP); acute time point: evaluation immediately after adjustment of the SP; chronic time point: chronic evaluation after adjustment of SP (for A2: 2 months).

For “no adjustment needed”, the acute time point was not measured and therefore no values are given.

Table 1.8. Differences of UPDRS III hemibody scores at the different time points of A2 by type of adjustment

UPDRS III hemibody differences	Total	No change	Change in voltage	Change in contact	NAN
Baseline-acute					
Mean	0.98	0.26	0.77	2.88	NA
P value	(<0.001)	(1.000)	(0.295)	(<0.001)	
Acute-chronic					
Mean	-0.94	-1.37	-1.46	0.25	NA
P value	(0.009)	(0.023)	(0.054)	(1.000)	
Baseline-chronic					
Mean	0.04	-1.11	-0.69	3.13	-1.17
P value	(1.000)	(0.265)	(1.000)	(0.007)	(0.240)

Abbreviations: NA: not applied; NAN: no adjustment needed.

A minus sign means deterioration. For each column, the first value represents the mean difference on UPDRS III hemibody scores and the p value is shown in brackets. P values were corrected according to Bonferroni adjustment.

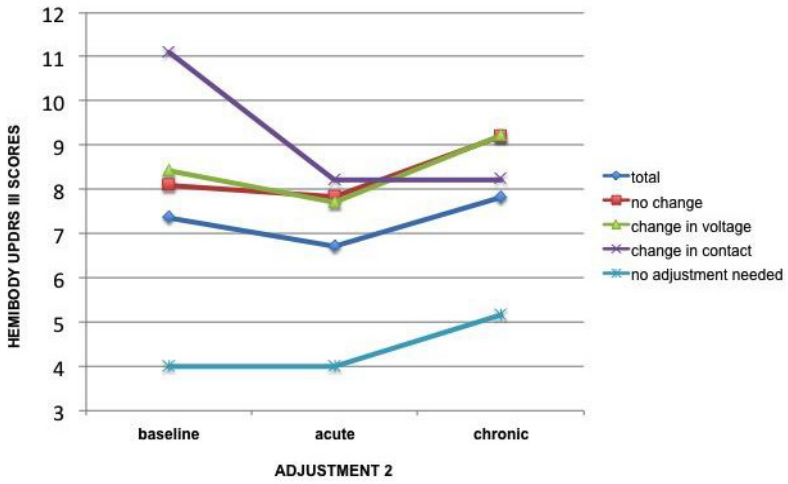

Figure 1.5. UPDRS III hemibody scores along A2 time points grouped by type of adjustment. Rhombus, square, triangle, cross and asterisk represent mean values of UPDRS III hemibody scores at each time point of the adjustment session. Blue line denotes total scores, red line shows no change,

green line indicates change in voltage, purple line shows change in contact and light blue line indicates no adjustment needed.

Table 1.9. UPDRSIII hemibody scores at the different time points of 3 (baseline, acute and chronic) by type of adjustment

A3		Total	No change	Change voltage	Change contact	NAN
BASELINE	**n**	46	11	6	7	22
	Mean	7.93	9.08	8.88	12.75	5.18
	SD	5.08	4.38	4.32	6.43	2.79
	Range	2-27	3-17	5-19	5-27	2-11
ACUTE	**n**	46	11	6	7	22
	Mean	7.02	8.42	7.25	9.75	5.18
	SD	3.95	3.78	3.99	4.13	2.79
	Range	2-18	3-14	2-16	4-18	2-11
CHRONIC	**n**	46	11	6	7	22
	Mean	6.35	6.27	5.83	9.571	5.50
	SD	3.52	2.37	2.56	4.99	3.29
	Range	1-19	3-10	4-11	3-19	1-13

Abbreviations: NAN: no adjustment needed. Baseline: evaluation before adjustment of the stimulation parameters (SP); acute time point: evaluation immediately after adjustment of the SP; chronic time point: chronic evaluation after adjustment of SP (for A3: 3 months).

Table 1.10 Differences of UPDRS III hemibody scores at the different time points of A3 by type of adjustment

UPDRS III hemibody differences	Total	No change	Change in voltage	Change in contact	NAN
Baseline-acute					
Mean	1.48	0.64	1.83	3.43	NA
P value	(<0.001)	(0.478)	(0.012)	(<0.001)	
Acute-chronic					
Mean	1.02	2.27	1.83	0.29	NA
P value	(0.052)	(0.012)	(0.227)	(0.932)	
Baseline-chronic					
Mean	2.49	2.91	3.68	3.71	-0.32
P value	(<0.001)	(0.002)	(0.005)	(0.002)	(1.000)

Abbreviations: NA: not applied; NAN: no adjustment needed.

A minus sign means deterioration. For each column, the first value represents mean difference on UPDRS III hemibody scores and p value is shown in brackets. P values were corrected according to Bonferroni test.

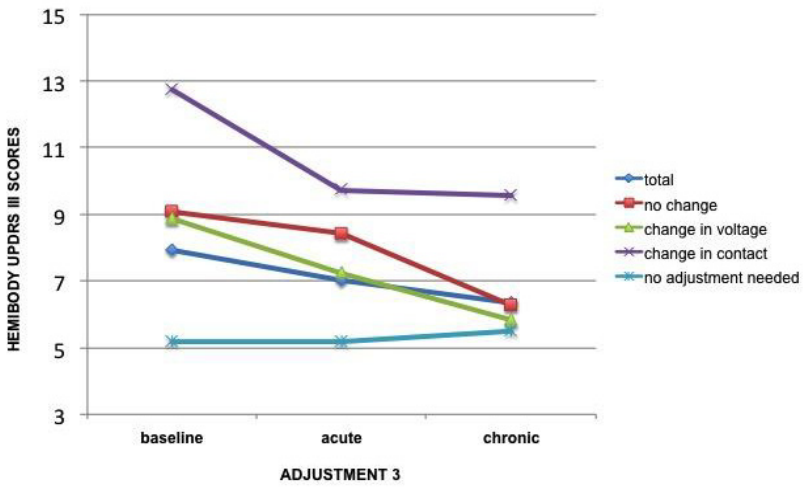

Figure 1.6. UPDRS III hemibody scores along A3 time points grouped by type of adjustment. Rhombus, square, triangle, cross and asterisk represent mean values of UPDRS III hemibody scores at each time point of the adjustment session. Blue line indicates total scores, red line denotes no

change, green line shows change in voltage, purple line indicates change in contact and light blue line shows no adjustment needed.

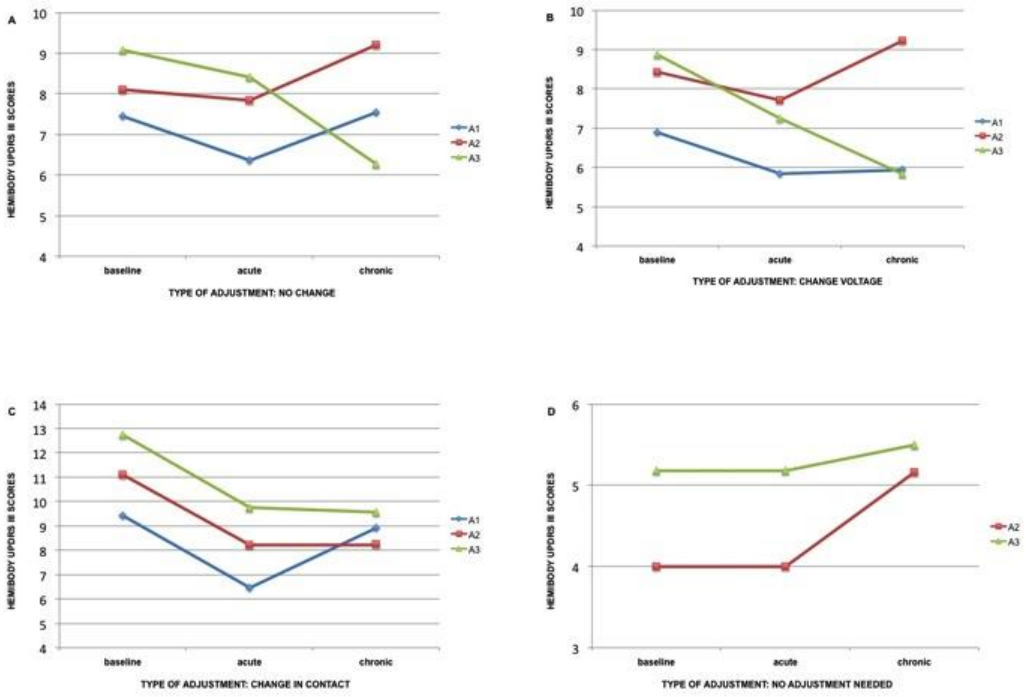

Figure 1.7 UPDRS III hemibody scores for each type of adjustment at A1, A2 and A3. Abbreviations: A: adjustment session; UPDRS III: motor part of Unified Parkinson's Disease Rating Scale.

1.3 IMPACT OF ADJUSTMENT SESSIONS ON "ON MEDICATION/ON STIMULATION" SCORES

Statistical considerations

None of the variables analysed followed a normal distribution (Shapiro-Wilk test, $p<0.05$); therefore, non-parametric tests were used: comparisons for related samples were carried out using Friedman test and Wilcoxon signed ranks test with Bonferroni correction for pairwise comparisons (p value set at 0.016 for three samples comparison).

UPDRS III SCORES, UPDRS III AXIAL SCORES AND TOTAL AND AXIAL DYSKINESIAS SCORES ON-MEDICATION/ON STIMULATION

UPDRSIII scores on medication/on stimulation (onM/onS) varied throughout the study (Friedman test, p=0.017) experiencing a significant deterioration between A1 and A2 (p=0.009, Wilcoxon test) and a tendency to deteriorate between A1 and A3 (p=0.054, Wilcoxon test); however, there were no differences between A2 and A3 scores.

No differences were found for UPDRS III axial scores among adjustment sessions (p=0.137, p=0.0886 and p=0.690 respectively).

Neither total dyskinesia nor axial dyskinesia scores varied during the study (Friedman test, p=0.861 and p=0.788) (table 1.11).

Table 1.11 ON medication/On stimulation scores

	A1	A2	A3
	Mean (SD)	Mean (SD)	Mean (SD)
UPDRS III	14.48 (8.64)	17.56 (9.59)	17.11 (9.23)
UPDRS III axial	1.30 (1.71)	1.44 (1.31)	1.52 (1.22)
UPDRS III hemibody	4.10 (2.93)	4.91 (3.68)	4.35 (3.09)
Dyskinesia total	4.52 (3.19)	3.59 (3.41)	3.37 (2.55)
Dyskinesia axial	1.81 (2.30)	1.30 (1.96)	1.26 (1.70)
Dyskinesia hemibody	1.52 (1.07)	1.13 (1.15)	0.90 (0.85)

Abbreviations: A: adjustment session; SD standard deviation

UPDRS III HEMIBODY SCORES AND HEMIBODY DYSKINESIAS SCORES ON-MEDICATION/ON-STIMULATION

Variations of UPDRS III hemibody scores were found for the three adjustment sessions (Friedman test, p=0.02): a tendency to deteriorate from A1 to A2 (p=0.02, Wilcoxon test) and no differences for A2 vs. A3 (p=0.12) and A1 vs. A3 (p=0.28) (table 1.11). A tendency towards an improvement was observed for hemibody dyskinesia (Friedman test, p=0.08; hemibody dyskinesia at A1 vs. hemibody dyskinesia at A3 p=0.03, Wilcoxon test) (table 1.11)

1.4 ADDITIONAL VISITS

Six patients required one additional visit. Two patients had an additional visit between adjustment 1 and 2 (2 hemibody sides), one between adjustment 2 and 3 (one hemibody side) and 3 after adjustment 3 (5 hemibody sides). Type of adjustment that prompted the additional visit was “change in contact” in all cases. Type of adjustment performed at the additional visit was “change in contact” in all but two sides where only voltage was adjusted. Hemibody motor scores deteriorated in 5 sides, whereas in three it was the presence of dyskinesia what prompted the additional adjustment.

1.5 PREDICTIVE FACTORS FOR GLOBAL IMPROVEMENT AT EACH ADJUSTMENT SESSION

Predictive variables for global outcome at each adjustment session were studied using multivariate regression. Global outcome for each adjustment session was defined as the difference on UPDRS III total and hemibody scores between chronic and baseline time points. The regression model (backward method) was checked for independence of the residuals (Durbin-Watson statistic), co-linearity, normality and homoscedasticity of the residuals. The independent variables analysed are shown in table 1.12.

Table 1.12. Variables considered for the multiple regression analysis

Dependent variable	Global outcome for each Adjustment session
Independent variables for UPDRS III total scores	Acute total UPDRS III effect Acute axial UPDRS III effect Acute total dyskinesia UPDRS IV total, off and dyskinesia Global effect on axial UPDRS III Global effect on total dyskinesia Type of adjustment
Independent variables for UPDRS III hemibody scores	Acute UPDRS III hemibody effect Acute limb dyskinesia Difference in voltage* TEED LEDD Change in contact** Time between visits

* difference in voltage between baseline and final time point of the adjustment

** Change in contact was redefined as an ordinal variable taking into consideration the depth of the change (change towards a more inferior or superficial position).

For total body analysis, “type of adjustment” was reclassified taking into account the type of adjustment performed at both DBS electrodes:

- No change in any of the DBS electrodes

- Change in voltage in at least one of the DBS electrodes and no change in contact
- Change in contact in at least one of the DBS electrodes
- No adjustment needed in any of the DBS electrodes

1.5.1 TOTAL UPDRS III

Thirty-one patients were included in this part of the study. Patients with additional visits were excluded from the analysis. Two patients required additional visits at A1, one at A2 and, 3 at A3.

IMPACT OF TYPE OF ADJUSTMENT ON GLOBAL OUTCOME AT EACH ADJUSTMENT SESSION

No impact of type of adjustment on global effect of the adjustment was seen at A1. At A2, there was a strong tendency towards a total UPDRS III global improvement for those patients that had at least one change in the stimulated contact and towards stable scores for those with at least one change in voltage. At A3, there was a total UPDRS III global improvement of approximately 8 points for those patients who had at least one change in voltage or one change in contact. Those not requiring additional adjustments at A3 had steady scores (table 1.13 and figure 1.8).

MULITIVARIATE REGRESION ANALYSIS

At A1, the global effect of axial UPDRS III scores predicted the global effect (R^2 = 0.69). For each unit of improvement on axial UPDRS III global scores there was a 3.22 improvement on total UPDRS III global scores. At A2 and A3, a strong association between total acute effect and global outcome was

found [(R^2 = 0.59 (A2); R^2 = 0.63 (A3)]. Acute effect had a direct impact on global outcome (for each unit of improvement on acute UPDRS III scores there was approximately 0.8 points improvement on global scores) (table 1.14).

Table 1.13 Global outcomes of adjustment sessions on total UPDRS III scores according to type of adjustment

		Total	No change	At least one change in voltage	At least on change in contact	NAN	p*
Global outcome at A1	**n**	29	2	5	22	NA	
	Mean	-1.41	-2.00	-2.00	-1.23	NA	0.816
	SD	9.55	2.83	1.58	10.98	NA	
Global outcome at A2	**n**	29	3	10	7	9	
	Mean	0.48	5.33	0.90	-5.29	2.89	0.070
	SD	6.89	9.29	5.11	8.30	4.34	
Global outcome at A3	**n**	23	2	4	6	11	
	Mean	-3.83	-5.00	-8.00	-8.83	0.66	0.009
	SD	6.17	2.83	5.16	6.24	5.16	

Abbreviations: A: adjustment session; NA: not applicable; NAN: no adjustment needed; SD standard deviation. A minus sign means improvement.

* Kruskal Wallis Test

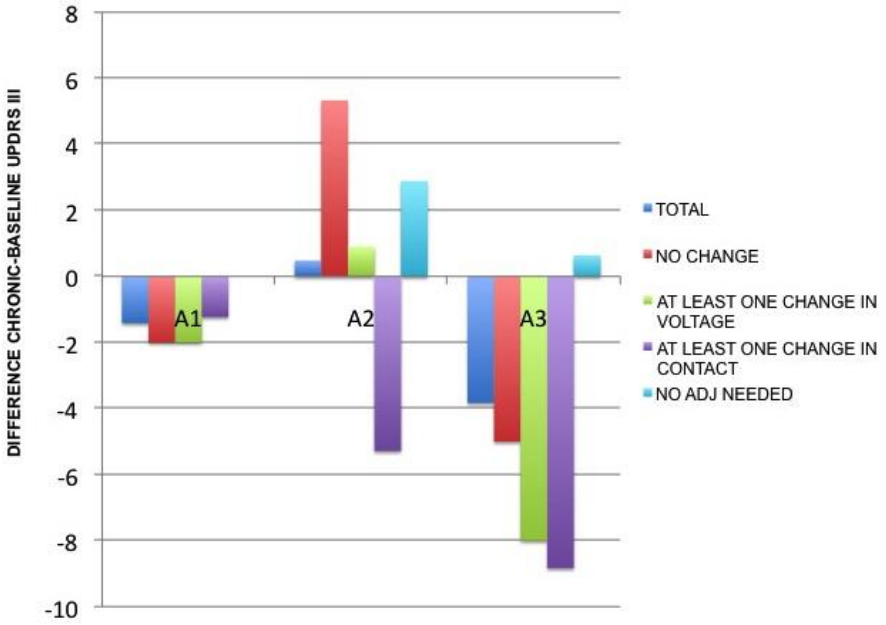

Figure 1.8. Global outcome of adjustment sessions on total UPDRS III scores according to type of adjustment. Type of adjustment by adjustment sessions were re-codified as: no change in any of the electrodes, at least one change in voltage, at least one change in contact and no adjustment needed. Negative values show an improvement in global UPDRS III scores.

Table 1.14 Multivariate regression analysis of total UPDRS III global outcome at each adjustment session

		B coefficient	Beta	p-value
A1	**Axial UPDRS III global scores**	3.225	0.664	0.001
A2	**Total UPDRS III acute effect**	0.782	0.360	0.053
A3	**Total UPDRS III acute effect**	0.766	0.406	0.018

Abbreviations: A: adjustment session 1, 2 and 3.

1.5.2 HEMIBODY UPDRS III

Patients with additional visits were excluded from the analysis. At A1, one hemibody side with a bipolar electrode geometry configuration at baseline was also excluded. A total of 55, 58 and 46 hemibody sides were included for the analysis at A1, A2 and A3, respectively.

Acute effect on UPDRS III hemibody scores predicted global outcome in all the adjustment sessions (table 1.15). There was a linear relationship between acute UPDRS III hemibody effect and global effect (figure 1.9). For each unit of improvement on the acute effect on UPDRS III hemibody scores, there was a global hemibody improvement of 0.91 points at A1, 1.17 points at A2 and 0.66 points at A3.

The magnitude of the acute effect necessary to ensure improvement/stability or improvement on global effect decreased as stimulation was optimised throughout the adjustment sessions. At A1, at least 3 points of acute improvement were needed to provide a global improvement or stability (95% confidence interval (CI) ranging from -2.65 to 0.14). All of the hemibody sides that experienced an acute improvement of at least 5 points did show global improvement (95%CI ranging from -5.47 to -2.43). At A2, at least 2 points of acute improvement were needed to provide a global improvement or stability and 3 points to guarantee a global improvement (95%CI ranging from -1.84 to -0.43 and from -3.23 to -1.39 respectively). At A3, at least 1 point of improvement on the acute effect was necessary to provide a global improvement (95%CI ranging from -3.28 to -1.50).

At A1, an increase in the depth of the active contact produced deterioration on the global effect of 5.06 points. Conversely, at A2 change contact towards a

more superficial position showed a tendency towards a global improvement (2.305 points) (table 1.15).

Time between visits had a negative impact on motor scores only at the third adjustment session. This session had a longer interval between acute and chronic evaluations (3 months). For each day of delay, there was an increment of 0.063 points on the UPDRS III hemibody scores.

Table 1.15. Multivariate regression analysis of global hemibody outcome at each adjustment session

PREDICTIVE VARIABLE	B Coefficient	Beta	p value
A1*			
Acute effect UPDRS III hemibody scores	0.908	0.623	<0.001
Increase contact depth	5.058	0.479	<0.001
A2 §			
Acute effect UPDRS III hemibody scores	1.177	0.714	<0.001
Decrease contact depth	-2.0305	-0.231	0.087
A3**			
Acute effect UPDRS III hemibody scores	0.665	0.395	0.001
Time between visits (days)	0.063	0.463	<0.001

Abbreviations A: adjustment session.

