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Adaptive Deep Brain Stimulation for Parkinson's Disease and Dystonia

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DOI:
[10.33612/diss.168446465](https://doi.org/10.33612/diss.168446465)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Piña Fuentes, D. (2021). *Adaptive Deep Brain Stimulation for Parkinson's Disease and Dystonia*. [Thesis fully internal (DIV), University of Groningen]. University of Groningen.
<https://doi.org/10.33612/diss.168446465>

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ADAPTIVE DEEP BRAIN STIMULATION FOR PARKINSON'S DISEASE AND DYSTONIA

Dan Piña Fuentes

Printing of this thesis was financially supported by the University of Groningen (RuG), the University Medical Center Groningen (UMCG), the Research School of Behavioural and Cognitive Neurosciences (BCN), and the Parkinson Vereniging (Proj. nr. 2021-02P). Additionally, Dan has personally been supported by a grant from the the National Council of Science and Technology (CONACYT Mexico), the RuG, and the UMCG.

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Adaptive Deep Brain Stimulation for Parkinson's Disease and Dystonia
Dan Piña Fuentes

ISBN/EAN: 978-94-6421-310-2

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Adaptive Deep Brain Stimulation for Parkinson's Disease and Dystonia

PhD thesis

to obtain the degree of PhD at the
University of Groningen
on the authority of the
Rector Magnificus Prof. C. Wijmenga
and in accordance with
the decision by the College of Deans.

This thesis will be defended in public on

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1

INTRODUCTION

**(Adaptive) Deep Brain Stimulation in
Parkinson's disease and dystonia:
Concepts**

Parkinson's disease (PD) and dystonia are two of the most common movement disorders. PD has a prevalence of 1% of the population ≥ 60 years of age;¹ dystonia is found in 16.43 per 100,000.² PD is a hypokinetic movement disorder, that is characterized by bradykinesia, rigidity and/ or tremor.³ In addition to this characteristic phenotype, non-motor features are virtually always present, such as psychiatric and autonomic disorders. Dystonia is a hyperkinetic movement disorder, in which involuntary muscle contractions are present in one body part (focal), two or more body regions (segmental), or spread throughout the whole body (generalized).⁴ These contractions can be either brief (phasic), sustained (tonic), or a combination of both, and be accompanied by other movement disorders, e.g. myoclonus or tremor. Furthermore, non-motor symptoms are also frequently present in dystonia patients.

Both PD and dystonia are initially treated with medication. Levodopa is the basis of the medical treatment for PD, with excellent results in the initial phases of the disease.^{5,6} However, after approximately five to seven years of treatment, fluctuations in the response to levodopa can occur, together with so-called levodopa-induced dyskinesias. In dystonia, periodic botulinum toxin injections are the treatment of choice when dystonia is focal or segmental.⁷ In patients with generalized dystonia, oral medication is the first treatment option. Anticholinergics and benzodiazepines are most often prescribed.⁸ However, anti-dystonic drugs are often unsatisfactory in providing an adequate symptom relief. Next to this, those drugs often give side effects if moderate to high doses are required, such as excessive somnolence, dizziness, and impaired coordination. For both PD and dystonia, surgical treatment with Deep Brain Stimulation (DBS) is one of the best alternatives when medication is not effective, or when medication-induced side effects become troublesome.⁹

DBS therapy consists in the neurosurgical implantation of multi-contact electrodes into deep brain regions where electrical pulses are delivered.¹⁰ These electrical pulses are provided by an extracranial battery (usually placed below the clavicle) that is connected with the electrodes through extension wires (Figure 1). The regions targeted with DBS are components of widespread brain networks. In movement disorders, the main targets for DBS are nuclei of the basal ganglia, which are crucial elements of networks involved in motor control, together with cognitive and affective functions. For that reason, by modulating the neural activity of the basal ganglia nuclei where the electrodes are located, the electrical stimulation provided by DBS is able to influence the functioning of these networks.¹¹ The principal target in PD is the subthalamic nucleus (STN),¹² whereas in dystonia the main target is the internal globus pallidus (GPI).¹³ Nevertheless, the STN is also an effective target for dystonia¹⁴ and

the GPI is similarly an effective target for PD.¹⁵ Therefore, the stimulation of any of these nuclei in both diseases leads to an improvement in motor symptoms.

Figure 1. Schematic representation of a DBS system. The electrodes implanted in one of the basal ganglia nuclei (GPI in this case) are connected to a pulse generator, which is usually placed subcutaneously in the chest of the patient.

Although DBS has been successfully applied for more than 30 years in PD and 20 years in dystonia,¹⁶ the exact mechanism by which DBS is able to lead to a significant benefit in both diseases has not yet been fully elucidated. Due to this gap in knowledge, DBS therapy currently faces a number of limitations (Table 1). First, until now DBS has only been applied in the clinical setting using an open-loop system (*conventional DBS*).¹⁷ This indicates that when DBS is on, stimulation is constantly delivered, without taking into account variations in the clinical state throughout the day, or symptom fluctuations induced by medication. For that reason, conventional DBS is being referred to as continuous DBS (cDBS). During cDBS, stimulation-dependent side effects can occur, such as parkinsonism in dystonia patients, or dystonia in PD patients,¹⁸ which may be related to the uninterrupted delivery of stimulation. These side effects can be addressed by choosing either less optimal settings or stimulation contacts further from the ideal target. However, it is clear that reducing stimulation-dependent side effects should not come at the expense of providing the most optimal therapeutic effect. In addition to this, cDBS has to be manually programmed by a trained clinician based solely on the clinical response of each patient to cDBS,¹⁹ since no other variables that indicate whether DBS is working are currently available in the clinical setting. Therefore, cDBS programming is up until now a rather empirical task. This often drawn-out process starts shortly after cDBS implantation, in which

the programming clinician manually adjusts stimulation settings based on the acute response of motor symptoms to cDBS. After the initial DBS settings have been selected, it is necessary to wait for stimulation to induce a chronic symptom improvement, which in many cases can take days or weeks, or might not happen at all.²⁰ Therefore, cDBS outpatient clinics are usually saturated, due to the constant follow-up that these patients require. Even after an adequate set of stimulation parameters has been found, residual symptoms are usually present. Because of this, it is difficult to establish when the maximum clinical benefit of cDBS has been achieved, as an objective indicator of the maximum response to stimulation is still lacking.

Benefits of cDBS	Limitations of cDBS
<ul style="list-style-type: none">• Significant improvement of motor symptoms.• Reduction in the amount of medication required• Reversible and manually adjustable to symptom response.	<ul style="list-style-type: none">• Can induce stimulation-related side effects.• Maximum efficacy can be limited.• Programming is performed empirically, and it is time-consuming

Table 1. Benefits and limitations of cDBS.

Fortunately, cDBS has opened the possibility to study the physiological mechanisms of the basal ganglia functioning, which helps to understand how stimulation works, and to apply this knowledge into the development of new DBS-systems. Nowadays, it is possible to record the neurophysiological activity from the brain regions where the cDBS electrode leads are implanted. This offers a unique opportunity to investigate areas of the living brain, which otherwise would not have been accessible to common electrical recording techniques (e.g. electroencephalography).²¹ The local neural activity observed in these recordings—the so-called local field potentials (LFP), represents the combined oscillatory activity of neurons surrounding the electrode where the recordings are obtained (Figure 2). LFP-recordings can be studied at three levels: in the time domain, by looking at changes in amplitude of the recorded signal after one or more filters have been applied; in the frequency domain, by estimating the power of a signal across a defined frequency spectrum; or a combination of both (time-frequency analysis), in which the power spectrum of a signal is estimated at short, consecutive epochs over a time period. The oscillations embedded in the LFPs convey information regarding physiological processes, and can be present as baseline activity, or be elicited in response to intrinsic or extrinsic stimuli.²²

When a disturbance in the physiology of the brain is present, as it is the case for movement disorders, oscillations can become pathological.²³ For that reason, the

term ‘oscillopathies’ has been suggested to refer to the group of diseases in which aberrant oscillations have been detected. PD and dystonia are part of this group, since prominent oscillations present at certain frequency bands have been associated with specific symptoms in these disorders.²⁴ In PD, prominent beta oscillations (13-35 Hz) have been detected both the GPi and the STN of PD patients in the resting state,²⁵ and they have been correlated with the presence of bradykinesia and rigidity.²⁶ In dystonia, low-frequency oscillations (4-12 Hz) have been detected in the GPi and STN of dystonia patients in the resting state, and they have been correlated with the severity of dystonic symptoms.²⁷⁻²⁹

Figure 2. Schematic representation of the Fast Fourier Transformation of a local field potential (LFP), which evidences the presence of both prominent low-frequency and prominent beta oscillatory activity.

The aim of this thesis is to explore the characteristics of abnormal oscillations detected in the basal ganglia of PD and dystonia patients. These oscillations can be used in adaptive DBS systems as physiological biomarkers (physiomarkers) to titrate stimulation, since they correlate with the clinical state of the patients.^{30,31} Throughout this thesis, the acute efficacy of these closed-loop systems is being tested in PD and dystonia patients, in order to incorporate this knowledge into the development of future aDBS devices.

This thesis is divided into three main sections:

Part I: Low-frequency and beta oscillations in Parkinson's disease and dystonia

In this first section, we describe the characteristics of aberrant oscillations detected in the STN and GPi of PD and dystonia patients. We focus on the description of

beta and low-frequency oscillations, since they have been postulated as the most promising physiomarkers for PD and dystonia, respectively. The lack of intra-operative recordings from healthy controls is addressed by using recordings of patients with either PD or dystonia as each other's controls. In the first part (**chapter two**), we summarize all the direct comparisons of low-frequency and beta power that have been performed in the literature between PD and dystonia, and pool the results into a meta-analysis. Afterwards, we compare the temporal characteristics of these oscillations (**chapter three**), and explore how these can be incorporated into aDBS systems for the GPi, by testing their application in both a PD and a dystonia patient.

Part II: Adaptive Deep brain stimulation in Parkinson's disease

The main objective of this section is to explore the immediate effects of beta-based aDBS in PD patients with electrodes implanted in the STN, which is the main target for cDBS. For this part, we only assess PD patients who underwent cDBS implantation several years before the recordings take place. The reason for this is to bypass the micro-lesion effect caused by the implantation itself, as this effect can cause a temporary symptom improvement, thereby masking the true effects of aDBS. Firstly, we investigate the feasibility of performing intra-operative LFP-recordings during the battery replacement surgery in a single patient (**chapter four**). Subsequently, we expanded this approach by performing a clinical trial, in which we tested the immediate effects of aDBS in a group of PD patients undergoing battery replacement.

Chapter five describes the protocol used for this clinical trial, while the results of this protocol are presented in **chapter six**. The future perspectives of aDBS for PD are briefly discussed in **chapter seven**.

Part III: Adaptive deep brain stimulation for dystonia

This last section addresses the potential of aDBS to be implemented in dystonia, using low-frequency oscillations as the physiomarker to close the stimulation loop. **Chapter eight** presents a review of the reasons that led to the postulation of low-frequency oscillations as a physiomarker for aDBS, together with the unique characteristics of dystonic symptoms and their response to stimulation. In order to translate theory into practice, we perform a pilot study in which we explore the acute and chronic response of low-frequency oscillations to stimulation, and test for the first time the immediate effects of aDBS in dystonia (**chapter nine**). This chapter ends with a discussion of how low-frequency oscillations can be incorporated into prospective aDBS systems.

Finally, **chapter ten** presents a general discussion is presented, in which we summarize the results presented throughout this thesis and debate the future directions that aDBS will take in the upcoming years.

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Low-frequency and beta oscillations in Parkinson's disease and dystonia

2

Direct comparison of oscillatory activity in the motor system of Parkinson's disease and dystonia: A review of the literature and meta-analysis

D. Piña-Fuentes, J.M.C. van Dijk, G. Drost, J.C. van Zijl, T. van Laar, M.A.J. Tijssen, M. Beudel. *Clinical Neurophysiology* 130 (2019) 917–924.

HIGHLIGHTS

- The distribution of low-frequency (LF) and beta oscillatory power differs between Parkinson's disease (PD) and dystonia.
- Increased LF power is present in subcortical local field potentials (LFPs) of dystonia when compared to PD.
- Increased beta power is present in subcortical LFPs of PD when compared to dystonia.

Abstract

Objective: To outline the current knowledge of (sub)cortical oscillations in Parkinson's Disease (PD) and dystonia, and to quantitatively summarize the results of direct comparisons of local oscillatory power between both diseases in the resting state, without medication or stimulation, in both the low frequency (LF, ± 4 -12 Hz) and beta (± 13 to ~ 30 Hz) range.

Methods: Eight relevant studies were included. Recordings from 127 dystonia-, and 144 PD-patient hemispheres were analyzed. Ratios of LF and beta power between diseases were obtained.

Results: Beta oscillations in dystonia were lower when compared to beta oscillations in PD, ratio = 0.72, $Z = 3.56$, $p = 0.0004$, 95% CI [0.60, 0.86]. Subgroup analyses showed significant differences only in the GPi, whilst conflicting evidence was shown in the STN. LF oscillations in PD were lower when compared to LF oscillations in dystonia, ratio = 0.77, $Z = 2.45$, $p = 0.01$, 95% CI [0.63, 0.95]. Subgroup analyses showed significant differences in the GPi and the STN, but not in the M1.

Conclusions: LF and beta oscillations are present in the resting-state motor network of both PD and dystonia patients. However, the power distribution of those oscillations differs between diseases.

Significance: This meta-analysis provides high-level evidence which supports the presence of exaggerated oscillations across the parkinsonian/dystonic motor networks.

2. Introduction

Parkinson's disease (PD) and dystonia are movement disorders with different phenotypes, showing respectively paucity and an excess of movements. Despite these clinical differences, deep brain stimulation (DBS) is an effective treatment for both disorders (Vidailhet et al., 2005; Kupsch et al., 2006; Odekerken et al., 2013).

The preferred target for DBS is the internal globus pallidus (GPi) in dystonia, and the subthalamic nucleus (STN) in PD. However, recent studies have demonstrated that a similar symptomatic improvement can be obtained either when the GPi is the target chosen for DBS in PD (Mansouri et al., 2018), or the STN in dystonia (Ostrem et al., 2017), using roughly similar stimulation parameters when comparing nuclei of the same disease. Currently, the exact mechanisms behind this duality on stimulation targets are not fully understood.

2.1. Pathological oscillations model

An emerging theory that provides some insight to this target duality phenomenon is the presence of pathological oscillatory patterns extended throughout the cortico-basal ganglia-thalamocortical (CBGTC) network of PD and dystonia patients (Guridi and Alegre 2017). This (pathological) local oscillatory activity in the CBGTC network can be explored by means of recordings of grouped neuronal activity obtained either from the same electrodes used for stimulation (local field potentials, LFPs), or from electrodes placed on cortical areas (electrocorticography, ECoG). In animal research, the GPi-LFPs of non-human primate PD models have shown exaggerated oscillations in the beta range (13 to ~30 Hz) compared to healthy animal controls (Leblois et al., 2007). On the other hand, none of the current dystonia animal models available (Chaniary et al., 2008; Ip et al., 2016) have been yet employed for such comparison; only non-human primate data of parkinsonian animals has been compared with human dystonia and PD data (Starr et al., 2005). In human PD subjects, prominent beta oscillatory activity has been found in the rest OFF medication state, in both the GPi and the STN (Brown et al., 2001). This subcortical beta activity decreases both after the application of DBS (Eusebio et al., 2011; Wang et al., 2018) and administration of levodopa (Kuhn et al., 2006). Similarly, prominent low-frequency (LF, 4–12 Hz) activity has been described in the GPi of dystonia patients (Chen et al., 2006), which is regulated after the application of DBS (Barow et al., 2014). In the motor cortex (M1), the interaction of beta oscillations with other frequency bands (beta-broadband phase-amplitude coupling (de Hemptinne et al., 2013, 2015)), or with signals from subcortical regions (beta coherence (Hirschmann et al., 2013, Wang et al., 2018)), rather than the oscillatory power, has been shown to be altered in PD, and regulated

after the application of DBS, in both the STN and the GPi. In the aforementioned study, the LF cortical-GPi rest coherence of dystonia patients was also increased.

1.2. Limitations of studies of pathological oscillatory activity

It is well known that oscillations play a role in physiological functions in the nervous system. For that reason, the detection of prominent oscillatory activity in a determined neuronal structure, does not necessary imply that such activity is exaggerated. Only a comparison with a healthy structure could determine whether oscillations detected on the affected network are pathologically increased. However, unlike animal research, studies that investigate local oscillatory activity in PD or dystonia patients usually cannot be contrasted with healthy human subjects, due to the invasive nature of (sub)cortical electrode placements. Occasional invasive recordings carried out on patients with functional movement disorders (Kobayashi et al., 2011; Ramos et al., 2015) or epilepsy (Aulicka et al., 2014; Kondylis et al., 2016) have demonstrated that certain neurophysiological features, previously only demonstrated on PD or dystonia, are not restricted to such organic movement disorders. Recently, prominent beta oscillations were described in the dorso-lateral STN of patients with obsessive compulsive disorder (Wojtecki et al., 2017; Rappel et al., 2018). For those reasons, while experiments that compare either PD or dystonia patients before and after treatment are helpful to explore the effect of treatment on LF and beta oscillations on the parkinsonian/ dystonic CBGTC network, they cannot determine whether such oscillations were increased on the first place. Given the lack of healthy controls as reference, the modulatory effect of both DBS and medication on the oscillatory activity could be interpreted as either a suppression of aberrantly increased oscillations, or a compensatory mechanism, in which physiological activity is suppressed, in order to counterbalance disturbances located elsewhere in the network. Therefore, there is a theoretical possibility that prominent oscillatory activity would also be present in healthy control subjects, and that either DBS or medication could induce a similar desynchronization on both the healthy and parkinsonian/ dystonic CBGTC network.

1.3. Comparison of oscillatory patterns between dystonia and PD

A feasible alternative for the lack of healthy controls in CBGTC oscillation research is the use of diseases with different phenotypes as controls. Thanks to the target duality mentioned before, dystonia and PD patients seem to be the best control for each other, since it is possible to perform invasive recordings from the same target for both diseases and under similar conditions. Although the comparison of oscillatory activity between two different diseases cannot reveal whether prominent oscillations are pathological, the presence of increased LF or beta activity in only one of the diseases, when all the other factors are similar, could indicate that such oscillations

are indeed exaggerated in patients with that disease. This knowledge, together with the modulation caused by treatment, could provide a better estimation to determine in which degree the presence of an increment in the LF or beta oscillatory activity is considered to be pathological.

1.4. Limitations of comparison studies

A modest number of studies have directly compared CBGTC structures between PD and dystonia patients. However, numerous factors considerably limit the generalizability of the findings encountered on individual articles. One of the major constraints regarding neurophysiological studies comparing PD and dystonia, is the small number of subjects included on each study (Table 1). This low number of subjects could be explained by the fact that the preferred DBS targets in PD and dystonia are different. This preference makes it difficult to plan prospective studies in which PD and dystonia are implanted in the same structure. Next to this, neurophysiological changes can be studied at different spatiotemporal levels. Besides the recording of synchronous populations of neurons by means of LFPs or ECoG, neuronal activity can be explored using micro-electrode recordings (MER), which collect spiking activity of single neurons. Furthermore, from these two signal types, a plethora of neurophysiological characteristics can be studied in which the spike rate for the MER and power spectral density (PSD) estimates for LFP or ECoG recordings are the most well studied. In order to address more widespread variations in CBGTC loops, simultaneous or additional cortical recordings can be made invasively (de Hemptinne et al., 2015) or non-invasively (Oswal et al., 2016). From an analysis perspective, local activity in interaction with other regions in the CBGTC network can be studied, using coherence analyses or phase-amplitude coupling (PAC, (de Hemptinne et al., 2015)), among others. The pipelines to analyze LFPs can vary at different levels of the procedure, from one of the many elements of preprocessing (filtering, standardizing) to the methods of performing the frequency analysis and postprocessing techniques to specifically analyze the frequency bands of interest and their characteristics, together with the units in which the results are expressed (normalized units, log-power, etc.). This interaction of parameters can contribute to a greater or lesser extent to the divergence of results. Moreover, neurophysiological changes can be studied in different experimental conditions; examples of these are rest, tonic contraction, pinch and start-stop paradigms, all requiring different motor programs. Given these various approaches at different stages of the scientific process, the a priori chance of two studies using a similar approach is rather low, which makes it difficult to replicate findings (Errington et al., 2014).

First Author	Year of Publication	Recording Site	Method	N hemispheres PD	N hemispheres dystonia	Status
Silberstein et al.	2003	GPI	LFP	19	17	Included
Crowell et al.	2012	M1	ECoG	10	10	Included
Neumann et al.	2012	STN	LFP	10?	2	Excluded. No measures of dispersion reported for PD patients.
Miocinovic et al.	2015	M1	ECoG	14	22 (8 ARM Dys) (14 No ARM Dys)	Included
Geng et al.	2017	STN	LFP	22	16	Included
Wang et al.	2016	STN	LFP	28	12	Included
Wang et al.	2018	GPI	LFP	20	14	Included
		M1	ECoG	13	12	
Piña-Fuentes et al.	2018	GPI	LFP	8	14	Included
Lofredi et al.	2018	GPI	LFP	10	10	Included
Starr et al.	2005	GPI	MER	101	302	Included in MER analysis.
Tang et al.	2007	GPI	MER	168	173	Included in MER analysis.
Weinberger et al.	2012	GPI	LFP + MER	94	273	Excluded. Peaks were not divided into LF or beta; mean LFP-PSD estimates not reported.

Table 1. Summary of articles directly comparing patients with Parkinson’s disease (PD) and dystonia using invasive recordings. GPI = internal part of the globus pallidus, M1 = primary motor cortex, STN = subthalamic nucleus, LFP = local field potential, MER = micro electrode recording, ECoG = electrocorticography, N = number.

In summary, information regarding the comparison of the oscillatory activity in dystonia and PD patients is scarce, and it is difficult to draw general conclusion from individual articles, due to all the constraints aforementioned. For that reason, the objective of the following meta-analysis is to quantitatively summarize the findings of articles that compared the oscillatory activity in dystonia and PD patients, in the LF and beta range, while taking into account the limiting factors mentioned above in the analysis, in order to provide high-level evidence that could help to determine whether LF and beta oscillations are increased in the dystonic and parkinsonian CBGTC networks, respectively. We aimed to control for all the factors mentioned above with our inclusion criteria and methods mentioned on the next section.

2. Methods

A PubMed search was performed until end November 2018 on all invasive studies reporting local oscillatory activity in recordings from dystonia and PD patients, using the terms ((("dystonic disorders"[MeSH Terms] OR ("dystonic"[All Fields] AND "disorders" [All Fields]) OR "dystonic disorders"[All Fields] OR "dystonia"[All Fields] OR "dystonia"[MeSH Terms]) AND ("parkinson disease" [MeSH Terms] OR ("parkinson"[All Fields] AND "disease"[All Fields]) OR "parkinson disease"[All Fields] OR ("parkinson's"[All Fields] AND "disease"[All Fields]) OR "parkinson's disease"[All Fields])) AND (local[All Fields] AND field[All Fields] AND potentials[All Fields])).