*A1: R^2=0.504; F=13.215, p<0.001.

A2§: R^2=0.509; F=58.121, p<0.001.

**A3: R^2=0.497; F=21.225, p<0.001.

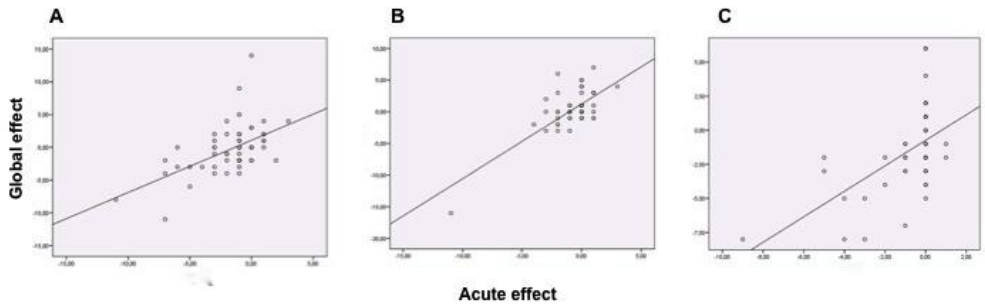

Figure 1.9 Correlation between acute effect and global effect for each adjustment session. A) Adjustment 1; B) Adjustment 2; and C) Adjustment 3. Global effect: chronic-baseline UPDRS III hemibody scores; acute effect: acute-baseline UPDRS III hemibody scores.

In view of these results, global outcome at each adjustment session seemed mainly dependent of the acute effect. However, we aimed to explore whether the type of adjustment acted as a confounding factor distorting the global outcome scores regardless of the acute effect. For this purpose, a new regression model was run considering the global outcome for each session as a dependent variable and the acute effect and type of adjustment as independent variables. Later on the same model was operated, excluding the type of adjustment, and the B coefficients compared.

At A1 and A2, only the acute effect had an impact on global outcome (A1: B coefficient 1.002; beta 0.726; $p<0.001$ when type of adjustment was considered in the model and B coefficient 0.881; beta 0.639; $p<0.001$ when type of adjustment was excluded; A2: B coefficient 1.059; beta 0.642; $p<0.001$ when type of adjustment was considered in the model and B coefficient 1.177; beta 0.714; $p<0.001$ when type of adjustment was excluded).

At A3, global outcome was influenced by the acute effect and by the type of adjustment (change in voltage). For each unit of improvement on the acute

effect there was a global improvement of 0.726 units on UPDRS III hemibody scores. However, when the type of adjustment corresponded to “change in voltage” there was a further benefit beyond the acute effect of 2.6 points. Therefore, there is a good proportion of the global effect that cannot be explained by acute effect. When a “change in contact” was applied no further benefit from the acute effect was observed (figure 1.6).

SUMMARY

Stimulation parameters of STN DBS were reprogrammed in 31 patients (62 DBS electrodes; 19 male, mean age 56.35±6.8 years old; mean disease duration 12.39±5.3 years) during three consecutive adjustment sessions. STN DBS produced a 49.53% improvement in UPDRS III scores (off-medication) at baseline of the study (comparison with pre-DBS). The impact of SP adjustment was similar for total and hemibody UPDRS III scores and subscores. Reprogramming produced an acute benefit in all of the adjustment sessions (A1, A2 and A3); however, this benefit was only maintained at A3. The type of adjustment influenced the response of hemibody UPDRS III subscores to SP adjustment. “No changes” in SP produced neither an acute nor sustained benefit except for at A3, where a chronic improvement was detected. “Change in voltage” did not produce either an acute or sustained benefit at A1 or A2. At A3, an immediate maintained benefit was achieved. “Change in contact” was the type of adjustment producing a major impact on SP. In all of the adjustment sessions, this type of adjustment produced an immediate benefit; however, it was only maintained at A2 and A3. For those hemibody sides not requiring any

adjustment of the stimulation parameters, motor scores were significantly lower and were kept stable throughout the study.

The best predictive factor for a global improvement at each adjustment session was an acute improvement on total and hemibody UPDRS III. A linear relationship was found between the acute and global effect on hemibody UPDRS III. The magnitude of the acute effect necessary to ensure a sustained benefit decreased with progressive adjustment of SP [A1: 5 points (range -5.47 to -2.43, 95% CI); A2: 3 points (range -3.23 a -1.39, 95% CI) and A3: 1 point (range -3.28 a – 1.50, 95% CI)]. At A1, stimulating a more caudal contact predicted a global deterioration, while, at A2, stimulating a more rostral area showed a tendency towards an improvement.

2. CLINICALOUTCOME OF STN DBS WITH REPROGRAMMING

2.1 IMPACT OF SUCCESSIVE ADJUSTMENT SESSIONS ON CLINICAL OUTCOME

Final UPDRS III scores were compared to scores at baseline. Baseline and final time point of the study corresponded to baseline scores at A1 and chronic time points of A3, respectively. All scores were performed off-medication/on-stimulation. Patients were included regardless of the need for additional visits between adjustment sessions. A total of 26 patients (52 hemibody sides) were included in this part of the analysis.

A significant improvement in UPDRS III total and hemibody scores and a tendency towards improvement on axial subscores was observed at the final time point compared to baseline. UPDRS I and activities of daily living (UPDRS II) off-medication improved as well. LEDD was significantly reduced after 6 months. However there was no further benefit on motor complications or in activities of daily living on-medication (table 2.1).

Table 2.1 Comparison of UPDRS scores at baseline and final time point of the study

	Baseline	Final	P value*
UPDRS III	27.85 (15.31)	22.96 (10.06)	<0.001
UPDRS III hemibody subscores	8.38 (5.33)	6.63 (4.04)	<0.001
UPDRS III axial subscores	2.54 (2.63)	1.92 (1.65)	0.08
UPDRS I	2.27 (1.39)	1.55 (1.41)	0.017
UPDRS II OnM/OnS	10.41 (5.15)	10.68 (4.86)	0.683
UPDRS II OffM/OnS	16.41 (7.39)	13.36 (4.49)	0.003
UPDRS IV dyskinesia	2.00 (1.85)	1.41 (1.79)	0.158
UPDRS IV off-time	1.68 (1.64)	1.05 (1.21)	0.125
LEDD	660.15 (403.98)	454.77 (224.18)	0.016

Abbreviations A: adjustment session; OffM: off-medication condition; OnM: on-medication condition; OnS: on-stimulation condition; SD: standard deviation. Values of UPDRS scores and subscores are given as means (SD). UPDRS IV dyskinesia comprises items 32, 33, and 34; UPDRS IV off-time comprises item 39. *Two-tailed t test.

Multivariate regression analysis at each adjustment session highlighted the importance of changing the stimulated contact. To analyse the impact of this type of adjustment on final outcome, patients (by hemibody sides) were grouped according to the following classification **"Adjustment of stimulation parameters throughout the study"** (table 2.2):

- "No changes": No changes of stimulation parameters (includes "no changes" and "no adjustment needed") throughout the study.
- "Change in voltage": One or more change in voltage (or pulse width or frequency) but no changes of stimulated contact.
- "One change in contact": One change of stimulated contact.
- "≥ 2 change in contact": Two or three changes of the stimulated contact.

Table 2.2. UPDRS III hemibody scores by type of adjustment of stimulation parameters throughout the study (comparison baseline time point of A1 and chronic time point of A3)

UPDRS III hemibody		Total	No change	Change in voltage	One change in contact	≥ 2 changes in contact
	N	52	6	13	21	12
Baseline	**Mean (SD)**	8.385 (5.33)	5.50 (2.07)	7.923 (4.63)	8.619 (5.38)	9.917 (6.82)
Final	**Mean (SD)**	6.635 (4.04)	4.50 (3.08)	6.385 (3.45)	5.857 (2.67)	9.333 (5.80)

Abbreviations: SD: standard deviation.

Repeated measures analysis with main factor TIME (2 levels baseline and final time point) and between-subjects factor “adjustment of stimulation parameters throughout the study” was performed. The analysis revealed a significant effect for Time (Pillai’s Trace, p=0.019) but not for adjustment (Pillai’s Trace, p=0.457; F=1.789; p=0.162). *Post-hoc* tests showed a significant improvement of UPDRS III hemibody scores for “one change of stimulated contact” (p=0.003), while “change in voltage” showed a tendency towards improvement (p=0.068). The remaining types of adjustment led to stable UPDRS III hemibody scores. Multiple comparisons did not show any significant differences among groups of type of adjustment. However, those included in “more than one change of stimulated contact” seemed to have higher baseline and final scores, especially when compared to “no changes” (figure 2.2).

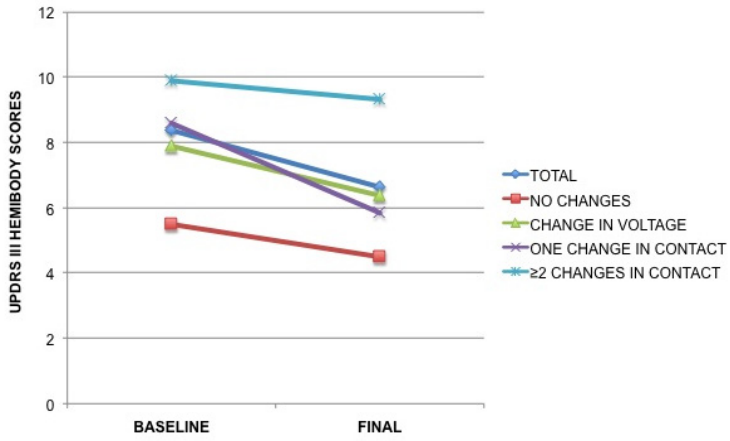

Figure 2.2. UPDRS III hemibody scores at baseline and final time point by type of adjustment throughout the study. Mean UPDRS III hemibody scores are represented by rhombus, squares, triangles, crosses and stars.

2.2 PREDICTIVE FACTORS FOR FINAL IMPROVEMENT

Final outcome variable was defined as the differences between chronic time point of A3 and baseline scores of the study (baseline time point of A1).

Final outcome variable = chronic scores of A3 - baseline scores of A1

A minimal clinical important difference was established on 2.5 points for total UPDRS III based on the study by Shulman (2010). Final outcome variable was re-codified into a qualitative variable where differences equal or below -2.5 points were defined as improvement and equal to or above +2.5 points as deterioration. Values in between were considered stable scores. For logistic regression analysis, the variable was dichotomised into improvement or no improvement (including stable and deterioration). For hemibody scores, the cut-off value was calculated at 0.825 points. Final outcome variable was re-codified

into a qualitative variable. Differences equal or below -0.825 points were defined as improvement and equal to or above +0.825 as deterioration. The global outcome variable for each adjustment session was categorised into improvement (differences equal or below -0.825) and deterioration (equal or above 0.825).

IMPROVEMENT OF UPDRS III SCORES ALONG THE STUDY

Twenty-six patients (52 hemibody sides) completed all adjustment sessions. Eleven patients (42.3%) had a global improvement, eleven remained stable and four (15.4%) deteriorated. For hemibody side: 31 (59.6%) improved, 7 (13.4%) remained clinically stable and 14 (26.92%) deteriorated. At A1, half of these hemibody sides improved (51.1%). At A2 only 30% improved. At A3 most of the hemibody sides improved (68.9%).

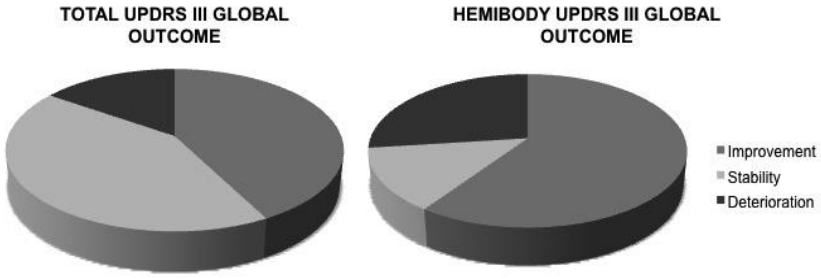

Figure 2.3. Final outcome for total and hemibody UPDRS III global outcome. Area in the circles represents the percentage of patients and hemibody sides, respectively.

LOGISTIC REGRESSION OF GLOBAL OUTCOME AND OUTCOME AT ADJUSTMENT SESSIONS

The probability of a global improvement on hemibody motor scores was studied using logistic regression analysis (stepwise method). The dependent variable was the final outcome defined as improvement or deterioration (cut-off value 0.825 points). The independent variables considered for the analysis were: improvement at A1, improvement at A2 and improvement at A3, as well as interactions between them.

The best predictive factor for a global improvement was improvement at A3 on hemibody UPDRS III scores (Exp (B) = 22.455, p=0.006) followed by improvement at A1 (Exp (B) 13.598, p=0.021) (table 2.3). Improvement at A2 and interactions between adjustment sessions were not significant and were left out of the equation. Thus, the probability to improve after improvement at A3 or improvement at A1 was of the same magnitude regardless of whether there was an additional improvement at A1 or A3, respectively.

The percentage of cases predicted by the model was of 73.1% (for total UPDRS III) and 77.8% (for hemobidy UPDRS III)

The models were checked for Hosmer test (p=0.86 and 0.65), normality of the residuals (p=0,073 and 0.077) and Nagelkerke coefficient (0.32 and 0.44).

Table 2.3. Logistic regression for global outcome by outcome at each adjustment session

	B	Exp (B)	p-value
Total UPDRS III			
Improvement at A1	2.065	7.888	0.064
Improvement at A2	2.106	8.212	0.072
Hemibody UPDRS III			
Improvement at A1	2.610	13.598	0.021
Improvement at A3	3.111	22.455	0.006

Abbreviations: A: adjustment session (1, 2 and 3)

LOGISTIC REGRESSION ANALYSIS OF GLOBAL OUTCOME AND SOCIO-DEMOGRAPHIC VARIABLES

The impact of sex, age at DBS and duration of DBS therapy on global outcome UPDRS III total and hemibody scores (final time point – baseline time point of the study) were studied using logistic regression (user-controlled backward stepwise method).

For UPDRS III total scores, none of these variables predicted global outcome (p-values: 0.581, 0.519 and 0.157).

For UPDRS III hemibody scores, there was a tendency towards an influence on final outcome for sex and, to a lesser degree, for age at DBS (table 2.4). Women presented a higher probability for improvement than men (Odds ratio 5.412) (table 2.5). There was a tendency as well for older patients to present a decreased probability to improve compared to younger patients (Odds ratio 0.892). For each year of age difference at the time of DBS, the probability of improvement decreased by 11%.

Table 2.4. Logistic regression analysis of sociodemographic variables on final outcome on hemibody UPDRS III scores

	B	Exp (B)	p
Sex	1.689	5.412	0.058
Age at DBS	-0.114	0.892	0.077

Abbreviations: DBS: deep brain stimulation; p: p value

Table 2.5. Final outcome on hemibody UPDRS III scores according to sex

Final outcome	Total	Male	Female
Total	45	30	15
Deterioration	14	12	2
Improvement	31	18	13

ANALYSIS OF GLOBAL OUTCOME AND TEED, LEDD AND UPDRS III AT BASELINE

Total UPDRS III scores

Univariate analysis for change in TEED from baseline to final time point (mean difference for both hemibodies) and for change LEDD did not showed differences between those patients that improved and those that did not (Mann-Whitney U test p=0.357 and p=0.157, respectively). However, those with higher UPDRS III scores at baseline (off-medication/on-stimulation) had a higher probability of a final improvement (logistic regression: B=0.141, Exp(B)=1.151, p=0.024). For each unit of increment in UPDRS III baseline scores, the odds probability for global improvement increased by 11.51% (95%CI, 1.018-1.301) (table 2.6).

Table 2.6 Global outcome according to UPDRS III at baseline of the study

	Global outcome		
UPDRS III scores at BL	**Total**	**Improvement**	**No improvement**
n	26	11	15
Mean (SD)	27.8 (15.3)	37.6 (18.5)	20.7 (6.7)

Abbreviation: BL: baseline of the studySD standard deviation; UPDRS III: motor part of Unified Parkinson's Disease Rating Scale.

Mann-Whitney U test p=0.004.

Hemibody UPDRS III scores

Logistic regression analysis was used (user-controlled backward stepwise methods for main effects and stepwise for interactions) with independent variables: change in TEED from baseline to final time point, change in LEDD from basal to final time points, UPDRS III hemibody scores at baseline of the study and type of adjustment throughout the study.

Only UPDRS III hemibody scores at baseline were significant (B=0.291, Exp (B)= 1.337, p=0.030 (95%CI 1.029-1.738)). For one point of increment in UPDRS III hemibody scores at baseline, the probability for improvement increased by 33.7% (odds ratio 1.337) (table 2.7).

Table 2.7 Global outcome according to UPDRS III hemibody scores at baseline of the study

	Global outcome		
Hemibody UPDRS III BL	**Total**	**Improvement**	**Deterioration**
n	45	31	14
Mean (SD)	8.6 (5.58)	10.1 (5.92)	5.29 (2.70)

Abbreviation: BL: baseline of the study; SD standard deviation; UPDRS III: motor part of Unified Parkinson's Disease Rating Scale.

SUMMARY

Forty-two per cent of the patients (59.6% of hemibody sides) showed a motor improvement with reprogramming at the end of the study. A significant improvement was found for total (p <0.001; two-tailed t test) and hemibody UPDRS III (p <0.001; two-tailed t test), UPDRS I and activities of daily living off-medication (p=0.017 and 0.003 respectively, two-tailed t test). Dopaminergic medication requirements were reduced by 30% (p=0.016, two-tailed t test). DBS electrodes where a single change in the stimulated contact during the study period was conducted showed a statistically significant final improvement (p=0.003), while those undergoing "change in voltage" showed a tendency towards improvement (p=0.068). "No changes" or "two or more changes in active contact" did not produce any final effect.

Younger patients (B=-0.114, p=0.077), women (B=1.689, p=0.058) or higher UPDRS III scores at baseline (total: B=0.141, p=0.024; hemibody: B=0.291, p=0.030) showed a higher probability for final improvement.

3. OPTIMAL STIMULATION SITE IN STN DBS FOR PARKINSON'S DISEASE

The position of the DBS electrode and therapeutic contact (active contact) was evaluated in 31 patients. Demographic data are described in part 1 of the results. All patients underwent bilateral STN DBS for at least 12 months. Stimulation parameters were optimised after three consecutive adjustment sessions with objective quantification of symptoms. This ensures that final active contact represents the optimal stimulation site for a given electrode.

Pre- and postoperative stereotactic MR image acquisition and electrode contacts positions were obtained as previously described in methodology. Two neurosurgeons blinded to the clinical outcome and stimulation parameters independently assessed and agreed on the anatomical position of each contact in relation to the visualised STN on the axial and coronal MRI planes. The visualised STN was divided into five segments: superior (A), anterior-medial (B), central (C), postero-lateral (D) and inferior (E). Each contact was localised in relation to the closest STN segment and classified as being inside, superior, medial, inferior or lateral to that segment. Final anatomical position for each DBS electrode's contact was defined by the anatomical localisation around the STN and its surrounding structures and the STN segment. The optimal stimulation area was considered to be the central, superior, posterolateral segment of the STN or the area adjacent to the superior border of the STN (located less than 1 mm from the border of the nucleus).

This study will analyse three points:

1) Analysis of the anatomical position of the DBS electrode. This part will focus on the position of the DBS electrode (regardless the position of the stimulated contact). Electrode's position will be resumed in two groups:
    a. Group I electrode's position (Group Ie, good location), when at least one of the four contacts of the electrode was within the defined optimal area (not necessarily corresponds to the active contact).
    b. Group II electrode's position (Group IIe), when none of the contacts was within the defined optimal area.
2) Analysis of the anatomical position of the active (therapeutic) contact. This part will define the optimal stimulation site. Active contact position will be classified as:
    a. Group I contact's position (Group Ic, good location) the active contact is within the defined optimal area - the central, superior, posterolateral segment of the STN or the area adjacent to the superior border of the STN.
    b. Group II contact's position (Group IIc) consisted of those active contacts not fulfilling the above criteria.
3) The value of postoperative imaging in the selection of the optimal therapeutic contact. This part of the study will investigate the usefulness of an image-guided selection of the active contact. One of the neurosurgeon, blinded to the stimulation parameters and clinical outcome, selected one or two contacts considered to be optimally placed according to MRI data (MRI contact), assuming that the best site of stimulation is the STN nucleus and not the surrounding tracks. If no

contact was found within the nucleus, the best contact was considered to be the one closest to the superior tip of the STN. Concordance of the best located contact (MRI contact) with active contact (clinical contact) was evaluated. Contacts were classified into two groups: “no concordance clinical/MRI contact” and “concordance clinical/MRI contact”.

3.1 ANALYSIS OF ANATOMICAL POSITION OF THE DBS ELECTRODE

Data regarding electrode’s position was available for 50 electrodes (24 patients information available for both DBS electrodes and in 2 patients, for one DBS electrode). Figure 3.1 shows number of electrode contacts within (group I) and outside the optimal stimulation area (group II): eighty-eight per cent of the electrodes had one or more contacts within the optimal stimulation area and; 60% had two or more contacts. In 12% of the electrodes, all contacts were outside the defined optimal area. This accounts for nineteen patients (79%) having both electrodes (right and left brain sides) with at least one contact within the optimal area and, 5 patients with one of the DBS electrodes sub-optimally placed. No differences were found for right or left hemisphere (table 3.1).

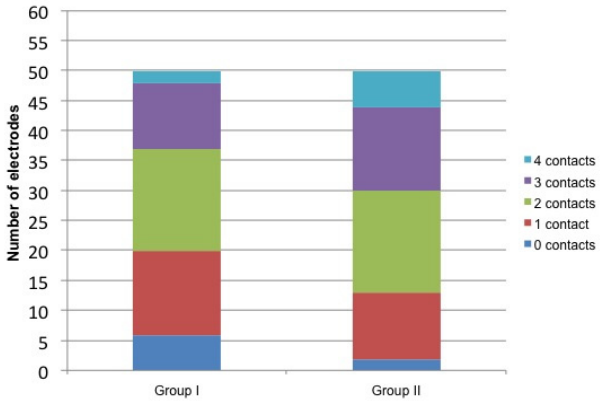

Figure 3.1. Number of electrode's contacts within (group I) and outside (group II) the optimal stimulation area for patients included in the clinical study.

Table 3.1. Electrodes classification in group Ie by brain hemisphere for patients of the study

Group Ie	Right hemisphere	Left hemisphere	Total
0 contacts	3	3	6 (12%)
1 contact	5	9	14 (28%)
2 contacts	11	6	17 (35%)
3 contacts	5	6	11 (22%)
4 contacts	1	1	2 (4%)
Total	25	25	50 (100%)

TYPE OF ADJUSTMENT AND ELECTRODE'S POSITION

From a descriptive point of view, electrodes sub-optimally placed required more frequently multiple changes in the active contact, whereas "no changes" in the SP only occurred in those electrodes with a good location (Chi-square test p=0.988; figure 3.2). No statistically significant differences were found for

number of contacts per electrode classified as group Ie and either type of adjustment performed at the different adjustment sessions (Kruskal Wallis test A1 p=0.880; A2 p=0.774; A3 p=0.122).

DBS EFFICACY AND ELECTRODE'S POSITION

There was a strong tendency towards lower UPDRS III hemibody scores at baseline and final time point when the electrode has one or more contacts optimally placed. Both groups (Ie and IIe) obtained similar benefits on UPDRS III hemibody scores at the end of the study. No statistically significant differences were found for DBS efficacy at baseline (compared to preoperative scores) and number of contacts classified as group I (table 3.2).

TEED, VOLTAGE, LEDD AND ELECTRODE'S POSITION

TEED at baseline (statistically significant) and final time point (nearly significant) was lower for those electrodes classified as group Ie (table 3.2, figure 3.3). Lower values were also found for voltage at baseline in this group (table 3.2, figure 3.4).

Considering both DBS electrodes, LEDD was significantly lower for those patients having both electrodes at group Ie at the final time point but not at baseline. No differences were found for reduction of LEDD at the end of the study within or between groups (table 3.3).

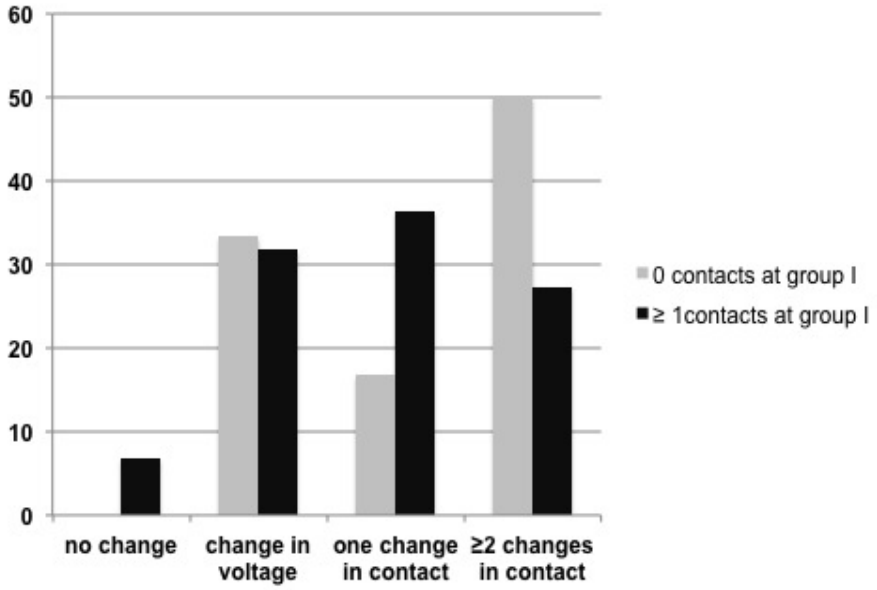

Figure 3.2 Percentage of electrodes with 0 or ≥ 1 or more contacts of the DBS electrode at group Ie by type of adjustment during the study. *Y axis*: percentages respect to the total number of electrodes with 0 contacts at group I or ≥ 1 more contacts at group I.

Table 3.2 Comparison of DBS efficacy, global outcome, TEED and voltage by number of contacts at group Ie at baseline and final time point

	0 contacts at group Ie Mean (SD)	≥1 contacts at group Ie Mean (SD)	P value
N at BL	6	44	
N at final	6	37	
DBS efficacy at BL (%)	54.52% (14.60)	54.63% (17.84)	0.744*
DBS efficacy at final (%)	60.01% (16.50)	58.17% (15.47)	0.744*
UPDRS III hemibody BL	7.90 (3.28)	7.43 (4.68)	0.082**
UPDRS III hemibody final	6.33 (3.03)	5.46 (2.86)	0.062**
Global outcome	-1.60 (2.34)	-0.54 (2.96)	0.44**
TEED BL	138235.5 (41651.47)	93247.94 (50801.28)	0.044**
TEED final	157351.0 (91661.11)	102.503.7 (56206.65)	0.075**
Change TEED	19115.75 (72860.35)	8929.95 (26612.26)	0.55**
Voltage BL	3.73 (0.41)	3.13 (0.75)	0.060*
Voltage final	3.73 (0.39)	3.22 (0.76)	0.113*
Change voltage	0.00 (0.46)	0.10 (0.36)	0.54*

Abbreviations: BL: baseline; SD: standard deviation; TEED: total electrical energy delivered

DBS efficacy: [(UPDRS III off medication pre DBS – UPDRS III off medication/on stimulation at baseline)/UPDRS III off medication pre DBS] x 100.

Global efficacy: UPDRS III final time point of the study - UPDRS III baseline time point of the study (both off medication/on stimulation). A minus sign means improvement.

* T-test.

** Mann-Whitney U test.

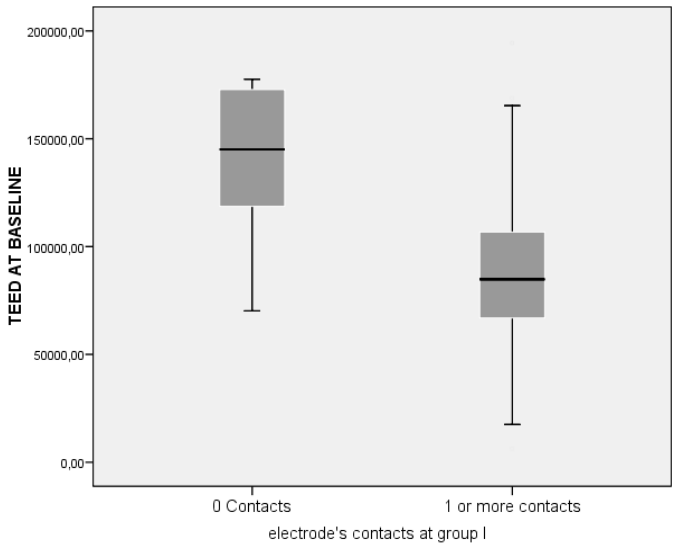

Figure 3.3. TEED at baseline by number of contacts per electrode classified as group Ie. Inside horizontal line: median TEED value; whiskers: first and third quartile.

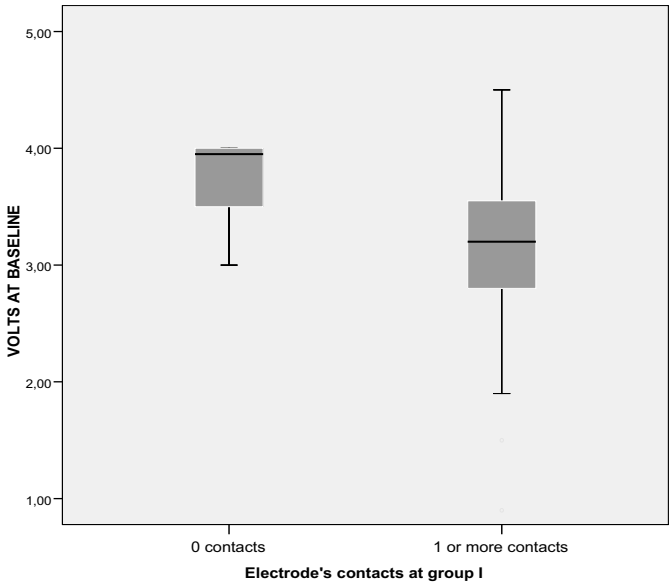

Figure 3.4. Voltage (in volts) at baseline by number of contacts per electrode classified as group Ie. Inside horizontal line: median voltage value; whiskers: first and third quartile.

Table 3.3 LEDD at baseline and final time point classified by number of electrodes having at least one contact at group Ie

	One electrode with at least one contact at group I	Two electrodes with at least one contact at group I each	P*
n	5	19	
LEDD baseline	864.71 (144.73)	667.77 (476.86)	0.430
LEDD final	735.00 (114.74)	373.63 (213.39)	0.005
Change LEDD	-129.71 (112.13)	-105.21 (180.95)	0.80

Abbreviations: LEDD: Levodopa equivalent daily dose; SD: standard deviation. Change LEDD: difference between final and baseline LEDD

* T- test.

3.2. ANALYSIS OF THE ANATOMICAL POSITION OF THE ACTIVE CONTACT

Contact location information was available for 50 electrodes at baseline and 43 at final time point. At baseline, 54% of active contacts (stimulated contacts) lay inside the STN, 40% were medial and the remaining 6% were located lateral, superior or inferior to the STN. Those active contacts inside the nucleus were mainly at its centre (55.5%) or its superior part (30%). Those located medial to the nucleus were mainly medial to the centre (30%) or to the superior part (60%), i.e. in the zona incerta that stretches from just above the STN and along its medial border and terminates medial and posteromedial to the STN's posterior tail (figure 3.5).

At the final time point, 58.1% of the active contacts projected inside the STN and 30.2% were medially located. The remaining 11.6% were positioned lateral, superior or inferior to the nucleus. Active contacts located inside the nucleus

were placed at its centre (40%) or at its superior part (52%); those located medially were more frequently located medially to the superior part (46%) and to the centre of the nucleus (30%). A description of the active contacts according to the Schaltenbrand atlas is given in figures 3.5 and 3.6. Figure 3.7 shows the evolution of the active contact towards a more rostral position.

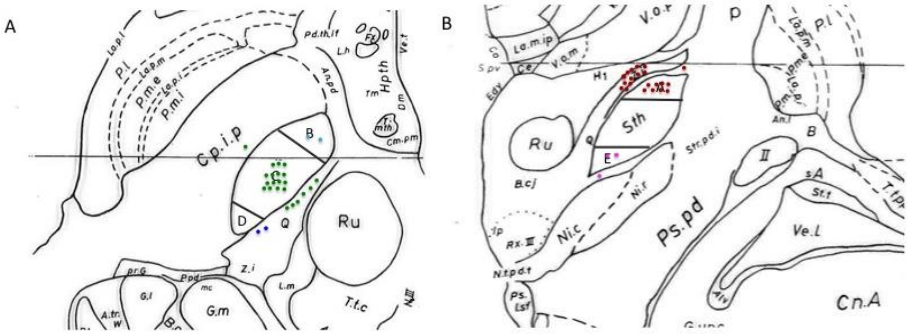

Figure 3.5. Location of active contacts at baseline as transposed onto the Schaltenbrand atlas. A) Axial view adapted from plate 55, *H.v 4.5.* Contacts related to the antero-medial (light blue dots), central (green dots) and postero-lateral (dark blue) segments of the STN. B) Coronal view adapted from plate 27, *f.p 3.0*. Contacts related to the superior (red dots) and inferior segments (pink dots) of the STN.

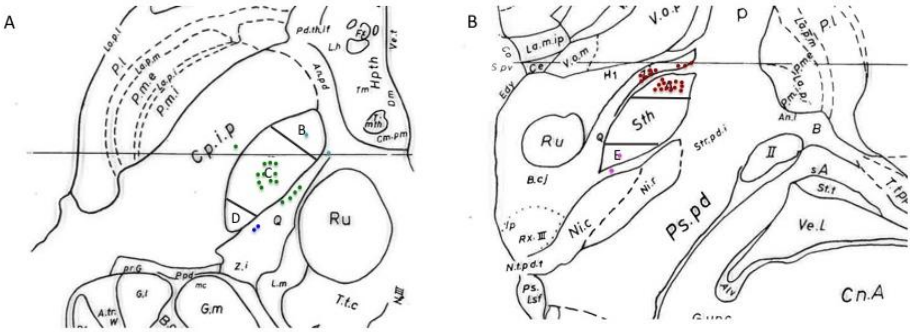

Figure 3.6. Location of active contacts at final time point as transposed onto the Schaltenbrand atlas. A) Axial view adapted from plate 55, *H.v 4.5.* Contacts related to the antero-medial (light blue dots), central (green dots) and postero-lateral (dark blue) segments of the STN. B) Coronal view adapted from

plate 27, *f.p 3.0*. Contacts related to the superior (red dots) and inferior segments (pink dots) of the STN.

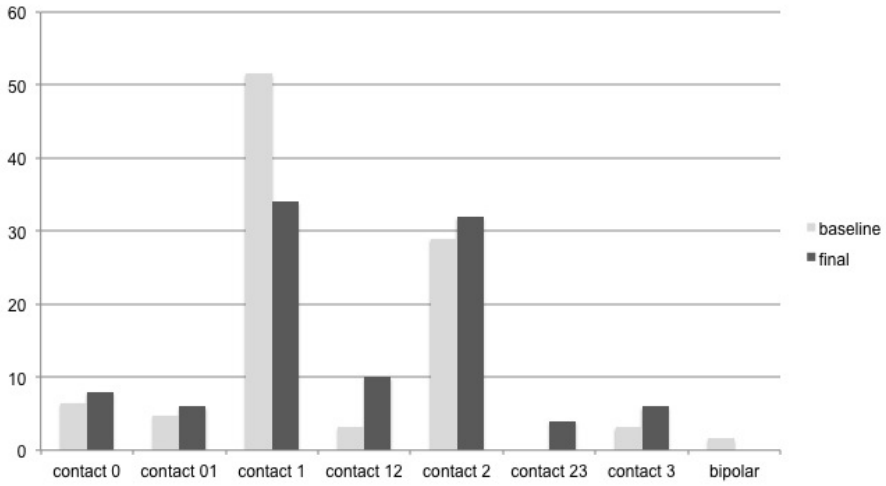

Figure 3.7 Evolution of the active contact of the quadripolar DBS electrode from baseline to final time point. The DBS electrode has four contacts named from 0 to 3 (contact 3 being the upper most and contact 0 the lowest most). Contact 0, 1, 2, 3 refers to single monopolar stimulation (carcase of the neurostimulator as anode and contact as cathode). Contact 01, 12 and 23 refers to double monopolar stimulation. Bipolar refers to bipolar configuration with one or more contacts as the cathode and one contact as the anode. Numbers in the *y-axis* represent percentages.

Figure 3.8 and table 3.4 shows distribution of active contacts to group Ic or IIc at different time points. Nearly 12% of the active contacts moved to a more optimal anatomical position at the end of the study.

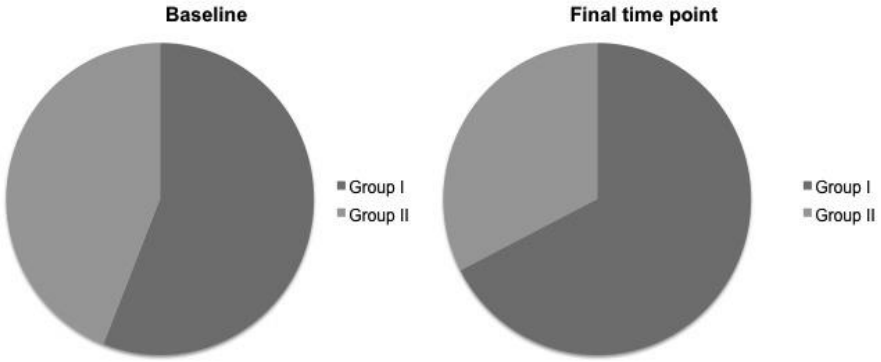

Figure 3.8 Anatomical location group of active contact at baseline and final time point. Group Ic (good location): the contact was inside the STN or at least adjacent the superior border of the STN. Group IIc: contacts not fulfilling the above criteria.

Table 3.4 Anatomical location group of the active contact at different time points of the study

	Total (%)	Group Ic (%)	Group IIc (%)
Baseline time point	50 (100%)	28 (56%)	22 (44%)
Chronic time point A1	50 (100%)	30 (60%)	20 (40%)
Chronic time point A2	49 (100%)	30 (61.2%)	19 (38.8%)
Final time point	43 (100%)	29 (67.4%)	14 (32.6%)

Abbreviations: A: adjustment session.

CLINICAL AND STIMULATION PARAMETER VARIABLES

A tendency towards a larger STN DBS induced improvement and lower UPDRS III hemibody scores were observed when the stimulated contact was at group Ic. In this group, stimulation was also more efficient, as lower TEED was required. TEED increased in both groups (change in TEED group Ic and IIc p=0.74, Mann-Whitney U test) and both groups showed a similar improvement

at the end of the study (global outcome). LEDD requirements were lower for group Ic at baseline, although no differences were found at the final time point as medication was reduced in both (change in LEDD final–basal, Mann-Whitney U test, p=0.23) (table 3.5).

It is worth mentioning that 11 patients (13 hemibody sides) had stimulation-induced dyskinesia at one or both hemibodies at some points of the study (dyskinesia rating scale for arm, leg scoring 2 or more points). Dyskinesia scores did not change from baseline to final time point [mean (SD), baseline 0.89 (1.125) and final time point 1.21 (1.478); Wilcoxon test, p=0.49]. In 8 sides, dyskinesia appeared or was aggravated readily after the adjustment of the stimulation. In none of the patients, dyskinesia was disabling enough to prevent stimulation. Active contacts were located inside the STN in all but two, where the contact was adjacent to the rostral border of the superior segment (1 side missing). Therapeutic contact position distribution at the final time point was as follows: central segment of STN (6 sides), superior segment of STN (4), rostral to superior segment of STN (2) and, inferior segment of STN (1). Stimulation-induced dyskinesia did not differ between baseline and final time point. Contacts eliciting dyskinesia were more frequently inside the nucleus at both basal and final time points compared to the group without dyskinesia. Hemibody sides with stimulation-induced dyskinesia had significantly lower hemibody motor scores both at baseline and final time points, lower TEED at baseline and lower LEDD at final time points. Both groups improved with reprogramming to a similar extent (table 3.6).