2.1. Our inclusion criteria were:

- Articles directly comparing oscillatory activity in PD and dystonia from the same anatomical structure. By including PD and dystonia recordings coming from the same center, we ensured that both data were subjected to the same techniques used for data acquisition and signal (pre)processing.
- Articles including recordings from the GPi, STN or M1. N.B.: studies comparing other CBGTC structures are seldom reported.
- Articles reporting oscillatory activity in the rest state and without medication nor stimulation. This condition is the most common for all the recordings. Other conditions often diverge across studies.

2.2. Our exclusion criterium was:

- Articles not reporting sufficient information to perform the meta-analysis (e.g. not reporting measures of dispersion or results not divided into LF and beta frequencies).

Our search resulted in 32 articles from 2003 to 2018, from which twelve studies met the inclusion criteria. (Silberstein et al., 2003; Starr et al., 2005; Tang et al., 2007; Crowell et al., 2012; Weinberger et al., 2012; Neumann et al., 2012; Miocinovic et al., 2015; Wang et al., 2018, 2016; Geng et al., 2017; Lofredi et al., 2018; Pina-Fuentes et al., 2019) Of these twelve studies, two studies met the exclusion criterium and therefore were not included in the analysis (Table 1). Of these 10 studies, 2 studies only reported MER data. As MER data uses a different outcome measure (count of single-unit peaks), we will focus this meta-analysis on local oscillatory power (LFPs or ECoG), in order to harmonize the results. A small analysis of MER data can be found in Supplementary Figs. 1–2. Therefore, eight studies were used to perform the meta-analysis. Recordings from 127 dystonia-, and 144 PD-patient hemispheres were included in the meta-analysis. Spectral power was reported at different structures: the STN ($n = 2$ articles), the GPi ($n = 4$ articles) and the M1 ($n = 3$ articles).

2.3. Data approximation

Data reported in the articles, as either power spectral density (PSD) estimates or box plots/scatter plots, were approximated, using a reverse engineering software (WebPlotDigitizer, Texas, USA (Rohatgi (2011))). This allowed us to determine the mean/median power across the LF-beta range and a measure of dispersion (e.g. standard deviation (SD), standard error of the mean (SEM) or interquartile range (IQR) and minimum and maximum) from the plots presented. All subsequent calculations were performed in MATLAB (ver. 2018a, Mathworks, Inc. Natick, 151 Massachusetts, USA). Data obtained from the approximation of each PSD estimate were interpolated, in order to obtain the values for the mean power $\pm$ SD/SEM in the range of 4–30 Hz, in frequency bins of 0.25 Hz, for both conditions. SEM were transformed to SD by multiplying the SEM by the square root of the sample size. Data expressed as mean $\pm$ SD of log-transformed units (mean(Log) and SD(Log)) were transformed back to their raw scales by using the estimation methods proposed by Higgins et al. (Higgins et al., 2008). If PSD estimates were approximated, the average mean power for the LF and beta band was obtained; average SDs were obtained by calculating the square root of the averaged variance (SD^2). When box plots were employed in the articles, means and SD were approximated using the sample size, median, IQR, and minimum and maximum reported, according to the methods developed by Wan et al. (Wan et al., 2014). When power data reported was divided into frequency bands, the mean $\pm$ SD

LF power was obtained by averaging the mean $\pm$ SD power of theta and alpha bands, weighted according to the number of Hz included on each band; a similar procedure was performed to calculate the mean $\pm$ SD beta power from both low and high mean $\pm$ SD beta power.

2.4. Statistical analysis

Means of individual studies could not be grouped, since each article used different units to express PSD values, e.g. percentage of total power, normalized power (arbitrary units, a.u.), or log power (mV^2/Hz). For this reason, values of average LF power in the different studies in PD were expressed as a fraction relative to dystonia (e.g. an average LF value of 2.2 a.u. in dystonia and 1.5 in PD would give a ratio of 0.68). Similarly, this was performed for average beta power in dystonia relative to PD (e.g. an average beta value of 1.2 a.u. in PD and 0.7 a.u. in dystonia would give a ratio of 0.58). Ratios can be grouped, since they are unitless, while keeping the proportion of power between PD and dystonia constant. Ratios were Log-transformed (LogRatio) for further statistical analysis. The variance of LogRatios was approximated by using the delta method described by Friedrich et al. (Friedrich et al., 2008). Statistical analysis was performed using RevMan (v 5.3, Copenhagen, Denmark (The Nordic Cochrane Centre (2014))). An overall estimate using LogRatios was calculated through the generic inverse variance method with a random effects model. The weight of each study was calculated according to the formula ($1/\text{variance of the effect estimate}$). Outcomes were divided in subgroups according to the localization of the recording. Ratios were transformed back to raw scales after the analysis.

3. Results

3.1. LF ratios

The overall ratio was 0.77 for LF oscillations in PD compared to dystonia, $Z = 2.45$, $p = 0.01$, 95% CI [0.63, 0.95] (Fig. 1). Subgroup analyses revealed a strong effect of subcortical structures: GPi LF ratio = 0.61, $Z = 4.96$, $p \leq 0.00001$, 95% CI [0.50, 0.74]; STN LF ratio 0.67, $Z = 2.09$, $p = 0.04$, 95% CI [0.46, 0.98]. No differences in cortical ratios were found, M1 LF ratio 1.02, $Z = 0.51$, $p = 0.61$, 95% CI [0.94, 1.11]. The concordance of results within subgroups was high, with $I^2 = 0\%$ for all structures.

Figure 1. Forest plot summarizing the ratios of low-frequency power in Parkinson's disease in relation to dystonia across the different articles included. LF = low-frequency, GPI = internal part of the globus pallidus, M1 = primary motor cortex, STN = subthalamic nucleus, PD = Parkinson's disease, Dys = Dystonia, SE = standard error, CI = confidence interval.

Figure 2. Forest plot summarizing the ratios of beta power in dystonia in relation to Parkinson's disease across the different articles included. GPI = internal part of the globus pallidus, M1 = primary motor cortex, STN = subthalamic nucleus, PD = Parkinson's disease, Dys = Dystonia, SE = standard error, CI = confidence interval.

3.2. Beta ratios

The overall ratio was 0.72 for beta oscillations in dystonia compared to PD, $Z = 3.56$, $p = 0.0004$, 95% CI [0.60, 0.86] (Fig. 2). Subgroup analyses revealed a strong effect in the GPi: beta ratio = 0.62, $Z = 7.26$, $p \leq 0.00001$, 95% CI [0.55, 0.71], which showed a high concordance within studies, $I^2 = 0\%$. Beta ratio effects in the STN and M1 were not significant, STN beta ratio 0.63, $Z = 0.97$, $p = 0.33$, 95% CI [0.24, 1.61]; M1 beta ratio 0.82, $Z = 1.65$, $p = 0.10$, 95% CI [0.65, 1.04]. The concordance of results within STN and M1 subgroups was low, STN $I^2 = 87\%$, M1 $I^2 = 79\%$.

4. Discussion

Based on the findings of the articles included in this meta-analysis, the distribution of local oscillatory power, observed in the LF-beta range of the CBGTC network, differs between PD and dystonia patients in the resting state, without medication nor stimulation. Resting-state LF oscillatory activity in dystonia patients is increased when compared to PD patients. On the contrary, resting-state beta oscillatory activity is increased in PD patients, when compared to dystonia patients. Subgroup analyses revealed primarily a subcortical predominance of such distribution (GPi and STN).

4.1. Significance of LF oscillations

In this meta-analysis, the presence of LF oscillations was increased in both the resting-state GPi and STN of dystonia patients when compared to PD patients, while the LF oscillatory power in the resting-state M1 was virtually similar between diseases. The high degree of concordance within articles supports a selective role for exaggerated subcortical LF activity in dystonia. However, the functional significance of increased LF oscillations is up to now a topic for debate. Nevertheless, increasing evidence points out toward their relation with a hyperkinetic state. It has been proposed that exaggerated LF oscillations carry a dystonic drive with them, as suggested by studies showing an increased coherence in the LF range between GPi and electromyography (EMG) of dystonic muscles (Sharott et al., 2008), or between dystonic muscles (EMG-EMG) (Tijssen et al., 2000). Next to this, such oscillations are increased in both the GPi and STN during the performance of ballistic movements (Singh et al., 2011). While LF oscillations in the dystonic M1 seem not to be exaggerated, an increased coherence in the LF range between the M1 and subcortical structures, such as the GPi (Wang et al., 2018) or the cerebellum (Neumann et al., 2015), possibly indicates that an abnormal regulation of downstream flow of prokinetic oscillatory information is present in dystonia. Notwithstanding the evidence accumulated, certain difficulties need to be addressed in order to unify this theory. Firstly, it is important to point out that a potential confounding factor is the fact that diverse forms of dystonia (e.g. postural

deformities, OFF-dystonia, striatal toe, torticollis, among others) could be present in the phenotype of unmedicated PD patients (Doherty et al., 2011), potentially incrementing the LF power in PD, if present at the moment of the recordings. This is relevant when using PD as a control for comparisons with dystonia recordings, since these features might be not actively investigated during the clinical examination and possibly not reported on the information of the patients that were included on the studies. However, even with this confounding factor against them, subcortical LF oscillations were found to be more prominent in dystonia. Secondly, the range of LF oscillations (4–12 Hz) does not coincide with those of the typical frequency bands used in electroencephalography (EEG), which divides LF into theta and alpha activity. This could lead to heterogeneity when reporting findings on the LF range. Whether there is a relevant functional division between theta and alpha bands in dystonia is yet unknown. Lastly, the exact role of LF oscillations on each dystonia subtype is still unclear. This is especially important as dystonia is an etiologically heterogeneous disorder in which various (genetic) types respond differently to DBS (Fox and Alterman 2015). It was not possible to control for this factor in the present meta-analysis, due to the inclusion of mixed types of dystonia in the studies approached.

4.2. Significance of beta oscillations

An overall agreement across studies included in this meta-analysis, indicate that beta oscillations are increased in the GPi of PD patients when compared to dystonia patients. On the other hand, articles showed a high degree of heterogeneity among them, when reporting results in the STN and M1. From the two included articles reporting STN-LFPs, a maximum degree of homogeneity in their results regarding LF power was observed; however, they showed contrasting results in the beta range. One article showed increased beta power in PD (Geng et al., 2017), whereas the other showed no differences in the beta range between diseases (Wang et al., 2016). However, while the presence of exaggerated beta oscillations in the dystonic STN is in theory physically possible, the role of other potential confounding factors might have contributed to discrepancy of results across studies. In the study of Geng et al., only one of the eight dystonia patients included received aripiprazole/clonazepam during the recordings. This patient showed an increment on beta oscillations, compared with the OFF-medication dystonia patients. In contrast, 11 of the 12 patients included in the Wang et al. study were regularly treated with either anticholinergics or benzodiazepines. Although medication was stopped at least 12 h prior the measurements in this study, it is well known that many benzodiazepines possess a long half-life (being 15 h for alprazolam, 10–20 h for Lorazepam, and 30–40 h for clonazepam (Mihic et al., 2017)). This is relevant, as it has been observed that benzodiazepines produce an increment in beta activity, and a reduction of theta

activity in the human motor system (Jensen et al., 2005). Therefore, it is possible that the increment in beta activity observed in those dystonia patients could be due to a potential incomplete washout. A third article ((Neumann et al., 2012), excluded from the analysis) also showed increased beta power in STN recordings of PD patients when compared to dystonia. Furthermore, a recent study found that beta oscillations were significantly increased in the ventromedial STN of PD patients, when compared to OCD patients (Rappel et al., 2018). In the aforementioned study, beta oscillations also seemed to be increased in the dorsolateral STN of PD patients in comparison to OCD patients. However, this difference was not significant, probably due to the use of Bonferroni correction in the PSD estimates, as it tends to be hyper-conservative when tests are correlated (consecutive frequency bins) (Conneely and Boehnke 2007). Therefore, an overall increased beta power in the parkinsonian STN cannot be confirmed or excluded with the data available. Regarding the pooled ratios of beta power in the resting-state M1, they showed no significant differences between diseases. Nevertheless, slight, but significantly increased beta power in the parkinsonian M1 could be appreciated in two of the three articles included. It could be possible that beta oscillations in cortical PD motor structures slowly become increased as the progression of the disease gradually affects cortical structures (Braak et al., 1996). Another option is that, similarly to LF oscillations in the M1, the interaction of beta oscillations with either other frequency bands, or in the information flow to subcortical structures in terms of coherence, could play a bigger role in the pathophysiology of the disease on the M1, rather than the increase of beta power itself. The clinical significance of beta oscillations has been more widely described than that of LF oscillations. The physiological role of beta oscillations in the suppression of voluntary movements has been broadly described on EEG studies with healthy subjects (Heinrichs-Graham et al., 2017). Exaggerated beta oscillations are a well-known phenomenon in the PD motor system (Brown and Marsden 1999). Nevertheless, there is an ongoing debate whether these are causative or an epiphenomenon of pathological features. Evidence of their causative role comes from studies indicating that bradykinesia is exaggerated if DBS is applied with stimulation frequencies in the beta range (Eusebio et al., 2008). The same holds when the motor cortex is stimulated with stimulation frequencies in the beta range using transient alternating current stimulation (Joundi et al., 2012). Recently, it has been shown that beta oscillations present a bursting behavior (Tinkhauser et al., 2017), and the amplitude of such bursts is higher in PD when compared to dystonia (Wang et al., 2018; Pina-Fuentes et al., 2019). Given that higher beta power was found in the PSD estimates of PD, in comparison with those of dystonia, higher burst amplitudes are expected in PD, as amplitude and power are representations of the same phenomenon, in either the time or the frequency domain (i.e. a high beta

peak in the PSD estimates of a signal is expected to translate into high amplitudes of such signal filtered around the frequency of the peak). However, the fact that burst amplitudes are consistently increased in PD, indicates that the power difference found between PD and dystonia is evenly distributed over time, which support the role of increased beta oscillations in the maintenance of a continuous hypokinetic state.

4.3. Symptom-related oscillatory profile

While particular oscillatory patterns for dystonia and PD have been shown in this meta-analysis, certain studies have suggested that abnormal oscillations could be primarily linked to certain features of each disease, rather than the whole pathology. Increased LF oscillations in the GPi and LF coherence with other CBGTC structures have been associated with phasic components of dystonia (Liu et al., 2006; Barow et al., 2014), whereas tonic components have been associated with coherence in the delta (0–4 Hz) range (Chung and Huh 2016). Similarly, beta oscillations in the parkinsonian STN have been correlated with motor symptoms (Neumann et al., 2016), especially bradykinesia and rigidity, but not tremor (Beudel et al., 2017). However, the presence of increased beta oscillations in bradykinetic-rigid syndromes other than PD is yet to be explored.

4.4. Implications for adaptive DBS systems

Currently, adaptive DBS systems are being explored, which could employ either beta amplitude in PD (Little et al., 2016; Piña-Fuentes et al., 2017; Arlotti et al., 2018) or LF amplitude in dystonia (Neumann et al., 2017; Pina-Fuentes et al., 2018, 2019) as physiomarkers in closed-loop algorithms. However, as shown in the articles included in this meta-analysis, LF and beta oscillations are present, to a greater or lesser extent, in both PD and dystonia networks, which is probably due to the physiological role that both oscillations have in the regulation of movement. Therefore, it is up to now not yet established in which degree LF and beta activity are considered to be pathologically increased, and to which extent stimulation should be aimed to suppress them. This is relevant for aDBS systems, as currently an arbitrary threshold has been used to determine the moments in which oscillations are considered to be increased, and subsequently triggering stimulation (Little et al., 2013; Arlotti et al., 2016). In this meta-analysis, LF power in PD was consistently found to be roughly two thirds the amount found in dystonia, in both the GPi and the STN. Similarly, beta power in dystonia was found to be roughly two thirds the amount found in PD in the GPi. These findings could provide a rationale to explore stimulation paradigms in which a threshold for stimulation could be set at two thirds of the maximum LF or beta activity, in dystonia and PD, respectively.

4.5. Limitations

Although we strived to homogenize the data included on the meta-analysis, potential sources of bias have to be pointed out. First, data had to be extrapolated from PSD estimates or plots, since direct descriptions of means $\pm$ SDs of LF or beta power were not reported in the articles. Second, some articles use measures of central tendency/dispersion other than mean $\pm$ SD to report differences in local oscillatory activity between PD and dystonia, and outcomes were presented on different power units. For this reason, means and/or SDs had to be often estimated from other measures of central tendency/dispersion. This may have led to both over- and underestimations of the differences between PD and dystonia. Nevertheless, as information had to be extrapolated for all articles, individual data was exposed homogenously to this bias. Next to this, ratios are robust parameters, which allow to maintain the power relation between conditions relatively constant, and the use of random-effects on the analysis took into account aleatory variations on the data. Furthermore, although a publication bias towards positive results could be present in the literature, articles with negative findings were also included. Moreover, recordings sites were different among studies. However, each structure belonged to the core motor network of the CBGTC loop (motor cortex, STN or GPi), and the statistical analysis was divided into sub-groups according to the anatomical structure recorded. Given the heterogeneity of the experimental paradigms, only rest recordings could be included. The use of different tasks or comparison methods, such as coherence, could possibly lead to more insight. Finally, the pathological role of prominent oscillations can only be inferred, since we only described studies directly comparing PD and dystonia, in the absence of controls.

4.6. Future perspectives

Since currently data comparison of PD and dystonia patients from similar subcortical structures faces many difficulties, several approaches can be explored to study the disease-related neurophysiological characteristics beyond PSD estimates. One exciting possibility is the use of modelling basal ganglia modulation and the effects of DBS (Guo et al., 2013). Also, following other fields within neurosciences (e.g. fMRI), anonymous data sharing in uniform reporting styles might be useful (Poldrack and Gorgolewski 2017). Furthermore, the development of implantable DBS systems that are able to provide chronic recordings will counteract some of the physical limitations that intraoperative recordings currently face (Swann et al., 2018), such as the limited time available for recording, or the necessity of having the electrodes externalized in order to record.

5. Conclusion

The current meta-analysis provides quantitative high-level evidence which confirms that LF are increased in the GPi and STN of dystonia patients, while beta oscillations are increased in the GPi of PD patients. More studies are required to provide a more definite answer regarding increased beta oscillations in the parkinsonian STN.

Relevant conflicts of interests/financial disclosures

None of the authors have potential conflicts of interest to be disclosed.

Funding

The present review/meta-analysis was carried out thanks to public funds received from the Dutch Brain Foundation ('Hersenstichting Nederland') grant number F2015(1)-04, the National Mexican Council of Science and Technology (CONACYT) grant number CVU 652927, and the University of Groningen/University Medical Center Groningen (RuG/UMCG).

Author contributions

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing of the first draft, B. Review and Critique, C. Modification of subsequent versions.

DPF 1BC 2ABC 3BC, JMvD 2C 3B, GD 2C 3B, JvZ 2C 3B, TvL 2C 3B, MT 2C 3B, MB 1ABC, 2AB, 3AC.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clinph.2019.02.015>.

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Appendix A. Supplementary material

Supplementary Figure 1: forest plot summarizing the odds ratios of single-unit low-frequency power peaks in Parkinson's disease in relation to dystonia across the different articles included. LF = low-frequency, GPI = internal part of the globus pallidus, M1 = primary motor cortex, STN = subthalamic nucleus, PD = Parkinson's disease, Dys = Dystonia, CI = confidence interval.

Supplementary Figure 2: forest plot summarizing the odds ratios of single-unit beta power peaks in dystonia in relation to Parkinson's disease across the different articles included. GPI = internal part of the globus pallidus, PD = Parkinson's disease, Dys = Dystonia, CI = confidence interval.

3

The characteristics of pallidal low-frequency and beta bursts could help implementing adaptive brain stimulation in the parkinsonian and dystonic internal globus pallidus

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HIGHLIGHTS

- Oscillatory burst profiles in the resting-state GPi differ between dystonia and PD.
- LF burst amplitude in the GPi is increased in dystonia when compared to PD.
- Beta burst amplitude in the GPi is increased in PD when compared to dystonia.
- Oscillatory LF and beta burst profiles are similar in the parkinsonian GPi and STN.
- First attempt to apply aDBS-GPi in dystonia and PD was feasible and well tolerated.

Abstract

Introduction: Adaptive deep brain stimulation (aDBS) has been applied in Parkinson's disease (PD), based on the presence of brief high-amplitude beta (13–35 Hz) oscillation bursts in the subthalamic nucleus (STN), which correlate with symptom severity. Analogously, average low-frequency (LF) oscillatory power (4–12 Hz) in the internal globus pallidus (GPi) correlates with dystonic symptoms and might be a suitable physiomarker for aDBS in dystonia. Characterization of pallidal bursts could facilitate the implementation of aDBS in the GPi of PD and dystonia patients.

Objective and methods: We aimed to describe the bursting behaviour of LF and beta oscillations in a cohort of five GPi-DBS PD patients and compare their amplitude and length with those of a cohort of seven GPi-DBS dystonia, and six STN-DBS PD patients (n electrodes = 34). Furthermore, we used the information obtained to set up aDBS and test it in the GPi of both a dystonia and a PD patient (n = 2), using either LF (dystonia) or beta oscillations (PD) as feedback signals.

Results: LF and beta oscillations in the dystonic and parkinsonian GPi occur as phasic, short-lived bursts, similarly to the parkinsonian STN. The amplitude profile of such bursts, however, differed significantly. Dystonia showed higher LF burst amplitudes, while PD presented higher beta burst amplitudes. Burst characteristics in the parkinsonian GPi and STN were similar. Furthermore, aDBS applied in the GPi was feasible and well tolerated in both diseases.

Conclusion: Pallidal LF and beta burst amplitudes have different characteristics in PD and dystonia. The presence of increased burst amplitudes could be employed as feedback for GPi-aDBS.

1. Introduction

The internal part of the globus pallidus (GPi) is currently the preferred target for conventional (continuous) deep brain stimulation (cDBS) in dystonia (Balint and Bhatia, 2014) and one of the two main targets for cDBS in Parkinson's disease (PD), together with the subthalamic nucleus (STN) (Odekerken et al., 2016). In both diseases, patients show a significant improvement after cDBS implantation, being around 30% improved in the Unified PD Rating Scale (UPDRS) part III in PD and demonstrating a motor and disability improvement up to 60% in isolated dystonia (Moro et al., 2017). However, despite its clear clinical benefit, cDBS still has some limitations. cDBS programming can be troublesome and time-consuming, especially in dystonia, in which a visible clinical response is usually delayed for weeks or months, and the overall response across dystonia subtypes to cDBS can be limited and difficult to predict (Picillo et al., 2016). Furthermore, side effects such as dystonia / dyskinesias (in PD), parkinsonism (in dystonia) or dysarthria (in both conditions) may occur (Odekerken et al., 2016; Vidailhet et al., 2013).