Table 3.5 Differences between contacts at group Ic and IIc for clinical and stimulation parameters variables and LEDD

	Group Ic Mean (SD)	Group IIc Mean (SD)	p value†
DBS improvement*	52.737 (14.155)	48.122 (12.532)	0.08
Normalized DBS improvement^	0.0010 (0.0012)	0.0005 (0.0002)	0.06
UPDRS III hemibody BL	5.878 (2.035)	7.891 (2.102)	0.07
UPDRS III hemibody final	5.707 (2.763)	6.629 (2.656)	0.13
Global outcome (hemibody)**	-0.79 (3.256)	-0.50 (1.990)	0.548
TEED BL	89919.53 (30510.11)	119753.78 (31610.23)	0.07
TEED final	99649.65 (40698.02)	141921.67 (52598.58)	0.08
LEDD BL	634.07 (221.54)	773.86 (357.55)	0.07
LEDD final	430.07 (212.15)	509.23 (280.84)	0.12

Abbreviations: BL: baseline; DBS deep brain stimulation; LEDD: levodopa equivalent daily dose; SD: standard deviation; TEED total electrical energy delivered; UPDRS: Unified Parkinson's Disease Rating Scale.

*Calculated respect to the off medication/on stimulation versus off medication/off stimulation condition at baseline for UPDRS III hemibody scores.

^ Percentage of DBS improvement on UPDRS III hemibody scores (respect to off medication/off stimulation) divided by TEED at baseline.

** Global outcome of UPDRS III hemibody scores: UPDRS III hemibody scores at final time point - UPDRS III hemibody scores at baseline time point (a minus sign means improvement).

† Mann Whitney U test

Table 3.6. Comparison between group with stimulation-induced dyskinesia and group without dyskinesia

	Dyskinesia +	Dyskinesia -	p
UPDRS III hemibody BL	6.43 (3.13)	8.55 (5.45)	0.073*
UPDRS III hemibody final	4.54 (2.73)	7.34 (4.24)	0.031*
Global outcome (hemibody)**	-1.85 (2.70)	-1.79 (4.36)	0.965*
Voltage BL	2.90 (0.63)	3.22 (0.80)	0.171*
Voltage final	3.00 (0.70)	3.26 (0.83)	0.297*
TEED BL	79499.04 (39700.80)	10.3596.83 (53392.53)	0.078*
TEED final	87714.69 (48274.25)	114330.32 (67994.52)	0.200*
LEDD BL	548.75 (331.21)	690.87 (411.33)	0.258*
LEDD final	346.72 (217.83)	490.45 (217.73)	0.064*
Active contact in/outside the STN at baseline (%)	92.3/7.7	44.7/55.3	0.003**
Active contact in/outside the STN at final (%)	91.7/8.3	54.8/45.2	0.023**

Abbreviations: BL: baseline; LEDD: levodopa equivalent daily dose; SD: standard deviation; STN: subthalamic nucleus; TEED total electrical energy delivered; UPDRS: Unified Parkinson's Disease Rating Scale. Dyskinesia + refers to the group displaying stimulation induced dyskinesia. Values are expressed as means (SD).

* T-test.

** Fisher's exact test.

TYPE OF ADJUSTMENT THROUGHOUT THE STUDY AND ACTIVE CONTACT ANATOMICAL GROUP

At final time point, those electrodes requiring only "one change in contact throughout the study" belonged more frequently to group Ic [48.3% (group I) *versus* 14.28% (group II)]. On the other hand, those electrodes requiring "more than one change in contact" belonged more frequently to group IIc [13.7% (group I) vs. 42.85% (group II)] (table 3.7 and figure 3.8).

In terms of evolution of the active contact, those electrodes requiring only "one change in contact" did not change the anatomical group in 81.3% of the cases (68.8% remained in group Ic and 12.5% in group IIc), while anatomical position

moved from group IIc to Ic in 18.8% of the cases. In the same way “2 or more changes in the active contact” did not change contact location in 90% of the cases but did improve contact position in 10% (table 3.8).

Table 3.7. Type of adjustment throughout the study by DBS electrode according to anatomical contact location group at baseline and final time point

Time point	Group	Total N (%)	No changes	Change voltage	One change in contact	>1 change in contact
Baseline	**Total**	**50 (100)**	**6 (100)**	**16 (100)**	**17 (100)**	**11 (100)**
	Ic	28 (56)	3 (50)	10 (62.5)	11 (64.7)	4 (36.4)
	IIc	22 (44)	3 (50)	6 (37.5)	6 (35.3)	7 (63.6)
Final	**Total**	**43 (100)**	**6 (100)**	**11 (100)**	**16 (100)**	**10 (100)**
	Ic	29 (67.4)	3 (50)	8 (72.7)	14 (87.5)	4 (40)
	IIc	14 (32.6)	3 (50)	3 (27.3)	2 (12.5)	6 (60)

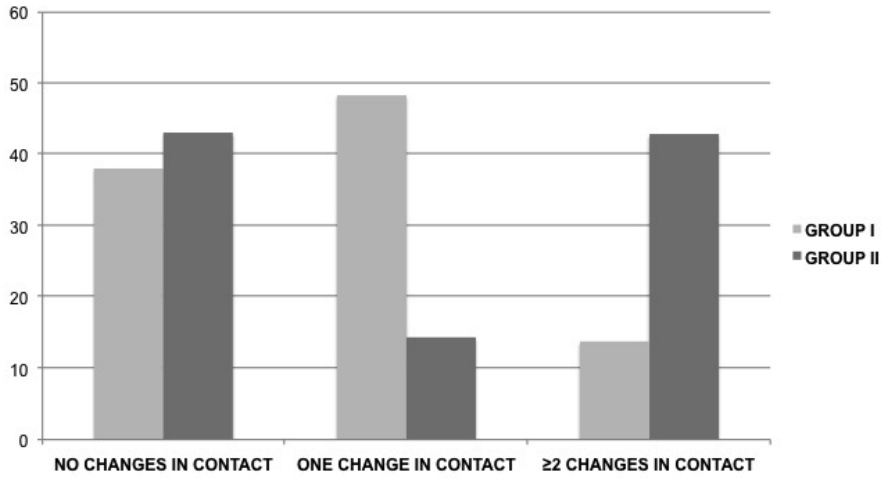

Figure 3.8 Percentage of active contacts by type of adjustment and anatomical group at final time point.

Table 3.8 Type of adjustment performed and evolution of anatomical group from baseline to final time point

Group	Total N (%)	No change in contact	One change in contact	>1 change in contact
Total	43 (100)	17 (100)	16 (100)	10 (100)
Ic (stable)	25 (58.1)	11 (64.7)	11 (68.8)	3 (30)
IIc (stable)	14 (32.6)	6 (35.3)	2 (12.5)	6 (60)
IIc→Ic	4 (9.3)	0 (0.00)	3 (18.8)	1 (10)

The term stable refers to those contacts that did not change anatomical group and IIc→Ic applies for those contacts that moved from group IIc to Ic. No contact moved from group Ic to IIc.

3.3 THE VALUE OF POSTOPERATIVE IMAGING IN THE SELECTION OF THE OPTIMAL THERAPEUTIC CONTACT

Anatomical data were available for 50 contacts at baseline and 43 at final time point. Concordance between clinically selected contact and MRI selected contact was seen for 33 contacts (66%) at baseline and increased up to 70% at the final time point (figure 3.10).

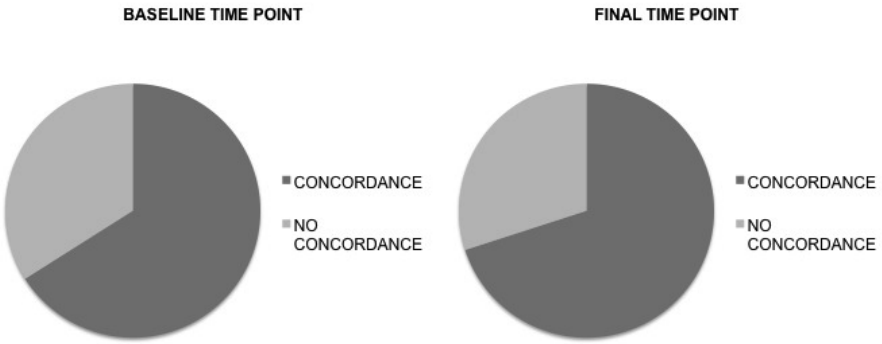

Figure 3.9 Distribution of concordance clinical/MRI contact at baseline and final time point

CONCORDANCE BETWEEN CLINICAL/MRI CONTACT AND CLINICAL, STIMULATION PARAMETERS AND LEDD VARIABLES

No clinical significant differences were found between “concordance” and “no concordance” groups for UPDRS III hemibody at baseline and final time points (p=0.509, p=0.339; Mann-Whitney U test), DBS efficacy, normalised DBS efficacy by hemibody (p=0.519, p=0.952; Mann-Whitney U test) or global effect of adjustments (p=0.927; Mann-Whitney U test).

Increases in voltage and TEED at the end of the study were larger when no concordance existed between clinical/MRI contact (table 3.9).

CONCORDANCE BETWEEN CLINICAL AND MRI CONTACT ACCORDING TO ANATOMICAL GROUP

There was a statistically significant higher degree of concordance for those contacts located in group Ic than in group IIc at the final time point (p=0.049; Fisher's exact test; table 3.10).

However, 4 active contacts at group Ic showed a discrepancy with MRI contact. In two of them, a contact located rostral to the superior segment of the STN was deliberately selected because of stimulation-induced dyskinesia with stimulation within the STN. In 2 cases, the MRI contact was inside the central segment of the STN, while the therapeutic contact was inside the superior segment; therefore, the selection of contact based on MRI data for these two cases may have been imprecise.

CONCORDANCE BETWEEN CLINICAL AND MRI CONTACT AND TYPE OF ADJUSTMENT DURING THE STUDY

Those contacts requiring more than one change in the active contact during the study had a higher frequency of discrepancy clinical/MRI contact (p 0.052, Chi-square test) (figure 3.11).

Table 3.9 Stimulation parameters variables and LEDD for concordance and no concordance groups

	Concordance	No concordance	P
Voltage baseline	3.11 (0.82)	3.37 (0.54)	0.365*
Voltage final	3.23 (0.78)	3.42 (0.66)	0.515*
Change Voltage	0.01 (0.35)	0.26 (0.35)	0.051*
TEED BASELINE	96818.32 (50947.81)	102195.176 (54168.32)	0.886*
TEED final	100208.90 (48385.48)	133113.578 (88295.42)	0.432*
Change TEED	53.80 (19630.48)	34114.50 (50725.57)	0.013*
LEDD baseline	636.78 (293.52)	801.79 (600.76)	0.292**
LEDD final	429.92 (232.14)	523.98 (260.87)	0.285**
Change LEDD	-104.28 (192.43)	-97.47 (99.14)	0.92**

Abbreviations: LEDD: levodopa equivalent daily dose; TEED total electrical energy delivered. Values are expressed as means (SD)

* Mann-Whitney U test.

** T-test

Table 3.10 Concordance between clinical and MRI contact in relation to anatomical group at final time point

	Total N (%)	Group I N (%)	Group II N (%)
Total	43 (100)	29 (100)	14 (100)
No concordance	13 (30.2)	4 (13.8)	7 (50.0)
Concordance	30 (69.8)	25 (86.2)	7 (50.0)

p value (Fisher's exact test) 0.049.

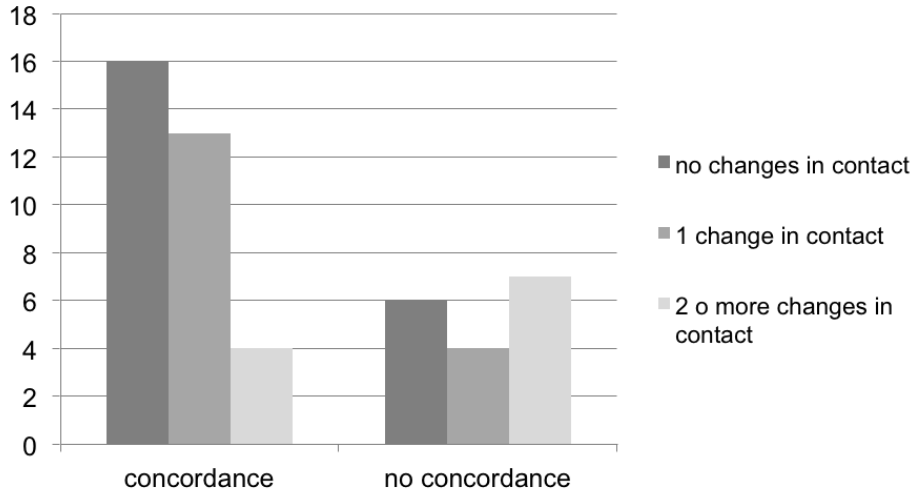

Figure 3.10 Concordance between clinical and MRI contact according to type of adjustment during the study. Numbers of therapeutic contacts are represented at *y*-axis.

SUMMARY

Postoperative anatomical information about the position of the four contacts of the DBS electrode was available for 50 electrodes. Eighty-eight per cent of the electrodes had at least one contact within the defined optimal stimulation area. Lower hemibody UPDRS III subscores were found at baseline and the final time point (p=0.082 and p=0.062; Mann-Whitney U test), TEED at baseline and the final time point (p=0.044 and p=0.075; Mann-Whitney U test) and voltage at baseline (p=0.60, two-tailed t test) for those electrodes that were optimally placed. LEDD at the final time point was significantly lower when both electrodes were optimally located (p=0.005, two-tailed t test).

Active contact evolved towards a more rostral position during the study (from central to superior STN segment). Reprogramming led to a more optimal active contact position in 12% of the electrodes. Larger DBS benefit (p=0.06, Mann Whitney U test) and lower hemibody UPDRS III subscores (P=0.07 Mann

Whitney U test) and TEED (baseline: p=0.07 Mann Whitney U test) were found for active contacts that were optimally placed. Nevertheless, reprogramming led to a similar improvement and allowed a similar reduction of dopaminergic medication, regardless the position of the active contact, but at the expense of higher TEED in sub-optimally located contacts (p=0.08 Mann Whitney U test). Stimulation-induced dyskinesia occurred more frequently with stimulation of contacts inside the STN.

Increases in TEED and voltage were higher when no concordance existed between clinical and MRI contact (p=0.013 and p=0.051, respectively, Mann-Whitney U test). Concordance was significantly higher when active contact was optimally placed (0=0.049, Fisher's exact test)

4. ANALYSIS OF TYPE OF ADJUSTMENT "CHANGE IN CONTACT"

This part of the study sought to describe the evolution of those sides that underwent "change in contact" from a clinical and anatomical point of view. Due to a progressive reduction of the sample, descriptive statistics were mainly used. Non-parametric tests were applied when appropriate.

4.1 CHANGES IN CONTACT AT ADJUSTMENT 1

At A1, the type of adjustment "change in contact" was performed on 28 hemibody sides (48.3%). Nearly all of them moved towards a contiguous contact (93%), and usually to the immediate rostral contact (64%). One contact changed from contact 1 to contact 3, and another changed from bipolar (contact 1 as cathode and 2 as anode) to monopolar configuration (contact 2 as cathode). In the remaining 8, the change was towards the immediate caudal contact.

Twenty-one of these contacts did not require a second change of contact at A2 (figure 4.1); These contacts evolved more frequently towards the immediate superior contact (76%). In 4 of these 21 contacts, active contact moved towards the immediate caudal contact (in three of these, active contact was changed again at A3) (figure 4.1). These 21 hemibody sides had a global motor improvement at A1 of 2.45 points. Type of adjustment performed at A2 was: no change (9), change of voltage (6), no adjustment needed (6). Anatomical position (available for 17 electrodes) before and after A1 is shown in figure 4.2. At the baseline of A1, 7 active contacts (41%) were close to the superior segment of the STN (inside, medial) and 8 (47%) were inside the central

segment. After A1, the number of active contacts adjoining the superior segment increased to 12 (70%), while only 3 contacts (17.5%) were located close to the central segment.

4.2 CHANGES IN CONTACT AT ADJUSTMENT 2

Of the 28 electrodes that had a change in contact at A1, 7 required a new change in contact at A2 despite showing an acute improvement after A1. Nevertheless, the acute benefit was significantly smaller and they suffered a larger deterioration afterwards compared to those not requiring a new “change in contact” (table 4.1). Most of these contacts (71.4%) corresponded to those moved caudally at A1. The newly stimulated contact at A2 corresponded to the same contact used at baseline in 85.7% of the electrodes. Anatomical position was available for 4 contacts (figure 4.3). One contact changed towards a new contact (different to that use at baseline). In this case, anatomical position evolved from the medial to the central segment of the STN (A1 before adjustment) to medial to the superior segment (A1 after adjustment) to inside the superior segment (A2 after adjustment).

Two contacts changed only at A2 (figure 4.4); however, anatomical data was available only for one of the electrodes. Contact moved to the immediate inferior contact (from contact 1 to contact 0). Both anatomical positions were considered to be inside the central segment of the STN.

4.3 CHANGES IN CONTACT AT ADJUSTMENT 3

Three electrodes underwent “change in contact” at all the adjustment sessions. Active contacts and their anatomical positions are outlined in table 4.2.

Five electrodes had a change in contact at A1 and A3 (prior type of adjustment at A2 was “no change” in 2, “change in voltage” in 1 and; “no adjustment needed” in 2). Three returned to the contact used at the baseline time point of A1. All of these sides experienced an improvement with respect to baseline of the study (mean global UPDRS III hemibody scores (final time point of the study-baseline time point of the study)= -5.00 points). Anatomical position was available for 4 contacts (table 4.3).

Table 4.1. Effects of adjustment 1 on UPDRS III hemibody scores for those contacts that underwent a “change in contact” at A1 classified by requirement of change of contact at A2

	Type of adjustment at A2		
A1 effect hemibody	**No change in contact**	**Change in contact**	**p**
N	21	7	
Acute	- 3.68 (3.71)	- 0.50 (2.00)	0.027*
Chronic	1.22 (2.86)	5.25 (4.59)	0.007**
Global	- 2.45 (4.13)	4.75 (4.71)	0.024*

Abbreviations: A adjustment session.

Values are expressed as means (standard deviation). A minus sign means improvement.

Acute effect: acute – baseline UPDRS III hemibody scores; Chronic effect: chronic - acute UPDRS III hemibody scores; global: chronic – baseline UPDRS III hemibody scores.

* Mann-Whitney U test.

** T-test.

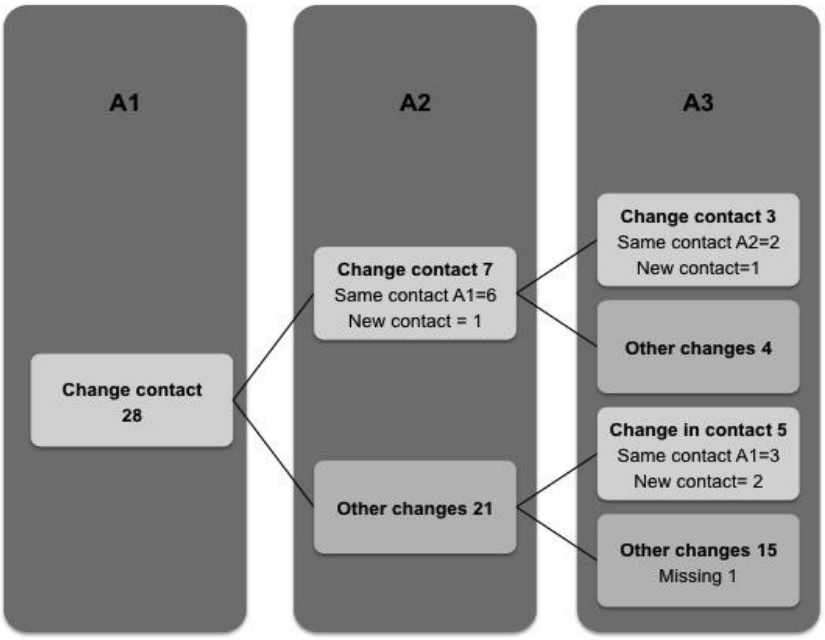

Figure 4.1 Flow chart of hemibody sides that underwent a "change in contact" at A1. Abbreviations A1: adjustment 1; A2: adjustment 2; A3: adjustment 3. The numbers refer to the number of electrodes. "Same contact" is used when a contact was changed towards the same contact used in the previous adjustment session. "New contact" is used when a different contact is selected. "Other changes" includes no changes, change in voltage and no adjustment needed.

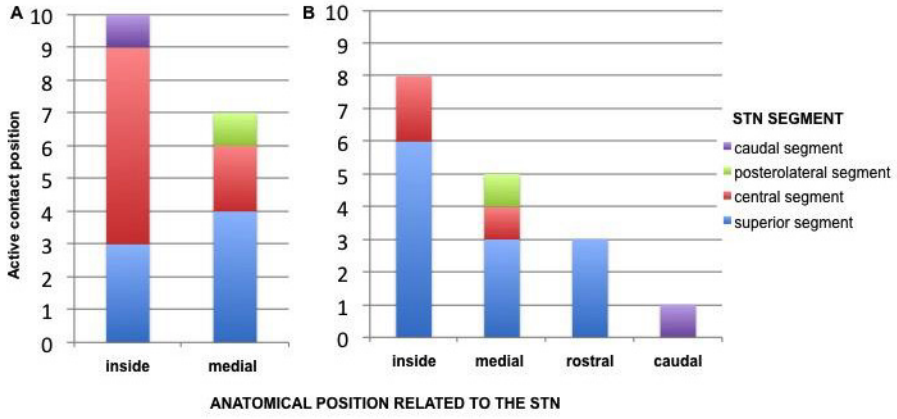

Figure 4.2 Anatomical positions of active contacts before (A) and after (B) adjustment 1 for those contacts that changed at A1 but not at A2. Number of active contacts are displayed on the *y-axis* and anatomical position related to the STN on the *x-axis*. Location with respect to STN segment is codified in different colours, as shown in the legend.

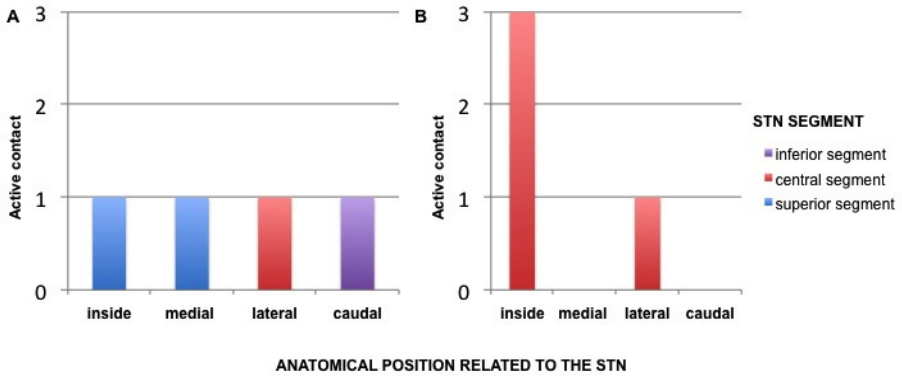

Figure 4.3 Anatomical position of active contacts that underwent "change in contact at A1 and A2: before (A) and after (B) adjustment 1. Number of active contacts are displayed on the *y-axis* and anatomical position related to the STN on the *x-axis*. Location respect to STN segment is codified in different colours, as shown in the legend. At A2, active contact was changed again to the contact used at the baseline of A1.

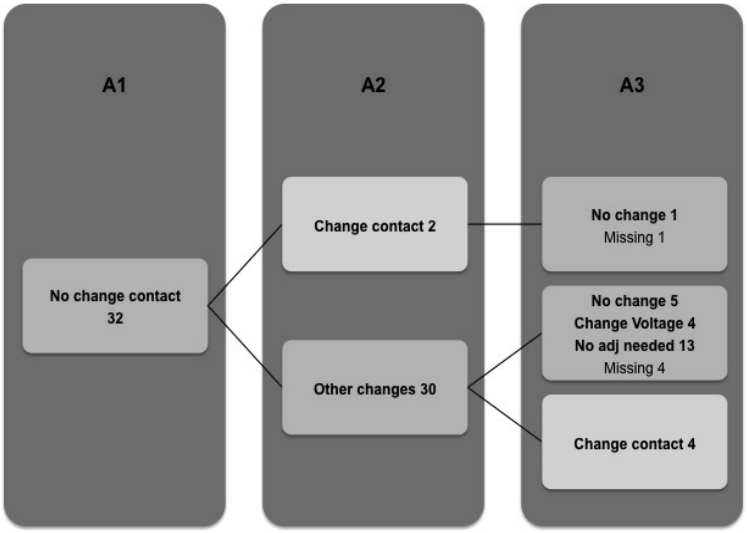

Figure 4.4 Flow chart of hemibody sides that did not underwent "change in contact" at A1. Abbreviations A1: adjustment 1; A2: adjustment 2; A3: adjustment 3. The numbers mean number of electrodes. "Same contact" is used when a contact was changed towards the same contact used in the previous adjustment session. "New contact" is used when a different contact is selected. "Other changes" includes no changes, change in voltage and no adjustment needed.

Table 4.2. Active contact and its anatomical position for those contacts that changed at A1, A2, A3

	Active contact				Anatomical position of active contact	
	A1b	**A1a**	**A2a**	**A3a**	**A1b**	**A3a**
Case 1	1	12	1	0	Medial to superior segment	Medial to anteromedial segment
Case 2	1	3	1	0	Inside central segment	Inside central segment
Case 3	2	1	2	1	Medial to superior segment	Inside central segment

Abbreviations: A1a: adjustment 1 after adjustment of stimulation parameters; A1b: adjustment 1 before adjustment of stimulation parameters; A2a: adjustment 2 after adjustment of stimulation parameters; A3a: adjustment 3 after adjustment of stimulation parameters.

Table 4.3. Active contact and its anatomical position for those contacts that changed at A1 and A3

	Active contact			Active contact position	
	A1b	**A1a**	**A3a**	**A1b/A3a**	**A1a**
Case 1	1	0	1	Inside inferior segment	Caudal to inferior segment
Case 2	1	0	1	Medial to dorsolateral segment	Medial to dorsolateral segment
Case 3	1	2	1	Inside superior segment	Rostral to superior segment
Case 4	2	3	23	NA	NA
Case 5	2	1	12	Medial to superior segment	Medial to superior segment

Abbreviations: A1a: adjustment 1 after adjustment of stimulation parameters; A1b: adjustment 1 before adjustment of stimulation parameters; A3a: adjustment 3 after adjustment of stimulation parameters; NA: not available.

SUMMARY

Twenty-eight electrodes underwent a "change in contact" at A1. Acute effect produced by the adjustment was significantly higher for those contacts in which the acute benefit was maintained compared to those that deteriorated and required a second change in the active contact at A2 (p=0.027, Mann Whitney U test). In the latter, most contacts moved caudally, while those not requiring a second change in contact moved rostrally. At A2, the new active contact selected corresponded to the contact stimulated at the baseline of A1.

5. THE VALUE OF THE INTRAOPERATIVE LFP RECORDINGS IN DBS TARGETING OF THE STN AND OPTIMIZATION OF STIMULATION PARAMETERS

Thirty-one patients (17 males) were included in this part of the study. Mean age at time of DBS was 57.0 years (SD 7.4; range 38-68). All patients had advanced PD with motor fluctuations and/or dyskinesias. Mean disease duration was 11.7 years (range 5-28). Before surgery, the mean UPDRS III scores off medication was 44.8 (SD 14.5) and on medication 13.9 (SD10.0) ($p<0.001$, two-tailed paired t-test). Clinical assessment of efficacy of chronic DBS could not be performed in 2 of the 31 patients. One patient developed unexplained confusion postoperatively and the DBS electrodes were removed in the immediate postoperative period. One patient succumbed to cancer a few months after surgery. Mean time of DBS treatment at time of clinical assessments was 19 months (range 6-51 months). UPDRS III scores fell from 44.7 (SEM 2.9) off-medication/off-stimulation to 21.2 ± 1.5 off-medication/on-stimulation. Electrode's contact configuration was monopolar in all but 5 sides where it was set as bipolar. Pulse with was set at 60 μseconds (90 in 4 sides) and frequency at 130 Hz (145 Hz in four sides, 150 Hz on two sides, 160 Hz on two sides, 180 Hz on five sides and 185 Hz on two sides).

A discrete peak between 11 and 35 Hz in power spectra of the LFP activity recorded at contact 01 was identified in all but two sides (both on the left). The power of this peak was clearly modulated during electrode descent, except on one side. Thus, three (5%) out of 57 sides did not have an obvious peak or step change in LFP activity along the electrode trajectory. There was no difference in the efficacy of DBS between the 54 sides, with evidence of a local beta

generator [improvement in contralateral UPDRS III hemibody score off-medication 8.2 (SD 0.7) points or 51.3% (SD 4.2) of preoperative score] and, those three sides without such evidence [improvement in contralateral UPDRS III hemibody score off-medication 13 points (97%), 3 (50%), 10 (62%), respectively] although the latter group was very small. No differences between stimulation parameters were found between both groups [evidence of beta generator: mean stimulation voltage 2.8 (SD 0.1) volts, pulse width 60 (90 on four sides) microseconds, frequency 139 (SD 2) Hz; no evidence of beta generator (3 sides): stimulation voltage 1.7, 3.8 and 1.9 v, pulse width 60 microseconds, frequency 130 Hz]. However, those sides with evidence of a local beta generator tended to have more optimal anatomical targeting (88% in group I) than those without evidence of a local beta generator (33% (1 side) in group I; Fisher's exact test, p=0.054).

Among the 54 sides in whom there was a focal beta peak, the subthalamic LFP peaks were distributed across 14-34 Hz (figure 5.1). The median power of the peak LFP activity recorded at the initial step in the beta activity (ie, the depth considered to be that of the local beta generator) was 3.3 μV (IQR 1.1 to 7.2 μV; Kolmogorov-Smirnov test for normal distribution, p=0.004); 2 mm above (below in four sides) this, the median power over the frequencies of the peak was 0.5 μV (IQR 0.1 to 1.2 μV; Kolmogorov-Smirnov test for normal distribution, p=0.003). The median percentage change between the two levels was 500% (z=6.393, p<0.001). There was no difference between the depth of the local beta generator recorded intraoperatively (mean 0.83 mm and median 0 mm above the surgical target point) and the depth of the contact independently chosen for chronic DBS (mean 1.01 and median 0.5 mm above the surgical

target point; Wilcoxon signed ranks test, z=-0.571, p=0.568). However, both differed from the depth of the target point aimed at during surgery (Wilcoxon signed ranks tests, z=-2.973, p=0.003 and z=-4.161, p<0.001, respectively).

There was a correlation between the depth of the local beta generator recorded intraoperatively and the depth of the electrode contact independently chosen for chronic DBS (Spearman's rho=0.35, p=0.01, n=54; figure 5.2). A potential association between the depth of the beta generator and the optimal site for amelioration of parkinsonism was strengthened by considering those sides in which there was a disparity between the depth of the generator and that of the contact chosen for chronic stimulation. There was a weak correlation between the absolute disparity in millimetres and the stimulation voltage used for chronic stimulation, such that a bigger difference between depths was associated with a higher stimulation voltage or TEED (rho=0.322, p=0.017, n=54 and rho=0.308, p=0.024, respectively). There was no such tendency between the stimulation voltage or TEED employed for chronic stimulation and the absolute difference between the surgical target point depth and that of the contact chosen for chronic stimulation (rho=0.103, p=0.468, n=54 and rho=0.127, p=0.368, respectively). This suggests more stimulation voltage had to be employed if a depth was selected for chronic stimulation that differed from that of the local beta generator but not if it differed in depth from the surgical target point. This relationship between the depth of the generator and the stimulation intensity was maintained even if we controlled for clinical effect of DBS. To this end we derived a measure of the normalised efficacy of DBS by dividing the DBS induced improvement in contralateral hemibody UPDRS III scores by TEED. There was a negative correlation between the normalised chronic DBS efficacy

and the absolute difference between the depth of the local beta generator and that of the contact chosen for chronic stimulation (rho=-0.315, p=0.021), so that chronic stimulation at the depth of the intraoperatively defined generator was associated with more effective long-term stimulation. As before, however, there was no correlation between the normalised chronic DBS efficacy and the absolute difference between the surgical target point depth and that of the contact chosen for chronic stimulation (rho=-0.116, p=0.411), so that the depth of the surgical target point was a relatively poor predictor of stimulation efficacy. Figure 5.3 highlights the scale of the effect of disparity between the depths of the generator and contact chosen for chronic stimulation. The normalised efficacy of DBS was more than halved when the contact was ≥2mm from the depth of the generator.

Finally, there was a positive correlation between the depth of the local beta generator and that of the optimally anatomically placed contact on those 46 sides (group I) in which a contact was inside or adjacent to the most superior part of the STN (rho=0.379, p=0.011). As expected, there was no such correlation in the remaining sides where the best situated contact was neither inside nor abutted the superior part of the STN (group II) although the numbers were much smaller (n=8, rho=0.226, p=0.55).

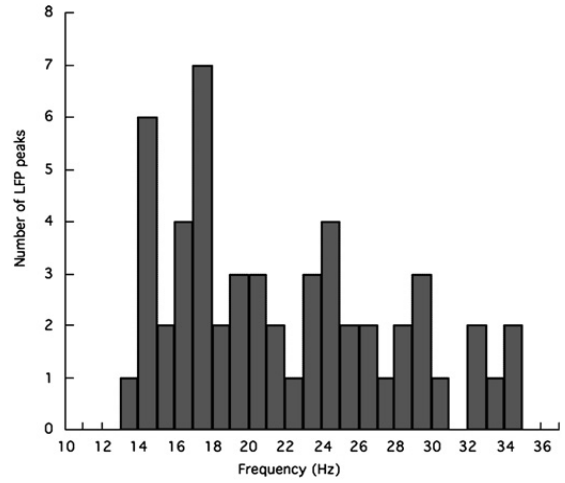

Figure 5.1. Distribution of spectral peaks, as recorded intraoperatively from the deep brain stimulation electrode (n=54. One peak per side).
Abbreviations: LFP local field potentials

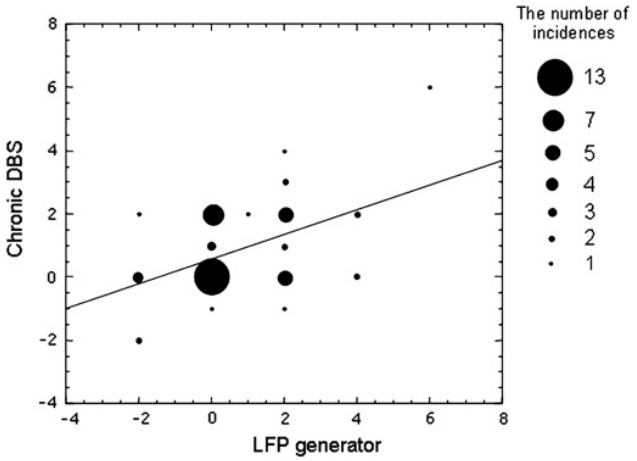

Figure 5.2. Correlation between the depth of the local beta generator recorded intraoperatively and the depth of the contact independently chosen for chronic deep brain stimulation (DBS). The size of the circle indicates the number of sides that shared these graphical coordinates. Depths are relative to the surgical target point. Spearman's rho=0.35, p=0.01, n=54. Abbreviations LFP: local field potentials

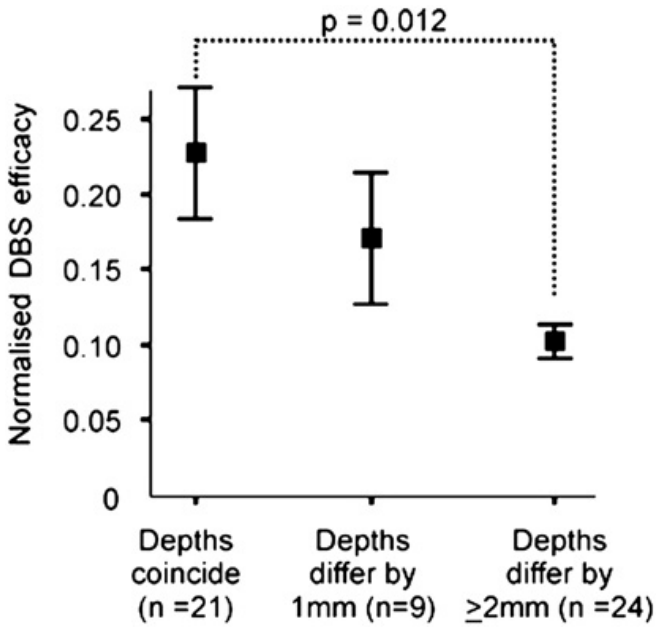

Figure 5.3. The effect of any difference between the depth of the local beta generator identified intraoperatively and the depth of the contact chosen for chronic stimulation on normalised DBS efficacy (DBS induced improvement in contralateral UPDRS III hemibody scores/total electrical energy delivered (in μJ). Chronic stimulation at the depth of the intraoperatively defined beta generator was associated with more effective long term stimulation. (p value is given following a t test for independent samples with unequal variances). Note that depths that differed by 1 mm occurred because the neurosurgeon advanced the electrode 1 or 3 mm beyond the target point before fixation.

SUMMARY

LFPs were recorded from the contacts of 57 DBS electrodes as the latter were advanced in 2 mm steps from above to below the intended surgical target point in STN.

A spectral peak in the bipolar LFP was recorded in the 11-35 Hz band at the lowest contact pair that underwent a steep but focal change during electrode descent in all but three sides. The depth of the initial intraoperative step increase in beta correlated with the depth of the contact independently chosen for chronic DBS (Spearman's rho=0.35, p=0.01). In addition, the absolute difference between the depths of the initial increase in beta and the contact chosen for chronic DBS correlated with the voltage used for chronic stimulation (rho=0.322, p=0.017). Thus, more voltage had to be employed if a depth was selected for chronic stimulation that differed from that of the beta generator.

V. DISCUSSION

1. LONGITUDINAL ASSESSMENT OF THE IMPACT OF CONSECUTIVE SESSIONS FOR ADJUSTMENT OF STIMULATION PARAMETERS OF STN DBS IN PD PATIENTS: EVALUATION OF THE ACUTE AND CHRONIC EFFECTS OF STIMULATION PARAMETERS

This study was designed to evaluate the acute and sustained effect on motor symptoms of three consecutive sessions of programming of stimulation parameters in chronically STN DBS-treated PD patients. The objective was to establish whether the acute effect consistently predicted a sustained benefit.

Our general results on DBS efficacy are in line with previously published studies (Krack et al., 2003, Fasano et al., 2010; Castrioto et al., 2011). In the present study, an improvement of almost 50% on motor UPDRS III scores was found after a mean time of DBS treatment of 30 months in the off-medication condition (compared to pre-DBS scores). This improvement was corroborated for total scores as well as for hemibody and axial UPDRS III subscores. However on-medication scores deteriorated when compared to pre-DBS scores, probably reflecting both a progression of PD with development of dopamine-resistant symptoms and stimulation induced-desensitisation in the dopaminergic system (Moro et al., 2002; Bejjani et al., 2000).

Currently, guidelines for selection of optimal stimulation parameters are based on the acute improvement produced by the combination of stimulation parameters. In routine practice, the improvement is subjectively assessed without proper quantification. The acute effect of stimulation parameters adjustment is firstly influenced by the complexity of the response to stimulation of Parkinsonian symptoms (Kuncel et al., 2004), need of cooperation from the patient and possible placebo effect (Mercado et al., 2006). This renders

programming of DBS dependent on several variables and there is no guarantee that a new setting will be optimal in the long-term.