With the aim of improving efficacy and limiting side effects, adaptive DBS (aDBS) systems which only stimulate when pathological neural activity and/or clinical symptoms are present are currently being explored (Beudel and Brown, 2016). Preliminary evidence shows that this new DBS technique is at least as efficacious as cDBS (Arlotti et al., 2018; Little et al., 2013; Piña-Fuentes et al., 2017), whereas aDBS may induce fewer side effects and reduce energy consumption (Little et al., 2016; Rosa et al., 2017). In PD, this adaptive form of DBS is based on the level of exaggerated beta (13–35 Hz) oscillations in the STN, which have been correlated with contralateral parkinsonian symptoms (Neumann et al., 2016). Beta oscillations occur in phasic bursts (Little et al., 2013), and the characteristics of those bursts are reactive to treatment response. Specifically, their amplitude and duration positively correlate with clinical symptoms, and a reduction on both parameters is seen after levodopa (Tinkhauser et al., 2017b) and aDBS (Tinkhauser et al., 2017a) (but only a reduction in amplitude in cDBS). Moreover, the coefficient of variation (CoV) of beta oscillations—an indicator of the variability of a signal over time—is negatively correlated with the severity of parkinsonian symptoms, and increases after levodopa administration (Little et al., 2012). Such dynamic properties of beta oscillations have made it possible to implement them as physiomarker in aDBS (Arlotti et al., 2018). These exaggerated oscillations are not only restricted to the STN, but also prominently present in the GPi of PD patients (Jimenez-Shahed et al., 2016; Silberstein et al., 2003; Tsiokos et al., 2017) and they are synchronized between nuclei when measured simultaneously

(Brown et al., 2001). This phenomenon indicates a general pathological oscillatory status within the basal ganglia circuitry (Chiken and Nambu, 2016).

Analogously, a prominent pallidal low-frequency (LF; $\pm 4\text{--}12$ Hz) oscillatory activity has been reported across many dystonia subtypes (Piña-Fuentes et al., 2018). Early studies revealed that an increased musculo-muscular dystonic drive in the theta (4–7 Hz) band was present in cervical dystonia (Tijssen et al., 2000), as well as a correlation of LF oscillations in the GPi with multi-unit neuronal activity and dystonic electromyogram (EMG) periods (Chen et al., 2006; Chu Chen et al., 2006). LF oscillations in the GPi have been shown to be especially coherent with EMG phasic dystonic components (Liu et al., 2006). Prominent LF oscillations in dystonia have been also found at a single-unit level of GPi microelectrode recordings (Starr et al., 2005). Further evidence for a role of GPi-LF power in dystonia comes from EMG and intra-operative local field potential (LFP) recordings, which showed that LF power and coherence are suppressed by DBS and that their rate of suppression correlates with the improvement of the phasic components of dystonia (Barow et al., 2014; Foncke et al., 2007; Neumann et al., 2017; Wang et al., 2018). In contrast, evidence of prominent LF oscillations in the STN of dystonia patients is scarce, mostly due to the fact that the GPi—and not the STN, is the preferred target for DBS in dystonia. From the two research groups that reported STN-LFPs in dystonia, one found more prominent STN-LF oscillations in dystonia compared to PD (Geng et al., 2017), while the other did not (Wang et al., 2016).

Oscillatory LF and beta pallidal power has been mostly determined by means of power spectral density (PSD) estimates. As PSD estimates only represent the average oscillatory power, understanding the properties of the parkinsonian and dystonic GPi bursts could provide further evidence of the behavior of oscillatory networks over time on each disease and allow aDBS algorithms to be implemented also in the GPi according to the physiomarker selected. In this study, we aimed to compare the burst characteristics of the dystonic and parkinsonian GPi, and the parkinsonian GPi versus the parkinsonian STN. This was performed with the goal of determining similarities or differences between diseases, or between different nuclei in the same disease. In addition, as a proof of principle, we tested aDBS in the GPi of both a dystonia and a PD patient.

Pt	Age	Sex	PD type	Disease duration (y)	Type of surgery	ON/OFF UPDRS PART III	Most affected side	Medication	Medical history of dystonia
PD-GPi 1	65	M	Akinetic-Rigid	25	Battery replacement		Right	Levodopa, amantadine 1200 mg LDED	No
PD-GPi 2	54	M	Akinetic-Rigid	8	New implantation	38/12	Left	Levodopa, entacapone 750 mg LDED	Yes. Peak-dose dystonia
PD-GPi 3	64	F	Akinetic-Rigid	23	Battery replacement		Left	Duodopa, amantadine 1759 mg LDED	Yes. Dystonic hand.
PD-GPi 4	64	M	Akinetic-Rigid	11	New implantation	29/11	Right	Levodopa, ropinirole, amantadine 1190 mg LDED	Yes. Cervical dystonia
PD-GPi 5 (aDBS)	58	F	Tremor	14	Battery replacement		Right	Levodopa, pramipexole, amantadine 1175 mg LDED	Yes (early morning dystonia)
PD-STN 1	71	F	Akinetic-Rigid	8	New implantation	31/11	Left	Levodopa, pramipexole 844 mg LDED	No
PD-STN 2	73	M	Akinetic-Rigid	17	New implantation	57/40	Right	Levodopa, apomorphine 2569 mg LDED	Yes. Biphasic dystonia
PD-STN 3	70	M	Akinetic-Rigid	10	New implantation	37/17	Right	Levodopa, ropinirole 1098 LDED	Yes (big toe)
PD-STN 4	47	F	Akinetic-Rigid	8	New implantation	38/14	Right	Levodopa, amantadine, apomorphine 651 mg LDED	No
PD-STN 5	55	M	Tremor	5	New implantation	46/20	Right	Levodopa, pramipexole, apomorphine 1808 mg LDED	Yes (torticollis)
PD-STN 6	59	F	Akinetic-Rigid	10	New implantation	19/6	Right	Levodopa, rotigotine, selegiline 1710 mg LDED	No

Pt.	Age	Sex	Dystonia type	Disease duration (y)	BFMDRS PRE/ POST†	TWSTRS PRE/ POST†	Etiology	Medication	Clinical presence of phasic dystonia
Dys- GPI 1	47	M	Generalized (secondary) + spastic hemiparesis	11	New 49/53 implantation		Prob. Perinatal hypoxia	Lorazepam	Yes. Dystonic tremor
Dys- GPI 2	52	M	Segmental dystonia (torticollis)	3	New 23/14.25 implantation		–	Clonazepam	Yes. Jerks, dystonic tremor. Improvement with Sensory trick.
Dys- GPI 3	52	F	Segmental dystonia (Myoclonus-dystonia)	33	New 25.25/12 implantation	22.5/17.5	–	Propranolol, zolpidem	Yes. Improvement with sensory trick
Dys- GPI 4	63	M	Cervical dystonia	20	New 19.5/11.25 implantation	16.5/13.5	–	Clonazepam	Yes
Dys- GPI 5	63	M	Segmental dystonia (torticollis and oromandibular) + Holmes tremor	63	New 13.75/5 implantation	20/8.5	Prob. Perinatal hypoxia	Clonazepam	Yes
Dys- GPI 6	65	F	Segmental dystonia (torticollis)	12	New 15.25/12 implantation	22/13	–	–	Yes, dystonic tremor
Dys- GPI 7 (aDBS)	65	F	Blepharospasm and oromandibular dystonia (Meige's syndrome)	9	Battery replacement		–	Botulinum toxin every 10 weeks	Yes

Table 1. Clinical information of PD and dystonia patients. Pt = patient, PD = Parkinson's disease, Dys = dystonia, GPI = internal globus pallidus, STN = subthalamic nucleus M = male, F = female, y = years, aDBS = adaptive deep brain stimulation, UPDRS = Unified Parkinson's Disease Rating Scale, LDED = levodopa daily equivalent dose, DBS = deep brain stimulation, R = right, L = left. †Clinical score after 1 year of DBS implantation.

2. Materials & methods

2.1. Patients

Eleven patients with PD and seven patients with dystonia who underwent either DBS placement or battery replacement surgery in the University Medical Center Groningen, the Netherlands, participated in this study (Table 1). All patients gave written informed consent to the study protocol, which was approved by the local ethical committee. Five PD patients (8 electrodes) and all dystonia patients (14 electrodes) were measured in the GPi, whereas six PD patients (12 electrodes) were measured in the STN. Either dopaminergic or anti-dystonic medication were suspended for least 12 h prior to the measurements.

2.2. Resting state recordings

2.2.1. Data acquisition

Intraoperative LFPs were bilaterally recorded from two quadripolar DBS electrodes (Medtronic lead model 3387/3389), while patients were in a supine resting state for approximately 90 s, using a sampling rate of 1000 Hz, except in two GPi-PD patients in which the recordings were unilateral (i.e. the first patient had only one side implanted in the GPi and a technical problem with the second patient caused that no signal could be registered on one of the electrodes). Recordings were initially performed either using a monopolar montage, and nasion-referenced using a EEG/PSG headbox, (SleepRT, Rumst, Belgium), or a bipolar montage, using contacts 0–2 and 1–3 for each DBS lead (Spike2 Version 8, Cambridge Electronic Design, Cambridge, United Kingdom). Signals were amplified, and bandpass filtered at 1–500 Hz (BrainRT™ software) for monopolar recordings and 3–37 Hz for bipolar recordings.

2.2.2. Signal processing

LFPs were analyzed offline using MATLAB (ver. 2018a, Mathworks, Inc. Natick, Massachusetts, USA) and FieldTrip toolbox (Donders Center for Cognitive Neuroimaging, University Nijmegen, Nijmegen, the Netherlands). Monopolar channels were filtered (band-pass at 4–35 Hz) and visually inspected, in order to select the largest segment without artifacts. Segments of 45 s were selected for further analysis for each channel. Monopolar LFPs were re-referenced using a bipolar montage. Remaining jump (~0–2 per recording) and electrocardiographic (ECG, 1 patient) artifacts were suppressed by means of a wavelet denoising filter (Taswell, 2000) (example shown in Supplementary Fig. 1). Signals were passed through a denoising filter with a sym4 wavelet, using a Bayes method with 10 levels and a soft (jump) or hard (ECG) threshold, with subsequent subtraction of the result from the original

signal. Artifact suppression (instead of rejection) was necessary, as continuity of the recording is essential for burst analysis. Cutting out remaining artifacts and attaching the rest of the recording would have induced artificial waveforms and broken such continuity. Additionally, subharmonic powerline noise at 24 Hz was suppressed by averaging the power of adjacent frequency bands using a symmetric nearest neighbor filter. Each bipolar channel was normalized to its root mean square (RMS) value to account for differences in voltage gains, and amplitude was expressed as arbitrary units (a.u.).

2.2.3. Power spectral density (PSD)

Individual PSD estimates were obtained using Welch's method with segments of 2000 discrete Fourier transform points and 50% overlap, and smoothed using a moving average filter. The channel per hemisphere that presented the highest combined LF-beta power (highest area under the 4–35 Hz band calculated by integration using a trapezoidal method) was selected for further analysis. The resulting PSD estimates for each group were selected for statistical analysis, using the values of PSD bins of 0.5 Hz between 4 and 35 Hz (Table 2).

2.2.4. Coefficient of variation (CoV)

To obtain the CoV of each bipolar channel, a continuous wavelet transformation was performed on the selected LFPs using Morlet wavelets, with a sampling frequency of 1000 Hz to perform the appropriate scale-to-frequency conversions (45 s = 45000 values per frequency bin and 140 scaled frequency bins). Afterwards, the CoV was calculated by dividing the standard deviation (SD) of each frequency bin over the mean value of the corresponding bin. CoV values were averaged in four frequency bands (theta 4–8 Hz; alpha 8–12 Hz; low-beta 13–20 Hz; and high beta 21–30 Hz) and used for statistical analysis.

2.2.5. Burst analyses

Normalized bipolar LFPs were re-filtered around the highest peak ± 3 Hz in the LF and beta range. If the peak was < 7 Hz, the LFP was bandpass-filtered around 7 Hz. Also, peaks at the edge of the LF/ beta transition were allowed to include frequencies of the opposite band only if a peak of the opposite band was not included on the ± 3 Hz range. This resulted in two peak-filtered LFPs per bipolar LFP processed, one around the low-frequency peak and one around the beta peak. As each filtered LFP contained amplitude values oscillating around zero (both positive and negative), the amplitude envelope of the filtered signal was calculated, which depicts the overall magnitude (absolute values) of the oscillatory activity. The amplitude envelope of each filtered

LFP was obtained by calculating the modulus of the analytical signal after applying a Hilbert transformation to the filtered LFP (68 amplitude envelopes in total) (Fig. 1).

Bursts were calculated for every amplitude envelope by selecting a percentile value of the total envelope as a threshold, according to Tinkhauser et al., 2017a, 2017b (50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th, and 90th percentile); individual bursts per amplitude envelope were then defined as the amount of time that the amplitude envelope remained above the selected threshold, from the moment the amplitude exceeded the critical value until the amplitude went down below such value. Burst amplitude was calculated by subtracting the maximum amplitude of every burst to the critical value of the threshold selected. Burst length was calculated as the amount of time each individual burst lasted, measured in milliseconds. Burst duration and amplitude were further divided in 9 arbitrary categories of equal intervals per condition (< 0.2 to ≥ 0.16 a.u. in steps of 0.2 a.u. for LF amplitude, < 0.1 to ≥ 0.8 a.u. in steps of 0.1 a.u. for beta amplitude, and 100 to ≥ 500 ms in steps of 50 ms for burst duration), in order to visualize progressive transitions between low and high values. The amount of bursts present in each category were further expressed as percentages of the total amount of bursts of each amplitude envelope. Moreover, the total amount of bursts from the Dystonia-GPi and PD-GPi amplitude envelopes were pooled and divided into quartiles. Each burst was then assigned into an amplitude quartile and a length quartile. The same procedure was repeated for the PD-GPi and PD-STN bursts.

2.3. aDBS recordings

2.3.1. Data acquisition aDBS

Additionally, aDBS was tested on both the last Dystonia-GPi and PD-GPi patients (Dys-GPi7 and PD-GPi5). Bilateral recordings were performed using a custom-made amplifier (Little et al., 2016) and script, either from the contacts 0–2 or 1–3, while stimulation was administered using contacts 1 or 2, respectively. Three conditions — namely no stimulation (NoStim), cDBS and aDBS, were applied while the patient was in a supine resting state, at a frequency of 135 Hz and with a pulse width of 60 μ s. Prior to the trials, a brief (± 30 s) recording was performed from both the upper and lower contact pairs, with the LFPs bandpass filtered at 3–37 Hz. For each contact, either the low-frequency (dystonia) or beta (PD) spectral peak were obtained and used to set the central frequency for online filtering ± 3 Hz (Fig. 2). Amplitude envelopes were obtained from the filtered LFPs, and a threshold was defined around ~50–60% of the total amplitude. Stimulation was switched on every time a burst was detected, and stimulation lasted until the burst ended. A ramping period of 250 ms was used

Patient	Side	Contact selected	Highest LF peak (Hz)	Highest beta peak (Hz)
PD-GPi01	Right	0-2	10.5	18.5
	Left	0-2	7	14
PD-GPi02	Left	1-3	9	18
PD-GPi03	Right	0-2	5.5	28.5
PD-GPi04	Right	1-3	7.5	15
	Left	1-3	7.5	16
PD-GPi05	Right	1-3	8	19.5
	Left	0-2	7	18.5
Mean freq Peak (± SEM)			7.7(0.5)	18.3(2.1)
Dys-GPi01	Right	0-1	11.5	18.5
	Left	2-3	11	16
Dys-GPi02	Right	0-1	5(7)	24
	Left	0-1	5(7)	23
Dys-GPi03	Right	1-2	5(7)	14.5
	Left	1-2	8	15
Dys-GPi04	Right	0-1	6(7)	20
	Left	0-1	12	19
Dys-GPi05	Right	0-1	10	14.5
	Left	2-3	10	18.5
Dys-GPi06	Right	2-3	5.5(7)	19.5

Patient	Side	Contact selected	Highest LF peak (Hz)	Highest beta peak (Hz)
Dys-GPi07	Left	0-1	7.5	22.5
	Right	0-2	10	17
	Left	0-2	10	20.5
Mean freq Peak (± SEM)			8.5(0.7)	18.7(0.8)
PD-STN 01	Right	1-2	11	16
	Left	2-3	12	17.5
PD-STN 02	Right	0-2	8	17.5
	Left	0-2	8	15.5
PD-STN 03	Right	2-3	6(7)	18
	Left	2-3	7	14.5
PD-STN 04	Right	1-2	6.5(7)	27
	Left	1-2	8.5	27
PD-STN 05	Right	0-1	6.5(7)	29
	Left	1-2	6.5(7)	28.5
PD-STN 06	Right	1-2	9.5	19
	Left	2-3	9	17.5
Mean freq Peak (± SEM)			8.7(0.8)	22.6(2.2)

Table 2. Peaks per contact in the low frequency and beta band for the selected bipolar LFPs per hemisphere in dystonia and PD. PD = Parkinson's disease, Dys = dystonia, GPi = internal globus pallidus, STN = subthalamic nucleus, SEM = standard error of the mean, LF = low-frequency, freq = frequency.

Fig. 1. Example of the determination of low-frequency bursts and beta bursts and their relationship with the bursting behavior of the LFP of one dystonia and one PD patient, respectively. A) LFPs filtered around 4–35 Hz. B) LFPs were bandpass filtered around the frequency peak. In this example the left LFP was filtered around ± 7 Hz, and the right peak was filtered around 20 Hz. C) The signal envelope was obtained using the modulus of the Hilbert transformed LFP. The continuous line indicate the median of the amplitude and the dashed line indicates the 75th percentile. D) Burst count D.1) Based on the moments that the power remains above the 75th percentile. D.2) Based on the moments that the power remains above the median.

every time the stimulation was either switched on or off, in order to avoid stimulation-induced capsular/visual responses. In the dystonia patient, aDBS recordings were conducted from each contact combination (2 left, 2 right, total 4), whereas in the PD patient the contacts with the most prominent beta peak per hemisphere were used. Intraoperative recordings lasted approximately 200 s per condition (sampling rate = 1000 Hz), and started with NoStim due to a potential incomplete wash-out effect by stimulation. During the PD trial, a clinical assessment using a short version of the UPDRS (finger tapping, hand movements, pronation-supination, rest tremor and postural tremor) was videotaped on each condition and blindly scored afterwards by a movement disorders specialist. In the Dystonia-GPi patient, we only focused on the presence of possible side effects derived from aDBS, due to the limited intraoperative recording time and the delayed clinical response in dystonia to DBS.

2.3.2. Stimulation fraction adaptive DBS

The total amount of time each aDBS trial lasted was divided into smaller segments (~20 for each recording). For each segment, the total time fraction that the stimulation was ON was determined, and expressed as a stimulation fraction of that segment. The

Fig. 2. Example of the application of adaptive DBS based on low-frequency oscillations in dystonia. Upper row: bipolar local field potential (LFP) derived from the internal part of the Globus Pallidus (GPI) filtered between 3 and 37 Hz. Second row: LFP filtered between the peak in low-frequency oscillations ± 3 Hz (i.e. 10 ± 3 Hz). Third row: average low-frequency amplitude envelope over 400 ms moving average. The red line depicts the threshold determined for providing stimulation, i.e. when the amplitude is exceeding the red line, stimulation is provided. Lower row: Stimulation trigger showing at which moments high-frequency stimulation was provided.

stimulation fraction is directly proportional to the amount of LF or beta amplitude detected (i.e. more amplitude above the threshold equals a higher stimulation fraction).

2.4. Statistical analysis

Statistical comparisons were performed between the Dystonia-GPI and the PD-GPI data, and between the PD-GPI and PD-STN data. All data were visually inspected for normality using Q-Q plots. The PSD estimates obtained with Welch's method were tested using a cluster based two-tailed permutation t-test for independent samples using a Montecarlo approach with 3000 permutations. The alpha level for the cluster threshold was set at 0.05 and an alpha of 0.025 to control the false alarm rate. CoV across frequency bands, burst amplitude and length, and burst amplitude and length

quartiles were tested using a two-way independent ANOVA test (4×2 design for CoV and burst amplitude and length quartiles, and 9×2 design for burst duration and amplitude intervals).

For the aDBS data, correlations between fraction of stimulation and time were conducted using Spearman's rho.

3. Results

No significant differences were shown in the PSD estimates, CoV or burst characteristics between PD-STN and PD-GPi datasets.

3.1. Power spectral density

The PSD estimates of Dystonia-GPi and PD-GPi showed two significantly different regions. (Fig. 3). The first was located at 9–10.5 Hz (cluster $t = 9.7542$, p corrected = 0.0427) and the second at 15.5–20 Hz (cluster $t = -28.4216$, p corrected = 0.0177).

3.2. Coefficient of variation

The CoV in Dystonia-GPi (0.63 ± 0.01) was significantly higher than in PD (0.57 ± 0.01), main effect: $F(1,87) = 4.9834$, $p = 0.0284$ (Fig. 4). Differences in frequency band ($F(3,87) = 0.95$, $p = 0.41$), and interaction between disease and frequency band ($F(3, 87) = 0.42$, $p = 0.73$) were not significant.

3.3. Bursts

In line with previous literature (Tinkhauser et al., 2017a, b), the results of the burst analysis using a 75th-percentile threshold were reported. Statistical results are summarized in Table 3. Complementary burst analyses were performed across different thresholds for validation (50th, 55th, 60th, 65th, 70th, 80th, 85th, and 90th percentile).

Briefly, analyses of amplitude showed significantly higher LF burst amplitudes in Dystonia-GPi (Fig. 5) and significantly higher beta burst amplitudes in PD-GPi (Fig. 6). Dystonic LF bursts were more prominent in the highest LF amplitude quartile, while parkinsonian LF bursts were more prominent in the lowest LF amplitude quartiles. On the other hand, dystonic beta bursts were more prominent in the lowest beta amplitude quartile, while parkinsonian beta bursts were more prominent in the highest beta amplitude quartile. These results remained significant across virtually

Fig. 3. Upper panel Averaged resting state LFP PSD estimates for Dystonia-GPi (blue) and PD-GPi (red) $\pm$ SEM. Shaded areas indicate clusters that significantly differed (Shaded blue for low frequency and shaded red for beta frequency bands). Lower panel. Same comparison for PD-STN and PD-GPi.

Fig. 4. A) Coefficient of variation (CoV, standard deviation (σ)/mean (μ)) of Dystonia-GPi and PD-GPi LFPs across different frequency bands (theta: 4–8 Hz, alpha: 8–12 Hz, low beta: 13–20 Hz, high beta: 21–35 Hz) and B) CoV of PD-STN and PD-GPi LFPs. ** = $p < 0.05$.

all thresholds when tested for both LF bursts and beta bursts. Differences in burst length were significant neither for LF bursts nor beta bursts. A thorough visual description of the different analysis using increasing thresholds can be found in the Supplementary Figs. 2–17.

3.4. Adaptive DBS

LFPs used for feedback in the closed-loop system of aDBS were filtered around 10 ± 3 Hz in Dystonia-GPi and a 18 ± 3 Hz in PD-GPi. The average stimulation voltage was matched up with the therapeutic voltage used in practice, being in dystonia 1 V and 2.3 V in PD. GPi-aDBS was well tolerated in both patients and only elicited transient contractions at supraliminal voltages in the extremities contralateral to the stimulation side. aDBS was provided in such a way that it stimulated on average 34% of the time in the dystonia patient and 26.7% of the time in PD. From the beginning to the end of the aDBS condition, despite fixed thresholds, the stimulation fraction dropped significantly, both in PD ($p = -0.42$, $p = 0.04$) and dystonia ($p = -0.45$, $p = 0.04$)

Fig. 5. Comparison of LF burst characteristics between dystonia-GPi and PD-GPi, and between PD-STN and PD-GPi. Upper row: LF burst amplitude and length divided on intervals. Lower row: LF burst amplitude and length divided on quartiles. Left columns: LF burst amplitude. Right columns: LF burst length. *** Significant effect of the interaction.