There is not a specific pattern of behaviour for the different types of adjustment, as the outcome of one setting would necessarily be influenced by the preceding ones. In line with this, minor changes in the stimulation parameters, such as “change in voltage”, did not produce either an acute or sustained benefit at A1 and A2 sessions. However, at the third adjustment session (A3), adjustment of voltage produced an acute benefit that was maintained over time. “Change in the active contact” – and therefore in the stimulated area – showed a more complex response. This type of adjustment always produced a significant acute benefit, but the chronic response showed more variability. Under this condition, while a chronic deterioration was seen at A1, a sustained benefit occurred at A2 and A3. The behaviour of this type of adjustment will be discussed later, as it is closely linked to the anatomical site of stimulation. “No change” in the stimulation parameters, as expected, did not produce either an acute or sustained benefit at A1 and A2 adjustments. However, at A3 a long-term improvement was seen. Whether this could be related to optimisation throughout previous adjustment sessions is not clear. Those sides where no adjustment of the stimulation was needed had lower motor scores, reflecting that the clinical decision to not modify the stimulation in this group was correct.

Our findings lead us to conclude that subjective assessment of the acute impact of stimulation parameters is not always translated into an objective acute effect and, moreover, long-term deterioration can occur even after an acute benefit, particularly when the new setting involves a change in the active

contact. Previous studies have shown a similar behaviour when the programming setup involved a change in the active contact. Fasano et al. (2010), in their long-term study, found that changes in the stimulated contact beyond the fifth year of DBS led to an improvement in motor signs in 52% of the patients while it produced deterioration in the remaining 48%. Moro et al. (2006) conducted a study with the aim to evaluate the evolution of chronically implanted patients after reprogramming. This study demonstrated an improvement of symptoms with reprogramming of the stimulation settings in the majority of patients. In those who improved, the most frequent type of adjustment was a change in the electrode's geometry. However, half of the patients who deteriorated also underwent a change in the electrode's geometry. In this study, evaluations were not blinded and although some clinical assessments were performed for selection of the optimal setting, the acute effect was not clearly quantified. Neither did they determine the anatomical position of the electrode's contacts.

It has been shown that the stimulation effect might take up to 3 hours to vanish once the stimulation is switched off (Temperli et al., 2003). Tremor returns first, followed by rigidity and bradykinesia. Impact on axial signs may take even longer to fade away. In the same way, improvement of Parkinsonian signs after switching the stimulation on follows a similar pattern with tremor improving first, followed by rigidity and bradykinesia, and later on by axial signs (Temperli et al., 2003). Even more, a two-step process for bradykinesia washout has been described (Cooper et al., 2011). This is most relevant for DBS programming. In fact, the acute effect observed during a programming session will represent just a part of the total stimulation effect for a given

contact, which may explain the additional sustained benefit observed at A3. More important for DBS programming is that the “carry over” effects of previous stimulation parameters may still be present when assessing a new setting. This might be of relevance when changing the stimulated contact and thus the stimulation area, and explains the delayed deterioration in Parkinsonian symptoms observed in our study.

Sustained benefit was only achieved after two consecutive adjustment sessions, reflecting the complexity of DBS optimisation even in expert hands.

Finally, PD is a disorder in which the placebo effect can play a significant role (De la Fuente-Fernandez et al., 2002). DBS therapy is not exempt from this effect (Mercado 2006; De la Fuente-Fernandez et al., 2004). Therefore, although patients were blinded to the new stimulation setting, they were familiar with the beneficial effect of STN DBS. Thus, we cannot rule out that patient expectations may have magnified the acute response to the new stimulation parameters. Furthermore, hemibody UPDRS III subscores comprise several items evaluating bradykinesia, which is one of the Parkinsonian symptoms more susceptible to the placebo effect (Mercado et al., 2006).

On-medication/on-stimulation total UPDRS III scores showed a tendency towards deterioration (18% deterioration), while hemibody dyskinesia showed a tendency towards an improvement. This could be explained by a statistically significant reduction of dopaminergic medication at the end of the study.

In this study we have demonstrated that the variable that most consistently predicts global motor outcome is the acute effect on motor symptoms produced by adjustment of the stimulation parameters. The magnitude of the chronic effect was directly related to the magnitude of the

acute effect. Interestingly, as optimisation of the stimulation progressed through consecutive adjustment sessions, smaller improvements in the acute effect were necessary to ensure a global benefit.

“Change in contact“ also influenced motor outcome. Changing the contact towards a more caudal position predicted a global deterioration at A1, while reversing this situation at A2 showed a tendency towards a global improvement. Change in active contact did not predict global outcome at A3, most likely because optimal contact was already established at previous adjustment sessions. Nevertheless, this capacity of “change in contact” to impact global outcome is mainly through its acute effect. In contrast, “change in voltage” added a further benefit on global outcome, which might reflect how optimisation is achieved through consecutive programming sessions.

In our study, the presence of acute dyskinesia did not predict global outcome of the adjustment. This aspect contrasts with previous studies where this sign seemed to be a good predictor for DBS outcome. Moro et al. (2006) found that more than half of the patients that improved after reprogramming of DBS settings had stimulation-induced dyskinesia after a mean time of 9.9 hours. Our acute evaluation did not extend that long, thus it is probable that mild and non-disabling dyskinesia may have occurred and not been eve perceived by the patient. Smaller increments of voltage at the programming session might be another factor. At A3, which had the longest interval between acute and chronic evaluations, time between visits had a negative impact on motor scores, which raise the question about a possible tolerance effect in DBS, a matter that has been widely discussed, in particular for essential tremor (Hariz et al., 1999;

Pilitsis et al., 2008; Zhang et al., 2010; Favilla et al., 2012). Nevertheless worsening due to natural disease progression cannot be completely rule out.

2. FINAL OUTCOME OF ADJUSTMENT SESSIONS

Consecutive adjustment sessions of stimulation parameters led to an additional benefit of DBS therapy of 17.5% on total UPDRS III scores and of 20.9% on hemibody subscores in the condition of off-medication/on-stimulation (comparison baseline *vs* final time point of the study). UPDRS III axial subscores showed a tendency towards improvement. Activities of daily living off-medication/on-stimulation improved as well, whereas on-medication/on-stimulation UPDRS II did not. Forty-two per cent of the patients experienced a motor improvement with reprogramming and 42% remained stable at the end of the study. Only 15% of the patients had a motor deterioration from their baseline situation. Furthermore, reprogramming led to a reduction of dopaminergic medication by 30%. Our results, along with those from Moro et al. (2006) support the fact that reprogramming in chronic implanted patients can lead to additional benefits and reduction of dopaminergic dosage, at least in a subgroup of patients.

Electrodes undergoing only “one change in the active contact” had a significant improvement whereas those requiring only adjustment of amplitude showed a tendency to improve. Electrodes needing “two or more changes in the stimulated contact” did not obtain additional benefits. This last scenario probably reflects suboptimal electrode location. Motor scores for electrodes in which stimulation parameters were not changed did not significantly vary. This implies that although the placebo effect may be present in STN DBS adjustments (Mercado et al., 2006), it is not maintained over time.

As expected, improvement at previous adjustment sessions predicted global outcome. This was the case for A1 and A3, which were the adjustment sessions

that showed a global benefit. At A2, sides that improved corresponded mainly to those that underwent a change in contact at A1 and A2. The new contact selected at A2 matched the contact used at baseline of A1, and therefore the adjustment at A2 consisted mainly of reversing an unsuccessful adjustment at A1.

In our series, there was a male preponderance, as it has been the case in other DBS populations (Hariz G-M et al., 2003) where women are under-represented and seem to be referred to surgery later on in the course of the disease. Interestingly, we observed a lower probability for men to improve with reprogramming. In general, benefits obtained after STN DBS are similar in both sexes (Hariz G-M et al., 2003, Accolla et al., 2007) although women experienced greater benefits in activities of daily living (Accolla et al., 2007; Hariz G-M et al., 2003) despite showing a poorer response in bradykinesia (Accolla et al, 2007). Differences in response to DBS for women and men are not easily explained. The fact that, in our study, these differences were seen only for hemibody motor subscores and not for total motor scores may imply a different behaviour between sexes for tremor, rigidity and bradykinesia but not for axial symptoms.

In general, our results showed that patients who improved with reprogramming were younger. This finding is in line with the study of Moro et al. (2006). A worse outcome after STN DBS has been described in elderly patients and related to the presence of less responsive axial symptoms (Derost et al., 2007; Welter et al., 2002). However, in our study, the reduced probability for improvement was only seen on motor UPDRS III hemibody scores. Thus, it is

possible that rigidity, tremor and bradykinesia also had a more limited response to DBS in the elderly population.

Patients with a worse motor performance at baseline of the study showed a greater probability of improvement. This could be explained by a suboptimal optimisation of DBS therapy prior to inclusion in the study.

3. OPTIMAL STIMULATION SITE IN STN DBS FOR PARKINSON'S DISEASE

DBS of the STN is nowadays a well-established treatment for advanced Parkinson's disease. Since its introduction, several studies have reported long-term benefits of this procedure for selected patients with advanced PD. However, although DBS mimics several clinical effects induced by therapeutic lesions, the precise mechanisms of action are poorly understood. Furthermore, it remains unclear which locus within the subthalamic area is optimal to obtain the best efficacy with lower stimulation consumption. Two sites have been more frequently proposed: the dorsal part of the STN, known to be its sensorimotor part (Herzog et al. 2004; Yelnik et al., 2003; Saint-Cyr et al., 2002); and the dorsal area adjacent to it, containing pallidofugal fibres and the rostral zona incerta (ZI) (Voges et al., 2002; Hamel et al., 2003; Godinho et al., 2006). Most studies have addressed this question through determination of the anatomical location of the active contacts at one time point of the follow-up, regardless of previous changes in the electrode's active contact and thus of the stimulation site. In this regard, we sought to study the evolution of the stimulation site through consecutive programming sessions with objective quantification of symptoms. The final position of the active contact will most likely represent the optimal stimulation site. Finally, we investigated whether an image-guided approach for selection of the optimal contact could complement and simplify the programming of stimulation.

Our optimal defined area comprised the central/superior STN segments and the rostral area adjacent to it, as long as the contact was adjacent to the rostral border of the STN. Almost 90% of the DBS electrodes had at least one

contact within the optimal stimulation site, which accounts for nearly 80% of the patients having both DBS electrodes with at least one contact lying on the optimal stimulation site. None of the patients had both electrodes outside the optimal stimulation site.

STN DBS-induced improvement was similar in both groups of electrodes. However, stimulation was more efficient, in terms of TEED consumption, when the electrode was optimally placed. UPDRS III hemibody scores showed a tendency towards lower values in this group both at baseline and final time point. Adjustment of the stimulation led to a similar improvement in both groups. Nevertheless, for those electrodes suboptimally placed, TEED requirement was larger at the end of the study. As voltage did not change for these electrodes, augmentation of TEED might be explained by increased pulse width or frequency, stimulation parameters that are usually modified when improvement cannot be achieved by increasing voltage. Intensive programming allowed a reduction of dopaminergic medication in both groups. Nevertheless, LEDD at the final time point was significantly lower for the electrodes that were accurately implanted. Optimisation of stimulation parameters were more easily achieved for optimally located electrodes. Indeed, no changes of the stimulation parameters only occurred in this group, whereas multiple changes in the stimulated contact were needed more frequently for suboptimally placed electrodes.

Accuracy of electrode implantation is a crucial factor to ensure a good clinical response and to avoid side effects (Guehl et al., 2007; Richardson et al., 2009; Hamid et al., 2005). Our findings support this vision but highlight how improvement can still be achieved for suboptimally placed electrodes, as a

benefit can be obtained as long as the contact is within 2-3 mm diameter from the optimal stimulation site (Richardson et al., 2009; Ellis et al., 2008; Anheim et al., 2008). Nevertheless, this improvement is at the expense of higher stimulation parameters and dopaminergic medication. Furthermore, suboptimally placed electrodes may involve more laborious programming, with the consequent discomfort for the patient and time consumption for the neurologist.

The position of active contacts was determined on MR images and defined by their position within the STN and surrounding structures, instead of using atlas coordinates or microelectrode recording (MER) data. We believe that this is a more reliable method than using the inter-commissural point as the reference, given the significant intra- and inter-individual variation in the relationship of the inter-commissural point with the STN (Littlechild et al., 2003; Patel et al., 2003; Richter et al., 2004). Furthermore, the description of the anatomical position based on MER findings does not take into account possible deviations from the selected MER trajectory that can occur when introducing the microelectrodes or the DBS electrode (Bakay et al., 2011). Basing identification and location of the electrodes' contacts on MR images presupposes that MR provides a reliable representation of brain anatomy, a fact that has been previously verified (Yelnik et al., 2003).

At baseline of the study, more than half of the active contacts were inside the STN, whereas the remaining contacts were mainly medial to the nucleus. Our practice comprises an image-guided approach with routine postoperative stereotactic imaging. In a preliminary analysis, a systematic error consisting of a medial and posterior deviation of electrode placement was noticed. Accuracy

was improved after calibration of this systematic targeting error (Holl et al., 2010). However, this series of patients belong to the pre-calibration era, which may explain why almost half of the contacts were medially located.

Nevertheless, reprogramming - “change in contact” - reduced the percentage of active contacts medially placed by 10%, while those inside the nucleus and rostral to the superior segment increased. Contacts located inside the STN evolved from the central to the superior segment, the latter being the most frequent stimulation site at the final time point. Besides, contacts located medially to the nucleus were more frequently medial to the superior segment, which corresponds to the ZI, a recognised target for symptoms of PD (Plaha et al., 2006). Our implantation procedure aims to implant contact 1 at the centre of the STN, ensuring that there is one contact at the superior segment and the next one rostral to it. Thus, these results strongly suggest that the theoretical target is the superior segment of the STN in accordance with previous publications (Herzog et al., 2004; Yelnik et al., 2003; Godinho et al., 2006). Others, however, have concluded that the white-matter area above the STN is equally effective but more efficient in terms of energy consumption (Voges et al., 2002; Saint Cyr et al., 2002). Specifically, Hamel et al., (2003) proposed this latter zone to be the optimal area as it was the most frequent stimulation site. However, a later publication from the same group, which included symptoms quantification, found stimulation to be equally effective in the sensorimotor STN and dorsal margin of the nucleus whereas stimulation above the dorsolateral border resulted in poorer benefits and higher energy consumption (Herzog et al., 2004).

These discrepancies may, in part, reflect differences in the accuracy of the methods used to localise the electrode's position. Nonetheless we also found that some active contacts evolved towards the rostral white-matter subthalamic area, although they only represented 6% of all the contacts studied. In any case, if one takes the current spread around the electrode contact with monopolar stimulation into account (2–3 mm diameter) (Ranck, 1975; Ashby et al., 1999; Saint Cyr et al., 2002), it is quite likely that stimulation of either the sensorimotor STN or white-matter subthalamic area would modulate the contiguous region. A patient-specific model study found greater STN DBS-induced improvement when the volume of tissue stimulated spread outside the atlas-defined borders of the STN compared to stimulation inside the nucleus (Maks et al., 2009).

One of the advantages of our study design over previous studies evaluating the optimal stimulation site is that we assessed stimulation area after a careful optimisation of the stimulation parameters while some of these studies have assumed that an active contact at a given time should represent the appropriate target (Voges et al., 2002; Hamel et al., 2003; Saint Cyr et al., 2002). This is based on the assumption that stimulation parameters are optimised during the first months after surgery and few changes are needed afterwards. However, we, along with other authors (Moro et al., 2006; Fasano et al., 2010) have probed that reprogramming in otherwise stable patients may lead to further benefits, especially when it involves a change in the active contact.

We found that stimulation within our defined optimal area – the central/superior segment of the STN or adjacent rostral area – to be more

efficient. Stimulation of this region not only provided a larger benefit but required less energy of stimulation and lower medication.

Despite the suboptimal position of some of the active contacts, both groups improved with reprograming to a similar extent and medication could be further reduced. This improvement may be explained by a change in the stimulation area and higher electrical stimulation parameters used at the final time-point. Nevertheless, it is important to stress that optimisation was much more laborious for suboptimally placed contacts, with multiple changes in the stimulated contact required more often in this group. These findings highlight how stimulation can be further optimised even for suboptimally placed electrodes, although they may require higher stimulation parameters to broaden the volume of the tissue stimulated.

Selection of the active contact by clinical assessment improved stimulation site in almost 10% of the electrodes. Our defined optimal site is wide enough to cover at least two contacts of the DBS electrode, which explains why some changes in contact did not result in a modification of the stimulated area, as long as the change is towards a contiguous contact. Some of the active contacts located at group Ic underwent a “change in contact”, which explains the evolution from central to superior STN segment.

In our results, in all but two cases, stimulation-induced dyskinesia occurred when the active contact was located inside the STN. In these, stimulation was applied adjacent to the superior border of the STN, which would necessarily have influenced the sensorimotor STN. The presence of stimulation-induced dyskinesia has been considered a good predictive factor of amelioration of Parkinsonian signs (Houeto et al., 2003; Moro et al., 2006).

Indeed, we found this group to have lower UPDRS III scores and TEED and medication requirements. These results also support the hypothesis of sensorimotor STN as the optimal target. Nevertheless, as not all patients in which contacts where located inside the STN had stimulation-induced dyskinesia, patient susceptibility factors may also be involved. Conversely, stimulation of the subthalamic white matter has been found to have an antidyskinetic effect (Herzog et al., 2007; Alterman et al., 2004). Herzog (2007) reported three patients in whom stimulation inside the STN induced disabling dyskinesia that was reduced with additional stimulation of the rostral white-matter area. We performed the same approach in one of our patients (not included in this study) and, although stimulation of a proximal contact suppressed stimulation-induced dyskinesia, Parkinsonian symptoms worsened, rendering this approach impracticable.

Additionally, we would like to stress that electrode implantation was performed without microelectrode recordings. A single brain-pass was used in the majority of patients. Most teams use three to five MER passes to define the functional sensorimotor STN segment with the consequent increase in the risk of intracranial haemorrhage and time of surgery (Hariz, 2002). We have corroborated that the clinically defined optimal stimulation site corresponds to the superior segment of the STN and that this functional segment can accurately be targeted using neuroimaging and macrostimulation criteria. Additionally the efficacy of our method on Parkinsonian symptom amelioration has been previously reported (Foltynie et al., 2011).

3.3 THE VALUE POSTOPERATIVE IMAGING IN THE SELECTION OF THE OPTIMAL THERAPEUTIC CONTACT

We have shown how anatomical position of the active contact is critical for DBS efficiency and optimisation. According to current guidelines for DBS programming, the best electrode contact is selected based on its clinical efficacy (the best contact will be the most effective at lowest voltage and higher threshold for side effects). However, the increased knowledge about the optimal stimulation site and advances in neuroimaging techniques may allow selection of the optimal contact based on its anatomical location. This approach represents a more rational strategy for selection of the therapeutic contact, avoiding confounding effects that may arise from traditional strategies of programming (patients' cooperation, neurologist capability, dopaminergic medication state, carry-over effects of previous stimulation) and shortening the time for programming.

Selection of the active contact by anatomical criteria matched clinical criteria in 66% of the electrodes at baseline. This percentage increased after consecutive adjustment sessions to 70%. For a similar global improvement, a lower increment in TEED and voltage were required in the concordance group. In the same way, optimisation of DBS was more easily achieved for the concordance group, where "multiple changes in the stimulated contact" was less-often needed. When the active contact was within the defined optimal area, a significantly higher degree of concordance was achieved. Yet, four optimally placed therapeutic contacts did not match MRI criteria. In two of them, stimulation was found to cause disabling dyskinesia and a more rostral contact

was selected for chronic stimulation. This area contains pallidofugal fibres conveying pallidal activity to thalamic nuclei and it is likely that high frequency stimulation of this area would modulate signals, which are primarily accountable for the emergence of dyskinesia. In the remaining two, MRI contact selection was probably inaccurate, assuming that the best contact was the one located inside the central segment of the STN (which showed to be inside the STN in coronal and axial MRI planes) while the contact in the superior segment was shown to be clinically more appropriate (which shown to be inside the STN in one of the MRI planes and adjacent in the other plane). Conversely, selection of suboptimally placed contacts based on MR data may be more inaccurate – only 50% of the therapeutic contacts matched MRI criteria.