Fig. 6. Comparison of beta burst characteristics between dystonia-GPi and PD-GPi, and between PD-STN and PD-GPi. Upper row: beta burst amplitude and length divided on intervals. Lower row: beta burst amplitude and length divided on quartiles. Left columns: beta burst amplitude. Right columns: beta burst length. *** Significant effect of the interaction

Variables	Mean percentage (% ± SEM)	Interaction effect (degrees of freedom)	Significance (p)
LF burst amplitude			
Intervals		F(8,197)=3.5181	0.0008
Quartiles		F(3,87)= 5.8939	0.0011
• Dystonia-GPi	Q1: 20.18 (2.18) Q4: 29.82 (2.76)		
• PD-GPi	Q1: 32.51 (5.50) Q4: 17.81 (4.65)		
Beta burst amplitude			
Intervals		F(8,197)= 2.2185	0.0280
Quartiles		F(3,87)= 4.3854	0.0066
• Dystonia-GPi	Q1: 28.97 (3.75) Q4: 22.08 (2.84)		
• PD-GPi	Q1: 22.08 (1.70) Q4: 31.21 (4.70)		
LF burst length			
Intervals		F(8,197)= 0.2172	0.9875
Quartiles		F(3,87)= 0.0916	0.9645
• Dystonia-GPi	Q1: 24.40(2.16) Q4: 25.35(2.43)		
• PD-GPi	Q1: 24.73 (1.89) Q4: 26.51 (2.52)		
Beta burst length			
Intervals		F(8,197)= 1.2648	0.2645
Quartiles		F(3,87)= 2.5687	0.0601
• Dystonia-GPi	Q1: 25.03 (2.34) Q4: 27.56 (1.90)		
• PD-GPi	Q1: 23.02 (2.08) Q4: 22.14 (2.60)		

Table 3. Statistical results of burst analysis. PD = Parkinson's disease, Dys = dystonia, GPi = internal globus pallidus, LF = low frequency, SEM = standard error of the mean.

(Fig. 7 A/B). The UPDRS subscores for the PD patient were 11 during OFF, 7 under cDBS (37% improvement) and 4 under aDBS (64% improvement). Even though no systematic clinical evaluation in the dystonia aDBS trial was performed, the patient reported a subjective symptom relief under cDBS/aDBS. However, as expected, no visual differences were perceived by the research team at the moment of cDBS/aDBS application, most probably due to the brevity of the recording.

Fig. 7. A. Relation between the fraction of time that stimulation is turned on (Fraction of Stimulation) and the advancement of the application of aDBS in a dystonia-GPi patient, together with its least square line. B. Similar relation in a PD-GPi patient.

4. Discussion

In the present study, we found that the characteristics of pallidal LF and beta bursts are similar between the parkinsonian GPi and STN, whereas significant differences were found in the amplitude/power of LF and beta oscillations between the parkinsonian and the dystonic GPi. These characteristics provided us a rationale to trial aDBS based on the LF burst amplitude in Dystonia-GPi or beta burst amplitude in PD-GPi.

4.1. Significance of disease burst profiles

Similar to other pathophysiological findings in movement disorders (Cilia et al., 2014; Shawky, 2014; Taylor et al., 2016) disease-related increased oscillations are not a sine qua non (Wang et al., 2016). Nevertheless, differences in basal-ganglia oscillatory resting spectral power of PD and dystonia have been consistently described (Geng et al., 2017; Silberstein et al., 2003; Tang et al., 2007; Weinberger et al., 2012). This indicates a more prominent role of certain oscillations in the pathology of movement disorders and further supports their use for aDBS. In this article, we found that those characteristic patterns are mainly caused by differences in burst amplitude. Wang

et al. also found that the main difference between parkinsonian and dystonic pallidal beta bursts is related to their amplitude (Wang et al., 2018). The presence of similar burst characteristics between the parkinsonian GPi and STN further supports this theory. In previous articles (Tinkhauser et al., 2017a, b), the burst characteristics were assessed in response to treatment, either stimulation or levodopa administration, using a common threshold between conditions. This raises the question about which burst characteristics (e.g. burst length) are more dependent to treatment response. During our aDBS trials based on LF and beta amplitude, we found a significant reduction in the fraction of stimulation over time. This indicates that burst length was also decreased (bursts remained above the threshold to trigger stimulation for less time). The clear correlation of amplitude and length (Supplementary Fig. 18) could explain why modifying one of both parameters can have repercussions for the other. Occasionally, brief periods of intense generalized dystonic activity are registered on the bipolar LFP recordings (Chen et al., 2006); this might explain the increased CoV in dystonia, showed in this article. The presence of (less prominent) LF oscillations in PD might be partially explained by the co-occurrence of dystonic symptoms that some PD patients experience (Tolosa and Compta, 2006).

Oscillations within the basal ganglia and cortical structures have been widely related to (patho)physiological motor performance (Lanciego et al., 2012). Beta oscillations are involved in maintaining a resting state, as they decrease during movement performance (Jurkiewicz et al., 2006). Analogously, LF have been associated with movement ideation and performance (Popovych et al., 2016). Therefore, the presence of subcortical exaggerated beta oscillations shown in PD, or LF oscillations in dystonia, might indicate that affected neuronal networks are under a oscillatory state that aberrantly promotes either maintenance of the resting state (hypokinetic) or the performance of movements (hyperkinetic), respectively.

4.2. Rationale for the implementation of aDBS to dystonia

Despite its proven effectiveness, cDBS still presents certain limitations. Given the correlation of LF with phasic dystonic symptoms (Barow et al., 2014; Liu et al., 2006; Neumann et al., 2017), aDBS devices based on LF amplitude might be able to reflect the real-time status of, at a minimum, mobile dystonia. The application of dynamic physiomarkers for DBS in dystonia would allow future devices to dynamically modulate stimulation and possibly, use LF as an adjuvant to facilitate the challenging endeavor of (initial) programming (Picillo et al., 2016). In this study, we demonstrate that the LF have a dynamic behavior over time, coming in the form of short-lived high-amplitude bursts, similarly to their beta counterpart in PD (Tinkhauser et al., 2017a). This fact provides a rationale for an aDBS ON/OFF intermittent approach

based on the setting of an amplitude threshold for LF, in order to selectively modulate high-amplitude bursts.

4.3. Testing aDBS in the GPI

To our knowledge, this is the first time that aDBS has been trialed in the GPI of both a PD and a dystonia patient. The particular presence of beta oscillations in our PD patient and their subsequent modulation by aDBS suggests that adaptive basal ganglia beta modulation might also be achieved from the GPI, in which clinical response was obtained with both cDBS and aDBS. We also showed that aDBS in dystonia based on the amplitude of LF bursts is technically possible and well tolerated in an experimental setting. Even though a visible clinical response could not be demonstrated due to the short duration of the setting, the reduction of LF burst amplitude/duration over time, even when stimulation is not continuous, might illustrate a form of short-term plasticity (Fenoy et al., 2014). At present however, we cannot yet say whether there would be any clinical benefit since a response in dystonia to DBS is usually delayed (Picillo et al., 2016). Long-term recordings (Swann et al., 2018), using an implantable device capable of stimulating and sensing neuronal activity, will be able to evaluate the clinical response of dystonia to aDBS and its ‘neurophysiological fingerprint’ over time.

5. Limitations

The main limitation of this study is the short intraoperative time in which we were able to perform the recordings. In many centers, DBS system implantation (electrodes and battery) takes place on the same day, which allows patients to quickly move forward to the recovery period. This gives a small intraoperative window of opportunity to perform the recordings. We also performed some recordings during battery replacement operations, which have the advantage of bypassing the stun-effect caused by electrode implantation. In light of the fact that recording from healthy subjects is not viable due to the invasive nature of the procedure, the comparison of normalized signals between diseases, or the use of pre-, and post-treatment recordings, seem to be reliable methods to determine which features are related to each disease. Also, signals were normalized to account for voltage differences between electrode positions. The limited number of patients included are mostly due to the intrinsic limitations of this type of intra-operative measurements, especially on interventions on dystonia patients without general anesthesia. However, even with this limitation, a significant difference in burst amplitude was found, which together with the literature available, likely indicates a real difference in amplitude between oscillations of PD and dystonia.

6. Conclusion

This study shows that the characteristics of high-amplitude short-lived bursts are similar between the parkinsonian GPi and STN, but different in the dystonic and parkinsonian GPi, giving the basis for formal trialing of GPi aDBS in dystonia and PD. Also, it indicates that applying aDBS in the GPi of both dystonia and PD using a phasic ON/ OFF burst approach is safe and well tolerated. Chronic studies will be able to determine the clinical efficacy of aDBS in dystonia.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nbd.2018.09.014>.

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Conflict of interest

All the authors declare no conflict of interest.

Funding

This project was publicly funded by the Dutch Brain Foundation ('Hersenstichting Nederland'), the National Mexican Council of Science and Technology (CONACYT) and the University of Groningen/ University Medical Center Groningen (RuG/ UMCG). G.T. is supported by a grant from the Swiss Parkinson Association. S Little is personally supported by the Wellcome Trust (105804/Z/14/Z).

Author contributions

M. Beudel and D. Piña-Fuentes had full access to the data and scripts of the study and take responsibility for the signal processing, statistical analyses and results derived from them.

Concept and design: M Beudel and D Piña-Fuentes.

Data collection, including patient inclusion, preparation for offline analysis and clinical scores of Dys-GPi and PD-STN DBS patients: JC van Zijl.

Chapter 3

Data collection, including patient inclusion and preparation for offline analysis of PD-GPi and aDBS patients: M Beudel and D Piña- Fuentes.

Surgical preparation of the patients and technical support for the measurements: JMC van Dijk and M Oterdoom.

Data (pre)processing, statistical analysis, interpretation and manuscript preparation and subsequent modifications, including visual elements: M Beudel and D Piña- Fuentes.

Critical advice regarding signal processing/statistical analysis: S Little and G Tinkhauser.

Manuscript revision: JMC van Dijk, JC van Zijl, S Little, G Tinkhauser, M Oterdoom MD, MAJ Tijssen.

Project supervision: JMC van Dijk, MAJ Tijssen, M Beudel.

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Supplementary figure 1. Example of artifact subtraction on a real recording using a wavelet denoising filter. A) Plot showing 30 s of a LFP recording. B) Zoomed-in plot showing a segment where a jump artifact is present. A,B 1) Original signal, bandpass filtered at 4–35 Hz. A prominent jump artifact can be observed at second 16. Section B.1 shows that the jump artifact is embedded on physiological activity. A,B 2) The components of the jump artifact were detected using a wavelet denoising filter (filter parameters discussed in Methods). A,B 3) LFP after the artifact has been subtracted from the signal. A,B 4) Comparison of the LFP before and after artifact suppression. Here it can be observed that the artifact was largely suppressed, while the rest of the signal remained intact (shaded blue area). Section B.4 shows that while most of the artifact component was suppressed, physiological oscillatory activity was preserved.

Supplementary figure 2. Comparison of the amplitude of low-frequency bursts in dystonia-GPi versus PD-GPi, using increasing thresholds for the determination of the burst amplitude (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 3. Comparison of the amplitude of low-frequency bursts in dystonia-GPi versus PD-GPi, divided into amplitude quartiles, using increasing thresholds for the determination of the burst amplitude (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 4. Comparison of the length of low-frequency bursts in dystonia-GPi versus PD-GPi, using increasing thresholds for the determination of the burst length (namely bursts above the percentile 50th, 55th., 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 5. Comparison of the length of low-frequency bursts in dystonia-GPi versus PD-GPi, divided into length quartiles, using increasing thresholds for the determination of the burst length (namely bursts above the percentile 50th, 55th., 60th, 65th, 70th, 75th, 80th, 85th and 90th).. *** Significant interaction effect.

Supplementary figure 6. Comparison of the amplitude of low-frequency bursts in PD-STN versus PD-GPi, using increasing thresholds for the determination of the burst amplitude (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 7. Comparison of the amplitude of low-frequency bursts in PD-STN versus PD-GPi, divided into amplitude quartiles, using increasing thresholds for the determination of the burst amplitude (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th).. *** Significant interaction effect.

Supplementary figure 8. Comparison of the length of low-frequency bursts in PD-STN versus PD-GPi, using increasing thresholds for the determination of the burst length (namely bursts above the percentile 50th, 55th., 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 9. Comparison of the length of low-frequency bursts in PD-STN versus PD-GPi, divided into length quartiles, using increasing thresholds for the determination of the burst length (namely bursts above the percentile 50th, 55th., 60th, 65th, 70th, 75th, 80th, 85th and 90th).. *** Significant interaction effect.

Supplementary figure 10. Comparison of the amplitude of beta bursts in dystonia-GPi versus PD-GPi, using increasing thresholds for the determination of the burst amplitude (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 11. Comparison of the amplitude of beta bursts in dystonia-GPi versus PD-GPi, divided into amplitude quartiles, using increasing thresholds for the determination of the burst amplitude (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 12. Comparison of the length of beta bursts in dystonia-GPi versus PD-GPi, using increasing thresholds for the determination of the burst length (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 13. Comparison of the length of beta bursts in dystonia-GPi versus PD-GPi, divided into length quartiles, using increasing thresholds for the determination of the burst length (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 14. Comparison of the amplitude of beta bursts in PD-STN versus PD-GPi, using increasing thresholds for the determination of the burst amplitude (namely bursts above the percentile 50th, 55th., 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 15. Comparison of the amplitude of beta bursts in PD-STN versus PD-GPi, divided into amplitude quartiles, using increasing thresholds for the determination of the burst amplitude (namely bursts above the percentile 50th, 55th., 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 16. Comparison of the length of beta bursts in PD-STN versus PD-GPi, using increasing thresholds for the determination of the burst length (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th). *** Significant interaction effect.

Supplementary figure 17. Comparison of the length of beta bursts in PD-STN versus PD-GPi, divided into length quartiles, using increasing thresholds for the determination of the burst length (namely bursts above the percentile 50th, 55th, 60th, 65th, 70th, 75th, 80th, 85th and 90th).. *** Significant interaction effect.

Supplementary figure 18. Correlation of all the low-frequency (upper) and beta (lower) burst included on the study. Even though duration and amplitude are linearly correlated, the intercept is different for Dystonia and PD.

Adaptive Deep Brain Stimulation for Parkinson's disease

4

Adaptive DBS in a Parkinson's Patient With Chronically Implanted DBS: A Proof of Principle

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Preliminary evidence from patients with Parkinson's disease (PD) suggests that deep brain stimulation (DBS) might work better, more efficiently, and with fewer side effects when applied in an adaptive manner (aDBS).¹⁻⁴ In each of these studies aDBS was delivered according to the amplitude of beta oscillations (13-30 Hz) in the subthalamic nucleus (STN), which itself has been shown to correlate with contralateral akinesia and rigidity (AR).⁵ The key limitations in these clinical aDBS studies are that they have been conducted in the immediate postoperative phase. In this period, clinical testing and stimulation titration are complicated by the "stun" effect, and the optimal chronic DBS settings are not yet known. Furthermore, AR has thus far only been assessed with ordinal clinical scores, a limited and subjective rating system. To circumvent these limitations, we applied aDBS in a PD patient who had been chronically implanted with DBS and already titrated to optimal stimulation parameters and assessed bradykinesia with a validated digital task. aDBS was applied during battery replacement surgery in a 68-year-old patient with a 27-year history of Parkinson's disease who had been implanted with bilateral STN electrodes for 14 years. The patient gave consent to the research protocol, which was approved by the local ethics committee. Bipolar local field potential (LFP) amplitude in the beta range ± 3 Hz was used as biomarker in such a way that conventional DBS was provided only when beta amplitude exceeded an estimated median value (for methods see references 1, 3, and 4). aDBS was applied for 12 minutes to the right STN (contralateral to the most affected side) with matched stimulation parameters to optimized conventional DBS (cDBS), namely, 2.8 V, 60-microsecond pulse width, and 135 Hz (with 250-millisecond ramping at onset and offset). Bradykinesia was assessed using a tablet-based version of the validated bradykinesia, akinesia, incoordination (BRAIN) task.⁶ The BRAIN task assesses the velocity of alternating finger movements between 2 buttons and provides an average "dwell time" (milliseconds). Bradykinesia assessments were performed following dopaminergic withdrawal for stimulation conditions OFF (OFF-stim) and during the application of aDBS and cDBS. Bipolar LFP amplitude of the right STN showed a marked peak around 20 Hz that was used as a feedback signal for aDBS (Fig. 1a). aDBS was well tolerated and only induced transient contralateral paresthesia in the left hand.

The average dwell times were compared for the 3 stimulation conditions and found to be lowest for aDBS compared with cDBS and OFF-stim (449, 556, and 861 milliseconds respectively; Fig. 1b).

Figure 1. (a) Adaptive DBS (aDBS) testing in a chronically implanted Parkinson's patient. Upper channel shows the averaged beta power over 400-millisecond episodes (moving average). The black line demarcates the threshold for applying stimulation. The middle channel shows the LFP filtered around the dominant beta frequency (20 $\pm$ 3 Hz). The bottom channel shows the stimulation copy that starts and ends with a 250-millisecond ramping period. The dotted blue lines illustrate the relation between the increase in beta power and the start of stimulation. (b) Average dwell time on a tablet tapping task during no stimulation, continuous DBS (cDBS), and aDBS.

Here we present the first case of aDBS in a parkinsonian patient with chronic STN-DBS treatment with parameters matched to optimized cDBS. We conclude that aDBS (1) can be applied in the chronically implanted DBS phase and (2) is at least as effective as cDBS when objectively assessed. With the development of implantable aDBS hardware capable of sensing and stimulating,⁷ similar studies may soon be conducted outside the operating theater, which would enable more extensive testing.

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Relevant conflicts of interest/financial disclosures: All authors reports no disclosures concerning this research.

5

Adaptive Deep Brain Stimulation as advanced Parkinson's disease treatment (ADAPT study): protocol for a pseudo-randomised clinical study

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STRENGTHS AND LIMITATIONS

- This protocol aims to assess both efficacy and side-effect profile of adaptive deep brain stimulation.
- The stun effect will not present in the patient population to be included in this protocol.
- Intraoperative testing will minimise exposure time for electrodes and risk of infection.
- Testing and washout periods will be limited by the intraoperative time available.
- The intraoperative setting will limit the tests available to be assessed in patients with Parkinson's disease.

Abstract

Introduction: Adaptive deep brain stimulation (aDBS), based on the detection of increased beta oscillations in the subthalamic nucleus (STN), has been assessed in patients with Parkinson's disease (PD) during the immediate postoperative setting. In these studies, aDBS was shown to be at least as effective as conventional DBS (cDBS), while stimulation time and side effects were reduced. However, the effect of aDBS on motor symptoms and stimulation-induced side effects during the chronically implanted phase (after the stun effect of DBS placement has disappeared) has not yet been determined.

Methods and analysis: This protocol describes a single-centre clinical study in which aDBS will be tested in 12 patients with PD undergoing battery replacement, with electrodes implanted in the STN, and as a proof of concept in the internal globus pallidus. Patients included will be allocated in a pseudo-randomised fashion to a three-condition (no stimulation/cDBS/ aDBS), cross-over design. A battery of tests will be conducted and recorded during each condition, which aim to measure the severity of motor symptoms and side effects. These tests include a tablet-based tapping test, a subscale of the Movement Disorder Society-unified Parkinson's disease rating scale (subMDS-UPDRS), the Speech Intelligibility Test (SIT) and a tablet-based version of the Stroop test. SubMDS-UPDRS and SIT recordings will be blindly assessed by independent raters. Data will be analysed using a linear mixed-effects model.

Ethics and dissemination: This protocol was approved by the Ethical Committee of the University Medical Centre Groningen, where the study will be carried out. Data management and compliance to research policies and standards of our centre, including data privacy, storage and veracity, will be controlled by an independent monitor. All the scientific findings derived from this protocol are aimed to be made public through publication of articles in international journals.

Trial registration number NTR 5456; Pre-results.

Introduction

Background and rationale

Deep brain stimulation (DBS) is currently one of the most effective advanced treatments for patients with Parkinson's disease (PD). At present, conventional DBS (cDBS) provides the continuous delivery of fixed-frequency and fixed-amplitude electrical pulses through the electrodes implanted mostly in either the subthalamic nucleus (STN) or the internal globus pallidus (GPi).^{1,2} Although cDBS is an effective treatment, it still has limitations in terms of efficacy, side effects and efficiency, and these have not undergone substantial improvements since the implementation of cDBS in clinical practice, approximately 20 years ago.³ However, new DBS systems directed to improve current stimulation algorithms are currently under development. These systems are often referred to as adaptive DBS (aDBS), as they aim to modulate the delivery of electrical stimulation, controlled by the detection of symptoms, such as tremor, or aberrant signals (biomarkers) that have been implicated in the pathophysiology of the disease.⁴ The ultimate goal of aDBS systems is to reduce the total amount of stimulation delivered, in a way in which beneficial effects of DBS are enhanced, while side effects are reduced.⁵ Furthermore, decreasing the total amount of stimulation delivered will allow to extend the battery life(span) of DBS devices.

Several biomarkers in PD have been proposed for use as a feedback signal for aDBS.⁶ Currently, the presence of prominent beta oscillations (13–35 Hz), in either the STN or the GPi, seems to be the most promising since it correlates with the severity of bradykinesia and rigidity.⁷ Evidence to date suggests that aDBS may be at least as effective as cDBS systems, while stimulation time and side effects are reduced.^{8–10} However, virtually all aDBS experiments based on beta oscillations have thus far only been tested in the immediate postoperative setting. Although aDBS has been evaluated mostly with regard to the STN, preliminary evidence indicates that aDBS could be equally effective when applied to the GPi.¹¹ The correlation of other prominent PD symptoms (such as tremor) with beta oscillations is far less robust. Therefore, the impact of aDBS on these symptoms is yet to be addressed.^{12,13}

Besides its effect on motor symptoms, a common side effect that could potentially be addressed by aDBS is stimulation-induced dysarthria. Preliminary data in the immediate postoperative phase showed that aDBS did not induce dysarthria, in contrast to cDBS.¹⁴ Likewise, due to the reduction in the total amount of stimulation that occurs in aDBS, this new technology could potentially help to tackle DBS-related side effects in executive functions, such as impaired response inhibition.^{15,16} Patients with PD treated with DBS are prone to make more mistakes in inhibitory control tests

(eg, the Stroop task).¹⁷ Response inhibition is a fundamental cognitive function, and its impairment could lead to impulsive conduct.¹⁸ For that reason, it is possible that stimulation-related impulsivity is the result of an impairment of response inhibition caused by DBS.^{19,20} It was first proposed that this side effect was due to unintended stimulation of limbic areas of the STN.²¹ However, it has been shown recently that DBS has a positive effect on risk-reward decision behaviour in patients with PD, and that such an effect was mostly dependent on stimulation of the motor part of the STN.²² This finding indicates that at least some of the non-motor effects of DBS are mediated through direct stimulation of the motor part of the STN. This is supported by increasing evidence that indicates that the motor and non-motor functions of the STN are not perfectly segregated.²³ It has been shown that beta oscillations in the motor STN play a significant role in adequate response inhibition.²⁴ For that reason, stimulation-induced impulsivity could be the result of an excessive beta suppression produced by continuous stimulation. Therefore, aDBS might be used as an additional option to address stimulation-induced impulsivity, since aDBS has the potential to provide a functional selectivity, by only triggering stimulation based on (primarily) motor biomarkers (eg, beta oscillations), only when a threshold is exceeded. As a result, only excessive beta activity would be suppressed.