Two previous attempts have been made to program DBS parameters based on neuroimaging anatomical location of the electrode contacts (Lee et al., 2010; Paek et al., 2011). In the former study, patients treated for at least 6 months with DBS therapy were reprogrammed stimulating as many contacts considered to be optimally placed (in the STN or, at worst, at its boundaries) by neuroimaging criteria. After reprogramming, most of the electrodes passed from a single to a multiple monopolar configuration. An additional improvement in motor UPDRS scores off and on medication along with a reduction in TEED and LEDD was found. This improvement was observed mainly for those leads considered to be well placed; which is in agreement with our findings. However, as multiple monopolar stimulation was used after reprogramming, a broader area was probably being stimulated, which might in part account for the further benefit observed and the reduction of TEED. In the study by Paek (2011), patients were programmed one month after surgery using neuroimaging criteria

for the selection of the active contact. Even though no control group was used, improvement at 3 and 6 months after surgery and reduction of LEDD were comparable to those previously described (Limousin et al., 1998; Rodriguez-Oroz et al., 2005) with the advantage that time of programming was markedly shortened.

Our results, along with those previously published, suggest that integration of anatomical contact location information on current strategies of programing of DBS may help to select the optimal therapeutic contact. Despite the present controversy regarding the optimal stimulation site, selection of therapeutic contact by an imaged-based programming may reduce the potential therapeutic contacts to two (given the Medtronic 3389 DBS electrode dimensions). This methodology would most likely simplify and shorten the programming of stimulation parameters, increase stimulation efficiency and alleviate patient discomfort. Moreover, this approach may be most valuable for future more complex leads and settings available and also for targets and other diseases where acute effect is less reliable. Nevertheless, intensive programming may still be necessary for suboptimally placed electrodes. Fortunately, these represent a small percentage of electrodes in the majority of centres performing DBS.

4. STUDY OF TYPE OF ADJUSTMENT "CHANGE IN CONTACT"

One of the key factors in the programming of stimulation is the selection of the optimal contact, as it represents the optimal stimulation site for a given electrode. Each contact of the DBS electrode stimulates a different area within the subthalamic region in the rostro-caudal axis (with an anterior-posterior and latero-medial direction). The optimal contact is selected based on the acute effect elicited by the stimulation. Nevertheless, the acute efficacy of one contact may be confounded with the carryover effects of a previous setting, as stimulation effect can take up to four hours to vanish (Temperli et al., 2003).

From the 28 electrodes that underwent a change in contact during the first adjustment session, 53.7% remained in that new contact at the end of the study. In 43% of electrodes, the contact changed again at the second and/or third adjustment session. In the majority of these electrodes (75%) the active contact returned to the same contact stimulated at baseline; thus, previous programming could be considered useless. Moreover, 10% of the electrodes required multiple changes in the active contact. For those contacts where the first "change in contact" was appropriate, the stimulation site moved mainly from the central to the superior segment of the STN or adjacent to it. For the remainder, stimulation site at the final time point was more heterogeneous, preventing us from drawing any conclusions.

These results, along with previous findings reported in this study, strongly suggest that the superior segment of the STN is the optimal area for stimulation. Active contact was selected based on its acute effect. However, although all contacts undergoing a "change in contact" at A1 had an acute benefit, this was significantly larger for those not requiring additional changes in the stimulated

contact at A2. In both groups, the acute effect was attenuated over time, but deterioration was only present for those requiring a second change at A2. Therefore, the magnitude of the acute effect seems to be closely related to the sustained benefit, as was seen in the multivariate regression analysis. The acute benefit observed in suboptimal selected contacts can be explained by the lasting effect of the stimulation. While tremor may return within minutes after switching the stimulation off (Temperli et al., 2003; Blahak et al., 2009), bradykinesia (Temperli et al., 2003, Cooper et al., 2013, Cooper et al., 2011, Waldau et al., 2011; Lopiano et al., 2003), rigidity and axial symptoms require longer washout periods (Temperli et al., 2003). In the same way, tremor readily improves after switching stimulation on, while improvements of bradykinesia and rigidity may take longer. Thus, when assessing the effects of stimulation of a new contact, and therefore, of a new anatomical area, the influence of the stimulation over the previous site is still present, unless stimulation has been turned off for a few hours. The complex response of symptoms to off and on stimulation conditions complicates any acute evaluation. Furthermore, this behaviour reflects different mechanisms of action of high frequency stimulation. Immediate effects may be related to the direct depolarisation of STN neurons or neurotransmission (Krack et al., 1998; Blahak et al., 2009), while other mechanisms, such as secondary messengers, long-term potentiation or a long-lasting modification of the basal ganglia activity by STN DBS, may be involved in the prolonged and even sometimes delayed effect of the stimulation (Temperli et al., 2003, Cooper et al., 2013). It has been suggested that a period of at least 3 hours with the stimulation turned off may be required to assess all

Parkinsonian signs (Temperli et al., 2003), which may be not only unbearable for patients but also unviable in routine practice.

Furthermore, some contacts changed at A2 or A3 without a previous change in contact. This reflects the difficulty in selection of the optimal contact when only clinical assessment is available and how this process may be dependent of many factors (i.e. clinician's expertise, patient cooperation, placebo effect, off-medication condition).

When a change in the active contact is involved in the reprogramming, the acute effect would comprise both the readily achieved effect of stimulation of a new contact and the long-lasting effect of the stimulation of the previous one. However, the delay-effects of the stimulation will not be present during the acute evaluation. This makes adjustment of the stimulated contact based on the acute effect quite unpredictable unless a large enough acute benefit has been obtained.

5. THE VALUE OF THE INTRAOPERATIVE LFP RECORDINGS IN DBS TARGETING OF THE STN AND OPTIMIZATION OF STIMULATION PARAMETERS

Online spectral analysis of LFPs recorded from the DBS electrode may provide information that would help to predict optimal stimulation settings during long-term follow-up. We previously shown that the same signals were quick to record and analysed intraoperatively, and correlated with successful targeting with respect to intraoperative implantation effect and postoperative imaging (Chen et al., 2006). The latter was also confirmed in this larger sample where most of the contacts considered to be optimally placed had evidence of a local beta generator. Together, these results point to the utility of the intraoperative spectral analysis of LFPs recorded from the DBS electrode in aiding the functional localisation of the STN.

No evidence for significant perioperative brain shift was found, in so far as there was no difference between the mean depth of the local generator and the depth of the contact independently used for chronic stimulation, although some individual variability existed. The limited delays introduced by our intraoperative functional localisation technique may have helped avoid significant subdural air collection. This contrasts with more prolonged microelectrode recording techniques where brain shift might be a problem (Miyagi et al., 2007). Furthermore, there were no perioperative haemorrhages in our series.

In this work we studied how well the intraoperative LFP recordings could predict the chronic contact and voltages independently selected for chronic stimulation.

The depth of the surgical target point was a relatively poor predictor of the depth of the local beta generator or the contact selected for chronic stimulation. We

concluded that although anatomical targeting based on preoperative stereotactic MRI may be very good at selecting an appropriate electrode trajectory towards and through the nucleus, it is relatively poor in identifying the precise rostro-caudal depth of the stimulation target, whether the latter is functionally defined as the local generator or clinically defined as the site of the best contact for chronic stimulation. There was even evidence that the local beta generator may be more indicative of the optimal depth for ameliorating parkinsonism than the contact level chosen for therapeutic stimulation over long-term follow up, perhaps because the latter represents a compromise between efficacy and side effects. Thus, higher stimulation voltage and energy tended to be delivered if a depth was selected for chronic stimulation that differed from that of the local beta generator. Stimulation efficacy was more than halved when the therapeutic contact was ≥ 2 mm from the depth of the beta generator; which is further explained by the fact that current spread around the electrode contact is of 2-3 mm of diameter (Ranck, 1975; Ashby et al., 1999; Saint-Cyr et al., 2002). In contrast, disparities in the depth selected for chronic stimulation and the depth of the surgical target point had no significant effect on stimulation voltage or energy. Further studies have confirmed a high concurrence between the center of the site used for chronic stimulation and the dorsolateral oscillatory region of the STN (Zaidel et al., 2010; Guo et al., 2013). In the same way stimulation of this area was correlated with a good outcome of STN DBS.

Intraoperative recording of local field potential activity directly from the DBS electrode may potentially provide an alternative to microelectrode recordings for identifying the depth of the STN, with attendant advantages in terms of the

duration of the operation and possible reduction in the risks of intraoperative haemorrhage and brain shift. Nevertheless, the technique relies on minimal error in the anterior-posterior plane, as a single trajectory cannot provide information about localisation in these dimensions, and the utility and safety of exploration of alternative trajectories with the DBS electrode remains uncertain. Thus the technique must be combined with accurate targeting in the anterior-posterior plane using stereotactic preoperative MRI. Yet, the present data provide further support for the clinical relevance of the local beta activity in the STN and suggest that the technique whereby LFPs are recorded from the DBS electrode also helps predict the optimal stimulation contact for use in chronic DBS. Nevertheless, further studies will be needed to assess the role of LFP in selection of the optimal stimulation parameters in DBS.

VI. CONCLUSIONS

1. LONGITUDINAL ASSESSMENT OF THE IMPACT OF CONSECUTIVE SESSIONS FOR ADJUSTMENT OF STIMULATION PARAMETERS OF STN DBS IN PD PATIENTS: EVALUATION OF THE ACUTE AND CHRONIC EFFECTS OF STIMULATION PARAMETERS

The aim of this study was to improve the current strategies for selection of the stimulation parameters. We have shown that the acute effect on motor scores is the factor that better predicts a sustained benefit. Nevertheless, although a lineal relationship between the acute and global benefit of the adjustment exists, the magnitude of the acute effect necessary for the adjustment to provide a sustained benefit may vary depending on previous optimisation of the stimulation. We can conclude that:

1. Subjective assessment of the acute effect of the stimulation is not always translated into an objective acute effect.
2. The most consistent predictive factor for a global motor improvement of a programming session of the stimulation parameters is the acute effect of the new setting on motor scores.
3. The magnitude of the acute effect necessary to ensure a global improvement varies depending on previous optimisation of the stimulation parameters.
4. The impact of the different types of adjustment on global outcome is mainly through its acute effect.

2. CLINICAL OUTCOME OF STN DBS WITH REPROGRAMMING

In this part of the study we have demonstrated that reprogramming, in otherwise stable PD patients treated with STN DBS, can lead to additional benefits; which contradicts what has been widely accepted that little changes on stimulation

parameters are required after the first six months of stimulation. While some patients will improve, others will remain stable and a minority will deteriorate. Patients requiring only “one change in the active contact” or “change in voltage” will show the greatest benefits. Necessity of “multiple changes in the stimulated contact” will not provide additional benefits and it may reflect a suboptimal electrode position. Women and younger patients showed the greatest probability for improvement. The following conclusions can be extracted from this part of the study:

1. Reprogramming of stimulation parameters in patients with chronic STN DBS can lead to additional benefits in terms of improvement on motor scores, activities of daily living off-medication and reduction of dopaminergic medication.
2. There is a lower probability for men and older patients to improve with reprogramming

3 and 4. OPTIMAL STIMULATION SITE IN STN DBS FOR PARKINSON’S DISEASE AND STUDY OF THE TYPE OF ADJUSTMENT “CHANGE IN CONTACT”

Intensive programming of the stimulation led to evolution of the active contact towards the superior part of the STN, strongly suggesting that this area is the optimal stimulation site. Accurate implantation of the electrode within the optimal area will provide a greater benefit of the stimulation and lead to more efficient stimulation parameters. Selection of the optimal therapeutic contact, based on its anatomical location, could simplify the programming of stimulation. The results of this part of the study lead to conclude that:

1. The best area for stimulation within the subthalamic area for STN DBS for Parkinson's disease is the superior segment of the nucleus.
2. Stimulation of central/superior segment of the STN provides a more effective and efficient therapy than stimulation of other regions of the subthalamic area.

5. THE VALUE OF THE INTRAOPERATIVE LFP RECORDINGS IN DBS TARGETING OF THE STN AND OPTIMIZATION OF STIMULATION PARAMETERS

LFP can be an alternative to microelectrode recordings to electrophysiologically define the functional target. Furthermore, we have demonstrated that this technique may help in the selection of the optimal therapeutic contact. We conclude that:

1. Online spectral analysis of local field potentials recorded from the DBS electrode aids in the functional localization of the STN.
2. Online spectral analysis of local field potentials recorded from the DBS electrode provides information that helps predict the optimal stimulated contact.

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VIII. APPENDIX I

APPENDIX I. STIMULATION PARAMETERS

Table 1.1 Voltage at different time points of the study

	n	Mean	SD	Range (min-max)
A1 before	62	3,15	0,764	0,90-4,50
A1 after	62	3,19	0,720	1,00-4,50
A2 after	62	3,25	0,746	1,20-4,50
A3 after	56	3,30	0,709	1,25-4,50

Abbreviations: A: adjustment session; SD: standard deviation.

Table displays the values of voltage (in volts) before A1, after adjustment of stimulation parameters in A1, after adjustment of stimulation parameters in A2 and after adjustment of stimulation parameters in A3

Table 2.1 Pulse widths at the different time points of the study

	n	Mean	SD	Range (min-max)
A1 before	62	62,90	8,942	60-90
A1 after	62	62,42	8,235	60-90
A2 after	62	63,39	9,572	60-90
A3 after	56	63,75	10,011	60-90

Abbreviations: A: adjustment session; SD: standard deviation.

Table displays the values of pulse width (in microseconds) before A1, after adjustment of stimulation parameters in A1, after adjustment of stimulation parameters in A2 and after adjustment of stimulation parameters in A3

Table 3.1 Frequency at the different time points of the study

	n	Mean	SD	Range (min-max)
A1 before	62	145,00	20,961	130-185
A1 after	62	147,90	22,716	130-185
A2 after	62	147,90	22,716	130-185
A3 after	56	149,82	23,100	130-185

Abbreviations: A: adjustment session; SD: standard deviation. Table displays the values of frequency (in Hertz) before A1, after adjustment of stimulation parameters in A1, after adjustment of stimulation parameters in A2 and after adjustment of stimulation parameters in A3

IX. APPENDIX II

APPENDIX II. SPANISH SUMMARY

OPTIMIZACION Y CUANTIFICACION DE LOS PARAMETROS DE ESTIMULACION EN LA ESTIMULACIÓN CEREBRAL PROFUNDA DEL NUCLEO SUBTALAMICO EN LA ENFERMEDAD DE PARKINSON

A. INTRODUCCION

La enfermedad de Parkinson (EP) es una de las enfermedades neurodegenerativas más prevalentes y discapacitantes. Sus síntomas incluyen lentitud de movimientos voluntarios (acinesia), temblor característico, rigidez muscular e inestabilidad de la postura y la marcha. Pese a no disponer un tratamiento curativo, actualmente existen tratamientos farmacológicos que mejoran los síntomas de los pacientes. La levodopa es el fármaco más eficaz; sin embargo, con el tiempo la medicación no logra controlar los síntomas y los pacientes desarrollan efectos secundarios (fluctuaciones motoras y discinesias) muy incapacitantes. En estos estadios de la enfermedad, la estimulación con alta frecuencia del núcleo subtalámico (NST), ha demostrado ser un tratamiento seguro y eficaz en pacientes seleccionados (Limousin et al., 1998; Krack et al., 2003; Fasano et al., 2010).

La estimulación cerebral profunda consiste en la implantación de un electrodo en una región cerebral concreta. Este electrodo es conectado, mediante una extensión, a un neuroestimulador que se coloca generalmente en la región infraclavicular.

El éxito de la estimulación cerebral profunda (ECP) del NST depende de una correcta selección de los candidatos, una precisa implantación de los electrodos y de una cuidadosa programación de los parámetros de estimulación y ajustes en la medicación dopaminérgica. Una correcta

programación de los parámetros de estimulación permitirá obtener el máximo beneficio de la estimulación, disminuir la incidencia de efectos adversos inducidos por la estimulación, optimizar el consumo de energía del neuroestimulador y disminuir los requerimientos de medicación dopaminérgica. Actualmente existen unas guías para la selección de los parámetros de estimulación (Moro et al., 2002; Rizzone et al., 2001). Éstas se basan en el efecto inmediato de las distintas combinaciones de los parámetros de estimulación sobre los síntomas. Sin embargo, hasta la fecha no ha sido estudiado si este beneficio inmediato predice una mejoría a largo plazo. Los parámetros de estimulación que se pueden programar son el voltaje, la duración de pulso y la frecuencia. Además, durante la programación hay que seleccionar el contacto del electrodo de ECP más eficaz. El electrodo dispone de cuatro contactos en su punta (dispuestos longitudinalmente) que se pueden estimular de forma independiente o en combinación. La selección del contacto más eficaz consiste en determinar cuál de los cuatro contactos presenta un mejor efecto clínico con menor consumo de energía y mayor ventana para la aparición de efectos secundarios. La programación de los parámetros de estimulación es un proceso laborioso, que depende de la experiencia del neurólogo que realiza los ajustes y de la colaboración del paciente. Además no está exenta de un posible efecto placebo (Mercado et al., 2006) y los ajustes deben hacerse con el paciente en la condición de off-medicación, es decir, tras retirar su medicación antiparkinsoniana 12 horas antes de la programación, lo que en ocasiones causa gran disconfort al paciente.

La zona óptima de estimulación dentro del área subtalámica (contiene el NST y las fibras que lo rodean) ha sido una cuestión ampliamente debatida

(Kuncel et al., 2004). Dos regiones son las que se han propuesto con mayor frecuencia: la región dorsolateral del NST que corresponde a su territorio sensitivo-motor (Lanotte et al., 2002; Saint-Cyr et al., 2002; Yelnik et al., 2003) y la región localizada rostralmente a este territorio que contiene la parte rostral de la *zona incerta* y las fibras palidofugales (Voges et al., 2002; Hamel et al., 2003; Godinho et al., 2006). Algunos grupos han encontrado que ambas zonas son igualmente efectivas pero que en la última los requerimientos de energía eléctrica suministrada por el neuroestimulador son menores (Voges et al., 2002; Hamel et al., 2003). El contacto óptimo de estimulación es seleccionado en base a sus efectos clínicos, por tanto su posición refleja el sitio más adecuado de estimulación. Esta estrategia ha sido utilizada en la mayoría de los estudios que han evaluado la zona más óptima de estimulación. Sin embargo, con la actuales guías clínicas, el contacto terapéutico es seleccionado en base a su efecto agudo y sin una cuantificación objetiva del impacto de su estimulación sobre los síntomas. Es más, generalmente se asume que los parámetros de estimulación y el contacto estimulado, una vez realizados los ajustes de los primeros meses tras la cirugía, no requieren de grandes cambios. Sin embargo, algunos estudios han obtenido un beneficio adicional con la reprogramación de pacientes crónicamente tratados con ECP del NST, especialmente cuando se cambia el contacto de estimulación (Moro et al., 2006; Fasano et al., 2010).

En los últimos años, los avances de la neuroimagen y los programas de planificación han permitido poder determinar la localización final de los electrodos implantados y por tanto de sus contactos. Sin embargo, no se ha desarrollado ninguna guía clínica que incluya estos datos anatómicos para la

selección del contacto óptimo para la estimulación. La información anatómica puede ser de gran utilidad, disminuyendo el número de contactos del electrodo que requieren ser evaluados y por tanto acortando el tiempo de programación y reduciendo la incomodidad que el procedimiento puede causar al paciente.

Por último, los potenciales de campo locales (PCL) son una técnica electrofisiológica que ayuda a identificar el NST durante la cirugía. Un pico en la actividad beta, propia del territorio sensitivo-motor del NST en pacientes parkinsonianos, tiene una buena correlación con la el alivio de los síntomas durante la implantación del electrodo y con la localización de éste en el NST evaluado con resonancia magnética postoperatoria (Chen et al., 2006). Sin embargo, se desconoce si los PCL pueden ayudar a seleccionar el contacto de estimulación y optimizar los parámetros de estimulación.

El objetivo fundamental de esta tesis doctoral es la optimización de los parámetros de estimulación. Para tal efecto se ha evaluado el efecto agudo y sostenido (crónico) de los ajustes de estimulación, qué variables pueden predecir un efecto mantenido tras la programación, el sitio óptimo de estimulación tras una optimización clínica y objetiva de los parámetros de estimulación y el papel de la información anatómica (RM) y los PCL en la selección del contacto más eficaz para la estimulación.