Objectives

The aim of this study is to assess whether aDBS provides a similar motor improvement compared with cDBS, while limiting the presence of stimulation-induced side effects in patients with chronically implanted electrodes. Stimulation efficacy is assessed using a battery of tests aiming to measure the motor response to different conditions and the severity of dysarthria and/or impulsivity. The goals of this protocol are summarised in three questions:

1. Is aDBS at least as efficacious as cDBS in terms of motor improvement?
2. Is the speech-related and response inhibition side-effect profile of aDBS lower than that of cDBS?
3. What is the amount of stimulation provided in aDBS compared with cDBS?

Trial design

This protocol describes an exploratory study in which patients with PD with DBS electrodes implanted in the STN are allocated to a three-condition (no stimulation (NoStim)/cDBS/aDBS), cross-over design (figure 1). The conditions are pseudo-randomised in a 2:1:1 format, in such a way that for every two patients who start

with no-stimulation, one patient will receive aDBS first and one will have cDBS first. The main reason for this proposed pseudo-randomisation is to minimise the impact that an incomplete washout effect derived from stimulation could have on the scores of NoStim condition, as this condition is the baseline for the comparison of the effect of the two stimulation modalities. In four patients, stimulation conditions will be separated by a NoStim condition to minimise the carryover effect that cDBS could have on aDBS (or vice versa). Lastly, NoStim will be the last condition in two patients in order to partially balance the effects of training or fatigue on the tasks. Additionally, pilot data could be collected from two patients in order to explore the effects of aDBS on the GPI.

The performance of several tasks during the three conditions will take place during the battery replacement surgery, when a temporal externalisation of the DBS extension wires is performed. This means that subjects to be included have had their DBS electrodes implanted for at least 3–5 years, and therefore the stun effect is not present in this patient population. It was decided to perform this protocol intraoperatively as it allows the surgery to be completed in one session, minimising the time that electrodes are externalised and patients are exposed to potential risks of infection.

Methods and Analysis

Methods: participants, interventions and outcomes

Study setting

This is a single-centre study at the University Medical Centre Groningen.

Inclusion criteria

- Patients with PD with DBS electrodes implanted bilaterally in the STN. A maximum of two patients with PD with electrodes implanted in the GPI would be allowed as pilot data.
- Patients are cognitively capable of performing the tests included in this protocol. This item is subjectively evaluated during the patient interview, by looking at the performance of the candidate when completing a trial set of the tablet-based tests used during the experiment.
- Able to provide written informed consent.

- Physical condition that enables 20–30 min of testing. This is evaluated according to the clinical records and the fragility of the patient (determined by the treating neurologist).
- Ability to undergo testing in the OFF dopaminergic state, determined by the clinical condition of the patient after medication withdrawal.

Exclusion criteria

- Patients who cannot tolerate battery replacement under local anaesthesia (eg, presence of severe OFF medication tremor, severe anxiety, etc).
- <18 years old.
- Clinical disorders or diseases that could interfere with clinical assessment (eg, vision impairment that cannot be corrected with glasses, severe limb movement restriction).
- Cognitive impairment sufficient to prevent the patient to consider and retain the necessary information to make a decision regarding the participation in the study.

Investigational device

The responsive (closed loop) aDBS is delivered through a custom-made stimulation-amplifier which allows local field potentials (LFPs) to be recorded during the application of DBS. With this device, LFPs are filtered in real time around a subject's specific beta frequency (± 3 Hz around peak).⁹ Afterwards, a median threshold is selected in order to deliver monopolar stimulation every time that beta activity in the rectified filtered LFP exceeds the predefined threshold. Stimulation pulses are charge-balanced and asymmetric, mirroring the waveform of the standard clinical Medtronic Activa PC. Pulses are delivered at 130 Hz with a pulse width of 60 μ s (standard clinical parameters) using a ramping period of 250 ms at onset and offset in order to help limit the presence of paraesthesias, autonomic or other non-specific side effects, such as dizziness or nausea.²⁵ From the four contacts available for each electrode lead, two electrodes are required to perform bipolar LFP recordings (either contacts 0–2 or 1–3), while one electrode (in between the two recording electrodes) is left available for stimulation (either contact 1 or 2). The stimulation-amplifier has been built to strict safety guidelines (Report 90 BS EN60601-1 safe design, construction of medical equipment) and extensively tested,^{8,9,11,26} and found to be safe and reliable.

Figure 1. Trial design and pseudo-randomisation block. aDBS, adaptive deep brain stimulation; cDBS, conventional DBS; GPi, internal globus pallidus; PD, Parkinson's disease; subMDS-UPDRS, subscale of the Movement Disorder Society-unified Parkinson's disease rating scale; SIT, Speech Intelligibility Test.

Procedure

Patients have to skip at least one medication dose and are not allowed to be under the effect of prolonged-release dopaminergic medication in order to be classified as OFF medication before surgery. Patients are brought to the operating theatre for their battery replacement procedure. After the battery is exposed, the old battery is detached from the DBS electrodes and explanted. At this moment, two temporary wires are attached to the DBS electrode extension cables and connected to a combined stimulator and amplifier (see previous section). A brief rest recording of 30–60 s is performed from each of the two bipolar montages (0–2 or 1–3) available for each hemisphere. Power spectral density estimates are obtained from each rest recording, and the bipolar contact pair (0–2 or 1–3) per hemisphere with the highest beta peak power is selected. Monopolar cDBS is then titrated using the available contact located between the selected recording contacts. The voltage for monopolar stimulation is titrated initially based on an approximation of the voltage used in clinical practice for each individual patient (independently of the montage used in clinical practice). Voltage is increased or decreased according to the presence of side effects, clinical effect and interference with LFP recordings (in practice, we have seen that voltages >3.5 V are more prone to cause interference with the recordings, and these are also rare stimulation parameters in clinical practice). Once an optimum stimulation voltage is established, the patients are assigned to each of three counterbalanced conditions in which the patient is either stimulated with aDBS or cDBS, or not stimulated, separated by washout periods of 1–3 min, according to the remaining time available. Stimulation parameters (voltage, frequency, pulse width and contact selection) remain constant for both aDBS and cDBS, differing only in the timing of stimulation delivered according to beta detection. As battery replacements are performed under local anaesthesia, we aim to limit the duration of the experiment to a maximum of 25–30 min.

Clinical tests and outcomes

Each patient performs the following tasks in each of the three pseudo-randomised conditions:

- a. Tablet-based tapping test: several analogue and digital versions of the tapping test have been validated to objectively measure the presence of bradykinesia in patients with PD.^{27–29} We developed a custom tablet-based finger tapping test using the PsyPad platform.³⁰ In this test, a tablet is presented to the patient, in which two squares appear at the left and right sides of the screen (figure 2). The patient then has to press the squares in an alternating pattern. We tested this set-up, as a proof of principle, on a patient with PD who underwent

battery replacement,²⁶ using 50 tapping iterations per condition. In order to optimise the time available for the battery of tests, it was decided to reduce the iterations to 20. Since the duration of each iteration was approximately 500 ms, 20 iterations (10 back-and-forth screen tapings) will be roughly equivalent to 10 finger tapings, which is the amount of taps required to measure tapping items from the Movement Disorder Society-unified Parkinson's disease rating scale (MDS-UPDRS).

Figure 2. Example of a trial of the tablet-based bradykinesia test.

- b. Subscale of the MDS-UPDRS (subMDS-UPDRS)³¹ (Part III, items 3.4, 3.5, 3.6, 3.15, 3.17 a, b): as patients are lying on the operating table during the experiment, only selected items can be performed by the patients. The items that are included and filmed are finger tapping, hand movements, pronation-supination, rest tremor and postural tremor.
- c. Speech Intelligibility Test (SIT): this is a modified version of the Assessment of Intelligibility for the Dysarthric Speech.^{32,33} In this test, the patient is instructed to read out a list of 18 sentences (approximately 110 words per condition), while the speech is recorded with a mobile application. The words that form each sentence are randomly chosen, taking into account that each sentence must follow the correct order of a proper grammatical construction. Voice recordings are sent to a speech therapist, who blindly evaluates the sentences and writes them down. Afterwards, the sentences written by the speech therapist are

compared with the original list, and the amount of words that coincide are expressed as a percentage of the total words.

- d. Tablet-based version of the Stroop test³⁴: in this test, 20 colour words are presented to each patient in a sequential order, and each word is coloured as shown in figure 3. From those 20 words, five are coloured in the same colour as the word written (congruent), while 15 words are coloured in a colour different from the word written (incongruent). We chose an unbalanced design as our main focus is the effect of stimulation on incongruent words between conditions, rather than the effect of stimulation between congruent and incongruent words. For each word presented, four buttons are presented at the bottom of the tablet screen, each containing different colour words. The patient has to select the button containing the colour word presented on the screen, independently of the colour in which the word is coloured in. Reaction times and accuracy for each trial are directly uploaded to an online database, from which they can be extracted for data analysis.

Figure 3. Example of two trials of the tablet-based Stroop test with congruent (left) and incongruent (right) conditions.

Order of the tests

After the battery is exposed, and before the performance of the clinical tests can start, a number of preparations are required in order to programme the aDBS (see the Procedure section). This requirement can lead to individual differences in the time available to perform the clinical tests due to the maximum amount of intraoperative time allowed for this experiment. Therefore, the sequence in which the clinical tests are performed on each condition is initially ordered according to the approximate time it takes the patient to perform each of them, the suggested order being as follows: (1) tablet-based tapping test, (2) subMDS-UPDRS, (3) Speech and Intelligibility Test (SIT), (4) tablet-based version of the Stroop test. If during the course of each individual experiment it is considered that the time will not be sufficient for a patient to complete

the full protocol, only the first test(s) could be selected to be performed in order to ensure that at least one of the tests will be completed for each of the three conditions.

Sample size

According to previous studies,³⁵ a difference of approximately four points in the total motor UPDRS could be considered clinically significant (3.7% of the total scale). This would be roughly equivalent to a limit of 1.5 points on a 10-item UPDRS scale, which is the one used in this protocol. Based on pilot data conducted in Oxford/ London on four patients,⁹ aDBS scores had a standard error of approximately two points (SD of 4). This is roughly equivalent to an SD of 1.5 points on a 10-item UPDRS scale. Using an α of 0.05, a power ($1-\beta$) of 0.8 and assuming similar variances, a sample size of 12 patients would be necessary to demonstrate that the efficacy of aDBS is not inferior to cDBS, while providing the potential benefits of facilitating programming, battery life optimisation and the potential to reduce stimulation-induced side effects. A potential extension of two patients (14 patients in total) would be pursued in order to explore the potential effects of aDBS on patients with electrodes implanted on the GPI.

5

Recruitment

Patients who are scheduled for a battery replacement at the University Medical Centre Groningen are contacted by telephone 2 weeks before their hospital admission to be informed about the study. Complementary written information is sent by mail to patients who show an interest in participating in the study. At the time of hospital admission, each patient is personally approached by one of the members of the research team, if they meet all of the inclusion criteria and none of the exclusion criteria. Patients who decide to participate in the study will then be given the opportunity to ask further questions and invited to sign the consent form.

Methods: assignment of interventions

Allocation

The ultimate goal of the allocation procedure is to have a pseudo-randomisation in which all the possible combinations of the block design are covered (ie, 2:1:1, see the Trial design section, figure 1). For that reason, patients will be sequentially allocated to each possible pseudo-randomisation scenario until 14 patients are allocated. Only successful bilateral measurements will be considered in the pseudo-randomisation list. At first, a pseudo-randomisation of 3:1:1 (10 patients) will be set as the allocation goal in order to ensure that all conditions of the pseudo-randomisation could be met by mid-2019. Depending on the number of aborted experiments and the deadline for

inclusion, two patients more may potentially be included to achieve the 2:1:1 pseudo-randomisation.

Blinding (masking)

Patients will be blinded to the stimulation condition. Video and voice recordings will be taken for the subMDS-UPDRS and SIT parts, and will be blindly evaluated by two neurologists experienced in movement disorders and a speech therapist, respectively. Analysis of tablet-based outcomes will be automated and matched across the three conditions.

Methods: data collection, management and analysis

Data management

Data are stored on a central database using REDCap storage system, being accessible only to the authorised personnel involved in this study.

Statistical methods

Simple scores from the subMDS-UPDRS, tablet-based tapping test, SIT and Stroop test during aDBS versus cDBS or NoStim will be checked for normality using Q-Q plots, and if normally distributed, will be compared using a linear mixed-effects model. If the data are non-normally distributed, a data transformation will be applied, or a distribution different from normal will be employed for the test.

Methods: monitoring

Harms

The experimental procedure does not substantially expose patients to increased risks, as there are no extra surgical procedures required, and patients are stimulated only with less electrical current than in their conventional setting. Given that the experiments take place in the operation room, and only add less than 30 min to the total surgery duration, there is no significant added risk of infection. Since patients are tested in the OFF dopaminergic state, this exaggerates their symptoms to certain extent. However, DBS remains active until the moment of the surgery, which limits the impact of medication discontinuation. In previous aDBS studies, electrodes were exposed for hours or days^{9,10} without any increased risk of infection. Therefore, as battery replacement is completed in one session, the amount of time in which the extension wires are exposed is considerably shortened in this study. Nevertheless, infections will be considered an adverse event and infection rates monitored.

Monitoring

Data management and compliance to research policies and standards of our centre, including data privacy, storage and veracity, are verified by an independent monitor from a different department within the hospital. As this is an investigator-initiated study, the project leader submits, once a year throughout the clinical trial, a safety report to the accredited local ethics committee. Serious adverse events, defined by the Central Committee on Research Involving Human Subjects in the Netherlands as 'any untoward medical occurrence or effect that at any dose results in death, is life threatening (at the time of the event), requires hospitalisation or prolongation of existing inpatients' hospitalisation or results in persistent or significant disability or incapacity', will be promptly reported to the corresponding governmental authorities.

Patient and public involvement

In order to make sure that the experiments are as comfortable as possible for the subjects, a short Patient Reported Outcome (PRO) questionnaire will be conducted on the first five patients (figure 4). This PRO consists of five questions in which patients can indicate whether the communication was adequate and empathetic and whether the procedure was not too demanding, uncomfortable or painful. The feedback of these reports will be used to evaluate the adequacy of the protocol, and changes will be incorporated into the following study procedures, if necessary via an amendment.

5

Ethics and dissemination**Protocol amendments**

The protocol presented here is the fifth version (9 December 2018) of the original protocol prepared for this study. The second version of the protocol (15 September 2015) got the approval of the ethical committee after several modifications of the first version (22 July 2015). In version 3 (12 April 2017), an attempt was made to include patients undergoing new implantations. However, this was dropped in subsequent versions, since (a) patients undergoing new implantations were often considerably fatigued at the moment of the measurement and could not perform all the tasks; (b) differences in total intraoperative time between new implantations and battery replacements meant that the time available for the measurement was considerably less during new implantations; (c) the stereotactic frame slightly restricted the visual field of the patients in new implantations. Version 4 (7 September 2017) and version 5 were meant to increase the total number of patients to be included, as several failed or incomplete measurements took place during the initial inclusions.

Patient Reported Outcome Form

1. Are you satisfied with the information you received before the experiment?

Yes ☐ No ☐

If not, could you indicate which kind of information would you have liked to receive regarding the experiment?

2. Was the experiment burdensome for you?

Yes ☐ No ☐

If this was the case, could you please specify which part of the experiment was burdensome for you?

3. Did you feel uncomfortable during the experiment?

Yes ☐ No ☐

If yes, could you please specify which part of the experiment made you feel uncomfortable?

4. Do you consider that the communication during the performance of the experiment and/or about what you could expect during the experiment was adequate?

Yes ☐ No ☐

If this was not the case, could you please specify in which part of the experiment the communication can be improved?

5. Did you experience any form of pain during the experiment?

Yes ☐ No ☐

If this was the case, could you please specify in which part of the operation you experienced pain?

Figure 4. Example of the Patient Reported Outcome questionnaire form conducted on the participants

Consent

During the inclusion interview, patients are informed that the participation in this study is on an entirely voluntary basis, and that they are therefore allowed at any moment to withdraw their consent. No economic reward is provided for the participation in this study.

Confidentiality

Only indirect personal data from each patient are stored as coded information in order to prevent the possibility that patient data could be traced back to an individual patient.

The coding list will be safeguarded in a secured facility located in our centre. Data derived from the clinical tests or recordings could be exported only as anonymised data to be used for statistical analysis.

Ancillary and post-trial care

Patients are insured up to €650000 for harm suffered directly from trial participation. Details of the insurance are provided on the patient information letter of this study.

Contributors

MB and JMCvD designed and prepared the first draft of the protocol, and initiated the study. DPF formatted the protocol according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and prepared the manuscript. SL, PB and DLMO critically reviewed the protocol procedures and manuscript. All authors reviewed and approved the final version of this manuscript.

Funding This study is publicly funded by grants received from the Dutch Brain Foundation ('Hersenstichting Nederland', grant F2015(1)-04), the National Mexican Council of Science and Technology (CONACYT) grant number CVU 652927 and the University of Groningen/University Medical Centre Groningen (RuG/UMCG). SL is personally supported by a Wellcome trust postdoctoral clinical research training grant (105804/Z/14/Z).

Disclaimer

All the scientific findings derived from this protocol are aimed to be made public through publication of articles in international journals.

Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

This protocol is approved by the local ethics committee of our institution, and all procedures are carried out according to the Declaration of Helsinki and the Dutch legislation on medical research involving human subjects.

Provenance and peer review

Not commissioned; externally peer reviewed.

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6

Acute effects of adaptive Deep Brain Stimulation in Parkinson's disease

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HIGHLIGHTS

- The acute effect of beta-based aDBS in PD is effective in controlling bradykinesia.
- Beta oscillations remain informative of the parkinsonian state 7 years after DBS.
- aDBS did not lead to stimulation-induced dysarthria, compared to conventional DBS.
- A minority of patients presented acute re-emerging tremor during aDBS.
- Modified aDBS control strategies might be required in some patients with tremor.

Abstract

Background: Beta-based adaptive Deep Brain Stimulation (aDBS) is effective in Parkinson's disease (PD), when assessed in the immediate post-implantation phase. However, the potential benefits of aDBS in patients with electrodes chronically implanted, in whom changes due to the microlesion effect have disappeared, are yet to be assessed.

Methods: To determine the acute effectiveness and side-effect profile of aDBS in PD compared to conventional continuous DBS (cDBS) and no stimulation (NoStim), years after DBS implantation, 13 PD patients undergoing battery replacement were pseudo-randomised in a crossover fashion, into three conditions (NoStim, aDBS or cDBS), with a 2-min interval between them. Patient videos were blindly evaluated using a short version of the Unified Parkinson's Disease Rating Scale (subUPDRS), and the Speech Intelligibility Test (SIT).

Results: Mean disease duration was 16 years, and the mean time since DBS-implantation was 6.9 years. subUPDRS scores (11 patients tested) were significantly lower both in aDBS ($p < .001$), and cDBS ($p = .001$), when compared to NoStim. Bradykinesia subscores were significantly lower in aDBS ($p = .002$), and did not achieve significance during cDBS ($p = .08$), when compared to NoStim. Two patients demonstrated re-emerging tremor during aDBS. SIT scores of patients who presented stimulation-induced dysarthria significantly worsened in cDBS ($p = .009$), but not in aDBS ($p = .407$), when compared to NoStim. Overall, stimulation was applied 48.8% of the time during aDBS. **Conclusion:** Beta-based aDBS is effective in PD patients with bradykinetic phenotypes, delivers less stimulation than cDBS, and potentially has a more favourable speech side-effect profile. Patients with prominent tremor may require a modified adaptive strategy.

Introduction

Parkinson's disease (PD) patients in advanced stages of the disease usually present with motor symptoms which are not sufficiently suppressed by dopaminergic medication, together with intolerable medication-related side-effects. Deep brain stimulation (DBS) is a successful treatment option as the disease progresses [1]. Although DBS is highly effective, both in terms of motor improvement and improvement in quality of life, there are still limitations. These include incomplete symptom suppression and side effects, such as stimulation-induced dysarthria (SID), and dyskinesias. In addition to this, most of the studies have documented the benefits of DBS only up to three years after implantation [2]. A handful of studies that have followed DBS patients in the long term (5-10 years after implantation) have suggested that the efficacy of DBS may reduce over time, especially with bradykinesia components, narrowing the therapeutic window [3,4]. Recent developments in adaptive DBS (aDBS) systems may help overcome some of these drawbacks [5]. In aDBS, the amount of stimulation is modulated according to variations in the clinical state, or in neural activity patterns underpinning clinical state. Here the aim is to only deliver stimulation as necessary to improve motor impairment, thereby avoiding side-effects when stimulation can be spared or lowered. Up to now, the majority of clinical studies investigating aDBS in PD have applied stimulation based on the amount of beta activity (13-35 Hz) in the subthalamic nucleus (STN) local field potential (LFP), as this biomarker is correlated with contralateral bradykinesia and rigidity [6,7], and is suppressed by DBS [8].

Although studies have confirmed the efficacy of 'beta-based' aDBS [9-13], and suggested a superior side effect profile compared to continuous, conventional, DBS (cDBS) [14,15], these have been mostly performed in newly implanted patients. Such studies are potentially compromised by the microlesion effect [16], as this confounding factor provides temporary symptom relief, which can mask the true effects of stimulation. Consequently, bradykinesia or tremor may be suppressed by the microlesion effect, and the impact of intermittent OFF stimulation periods, caused by alternately ramping stimulation up and down, thereby masked. For this reason, it is important to assess the acute effects of aDBS in chronically implanted patients. Currently it is feasible to investigate the utility of aDBS in chronically implanted patients using externalised electrodes [17], and in patients implanted with bidirectional devices [18]. Nevertheless, whether there is additional benefit over cDBS, particularly with respect to side-effects, remains unclear. One such side-effect is SID, and another is motor impulsivity, as measured by tests of response inhibition [19]. Here, we compare the clinical effect, efficiency and side-effect profile of aDBS

with both cDBS and no stimulation in PD patients with long implanted electrodes in the STN.

Materials and methods

Patients

We tested 13 patients with advanced idiopathic PD who were chronically treated with bilateral DBS of the STN and needed battery replacement surgery (Table 1). All patients gave written informed consent to the study protocol, which was approved by the local ethics committee. The study was registered in the Dutch Trial Register (trialregister.nl, trial # 5456) and the study protocol was published [20]. All patients stopped prolonged-release dopaminergic medication at least 24h prior to the measurements. In this group of advanced PD patients (mean disease duration: 16 years) the severity of OFF periods was considerably higher than in newly implanted patients. For that reason, we decided that patients skipped at least one dose of regular antiparkinsonian medication before the surgery, in order to achieve 6h of off-medication at the moment of the recordings. This washout period was enough to resemble the acute OFF periods that patients experience immediately after medication wears off. Battery replacement surgery was performed under local anaesthesia.

Recording procedure

In brief, the old battery was removed and a custom-made external stimulator-amplifier device (for details see Ref. [9]), which is able to record and stimulate simultaneously, was connected to the chronically implanted DBS electrodes (Fig. 1). From this point the protocol took about 25-30 min to be completed. Bipolar STN local field potentials (LFPs) were recorded in the resting state for 30-60 s, using contact pairs 02 and 13. Power spectral density estimates in the beta band range and their peak frequency were calculated. The contact (either 1 or 2) in the middle of the contact pair with the greatest beta activity on each side was selected for stimulation, and the beta activity in the bipolar channel bridging the stimulation contact used for the feedback control of aDBS. A common frequency range (± 3 Hz) that included the beta-peak frequencies of both hemispheres, was used in each patient to filter bilateral LFPs, based on the observation that beta peak frequencies are similar between sides [21,22]. Optimal stimulation voltages were determined before the experimental conditions, based on the response to monopolar cDBS, until either optimal symptom reduction (bradykinesia and/or tremor) was achieved, side-effects occurred or voltage-

dependent artefacts interfered with the recordings. Stimulation was monopolar, with the return electrode being a large skin electrode over the neck or shoulder [9].

Figure 1. Schematic representation of aDBS.

Upper part: During the operation, and after the old battery is exposed, the battery is detached from the DBS electrodes and explanted. At this moment, two temporary wires are attached to the DBS electrode extension cables at the level of the chest incision, and connected to a combined stimulator and amplifier (represented here).

Lower part: an aDBS recording is depicted. Left recordings are obtained from electrodes 0-2, while stimulation is provided from contact 1. Right recordings are obtained from electrodes 1-3, while stimulation is provided from contact 2. From top to bottom:

- Original signal from left (blue) and right (red) electrodes, using a bandpass filter from 3 to 37 Hz. At this stage it is possible to appreciate artefacts caused by stimulation.
- Left and right LFPs filtered around the beta peak. Here it is possible to observe the individual beta bursts.
- Left and right envelopes of the beta-filtered and rectified LFPs. The dotted lines represent the thresholds selected to trigger stimulation.
- Stimulation bursts, with a ramping period when stimulation is switched on and off.

Pt	S	A (y)	PD	Time since Start (y)	DBS use (y)	Most affected side	Tremor ^a	Medication	Clinical setting			Experimental setting		Freq used for filtering (±3Hz)	OFF Beta peak (Hz) ^b
									Contacts used	Parameters	Contacts used	Parameters			
PD01^c	M	58	24	9	9	Left		Levodopa, prami- pexole 1738 mg LEDD	L: -3/2+	2.9V 60µs 185Hz	L: -2/C+	1.8V 60µs 130Hz	15	L: 15	
									R: -10/C+	0.8V 60µs 185Hz	R: -10/C+	1.8V 60µs 130Hz		R: 15	
PD02	M	47	16	12		Right	No	Levodopa prami- pexole 1538 mg LEDD	L: -3/2+	3.5V 60µs 135Hz	L: -2/C+	2V 60µs 130Hz	15	L: 15	
									R: -11/C+	2.2V 60µs 135Hz	R: -10/C+	2.2V 60µs 130Hz		R: 13	
PD03	M	46	8	5	5	Left	No	Levodopa duodopa 1582 mg LEDD	L: -1/2+	2.2V 90µs 180Hz	L: -2/C+	1.86V 60µs 130Hz	20	L: 21	
									R: -11/10+	1.5V 90µs 180Hz	R: -10/C+	1.86V 60µs 130Hz		R: 21	
PD04	F	49	9	6	6	Left	Yes	Levodopa rotigo- tine 1558 mg LEDD	L: -1/2+	2.8V 60µs 180Hz	L: 1-/C+	2.8V 60µs 130Hz	17	L: 17	
									R: -9/10+	1.2V 60µs 180Hz	R: -9/C+	1.2V 60µs 130Hz		R: 19	
PD05	M	67	10	5	5	Left	Yes	Levodopa 1500 mg LEDD	L: -2/C+	1.7V 60µs 180Hz	L: -2/C+	1V 60µs 130Hz	20	L: 22	
									R: -11/C+	2.2V 60µs 180Hz	R: -10/C+	1.3V 60µs 130Hz		R: 21	
PD06^d	F	64	23	9	9	Left	No	Duodopa amanta- dine 1759 mg LEDD	L: -2/3+	3V 60µs 130Hz	L: -1/C+	2.54V 60µs 130Hz	22	L: 21	

Pt	S	A (y)	PD	Time since Start (y)	DBS use (y)	Most affected side	Tremor ^a	Medication	Clinical setting		Experimental setting		Freq used for filtering (±3Hz)	OFF Beta peak (Hz) ^b
									Contacts used	Parameters	Contacts used	Parameters		
PD07^e	M	59	19		9	Right	Yes	Duodopa 2540 mg LEDD	L: -0/1+	2V 60µs 1.85Hz	L: -1/C+	2V 60µs 130Hz	23	L: 21
											R: -9/C+	2V 60µs 130Hz		
PD08	M	54	7		3	Right		Levodopa prami- pexole 725 mg LEDD	L: -0/-1/- 2/3+	4.5V 90µs 190Hz	L: -1/C+	2.5V 60µs 130Hz	15	L: 16
									R: -9/10+	0.6V 60µs 190Hz	R: -10/C+	1.5V 60µs 130Hz		
PD09	M	66	32		8	Left	No	Levodopa, prami- pexole amantadine 1125 mg LEDD	L: -1/2+	4.5V 90µs 135Hz	L: -1/C+	2.05V 60µs 130Hz	18	L: 16
									R: -10/11+	4.8V 90µs 135Hz	R: -9/C+	2.05V 60µs 130Hz		
PD10	M	48	12		4	Left	Yes	Levodopa, prami- pexole amantadine 1081 mg LEDD	L: -1/C+	3.2V 120µs 130Hz	L: -1/C+	3.2V 60µs 130Hz	29	L: 29
									R: -9/C+	2.4V 120µs 130Hz	R: -9/C+	2.4V 60µs 130Hz		
PD11	M	81	15		6	Left	No	Levodopa, prami- pexole amantadine 900 mg LEDD	L: -1/2+	2.1V 60µs 135Hz	L: -1/C+	2.5V 60µs 130Hz	17	L: 17
									R: -10/9+	2.5V 60µs 135Hz	R: -10/C+	2.5V 60µs 130Hz		

Pt	S	A (y)	PD Start (y)	Time since DBS use (y)	Most affected side	Tremor ^a	Medication	Clinical setting		Experimental setting		Freq used for filtering (±3Hz)	OFF Beta peak (Hz) ^b
								Contacts used	Parameters	Contacts used	Parameters		
PD12	M	71	12	7	Right	No	0 mg LEDD	L: -2/C+	3.5V 80µs 90Hz	L: -2/C+	3V 60µs 130Hz	18	L: 18
								R: -11/C+	3.6V 80µs 90Hz	R: -10/C+	3V 60µs 130Hz		
PD13	M	72	21	7	Right	Yes	Levodopa aman- tadine 1098 mg LEDD	L: -2/C+	2.3V 70µs 185Hz	L: -2/C+	3V 60µs 130Hz	26	L: 26
								R: -8/C+	2.9V 90µs 185Hz	R: -10/C+	3V 60µs 130Hz		
Mean (±SE)		60.1 (3.0)	16 (2.0)	6.9 (0.6)			1318.7 (169.4)					19.6 (1.2)	19.2 (1.2)

Table 1. Clinical characteristics of the PD patients included in the study. Pt = patient, S = sex, A = age at the moment of the experiment, y = years, PD = Parkinson’s disease, M = male, F = female, LEDD = levodopa equivalent daily dose, L = left, R = right, C = case (used for monopolar stimulation).

^a Tremor present at the moment of the trial.

^b Peaks reported here were calculated offline. Therefore, they might slightly differ with the frequencies used to filter the signal intraoperatively.

^c Due to a technical failure in one of the LFP channels, this patient was measured unilaterally in both hemispheres.

^d This patient had the right electrode implanted in the GPI. Therefore, only results from the right hand (left electrode) were included in the analysis.

^e This patient had the right electrode off as their standard clinical setting, as only the right hemisphere required both stimulation and medication to suppress clinical symptoms. However, both electrodes were tested and included in the analysis.

Bilateral aDBS, cDBS and no stimulation (NoStim) were applied in a pseudo-randomised order, with a short washout period (2 min) between them (Fig. 2). aDBS was triggered on and off when rectified beta power crossed a median power threshold up and then down, respectively. Supplementary video 1 shows examples of the signals recorded on-line during NoStim, cDBS and aDBS.

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.brs.2020.07.016>

Tests and data processing

During each of the three conditions, the following four tests were performed (See Ref. [20] for a more detailed description of the tests):

- A short version of the motor Movement Disorders Society version of the Unified Parkinson's Disease Rating Scale (sub- UPDRS) [23] was assessed and video recorded for subsequent blinded rating. Items tested bilaterally included were finger tapping, hand movements, hand pronation-supination, rest tremor and postural tremor. Videos were evaluated by three clinicians with expertise in movement disorders. Total scores were calculated for each rater/patient combination. Subgroup scores were calculated for bradykinesia and tremor items.
- The speech intelligibility test (SIT) [14], in which each participant had to read out approximately 110 words divided into 18 sentences. Sentences were recorded, and the number of intelligible words of each SIT was blindly evaluated by a speech therapist. The total amount of intelligible words of each trial was determined. This score was normalised between 0 and 1, with 0 representing completely unintelligible speech.
- Response inhibition was assessed with a tablet-based version of the reverse Stroop effect (RST) [24], in which a colour word is presented, and the patient has to select the colour named by the word, independently of which colour the word is printed. The paradigm included 5 congruent words and 15 incongruent words randomly presented on each trial. Reaction times were determined for each word, and the amount of correct words for congruent and incongruent conditions were calculated. Reaction times with duration 200 or 5000 ms were discarded. It has been postulated that any impaired Stroop-test responses in PD patients might be a consequence of deficits in attentional resources, rather

Figure 2. Flowchart of the inclusion algorithm and pseudorandomisation order.

¹ The protocol and tests were modified after the inclusion of this patient, who was therefore excluded. Findings have been reported in Ref. [17].

² This patient was operated in the GPi, and therefore the results were reported separately in Ref. [54]

^{3,4} These randomisation orders belong to the same patient (PD01). As this patient had to be measured unilaterally in both hemispheres, due to a defect in one of the aDBS box channels, each hemisphere was assigned to a different randomisation order.

⁵ During patient surveillance, one patient presented a superficial infection on the surgical site, which was resolved completely after antibiotic treatment.

than impairments in impulse control [25]. Accordingly we chose the RST over the Stroop test as the former arguably is less attention demanding [26].

- A bradykinesia test was performed using a tablet-based version of a previously validated tapping test [27,28], in which patients had to press two separate squares in an alternating pattern (20 iterations). The first iteration of each trial was discarded, as it systematically differed from the rest, leaving 19 iterations for further analysis. Incorrect iterations were defined as each time a patient pressed the same square twice.

In the paradigm, the subUPDRS was the last test to be performed in each condition, in order to maximise the washout time between clinical scales. Hence, we use it as our benchmark measure of efficacy.

Statistical analysis

Statistical analysis were performed using R version 3.6.0, and the statistical packages lme4 [29] and lmerTest [30]. All items were assessed for normality using Q-Q plots. Iteration times of the tapping test, and RST reaction times were log-transformed prior to further analysis. subUPDRS scores, transformed iteration times, SIT scores and transformed RST reaction times were compared using a linear mixed-effects model. Condition was treated as a fixed effect in all tests and subject as a random effect. In addition, in the sub-UPDRS model, randomisation order was included as a fixed effect. Additionally, bradykinesia and tremor subscores were analysed using independent models. The intra-rater absolute agreement of UPDRS-subscores was analysed using 2-way random-effect intra-class correlation coefficient (ICC). In the SIT model, the presence of SID was included as a fixed effect, with SID defined as a decrement on the SIT score during cDBS, aDBS or both. In the RST analysis, congruency (congruent/incongruent) and accuracy (correct/incorrect) were added as fixed effects. In the tapping test, errors and their interaction with condition were added as fixed effects. Additionally, error counts of the tapping test and RST were analysed using a generalised linear mixed-effects model with a log-linear Poisson distribution model and an offset of 19 for each tapping- test trial, 5 for congruent words and 15 for incongruent words. In the RST error analysis, congruency was initially included as a fixed effect to test the presence of a reverse Stroop effect, and afterwards, its interaction with condition was added to the model, to test the selectivity of this effect to each condition. Models were compared using the Bayesian information criterion (BIC). The percentage time on stimulation was calculated for the aDBS condition. All results are expressed as mean $\pm$ standard error.

Results

Patients had a mean disease duration of 16 ± 2 years, and the mean time since DBS implantation was 6.9 ± 0.6 years. The average levodopa equivalent daily dose used was 1318.7 ± 169.4 mg. Of the 13 patients included in this study, all patients completed the bradykinesia test. Due to time and technical constraints, the rest of the tests were completed only by 11 patients each. All patients tolerated the test procedure, and stimulation-induced transient paraesthesias were present only at stimulation voltages above those used for the experiment.

Bilateral subUPDRS: Whereas 7/11 patients were classified as tremor dominant based on the clinical records, only five presented evident tremor during the recordings. Independent raters showed an excellent degree of agreement in the scores, (ICC = 0.939, $F(35,70) = 16.312$, $p < .001$). The linear mixed-effect model was significant for condition, ($F(2,88) = 8.144$, $p < .001$) (Fig. 3). sub-UPDRS scores were significantly lower in aDBS (12.30 ± 0.85) when compared to NoStim (15.81 ± 0.75), ($t(88) = -3.731$, $p < .001$), and in cDBS (12.57 ± 0.74) when compared to NoStim, ($t(88) = -3.252$, $p = .001$), but not between aDBS and cDBS, ($t(88) = -0.443$, $p = .659$). There was no significant effect of randomisation order, ($F(2,88) = 2.62$, $p = .07$). Bradykinesia subscores were significantly lower in aDBS (11.09 ± 0.58 , $t(88) = -3.096$, $p = .002$), and did not achieve significance during cDBS (11.87 ± 0.58 , $t(88) = -1.754$, $p = .08$), when compared to NoStim (12.90 ± 1.27). There was no difference in bradykinesia subscores between aDBS and cDBS ($t(88) = 1.341$, $p = .18$). Tremor subscores were reduced with both interventions (cDBS scores, 1.33 ± 0.73 vs NoStim 6.13 ± 0.92 , $t(40) = -6.572$, $p < .001$ and aDBS, 2.47 ± 0.73 vs No Stim, $t(40) = -5.02$, $p < .001$). There was no difference in tremor subscores between aDBS and cDBS ($t(88) = 1.189$, $p = .237$). However, although most patients showed tremor suppression even when stimulation was triggered off during aDBS, two patients demonstrated re-emergence of tremor when stimulation triggered off during this condition.

SIT: the linear mixed-effect model showed a significant effect for the interaction of condition and SID ($F(2,22) = 4.231$, $p = .027$). SIT scores of patients with SID significantly worsened only in cDBS (0.74 ± 0.08) when compared to NoStim (0.85 ± 0.08 , $t(22) = -2.833$, $p = .009$), but not in aDBS (0.84 ± 0.08) when compared to NoStim ($t(22) = -0.845$, $p = .407$).

Figure 3. Scatter plots of the subUPDRS (means of the scores from the three independent raters per condition per patient) and SIT scores. Boxplot indicates the standard error of the mean, and upper and lower lines the standard deviation. Lines connect data from the same patient. Left: total subUPDRS scores. Upper center: subscores of bradykinesia items of the UPDRS III. Lower center: subscores of tremor items of the UPDRS III. Right: SIT scores of patients with SID.

RST: the simpler model revealed a significant effect of congruency, ($\text{Chi}^2(1) = 4.576$, $p = .032$), where incongruent words had a significantly increased error rate, ($z = 2.139$, $p = .032$). No significant effect of condition was found, ($\text{Chi}^2(2) = 1.772$, $p = .41$). A model with an interaction factor was not a better fit (BIC 146.09 vs 138.34 for the simpler model), and interaction was not significant, ($\text{Chi}^2(2) = 0.586$, $p = .745$). No significant effect was found in reaction times for congruency, ($F(2626.03) = 0.266$, $p = .766$, condition, $F(1, 625.99) = 0.310$, $p = .577$), or their interaction, ($F(1, 626.02) = 0.723$, $p = .485$).

Tapping test: correct iteration times were reduced in cDBS (571.29 ± 9.83 ms) and aDBS (612.31 ± 10.14 ms) compared to NoStim (619.53 ± 10.35 ms). However, this reduction was only significant for cDBS, ($t(1412.29) = -2.388$, $p = .017$), and not for aDBS, ($t(1412.24) = -0.776$, $p = .438$). There was no significant difference between the two interventions, ($t(1412.04) = -1.620$, $p = .105$). No differences in errors were found between conditions, ($\text{Chi}^2(2) = 1.512$, $p = .469$).

Overall, stimulation was applied 48.8% (SEM 3.8) of the time during aDBS.

Discussion

Our study provides the first pseudorandomised and blinded acute comparison of both UPDRS scores and side-effects in aDBS versus cDBS in the chronically implanted

state. The results confirm previous findings that aDBS is well tolerated [9,11], performs equally well as cDBS, and does not compromise speech [14] in patients studied within days of electrode implantation. The effects in the chronically implanted state were seen despite stimulation being delivered about 50% of the time.

The patient cohort described in this study had DBS electrodes implanted for seven years on average (range 4-12 years), which provided the unique opportunity to observe the effects of aDBS in patients with advanced stages of the disease. It also confirms previous findings that beta oscillations remain informative of the clinical state of the patients [6,31], even several years after implantation.

There was significant improvement of the blindly evaluated subUPDRS during aDBS and cDBS. aDBS and cDBS did not differ significantly and improvements across both groups were relatively modest. However, this might reflect the reduction in the response of bradykinesia items to stimulation reported in some of the studies following DBS patients for more than 5 years [3,4]. This may also explain why the level of improvement in subUPDRS scores with both aDBS and cDBS (~20%) was at the lower limit of the range of improvements seen under similar blinded conditions when these interventions are contrasted acutely following electrode implantation [9,10,12,14,32]. Note too that scores from blinded video assessments are lower than those made during direct, unblinded clinical examination [9].

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.brs.2020.07.016>

Regarding tremor subscores, both cDBS and aDBS significantly suppressed tremor compared to NoStim (Supplementary video 2). Although differences in clinical scores between cDBS and aDBS were not significant, two patients demonstrated re-emergence of tremor when stimulation was off during aDBS (Supplementary video 3). This phenomenon was previously described in a similar proportion (2/12) of cases undergoing aDBS [18], and might be related to the fact that beta oscillations are only correlated with bradykinesia symptoms, but not tremor [6,7]. It remains unclear which factors determine the re-emergence of tremor. As observed in Supplementary video 3, one clue may be re-emergence of tremor even during cDBS. It has been shown that tremor is associated with a reduction in beta oscillations [33], so potentially when tremor is not successfully suppressed by stimulation, it may attenuate ongoing beta activity and temporally cause stimulation to turn off, until pathological beta resynchronisation overcomes tremor and triggers stimulation again. This 'flip-flopping' might cause the 'erratic' tremor suppression during aDBS. Therefore, patients with

stimulation-resistant tremor could require a lower threshold to trigger stimulation than their rigid-bradykinetic counterparts. Advances in tremor detection using LFPs [34] may provide additional biomarkers to control tremor in patients in which tremor cannot be effectively suppressed using only beta-based algorithms. Meanwhile in the minority of patients in whom tremor breakthrough does occur during aDBS, trials should assess the efficacy of control algorithms that have a minimum which is a low, rather than zero, stimulation intensity. Alternatively, the period between triggered stimulation bouts could be reduced in the aDBS condition, or the threshold dynamically changed to take account of medication state, which is linked to tremor.

A large number of patients classified as tremulous PD patients in the clinical records were included in this study. This could be explained by our inclusion criteria, which required patients with chronically implanted electrodes who were cognitively preserved. It has been shown that tremor-dominant PD patients usually present a more favourable cognitive prognosis [35]. However, it has also been observed that the presence of tremor in PD patients is not constant, and some patients who start with tremor as the main symptom may switch to a bradykinetic phenotype as disease progresses [36].

The potential benefits of aDBS regarding dysarthria are promising. SID is one of the most common side effects of cDBS, with a prevalence of around 10% in treated patients [37]. This usually adds to speech problems which are already present as consequence of the disease [38]. The pathophysiology of SID is up to now unclear. Stimulation spread to tracts adjacent to the STN has been proposed as a factor that contributes to the onset of SID [39]. New technologies, such as directional DBS [40] can improve the spatial accuracy of DBS, in order to avoid stimulation of unwanted tracts. However, increasing evidence indicates that the sensorimotor part of the STN itself is involved in speech production [41]. Therefore, the uninterrupted stimulation of the motor networks that are meant to be targeted with cDBS can also lead to SID. aDBS, by delivering stimulation only when it is necessary, reduces the overall electrical energy delivered and in this way limits speech-related side-effects. In this study, the benefits of aDBS were only seen when patients did present SID during cDBS. Nevertheless, the test used in our protocol only provides a general overview of the patient's speech. Studies using more sophisticated methods, such as articulography [42] or speech signal processing [43], might reveal even more insights about the potential benefits of aDBS. In addition to this, other activities in the STN LFP or biomarkers from the motor cortex could be used to monitor speech articulation, in order to further improve the efficacy of aDBS [44]. However, this is yet to be tested.

We found non-significant differences between cDBS and aDBS in the tapping test. Iteration times were shorter with cDBS, even though bradykinesia UPDRS subscores were lower with aDBS. The contrast might be explained by the effects of break-through tremor in the minority of patients on aDBS. In the RST, an interference effect was found, but this was not affected by stimulation (either continuous or adaptive).

Limitations

Some limitations of this study have already been highlighted, particularly the short duration of the stimulation conditions, but others remain. Because of the intra-operative nature of this study, not all the UPDRS items could be assessed. As operations were performed under local anaesthesia, the time available to complete the protocol was limited. Therefore, the results may potentially be affected by incomplete washouts between stimulation conditions. Pseudo-randomisation should have helped limit the impact of incomplete washout and condition order was not found to be a significant factor upon analysis. Moreover, wash-out has been considered a two-step process, consisting of an initial fast decrease in stimulation's therapeutic effect, followed by a further, slow decline. Our wash-out interval was sufficient for the former fast process [45,46]. Similar arguments may apply to the wash-in of effects, given that stimulation was only applied for about 5 min in each condition. The brief wash-out and wash-in periods necessitated by our intra-operative constraints should have served to reduce the differences between conditions, but significant differences were still detected. In a similar way, our baseline recording was limited to 30-60 s. However, beta oscillations in 'off' STN LFP-recordings are similar whether measured 1 min or 1 h later [47], and show relatively little variation over time [48]. Another possible confound in the present methodology is that both aDBS and cDBS were limited to monopolar stimulation at either contact 1 or 2, and higher voltages sometimes interfered with the recordings through stimulation-related artefacts, which led to the use of submaximal voltages in some instances. The resultant stimulation choices may therefore have differed from the chronically optimised contact selection and stimulation voltage prior to battery change (see Table 1). Still, voltages, pulse width and stimulation frequency were kept fixed between the cDBS and aDBS conditions, and the optimal voltages were estimated based on the response to cDBS during the assessment.

Nevertheless, the selection of cDBS contacts was more constrained than usual and bipolar stimulation was avoided so as to keep the two stimulation conditions as similar to one another as possible. Additionally, due to the bipolar recording configuration

focused on the middle contacts, the beta activity in outer contacts was not explored. Future aDBS experiments using non-segmented or segmented octopolar DBS electrodes may allow for more versatile stimulation montages [49].