B. OBJETIVOS

1. Evaluar el efecto agudo y mantenido del ajuste de los parámetros de estimulación sobre los síntomas motores de la EP

2. Evaluar el impacto agudo y crónico de los diferentes tipos de ajuste de los parámetros de estimulación sobre los síntomas motores.

3. Identificar qué factores involucrados en la programación de la ECP predicen el mejor efecto clínico a largo plazo en la ECP del NST en la EP.

4. Determinar si una programación minuciosa e intensiva de los parámetros de estimulación puede proporcionar un beneficio clínico adicional.

5. Estudiar la evolución del sitio de estimulación tras sesiones consecutivas de programación de los parámetros de estimulación.

6. Estudiar el sitio óptimo de estimulación en las ECP del NST tras una optimización de los parámetros de estimulación.

7. Evaluar si la información anatómica de la localización del electrodo y sus contactos puede ayudar a la selección de contacto terapéutico.

8. Estudiar el comportamiento del tipo de ajuste “cambio de contacto” durante sesiones consecutivas de programación.

9. Evaluar el papel de los potenciales de campo locales intraoperatorios en la predicción de los parámetros de estimulación en la estimulación cerebral profunda para la Enfermedad de Parkinson.

C. METODOLOGIA

Pacientes

Pacientes con EP tratados con ECP del NST con una duración mínima del tratamiento de 12 meses (6 meses en el estudio de los potenciales de campo locales) fueron reclutados para el estudio.

Se trata de un estudio prospectivo que consta de 5 subapartados:

1. Estudio longitudinal sobre el impacto de sesiones consecutivas de programación de los parámetros de estimulación en la ECP del NST en la EP
2. Resultado clínico de la reprogramación de la estimulación en la ECP del NST
3. Sitio óptimo de estimulación en la ECP del NST en la EP y papel de la información anatómica del electrodo de ECP y sus contactos en la selección del contacto terapéutico
4. Análisis del tipo de ajuste “cambio de contacto” en la ECP del NST en la EP
5. Papel de los potenciales de campo locales (PCL) intraoperatorios en la optimización de los parámetros de estimulación en la ECP del NST en la EP

1. Estudio longitudinal sobre el impacto de sesiones consecutivas de programación de los parámetros de estimulación en la ECP del NST en la EP

Los pacientes fueron evaluados en tres visitas: en el momento de la inclusión (visita 1), un mes (visita 2) y tres meses después de la inclusión (visita 3). En

cada visita los pacientes fueron evaluados con la parte motora de la escala UPDRS (UPDRS III) antes (tiempo basal) e inmediatamente tras el ajuste de los parámetros de estimulación (tiempo agudo). En la siguientes visita, la primera evaluación corresponde al tiempo crónico del ajuste previo y al basal del nuevo ajuste. Las valoraciones se hicieron en la situación off-medicación/on-estimulación. Tras la valoración "aguda" los pacientes tomaron su medicación antiparkinsoniana y fueron valorados on-medicación con la parte motora de la UPDRS y con la escala de discinesias. Una vez concluidas las valoraciones clínicas se completaron el resto de partes de la UPDRS (I, II y IV). El neurólogo que realizó las valoraciones clínicas y el paciente permanecieron ciegos a las modificaciones de los parámetros de estimulación.

El estudio consta por tanto de tres sesiones de ajuste: A1, A2 y A3 y cada una de éstas consta de tres tiempos de evaluación: basal, agudo y crónico (figura 2.1, apartado metodología).

Los ajustes de los parámetros de estimulación se clasificaron en:

- "sin cambios": se valoran nuevos parámetros de estimulación (PE) y finalmente no se modifican
- "cambio en voltaje": se modifica el voltaje de la estimulación (además se puede variar la duración de pulso y/o la frecuencia)
- "cambio en contacto": consiste en la modificación del contacto terapéutico. Se puede variar el voltaje, la duración de pulso y/o la frecuencia.
- "no necesidad de ajustes": tras A1, algunos electrodos presentan un beneficio clínico mantenido por lo que no requieren una nueva

programación de la estimulación. El efecto agudo por tanto no es valorado.

Los tipos de ajustes de los PE se consideran por electrodos y por tanto las valoraciones clínicas se realizan sobre el hemicuerpo contralateral utilizando los ítems 20 a 26 de la parte motora de la UPDRS (rango de puntuación 0-36). La medicación antiparkinsoniana se ajustó según las necesidades.

En el análisis estadístico se compararon las puntaciones en la UPDRS III (total y hemicuerpo) obtenidas en los tiempos basal, agudo y crónico de cada sesión de ajuste (variable intra-sujetos) utilizando el modelo general lineal de medidas repetidas ANOVA. En la valoración por hemicuerpos se incluyó el "tipo de ajuste" como variable entre-sujetos. El estudio de variables predictoras de beneficio mantenido del ajuste de la estimulación se estudió con un modelo de regresión multivariante.

2. Resultado clínico de la reprogramación de la estimulación en la ECP del NST

Se compararon las puntuaciones en las distintas escalas utilizadas en la situación basal del estudio (tiempo basal de A1) y final (tiempo crónico del A3) en la condición off-medicación/on-estimulación. Para evaluar el impacto de los ajustes de estimulación sobre la situación final se definió una nueva variable "tipo de ajuste a lo largo del estudio":

- sin cambios en los PE (incluye no cambios y no necesidad de ajustes)
- uno o más ajustes en voltaje pero no en contacto
- un cambio en contacto
- dos o más cambios en contacto.

El análisis estadístico se realizó utilizando un modelo de medidas repetidas con factor principal “tiempo” (UPDRS III total y por hemicuerpos basal y final del estudio) y variable entre-sujetos “tipo de ajuste a lo largo del estudio” para el análisis por hemicuerpos. Se determinaron las variables predictoras de mejoría final mediante un modelo de regresión logística. Para tal efecto, se redefinió una nueva variable cualitativa de “mejoría final”.

3. Sitio óptimo de estimulación en la ECP del NST en la EP y papel de la información anatómica en la selección del contacto terapéutico

Las imágenes de RM postoperatoria y el programa *Framelink* se utilizaron para determinar la posición de los contactos del electrodo. Las coordenadas de cada contacto se calcularon desde el centro del artefacto causado por el electrodo en la RM postoperatoria. El centro de cada contacto se calculó utilizando una plantilla del electrodo. Estas coordenadas se trasladaron a la RM preoperatoria con el fin de evitar el artefacto. Dos neurocirujanos ciegos a las valoraciones clínicas y parámetros de estimulación determinaron la posición de cada contacto que se definió con dos variables: segmento de NST (superior, anteromedial, central, posterolateral e inferior) y relación con estructuras que rodean al núcleo (dentro del núcleo, medial, lateral, superior, inferior al NST) (figura 2.3, apartado metodología). Para facilitar el análisis estadístico los contactos activos se clasificaron en: grupo Ic -buena localización- el contacto se encuentra dentro del NST (segmento central o superior) o adyacente al borde superior del NST y grupo IIc, para aquellos que no cumplían los criterios anteriores. Se utilizó un análisis univariante para estudiar el impacto de la posición del contacto activo sobre varias variables

dependientes: eficacia de la ECP, energía total suministrada, voltaje, tipo de ajuste de los PE durante el estudio y dosis diaria equivalente de levodopa.

Asimismo, un neurocirujano determinó qué contacto del electrodo era más óptimo para la estimulación en base a su localización anatómica en las imágenes de RM. Distintas variables clínicas y de PE se compararon entre aquellos contactos que coincidían con el seleccionado por el neurocirujano y los que no coincidían.

4. Análisis del tipo de ajuste "cambio de contacto" en la ECP del NST en la EP

Este apartado se centró en la descripción y análisis clínico y anatómico de aquellos electrodos que requirieron un "cambio de contacto" en el A1 y los que requirieron un "cambio de contacto" en A1 y A2 y/o A3. Se utilizaron pruebas no paramétricos cuando el tamaño de la muestra permitía realizar una comparación estadística.

5. Papel de los potenciales de campo locales (PCL) intraoperatorios en la optimización de los parámetros de estimulación en la ECP del NST en la EP

El registro de los PCL se realizó desde el electrodo de ECP en pasos de 2 mm desde 6-4 mm por encima de la diana hasta 2-4 mm por debajo (figura 2.4, apartado metodología). Un "pico" en la banda beta se definió como un aumento de al menos 100% de la media de la potencia de la banda beta en el contacto 01 del electrodo entre las sucesivas profundidades del registro. Las valoraciones clínicas y la programación de la estimulación fueron realizadas por un neurólogo ciego a los datos del registro. La localización anatómica de los contactos terapéuticos se definió en dos grupos: grupo Ic, el contacto se

encuentra dentro o al menos adyacente al borde superior del NST; y grupo IIc, el contacto se encuentra en una localización distinta a la del grupo I. La profundidad del contacto terapéutico también se describió con referencia a la profundidad planificada preoperatoria (misma referencia que la utilizada para la profundidad del pico en la banda beta). Para el análisis estadístico se utilizó la correlación de la Rho de Spearman para acomodar la distribución no paramétrica de la muestra y evitar observaciones aberrantes.

D. RESULTADOS

1. Estudio longitudinal sobre el impacto de sesiones consecutivas de programación de los parámetros de estimulación en la ECP del NST en la EP

1.1 Evaluación del efecto agudo y crónico de tres ajustes consecutivos de los parámetros de estimulación

Treinta y un pacientes con EP (19 hombres; edad 56.35±6.8; duración de la enfermedad 12.39±5.3 años) tratados con ECP del NST durante al menos 12 meses (media 29.94 meses) fueron incluidos en el estudio. El beneficio obtenido en la parte motora de la UPDRS con la ECP fue de 49.53% en la condición off-medicación (comparación tiempo basal del estudio con puntuaciones preoperatorias) (tabla 1.1, apartado de resultados).

El impacto producido por los ajustes en los parámetros de estimulación fue similar en la UPDRS III total y por hemicuerpos. Todos los ajustes produjeron un beneficio inmediato estadísticamente significativo, sin embargo en A1 y A2 este beneficio no se mantuvo y no se produjo un beneficio global del ajuste; mientras que en A3 sí que perduró, obteniéndose una mejoría global (tablas 1.2 a 1.10; figura 1.3 apartado de resultados).

El tipo de ajustes “no cambio” no produjo variaciones en la UPDRS III por hemicuerpos salvo en el A3 donde se observó una mejoría crónica significativa que se tradujo en una mejoría global (figura 1.7, apartado de resultados).

El “cambio en voltaje” no causó variaciones en la UPDRS III por hemicuerpos, salvo en el A3 donde se observó una mejoría en el efecto agudo que se mantuvo en el tiempo (figura 1.7, apartado de resultados).

El tipo de ajuste “cambio de contacto” fue el que produjo mayores variaciones en las puntaciones motoras. En el A1, se observó un beneficio inmediato, seguido de empeoramiento y sin obtener un beneficio global. Sin embargo en el A2 y A3, se volvió a producir un beneficio inmediato y mantenido, obteniéndose un beneficio global en estas dos sesiones de programación (figura 1.7, apartado de resultados).

Cuando no fueron necesarios ningún ajuste, las puntuaciones motoras se mantuvieron estables (figura 1.7, apartado de resultados).

1.2 Factores predictores de mejoría global en cada sesión de programación

El factor que mejor predijo una mejoría global en cada sesión de programación fue la mejoría aguda en la escala UPDRS III (total y por hemicuerpos) (tabla 1.14 y 1.15, apartado de resultados). En el A1, aumentar la profundidad de la zona de estimulación (es decir, seleccionar un contacto localizado más caudalmente) predijo un deterioro motor; mientras que en el A2, revertir esta situación (estimular un contacto más superficial) mostró una tendencia hacia la mejoría. La magnitud del efecto agudo sobre la UPDRS III-hemicuerpo presentó una relación lineal con la mejoría global de cada sesión de programación (figura 1.9, apartado de resultados). Conforme se progresó en las sesiones de programación, una menor magnitud de efecto agudo fue necesaria para asegurar una mejoría global [A1: 5 puntos (rango -5.47 a -2.43, 95% IC); , A2: 3 puntos (rango -3.23 a -1.39, 95% IC) y A3: 1 punto (rango -3.28 a – 1.50, 95% IC)].

2. Resultado final de ajustes consecutivos en los parámetros de estimulación en la ECP del NST en la EP

Se observó una mejoría significativa al final del estudio (comparación puntuaciones del tiempo crónico de A3 con tiempo basal de A1) en la UPDRS III total y por hemicuerpos, UPDRS I y II off-medicación. Los requerimientos de medicación dopaminérgica se redujeron en un 30% (tabla 2.1, apartado de resultados). La mejoría final se produjo en un 42.3% de los pacientes y un 59.6% de los hemicuerpos.

Los electrodos que sufrieron un solo cambio en el contacto de estimulación presentaron una mejoría final estadísticamente significativa. Aquellos en los que sólo se modificó el voltaje, mostraron una tendencia hacia la mejoría. En los que no se realizaron cambios de los PE o en los que requirieron dos o más cambios en el contacto de estimulación las puntuaciones motoras no variaron (figura 2.2, apartado de resultados).

Ser mujer, joven o tener puntuaciones basales de la UPDRS III total o por hemicuerpos más altas se relacionó con una mayor probabilidad de mejoría al final del estudio (tabla 2.4, apartado de resultados).

3. Sitio óptimo de estimulación en la ECP del NST en la EP

3.1 Análisis de la posición anatómica del electrodo de estimulación cerebral profunda

En 50 electrodos (24 pacientes) se disponía de la información sobre la localización anatómica del electrodo de ECP y de sus contactos. El 88% de los electrodos presentaban uno o más contactos en el área de estimulación definida como óptima y 19 pacientes presentaron ambos electrodos con uno o más contactos en dicha zona. Las puntuaciones en la UPDRS III-hemicuerpo

mostraron una tendencia hacia valores inferiores para aquellos electrodos con una óptima localización. También fueron inferiores los requerimientos de energía total suministrada y voltaje. Sin embargo, la programación intensiva de los PE permitió obtener beneficios similares en los dos grupos de electrodos (tabla 3.2, apartado de resultados). La dosis equivalente diaria de levodopa fue inferior en aquellos pacientes en los que ambos electrodos estaban correctamente implantados al final del estudio pero no en la situación basal (tabla 3.3, apartado de resultados).

3.2 Análisis de la posición anatómica del contacto activo de estimulación cerebral profunda

El contacto activo evolucionó hacia una posición más superficial a lo largo del estudio. Al inicio del estudio los contactos estimulados se encontraron con mayor frecuencia dentro del segmento central del NST o mediales al segmento central y superior del núcleo. Al final del estudio los contactos localizados en el segmento central del NST disminuyeron y aumentaron los localizados en el segmento superior o rostrales a él (figura 3.5, 3.6, apartado de resultados). Al final del estudio 12% de los contactos cambiaron hacia una posición más óptima para la estimulación.

Se observó una tendencia hacia un mayor beneficio de la ECP y valores más bajos de UPDRS III-hemicuerpo cuando el contacto activo estaba localizado en la zona de estimulación definida como óptima. En este grupo, la estimulación resultó también ser más eficiente (menores requerimientos de energía eléctrica suministrada por el neuroestimulador). Las dosis de medicación antiparkinsoniana también fueron menores en este grupo al inicio del estudio. Sin embargo, la energía eléctrica suministrada aumentó en los dos

grupos al final del estudio y la mejoría motora obtenida tras los ajustes de los PE no difirió entre ellos. Los requerimientos de medicación disminuyeron en los dos grupos a lo largo del estudio y no se observaron diferencias al final del mismo (tabla 3.5, apartado de resultados).

Once pacientes (13 hemicuerpos) presentaron discinesias inducidas por la estimulación del NST. En estos casos el contacto activo se localizó dentro del NST (fundamentalmente en segmento central o superior) en todos los casos, excepto en dos en el que el contacto se encontraba rostral al segmento superior del NST. Los contactos activos que provocaron discinesias se encontraron con mayor frecuencia dentro del NST en comparación con aquellos que no produjeron discinesias. Las puntuaciones en la UPDRS III-hemicuerpos, la energía total suministrada y las dosis de medicación dopaminérgica fueron significativamente menores en el grupo que presentaba discinesias inducidas por la estimulación (tabla 3.6, apartado de resultados).

3.3 Papel de la neuroimagen postoperatoria en la selección del contacto óptimo para la estimulación

No se encontraron diferencias significativas en las variables clínicas (UPDRS III hemibody, eficacia de ECP o efecto global del estudio) entre aquellos contactos que mostraban concordancia entre el contacto seleccionado clínicamente y el contacto seleccionado en la RM y los que no presentaban concordancia. Sin embargo, los incrementos del voltaje y de la energía total suministrada fueron significativamente superiores en el grupo sin concordancia. Se encontró un porcentaje significantemente superior de concordancia cuando el contacto activo se encontraba en una localización óptima. Así mismo, aquellos contactos que requirieron ser cambiados en más de una ocasión

mostraron mayor frecuencia de discrepancia entre contacto clínico y contacto de RM.

4. Análisis del tipo de ajuste "cambio de contacto" en la ECP del NST en la EP

Veintiocho electrodos requirieron un "cambio de contacto" en el A1. De éstos, 21 mostraron una mejoría del efecto agudo mantenida y no requirieron nuevos cambios en el contacto en el A2; mientras que siete, presentaron un claro empeoramiento clínico. En éstos últimos siete, aunque se produjo una mejoría aguda, esta fue significativamente menor que los 21 contactos que no requirieron un nuevo cambio de contacto (tabla 4.1, apartado de resultados). En la mayoría de estos siete, el nuevo contacto seleccionado tras A1 correspondió a un contacto localizado más caudalmente. Tras el A2, la mayoría volvieron al mismo contacto utilizado al inicio del A1. La mayoría de los contactos que no requirieron nuevo cambio en A2 cambiaron hacia un contacto más rostral, siendo la localización final más frecuente en este grupo dentro o adyacente al segmento superior del NST.

5. Papel de los potenciales de campo locales intraoperatorios en la optimización de los parámetros de estimulación en la ECP del NST en la EP

Treinta y un pacientes (17 hombres) se incluyeron en esta parte del estudio [edad media 57±7.4; duración media de la EP 11.7 años (rango 5-28); duración media del tratamiento con ECP 19 meses (rango 6-51)]. Se registró un pico en la banda beta (11-35 Hz) en todos los lados excepto en dos. Se encontró una correlación entre la profundidad en la que se detectó el pico de actividad beta y la profundidad del contacto terapéutico (Rho= 0.35, p=0.01;

figura 5.2, apartado de resultados). La diferencia absoluta entre la profundidad del generador beta y el contacto terapéutico mostró correlación con el voltaje utilizado para la estimulación crónica (Rho= 0.322, p=0.017); es decir, un mayor voltaje era requerido si la profundidad del contacto terapéutico difería de la del contacto que registró el pico en la actividad beta.

E. CONCLUSIONES

1. El efecto agudo valorado de forma subjetiva no se traduce siempre en un efecto agudo objetivo
2. La variable que mejor predice una mejoría motora de la programación de la estimulación es el efecto agudo sobre los síntomas motores producido por los parámetros de estimulación
3. La magnitud del efecto agudo necesaria para asegurar una mejoría mantenida depende de sesiones previas de optimización de la estimulación.
4. El impacto mantenido sobre los síntomas motores de los diferentes tipos de ajuste es fundamentalmente mediante el efecto agudo.
5. La reprogramación de la estimulación en pacientes tratados de forma crónica con ECP del NST puede aportar beneficios adicionales en cuanto a la mejoría de los síntomas motores y reducción en los requerimientos de medicación dopaminérgica.
6. Existe una probabilidad disminuida de mejorar con la reprogramación en pacientes varones y de mayor edad.
7. La zona óptima de estimulación en la ECP del NST es el segmento superior del núcleo.
8. Una implantación precisa en el segmento central/superior del NST proporciona una estimulación más eficaz y eficiente
9. La integración de la información anatómica de la localización de los contactos del electrodo de DBS ayuda en la selección del contacto óptimo para la estimulación.

10. Los potenciales de campo locales, registrados desde el electrodo de ECP, ayudan en la localización funcional del NST
11. Los potenciales de campo locales intraoperatorios son útiles en la selección del contacto óptimo para la estimulación