Furthermore, the effects of movement on beta oscillations were not directly assessed in this trial. It has been observed that the average STN beta power is modulated during voluntary movements [50] and walking [51]. However, we and others have not found a negative impact of these beta-effects on clinical scores during aDBS [9-11,18,32,52-54]. This may be due to the fact that while average beta power is reduced during voluntary movements, pathological beta bursts still occur on some trials [55,56]. Therefore, aDBS will continue to be triggered, as needed, by these bursts [57]. Although beta-based aDBS studies on non-human primates [58] and PD patients [12] have shown that aDBS improves overall bradykinesia and rigidity symptoms, more subtle elements of motor behaviour can be compromised, such as the speed or accuracy of the return phase during reaching tasks, when beta rebounds. On the other hand, these effects will also be shared by cDBS, which involves stimulation during all beta rebounds. The impact of these more subtle motor effects in real-life conditions will need to be further explored. Finally, it is still possible that the effects demonstrated here do not persist in the chronic setting. Ultimately, chronic trials are necessary that contrast the best possible cDBS parameters established during chronic therapy with aDBS.

Future perspectives

Several clinical trials [9-11,18,32,52-54], including the present study, have demonstrated that beta oscillations in the STN correlate with bradykinesia and rigidity in PD patients [59]. For that reason, beta oscillations are likely to play a central role in future aDBS trials [60,61]. With the advent of new stimulation devices that are able to perform chronic LFP-recordings, the next step towards implementing beta-based aDBS in the clinical practice will be to explore the clinical benefits and limitations of aDBS in real-life situations. One important aspect to take into account in the design of these trials is the interaction of beta oscillations with medication. Beta oscillations in the STN are reduced after levodopa administration [50]. For that reason, beta-based aDBS can avoid the delivery of excessive stimulation when the effect of levodopa is present. Preliminary evidence has shown that this could help reduce medication-induced dyskinesias in patients treated with aDBS [15,52,62]. Both low-frequency oscillations (4-12 Hz) [63] and gamma oscillations (35-80 Hz) [64] in the STN, and gamma oscillations in the motor cortex [65], are increased during

the presence of levodopa-induced dyskinesias. These biomarkers could also be incorporated into aDBS [66]. In addition, the stimulation technique could potentially be improved, so that the targeting of specific phases of synchronization, or plasticity-modulating patterns could replace regular, high frequency stimulation in aDBS [67,68]. However, the potential benefits of any prospective biomarker need first to be clinically contrasted with cDBS, as this is the present gold standard. Lastly, aDBS will need to continue working during sleep, in order to prevent problems related to turning in bed [69]. Algorithms that can recognise sleep, or that switch to cDBS over night, can be designed [70].

Conclusion

The acute therapeutic effects of beta-based aDBS are as great as conventional DBS in chronically implanted patients, just as immediately after electrode implantation [9]. This is in line with the evidence that beta oscillations remain present and informative over time [71]. The present findings are important, as the assessments in chronically implanted patients are not confounded by microlesion effects. Furthermore, comparisons were performed with cDBS, using stimulation parameters that were optimised for cDBS, with the exception of stimulation contacts. We found that SID was reduced with aDBS, most likely because stimulation was applied only as necessary. However, it remains to be seen whether aDBS remains effective with prolonged use, and whether stimulation algorithms have to be adjusted in some patients with tremor.

Funding

This study is publicly funded by grants received from the Dutch Brain Foundation ('Hersenstichting Nederland', grant F2015(1)-04), the National Mexican Council of Science and Technology (CONACYT) grant number CVU 652927, and the University of Groningen/ University Medical Center Groningen (RuG/UMCG). SL is personally supported by a Wellcome trust post-doctoral clinical research training grant (105804/Z/14/Z). PB is supported by the Medical Research Council [MC_UU_12024/1], National Institute of Health Research Oxford Biomedical Research Centre and Rosetrees Trust.

CRediT authorship contribution statement

Dan Piña-Fuentes: Patient inclusion, Data collection, Formal analysis, Data analysis-execution, Writing - original draft, Writing - review & editing, Writing of manuscript, Review and approval of the manuscript. J. Marc C. van Dijk: Surgical assistance during recordings, Supervision, Project supervision, Writing - original draft, Writing - review & editing, Writing of manuscript, Review and approval of the manuscript. Jonathan C. van Zijl: Blinded ratings, Writing - review & editing, Review and approval of the manuscript. Harmen R. Moes: Blinded ratings, Writing - review & editing, Review and approval of the manuscript. Teus van Laar: Writing - review & editing, Critical advice, Review and approval of the manuscript. D.L.Marinus Oterdoom: Surgical assistance during recordings, Writing - review & editing, Review and approval of the manuscript. Simon Little: Writing - review & editing, Critical advice, Review and approval of the manuscript. Peter Brown: Formal analysis, Supervision, Data analysis-Supervision, Project supervision, Writing - original draft, Writing - review & editing, Writing of manuscript, Review and approval of the manuscript. Martijn Beudel: Conceptualization, Conceptualization and design, Blinded ratings, Patient inclusion, Formal analysis, Supervision, Data analysis-Supervision, Project supervision, Writing - original draft, Writing - review & editing, Writing of manuscript, Review and approval of the manuscript.

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Declaration of competing interest

PB is a consultant with Medtronic.

Acknowledgements

We would like to thank all the patients for their participation in this study. We would also like to thank Renske de Vries for the evaluation of the voice recordings, Jasper Peeters for his assistance during the measurements, Alek Pogosyan for the facilitation of custom-made scripts, Cor Kliphuis for his assistance with the patient assessments, and the OR staff for their help during the recordings.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2020.07.016>.

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Supplementary text

Additionally, we performed correlations between disease duration and the percentage of improvement in the UPDRS scores of the cDBS and aDBS scores predicted from the model. Correlations are reported using Pearson correlation (R) coefficients and p -values (see figures below). We did not find a significant correlation with the improvement observed in cDBS or aDBS and age. However, it is important to remark that this is only valid for our cohort, since the generalisation of this statement is limited by our inclusion and exclusion criteria. We only included patients undergoing battery replacement, which means that more recently implanted patients, who usually respond better to stimulation, were not included. Additionally, we excluded patients with cognitive impairment, who are usually patients with a longer disease duration, and in whom the response to stimulation might be reduced.

7

Adaptive DBS in Parkinson's disease: Headlines, perspectives and challenges

Dan Piña-Fuentes, J. Marc C. van Dijk, Martijn Beudel. Adapted
from: *Brain Stimulation* 12 (2019) 1091-1092.

Conventional, continuous deep brain stimulation (cDBS) is one of the most effective treatments for patients with Parkinson's disease (PD). However, it currently has limitations in terms of efficacy and stimulation-induced side effects [1]. Adaptive deep brain stimulation (aDBS) is a novel stimulation approach designed to tackle these limitations. In aDBS, stimulation is titrated up or down according to neurophysiological biomarkers which are able to reflect the clinical state of PD patients. Preliminary studies have explored the feasibility of applying aDBS in the STN of PD patients [2]. However, only one study so far has shown the superiority of aDBS in the immediate postoperative phase, using unilateral recordings of 3 of the 33 motor items of the Unified Parkinson's Disease Rating Scale (UPDRS) [3]. A subsequent aDBS study in the immediate post-operative phase did not show significant differences between cDBS and aDBS, when tested in more ecological circumstances.[4] A potential confounding factor of such studies is that the measurements have been collected in the presence of the 'stun' or 'microlesion' effect. This effect is often present immediately after implantation of DBS, and causes temporary clinical improvement that cannot be further improved with stimulation.

In 2017, we reported the novel concept of performing aDBS recordings in a patient who already had DBS electrodes implanted for 14 years [5]. Apart from the absence of the stun effect in the chronic phase, another advantage of using this approach is that the response of the patient to DBS has already been verified before inclusion. This represented a step forward in establishing the true effect of aDBS. Velisar et al.[6] took this approach to the next level by using a fully implanted device, opening the possibility of more exhaustive recordings. In their article, the authors report their experience with a novel aDBS system, referred to as Neural Closed loop DBS (NclDBS), that was tested in 13 PD patients with chronically implanted DBS electrodes in the STN. The key finding of their study is that NclDBS was tolerated for at least 21 minutes, and led to the suppression of tremor and bradykinesia, while less energy was delivered than in cDBS. A substantial cohort of patients was reported, all implanted with an investigational sensing neurostimulator (Activa PC+S, Medtronic, Inc.). This type of neurostimulator was driven by an external control system (NexusD3, Medtronic, Inc) in the chronically implanted state. Their results showed a significant clinical improvement with both cDBS and aDBS conditions, compared to no stimulation. Unfortunately, clinical outcomes were measured using different techniques: a clinical rating scale for the former, and kinematic testing with an accelerometer for the latter. Therefore, comparison between aDBS and cDBS using equal rating scales or surrogate markers in both conditions should be a subsequent step to evaluate the clinical benefits of aDBS.

A. Spatial Accuracy

B. Temporal Accuracy

Figure 1. A.1: schematic representation of the current application of adaptive DBS (aDBS): a bipolar local field potential (LFP) derived from two contact points is used for the recording of beta oscillations. Monopolar stimulation is provided with the electrode in between. A.2: schematic representation of a potentially more refined form of adaptive stimulation by using 'steering' electrodes which would enable aDBS recordings at the sub-millimeter scale. B: illustration of the typical volatility of beta oscillations at the sub-second scale. Figure B Derived with permission from Tinkhauser et al. Brain 2017.

Given the necessity to prove the effectiveness of aDBS in a clinical setting, experimental studies on aDBS in PD, are received with great enthusiasm. The rapidly increasing number of publications on aDBS in PD reached approximately 500 in 2018 [2]. Paradoxically, the number of aDBS-subjects evaluated using clinical outcomes counted only approximately 50. Such a discrepancy illustrates the technical difficulties to translate conceptual aDBS prototypes into systems that can be tested in patients. Nevertheless, given the strong empirical evidence that indicates the existence of an optimal amount of stimulation [1], aDBS has a promising future in clinical practice.

An added challenge to compare the clinical effects of aDBS across studies is that several paradigms to modulate stimulation have been explored [3,6,7]. Also, feedback signals have been obtained from different recording sites [8]. In these studies, the DBS contacts used to obtain bipolar LFP recordings were different from the contacts used for stimulation. This means that the anatomical location where beta oscillations are recorded might be situated more than 2mm from the stimulation site. For that reason, stimulation might not be provided directly to the source of beta activity. This could be potentially circumvented by directing aDBS to the active DBS contact point used to sense neural oscillations, by means of ‘steering’ electrodes (Fig. 1A) [9].

Another fundamental question yet to be answered is how fast stimulation needs to be titrated. aDBS systems that titrate stimulation in a staggered way might provide a better control than intermittent ON/OFF systems to fast reacting symptoms, such as tremor. However, as beta bursts longer than 500ms have been positively associated with clinical impairment [10], the question is whether staggered control algorithms are volatile enough to selectively suppress pathological beta bursts (Fig. 1B). Finally, the applied stimulation algorithms for aDBS are virtually unexplored, which questions whether the same (high frequent) stimulation parameters as in cDBS need to be applied in aDBS.

Given all previous arguments, we consider that the availability of fully implanted DBS devices that are able to simultaneously record and deliver stimulation, will accelerate research in closed-loop systems. By comparing aDBS with cDBS, it will be possible to determine which candidates are the most suitable and for (a) sensing sites, (b) ‘physiomarker’ definitions and (c) stimulation algorithms.

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Adaptive Deep Brain Stimulation for dystonia

8

Toward adaptive Deep Brain Stimulation for dystonia

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KEYWORDS

- adaptive deep brain stimulation
- dystonia
- local field potentials
- electromyography
- low-frequency oscillations

Abstract

The presence of abnormal neural oscillations within the cortico-basal ganglia-thalamo-cortical (CBGTC) network has emerged as one of the current principal theories to explain the pathophysiology of movement disorders. In theory, these oscillations can be used as biomarkers and thereby serve as a feedback signal to control the delivery of deep brain stimulation (DBS). This new form of DBS, dependent on different characteristics of pathological oscillations, is called adaptive DBS (aDBS), and it has already been applied in patients with Parkinson's disease. In this review, the authors summarize the scientific research to date on pathological oscillations in dystonia and address potential biomarkers that might be used as a feedback signal for controlling aDBS in patients with dystonia.

Introduction

According to the latest expert consensus, dystonia is clinically defined as “a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.”² Dystonia can be caused by numerous etiologies, including acquired and different biochemical, cellular, or genetic substrates. The similarity of the clinical dystonia phenotype, however, suggests a unifying common pathophysiological pathway at a functional or network level.⁴ A currently leading hypothesis on its neurophysiological basis is that dystonia is the result of abnormal activity in cortico-basal ganglia-thalamo-cortical (CBGTC) and cerebellar networks.⁵² The treatment for the majority of dystonia subtypes only provides symptomatic relief, without addressing the underlying cause of the disease. Options currently available include oral medication (e.g., anticholinergic and antidopaminergic drugs, benzodiazepines, and baclofen), botulinum toxin (treatment of choice in focal dystonias), and deep brain stimulation (DBS).⁴

DBS in Dystonia

Given the limited efficacy and high prevalence of adverse effects associated with oral medication in generalized dystonia, DBS of the internal globus pallidus (GPi) has become the preferred therapy in this patient group.⁴ Several randomized controlled trials have demonstrated a sustained improvement in patients with (isolated) generalized dystonia following DBS, as shown by lower motor and functional scores on the Burke-Fahn-Marsden dystonia rating scale.²⁹ After 5 years of DBS, generalized dystonia is reported to show a reduction in the Burke-Fahn-Marsden dystonia rating scale score of 42%–61%.⁸ Furthermore, the health-related quality of life after DBS for dystonia improves significantly, by about 24%–51%, among several independent trials.²⁷ DBS therapy has also been utilized in other types of dystonia when an adequate response to botulinum toxin therapy could not be achieved.²⁴ A large, randomized clinical trial demonstrated that DBS is useful in medication-refractory cervical dystonia compared to sham stimulation, with a significant improvement of the Toronto Western Spasmodic Torticollis Rating Scale severity score (26% vs 6%, respectively), 3 months after implantation.⁷³

Despite its good effect, the exact mechanism of DBS in dystonia remains unclear,¹⁰ and clinical outcomes can differ from patient to patient, as well as among different subtypes of dystonia.⁸ Patients at an early stage of the disease and with less disability usually respond better to DBS. This is especially the case in patients with DYT1

mutations and tardive dystonia. In contrast, the response in other types of dystonia is less predictable, which makes the selection of appropriate candidates for DBS challenging.³

Drawbacks of Current (Continuous) DBS

More than 15 years of experience with DBS in dystonia has demonstrated the efficacy of the current model of continuous DBS (cDBS) once the optimal stimulation parameters have been achieved.⁴¹ Nevertheless, there are still limitations in terms of efficacy and side effects related to cDBS. Due to limited knowledge of CBGTC and cerebellar networks in dystonia, the modification of electrical stimulation parameters in DBS is essentially heuristic, and DBS programming is based on clinical records and examination. In this process, the clinician starts with the conventional initial settings of the DBS system, delivering a constant current or voltage through the selected electrode(s). The settings are then adjusted in a trial-and-error process, based on the clinical response and the absence of adverse effects.⁵⁰ However, an immediate response is often not possible to achieve, since it generally takes weeks to months to notice a perceptible change, especially in tonic dystonic components.⁵³ For this reason, it can take up to several weeks to modify the initial parameters.³⁰ In general, significant improvement can be expected approximately 3 months after the surgery, but it usually takes up to a year to achieve the maximum clinical effect.⁴¹ Another technical problem is the voltage required for stimulation in dystonia. While a mean of 3.0 V is usually effective to obtain an adequate clinical response in Parkinson's disease (PD) patients, with electrodes implanted either in the GPi or the subthalamic nucleus,⁴⁷ the effective voltage in dystonia is more variable. It depends, among other things, on the type of dystonia, the area of the body affected, and the patient's tolerance of high voltages (due to the subsequent emergence of stimulation-related side effects), ranging from 2.2 up to 7.0 V.²⁸ Therefore, non-rechargeable batteries need to be replaced more often, with a mean longevity of 28.1 months for dystonia compared with 47.2 months for PD.⁵³ This not only increases the treatment costs, but it also exposes the patient to more surgical procedures, as well as their attendant risks.

Finally, there are significant side effects induced by cDBS in dystonia patients, such as dysarthria (in up to 12%)²⁹ and parkinsonism (13%).⁷⁰ Among patients with cranial-cervical dystonia treated with GPi DBS, 90% reported at least one motor symptom associated with parkinsonism, such as handwriting problems, difficulty with standing up from a chair, and gait disturbances.⁷ In line with this, a correlation has been described between the increase in GPi stimulation frequency and the

development of bradykinesia.²⁶ The appearance of these side effects after stimulation suggests that DBS interferes with both pathological activity in the CBGTC circuits³⁹ and physiological activity that helps to control voluntary movements.^{9,29} To improve efficacy and limit side effects, much effort has been put into developing DBS systems that only stimulate when pathological activity and clinical symptoms are present.³⁹ Future DBS devices might be able to deliver electrical stimulation in response to pathological oscillations by increasing electrical current on demand—that is, only when, for example, the oscillatory power exceeds a threshold.⁴⁶ This adaptive form of DBS (aDBS) has already been successfully applied in nonhuman primate models of PD⁵⁶ by using the occurrence of cortical spikes as a biomarker. In patients with PD, there is also evidence of the effectiveness of aDBS.^{32,34,51,55} In these studies, the power of subcortical beta (13–30 Hz) oscillations, which correlate with bradykinesia and rigidity in PD,⁵⁴ was used as a biomarker. The most important positive effects of human aDBS studies in PD were increased efficacy, energy- saving properties, and potentially fewer side effects. This line of evidence strongly suggests that pathological oscillations can successfully be used as a biomarker for controlling DBS.

Preparing the Way for aDBS in Dystonia

Neural Oscillations as Biomarker

Neural oscillations are part of the physiological components present in the regulatory pathways of voluntary movements and are potentially a means by which neuronal structures communicate among one another and with muscular units.⁶¹ The relationship of oscillations between two different sources can be addressed by means of coherence analysis, which indicates the degree of mutual dependence.¹² Experiments carried out in healthy subjects have shown an increased coherence between cortical beta activity (13–30 Hz) and contralateral muscle discharges, respectively recorded with electroencephalography (EEG) and electromyography (EMG), suggesting that voluntary contractions are coupled with the physiological oscillatory activity of cortical neurons.^{12,60} In certain movement disorders, this physiological oscillatory activity is thought to be altered, since abnormal (pathological) oscillatory profiles have been detected.^{5,18,43} The use of subcortical beta oscillations as a biomarker for aDBS in PD was motivated by recordings of synchronized activity of large populations of neurons in the basal ganglia, known as local field potentials (LFPs). These LFPs can be recorded from the same DBS electrode contacts that deliver electrical stimulation. During a recording, LFPs are rapidly processed, and changes in power on a selected frequency band (e.g., beta range) are detected through spectral

analysis. The increase in frequency power triggers DBS in PD, which is continued until the power drops below a selected threshold.²⁵

One of the lessons learned from aDBS in PD patients is that the feedback signal of a biomarker needs to be both sensitive and specific. This means that the biomarker should correlate well in time with the severity of clinical symptoms (specificity)³³ and that the signal detected should be powerful enough to be differentiated from artifacts—e.g., the noise caused by the stimulation itself (sensitivity).⁵⁷

Figure 1. Potential interface for aDBS using low-frequency oscillations. In this figure, the presence of low-frequency oscillations on an LFP is visualized and used for an adaptive stimulation algorithm. Raw signals (LFP L and R) are dynamically recorded and filtered around the low-frequency peak registered (FILT LFP L and R). Afterwards, the filtered signal would be rectified, and an amplitude threshold would be set, in order to trigger the stimulation (STIM L and R) every time that an increment in low-frequency activity is detected. A brief delay in the activation of the stimulation would ensure that the stimulation is triggered only by actual increments of low-frequency activity and not by short-lived artifacts. AMP ENV = amplitude envelope of the rectified filtered signal; FILT LFP = LFP filtered around the low-frequency peak detected in order to visualize low-frequency oscillations embedded in the signal; L = left; R = right; STIM = channels representing stimulation amplitude.

Neural Oscillations in Isolated (Primary) Dystonia

As discussed above, increased beta oscillations have been found in patients with PD and used as a biomarker for aDBS. To answer the question of whether it is possible to transfer aDBS from PD to dystonia, it is necessary to identify biomarkers for the latter (Fig. 1, Table 1). Several studies have addressed the presence of (pathological) oscillations in patients with isolated dystonia. LFP recordings have shown increased

Biomarker	Advantages	Disadvantages	Further questions
I. GPI LFPs 4-12Hz magnitude/spectral power	Most studied oscillations. Correlated with phasic dystonia. Direct measurement of pathological network activity.	Not correlated with tonic dystonia. Noise generated by stimulation might interfere.	Evaluate the adequacy of the biomarker
II. Muscle activity (EMG) 4-12 Hz magnitude/spectral power	Coherent with LFP's. Direct measurement of dystonic activity.	Additional device required for EMG	Investigate applicability of subcutaneous EMG in aDBS.
III. Dystonic tremor (EMG) 4-12 Hz magnitude/spectral power	Potentially useful if tremor is the predominant symptom. Direct measurement of a clinical symptom.	Non-specific biomarker.	Develop algorithms capable of increased specificity in detection of dystonic tremor
IV. Electroencephalography 4-12 Hz spectral power	Potential alternative for aDBS use. High signal amplitude and less stimulation interference.	Subdural electrodes needed to be placed. Still at an early phase.	Elucidate which ECoG biomarkers could be used as a feedback for aDBS.
V. Coherence between biomarkers (e.g. LFP - EMG)	Correlates two different sources of pathological oscillations.	At least two different devices are required. Lower temporal resolution.	Examine whether coherence estimation is sufficiently fast for adaptive stimulation.
EMG agonist-antagonist ratio/sum	Identifies when dystonic activity is present. Good time resolution.	At least two different devices are required. Non-specific Not predictive (rather reactive)	Explore possibilities of using this statistic to increase the specificity and time resolution of aDBS biomarkers.
Common to all biomarkers is the need to establish their robustness across time and their reliability during brain states like sleep.			

Table 1. Potential biomarkers for aDBS in dystonia with their advantages, disadvantages, and challenges.

power in low frequencies (4–12 Hz) in dystonia patients.⁶⁴ Chen et al. demonstrated a positive correlation between pallidal low-frequency oscillations and muscle (EMG) activity in dystonia patients that was consistent among all contact pairs of the tested DBS-electrodes.⁹ In the same experiment, an additional correlation was found in the beta range (13–30 Hz), but this was not consistent among different contact pairs. Abnormal low-frequency oscillations have not only been found between GPi and EMG, but also in LFPs recorded in the subthalamic nucleus of dystonia patients^{17,45} and between different EMG signals.⁶⁹ Directed transfer analyses suggest that this excessive oscillatory GPi activity is mostly driven from the GPi to the affected muscles.⁶²

Furthermore, a sensorimotor modulation of GPi LFPs has been observed in response to active and passive movements, with a decreased LFP synchronization at 8–20 Hz and in dystonic involuntary muscle spasms with an increased activity in the range of 3–18 Hz.³⁵ This modulation of LFPs has also been observed in patients with an effective sensory trick (directing actions or movements to a specific part of their bodies where dystonia is present in order to alleviate their symptoms²).⁶⁷ In these patients, a suppression of the abnormally synchronized activity in the range of 6–8 Hz and beta bands was observed during the performance of the sensory trick, indicating a peripheral regulation of the CBGCT oscillations. In summary, information from peripheral stimuli also influences the behavior of neural oscillations, at least to a certain degree. A major finding that directly supports the use of low-frequency (4- to 12-Hz) oscillations as a biomarker for dystonia was described by Barow et al.⁵ In this study, increased low-frequency oscillations recorded from DBS electrodes of dystonia patients were significantly suppressed at the moment DBS was switched on, and they reemerged after stimulation was switched off. Additionally, increased coherence from EEG LFPs and EMG LFPs within the 4- to 12-Hz range was reduced after DBS stimulation. Another study showed that increased low-frequency activity in the cortex is normalized after applying DBS.⁴⁰ These findings indicate that the application of high-frequency GPi DBS modulates the abnormally increased low-frequency activity. For these reasons, a paradigm for aDBS in dystonia based on the level of low-frequency oscillations seems plausible (Fig. 2).

The studies mentioned so far in this section included a varying degree of patients with different types of local, segmental, and generalized forms of isolated dystonia (both sporadic and genetic/familial) in their cohorts. For that reason, the specific roles of low-frequency oscillations in each form of isolated dystonia are currently unclear. Recently, a study that only included patients with cervical dystonia showed that the power of low-frequency oscillations in the dystonic GPi positively correlates

with Toronto Western Spasmodic Torticollis Rating Scale scores, and an increased coherence is present between dystonic GPi and EMG signals in the low-frequency band.⁴⁴ This gives a rationale for the employment of low-frequency oscillations as a biomarker for aDBS in this particular group. Although several comparative studies have found increased subcortical low-frequency activity to be a characteristic of dystonia when compared to PD,^{17,64,75} this has not always been replicated.^{65,68,74} The co-occurrence of dystonia and PD might, at least partially, explain this phenomenon.⁷¹ However, the exact role of (pathological) low-frequency oscillations in dystonia is yet to be clarified.

Figure 2. Potential biomarkers and recording sites. Dystonic brain activity (A) (e.g., increased low-frequency oscillations) can be recorded either in the form of local field potentials—from the electrodes used for stimulation or from electrodes placed on the cortical surface of the brain (electrocorticography) (1). Dystonic muscle activity (B) can be recorded either from subcutaneous EMG (2) or through wearable devices (3), which could also detect dystonic tremor (C), thanks to integrated accelerometers. Signals can be instantaneously processed in the battery (4), to modulate stimulation according to the biomarker selected (to visualize a stimulation algorithm [see Fig. 1]).

Neural Oscillations in Other Types of Dystonia

Although virtually all neurophysiological studies described above have been carried out in patients with diverse forms of isolated dystonia, some studies have

shown similar results for increased low-frequency oscillations in other subtypes of dystonia, indicating at least a partially shared common pathophysiology for all of them. Prominent 5- to 18-Hz oscillations from the GPi and thalamus were recorded in a patient with acquired dystonia secondary to a cryptogenic stroke.⁷² Furthermore, studies based on LFP-EMG and EMG-EMG coherence analysis have found an increased abnormal coherence in the low-frequency range in patients with myoclonus-dystonia.^{15,16} These findings suggest that another potential biomarker to modulate the intensity of aDBS could include the low-frequency common drive to motor units detected through EMG; detection of this could be technically possible thanks to the development of subcutaneous EMG registers that can transmit the information wirelessly to the DBS generator.^{38,59}

Phasic and Tonic Components of Dystonia

While dystonia is usually composed of tonic (sustained) and phasic (rhythmic) abnormal movements,² increased low-frequency oscillations have only, thus far, been correlated with the phasic components of dystonia,^{36,44} including the reduction of such abnormal oscillations after cDBS.⁵ With conventional cDBS, the clinical improvement of phasic and tonic components differs in time; phasic components improve faster (sometimes even immediately) following the application of DBS, whereas improvement in tonic components can take weeks to months.¹¹ In contrast, when discontinuing stimulation, phasic components can recur rapidly, while tonic components recur in a more gradual manner.¹⁹ This temporal dissociation leads to the hypothesis that different pathophysiological mechanisms are involved.¹ The rapid improvement seen in the phasic components is thought to be due to a direct DBS effect, whereas changes in tonic components are attributed to stimulation effects on neuronal plasticity.²² It has been observed that the benefits of DBS may remain after stimulation is discontinued, even after the 1-year follow-up period.^{20,58,66} This could imply that DBS produces a series of readjustments in CBGTC and cerebellar networks that persist after stimulation has ceased. It remains to be elucidated how aDBS might influence the tonic components of dystonia.

Dystonic Tremor

A specific component of phasic dystonia in which aDBS might be considered is the presence of dystonic tremor. The prevalence of tremor in patients with dystonia varies from 11% to 87% among studies.¹⁴ Lee et al. contrasted data of patients with task-specific primary bowing tremor (a task-specific tremor especially occurring in string musicians) with data obtained in matched healthy controls, revealing coherence between the coactivation of wrist antagonist muscles (measured with EMG) and tremor fluctuation (measured with accelerometers on the metacarpal-phalangeal joint

of the index finger) in the low-frequency range only in the patient group.³¹ Whereas this might indicate an influence of the dystonic oscillatory activity in dystonic tremor, more studies are required to elucidate this relationship. At present, when the tremor is the most disabling symptom,²¹ the ventral intermediate/ lateral thalamus is used as a primary target in dystonia patients.⁴²

In a recent study, patients had an improvement of 77% on clinical tremor scales after DBS of the ventrolateral thalamus.⁴⁹ However, significant side effects also occurred, which raises the question of whether aDBS based on tremor amplitude/phase could be an alternative. However, at this moment, the assessment of tremor using current accelerometers is still nonspecific, owing to the difficulties in distinguishing accelerometer signals resultant from voluntary movements. Advanced tremor-specific accelerometer computation paradigms to treat patients with PD are currently being explored,³⁷ so in theory similar devices to assess dystonic tremor might be applied in the future.⁶³

Electrocorticography

Electrocorticography (ECoG) recording is another neurophysiological tool that might be considered for aDBS. It uses electrodes implanted in the subdural space, giving a powerful spatial resolution of local cortical activity. One of the first ECoG studies on movement disorders used this technique to measure cortical LFPs in patients with PD, essential tremor, and (cranio-)cervical dystonia.¹³ In the resting state, the authors found a peak in motor cortex LFPs that occurred in the high-beta band for PD and in the low-beta band for dystonia and essential tremor. They also found an impaired cortical beta desynchronization related to movement, present in both motor and somatosensory areas. Low-frequency oscillations (4–12 Hz) were not analyzed in this study due to roll-off interference of the high-pass filter in the recordings. Recently, the utility of ECoG to measure neural oscillations in the CBGCT network was addressed in a series of 189 patients (200 recordings) with movement disorders undergoing DBS surgery.⁴⁸ Some of the advantages of ECoG mentioned included higher-amplitude signaling, less DBS noise interference, and potentially a safe clinical profile (no significant adverse events added to the DBS procedure were reported in this study). These findings give rise to the potential use of ECoG to further investigate oscillations within the CBGTC network and, ultimately, find a potential biomarker for aDBS.

Temporal Dynamics of Prospective Biomarkers

One of the main questions that need to be answered before implementing aDBS in dystonia is what the temporal characteristics of the selected biomarker are. The

latency and duration of the biomarkers mentioned (e.g., GPi-LFPs), and how fast they react to electrical stimulation, should be investigated to determine how the aDBS system must be programmed and how well it can anticipate rather than react to the appearance of symptoms.

Combining Neurophysiological Techniques

In addition to single signals, the relation between oscillatory activity at two different sources, by means of coherence and/or other statistics might be used for aDBS. For example, LFP-EMG coherence or the EMG agonist-antagonist (AA) ratio might provide a more informative biomarker than a single-site recording. As mentioned before, increased coherence between LFP-EMG and EMG-EMG has been correlated with the severity of dystonic contractions.^{15,16} In relation to this, aDBS might be programmed based on the volatility in coherence. Nevertheless, to perform a “real-time” coherence analysis, the original signal has to be estimated over a finite period of time, limiting temporal resolution.

Besides coherence, other indicators of dystonic muscle activity can be obtained from EMG. This is based on the evidence that the co-contraction and overflow of AA muscles have been found on EMG measurements of dystonic patients.⁶ However, at present, an AA sum or AA ratio is not yet specific enough to differentiate signals of pathological contractions from voluntary contractions.²³ In the future, evaluation of the predictive value of combined signals through machine learning may lead to greater specificity.

Conclusions

After years of successful application in dystonia, the potential of cDBS is still limited in terms of efficacy, side effects, and efficiency. Next to this, the current lack of neurophysiological parameters that can predict the individual clinical response of dystonia to DBS makes programming difficult. For these reasons, improvements in knowledge about the neurophysiological alterations underpinning dystonia and the emergence of DBS devices capable of simultaneously recording neural activity and providing stimulation should allow aDBS to be developed for the treatment of dystonia in the future. At present, 4- to 12-Hz LFP oscillations appear to be the most promising candidate, but other neurophysiological signals (e.g., those from EMG and ECoG) and their interactions might also be suitable. However, many questions remain,

such as the effects of microlesion effects, sleep, and medication on DBS recordings. Regardless of the source of the biomarker or biomarkers selected for aDBS, their volatility and robustness over time will have to be established. Critical too, most of the potential biomarkers described here relate to phasic aspects of dystonia, and therefore the more delayed response of more tonic dystonic elements to aDBS remains to be established.

Acknowledgments

We would like to thank Prof. Peter Brown for his advice.

This review was carried out thanks to public funds received from the Dutch Brain Foundation (Hersenstichting Nederland), the National Mexican Council of Science and Technology (CONACYT), and the University of Groningen/University Medical Center Groningen (RuG/UMCG).

S.L. is personally supported by the Wellcome Trust (105804/ Z/14/Z).

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Piña-Fuentes, Beudel. Drafting the article: Piña-Fuentes, Beudel. Critically revising the article: Piña-Fuentes, Beudel, Little, van Dijk, Tijssen. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Piña-Fuentes. Administrative/technical/material support: Piña-Fuentes. Study supervision: Beudel.

9

Low-frequency oscillation suppression in dystonia: Implications for adaptive Deep Brain Stimulation

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Parkinsonism and Related Disorders 79 (2020) 105–109.

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HIGHLIGHTS

- A mild low-frequency oscillation (LFO) suppression in dystonia directly follows cDBS.
- Changes in dystonic symptoms might not occur directly after stimulation delivery.
- Patients with chronic cDBS present significantly lower LFO than DBS-naïve patients.
- LFO-suppression in dystonia, similar to symptom response to cDBS, might be gradual.
- aDBS could be programmed to track gradual changes in background LFO-power.

Abstract

Background: Low-frequency oscillations (LFO) detected in the internal globus pallidus of dystonia patients have been identified as a physiomarker for adaptive Deep Brain Stimulation (aDBS), since LFO correlate with dystonic symptoms and are rapidly suppressed by continuous DBS (cDBS). However, it is as yet unclear how LFO should be incorporated as feedback for aDBS.

Objectives: to test the acute effects of aDBS, using the amplitude of short-lived LFO-bursts to titrate stimulation, to explore the immediate effects of cDBS on LFO-modulation and dystonic symptoms, and to investigate whether a difference in the resting-state LFO is present between DBS-naïve patients and patients with chronic DBS.

Methods: seven patients were assessed during either DBS-implantation ($n = 2$) or battery replacement surgery ($n = 5$), and pseudorandomized in three conditions: no stimulation, cDBS, and aDBS. Additionally, resting-state LFP-recordings from patients undergoing battery replacement were compared to those obtained during DBS-implantation; LFP-recordings from a previous cohort of six dystonia patients undergoing DBS-implantation were incorporated into this analysis (total $n = 8$ newly implanted patients).

Results: we corroborated that a mild LFO-suppression rapidly occurs during cDBS. However, no acute changes in clinical symptoms were observed after cDBS or aDBS. Remarkably, we observed that resting-state LFO were significantly lower in patients who had been effectively treated with chronic cDBS compared to those of newly implanted patients, even when stimulation was suspended.

Conclusions: our results indicate that LFO-suppression in dystonia, similar to symptom response to cDBS, might be gradual, and remain after stimulation is suspended. Therefore, tracking gradual changes in LFO may be required for aDBS implementation.

1. Introduction

Conventional, continuous deep brain stimulation (cDBS) of the internal globus pallidus (GPi) is an advanced treatment for dystonia. Although cDBS is efficacious, it still has some drawbacks. It takes months to find the right programming settings, as dystonia reacts relatively slowly to stimulation [1]. Also, its clinical benefits can be limited, and stimulation-dependent side-effects, such as parkinsonism and dysarthria [1,2], can occur. In order to minimize the impact of stimulation-induced side-effects, while preserving the beneficial effect of stimulation, the development of adaptive DBS (aDBS) for dystonia has been proposed [3]. aDBS aims to reduce the total amount of stimulation by titrating stimulation up or down, according to the presence of dystonic symptoms. In order to predict whether symptoms are present, aDBS requires electrophysiological biomarkers (physiomarkers) that are able to reflect the clinical state of the patients [4]. Up to now, the most promising physiomaer for dystonia is the magnitude of low-frequency oscillations (LFO; 4–12 Hz) embedded in the local field potential (LFP) activity of the GPi. Those oscillations are increased in dystonia [5], and correlate with the severity of dystonic symptoms [4]. However, it is as yet unclear how LFO should be incorporated as a feedback signal for aDBS, given that these oscillations present distinctive characteristics at different timescales. On a millisecond timescale, it has been observed that LFO occur in the form of short-lived bursts, and that the amplitude of those bursts is increased in dystonia patients [6]. On a second-to-minute timescale, it has been shown that GPi-LFO power gets swiftly suppressed in dystonia patients during cDBS, predominantly in patients with phasic symptoms [7]. However, it is still unclear whether a fast LFO-suppression is synchronous with a reduction in dystonic symptoms during stimulation. On a longer timescale (minutes to hours or more), it has been observed that slow increments in background LFO-power take place in dystonia patients chronically treated with cDBS, after stimulation is suspended [8]. Those increments in LFO are proportional to the return of dystonic symptoms caused by switching off stimulation, which suggests that not only symptoms, but also LFO are chronically suppressed by cDBS. For the aforementioned reasons, aDBS could be programmed to respond either to dynamic changes in LFO-burst amplitude, to fast changes in LFO-power, or to gradual changes in background LFO-power.

In this study, we explore the effects of delivering stimulation at three different timescales in dystonia patients, in order to generate data-driven hypotheses about the incorporation of LFO as feedback signal in aDBS for dystonia. Firstly, we test the immediate effects of burst-based aDBS, in which the amplitude of LFO-bursts is used as feedback signal to dynamically titrate stimulation. Secondly, we explore the

acute effects of cDBS, in order to confirm the presence of a LFO-suppression directly after cDBS, and to investigate the relationship between this suppression and dystonic symptoms. Lastly, we estimate the chronic effects of stimulation on LFO-power, by comparing the recordings of DBS-naïve patients with those of patients with chronic cDBS.

2. Methods

2.1. No-Stimulation, cDBS and aDBS trials

2.1.1. Patients

Seven dystonia patients who underwent either DBS implantation ($n = 2$) or battery replacement surgery ($n = 5$) at the University Medical Center Groningen, the Netherlands, were included in the study. The protocol was approved by the local ethical committee; all patients provided written informed consent. Patients were operated under local anesthesia, and anti-dystonic medication was suspended at least 12 h before the procedure.

2.1.2. Recordings

LFP-recordings were obtained 20–30 min after intraoperative stimulation testing (DBS-implantation) or 20–30 min after DBS was turned off (battery replacement). The recording procedure lasted approximately 15 min, which has been previously described [6]. In brief, the extension wires that connect to the DBS leads were exposed and attached to a custom-made amplifier (Fig. 1A). This amplifier allows for bilateral LFP-recordings, using a bipolar montage from either contacts 0–2 or 1–3, and can simultaneously provide stimulation from either contacts 1 or 2, respectively. Bipolar recordings were obtained at a sampling rate of 2000 Hz, while applying a bandpass filter between 3 and 37 Hz.

Spike2 software (V.8, Cambridge, United Kingdom) was employed for the recordings. For each hemisphere, a baseline recording of approximately one minute was obtained from each bipolar contact (NoStim0) during rest, and periodograms were calculated for each bipolar LFP, in order to identify a low-frequency peak. The contacts selected to further record/stimulate for each hemisphere were chosen based on the contacts that met the most of these conditions: a) contacts that presented the highest low-frequency peak; b) contacts that provided a clear LFP signal; c) contacts that were used in the clinical care (in patients with chronic DBS).

Pt.	Age	Sex	Dystonia type	Disease duration (y)	Years with DBS ^a	Type of operation	Antidystonic medication	BFMDRS PRE/POST ^b	TWSTRS PRE/POST ^b	DBS parameters ^c	Channels used for recording
Adaptive Deep Brain Stimulation patients											
Dys aDBS-GPi 1	65	F	Blepharospasm and oromandibular dystonia (Meige's syndrome)	9	5	Battery replacement	Botulinum toxin every 10 weeks	22/13.5	14/9	L: 0-/C+: 1.5 V; 80 Hz; 300 µs R: -3/C+: 2.0 V; 60 Hz; 80 µs	L: 0-2 R: 1-3
Dys aDBS-GPi 2 ^d	64	M	Segmental dystonia + Parkinson's disease	4	0	New implantation	Botulinum toxin every 2 months	8/5	19/18	L: 0-/C+: 3.5 V; 135 Hz; 90 µs R: -2/C+: 3.5 V; 135 Hz; 90 µs	L: 1-3 R: 1-3
Dys aDBS-GPi 3 ^e	55	M	Segmental dystonia (torticollis)	5	2	Battery replacement	Clonazepam	23/14.25		L: -0/C+: 3.8 V; 135 Hz; 90 µs R: -0/C+: 3.7 V; 135 Hz; 90 µs	L: 0-2 R: 0-2
Dys aDBS-GPi 4	69	F	Blepharospasm and oromandibular dystonia (Meige's syndrome)	4	0	New implantation	Oxazepam	24/24	17/16	L: 0-/3+: 3.0 V; 135 Hz; 60 µs R: 0-/3+: 3.0 V; 135 Hz; 60 µs	L: 0-2 R: 0-2
Dys aDBS-GPi 5	83	F	Segmental dystonia (torticollis)	28	14	Battery replacement	Clonazepam, Pregabalin	9/6.5	19/16	L: -2/C+: 5.0 V; 130 Hz; 90 µs R: -2/C+: 5.0 V; 130 Hz; 90 µs	L: 1-3 R: 1-3

Pt.	Age	Sex	Dystonia type	Disease duration (y)	Years with DBS ^a	Type of operation	Antidystonic medication	BFMDRS PRE/ POST ^b	TWSTRS PRE/ POST ^b	DBS parameters ^c	Channels used for recording
Dys-aDBS-GPi 6	67	F	Oromandibular dystonia	9	3	Battery replacement	Clonazepam	17/18,25		L: -2/C+: 3.5 V; 130 Hz; 120µs R: -2/C+: 3.5 V; 130 Hz; 120µs	L: 1-3 R: 1-3
Dys-aDBS-GPi 7	53	F	Generalised dystonia	25	3	Battery replacement	Oxazepam, Trihexyphenidyl, Botulinum toxin	63.75/44.75		L: -0/1+: 4.0 V; 130 Hz; 120µs R: -0/1+: 3.5 V; 130 Hz; 120µs	L: 1-3 R: 0-2
Previous cohort dystonia patients											
Dys-GPi 1	47	M	Generalised (secondary) + spastic hemiparesis	11	0	New implantation	Lorazepam	49/53		L: -1/C+: 2.2 V; 135 Hz; 90µs R: -0/C+: 2.2 V; 135 Hz; 90µs	L: 0-2 R: 0-2
Dys-GPi 2	52	M	Segmental dystonia (torticollis)	3	0	New implantation	Clonazepam	23/14.25		L: -0/C+: 3.8 V; 135 Hz; 90µs R: -0/C+: 3.7 V; 135 Hz; 90µs	L: 0-2 R: 0-2
Dys-GPi 3	52	F	Segmental dystonia (Myoclonus-dystonia)	33	0	New implantation	Propranolol, zolpidem	25.25/12	22.5/17.5	L: -1/C+: 3.2 V; 130 Hz; 60µs R: -1/C+: 3.1 V; 130 Hz; 60µs	L: 0-2 R: 0-2
Dys-GPi 4	63	M	Cervical dystonia	20	0	New implantation	Clonazepam	19.5/11.25	16.5/13.5	L: -0/1+: 3.6 V; 130 Hz; 60µs R: -0/1+: 3.6 V; 130 Hz; 60µs	L: 0-2 R: 0-2

Pt.	Age	Sex	Dystonia type	Disease duration (y)	Years with DBS ^a	Type of operation	Antidystonic medication	BFMDRS PRE/POST ^b	TWSTRS PRE/POST ^b	DBS parameters ^c	Channels used for recording
Dys-GPi 5	63	M	Segmental dystonia (torticollis and oromandibular) + Holmes tremor	63	0	New implantation	Clonazepam	13.75/5	20/8.5	L: -1/C+: 3.4 V; 180 Hz; 120 µs R: -3/C+: 3.2 V; 130 Hz; 90 µs	L: 0-2 R: 1-3
Dys-GPi 6	65	F	Segmental dystonia (torticollis)	12	0	New implantation	-	15.25/12	22/13	L: -0/C+: 3.2 V; 135 Hz; 90 µs R: -0/C+: 2.7 V; 135 Hz; 90 µs	L: 0-2 R: 0-2

Table 1. Clinical details of patients with dystonia included in this pilot study. ^a Years in which patients have been treated with DBS at the moment of battery replacement. ^b Post-operative scores were obtained one year after DBS treatment. ^c Parameters used for cDBS in the clinical setting at the moment of battery replacement, or one year after implantation for patients measured during DBS-implantation. ^d This patient was included due to the presence of prominent segmental dystonia, which led to choose the internal globus pallidus as the DBS target, instead of the subthalamic nucleus. ^e This patient is the same as Dys-GPi 2.

After selecting the contacts, patients were pseudo-randomized into three balanced conditions: no stimulation (NoStim1), cDBS, and aDBS. Conditions were measured sequentially in a crossover fashion and lasted around two to four minutes each. During aDBS, LFPs were filtered around the frequency of the highest low-frequency peak (± 3 Hz), and the filtered signal was rectified. A threshold for stimulation was set at roughly 50% of the maximum amplitude of the smoothed-rectified LFP-envelope (Fig. 1 A.2). Similar settings were applied during cDBS and aDBS conditions (frequency 135 Hz, pulse width 60 μ s). The applied amplitude was the maximum voltage tolerated that did not corrupt the recordings and/or that approached the voltage used for cDBS in the clinical practice. In five of the seven patients, a short version of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and/or the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was videorecorded during each condition, using the facial and cervical subdomains. Afterwards, the aDBS amplifier was disconnected and the surgical procedure continued as usual. Videos were blindly assessed by an independent expert in movement disorders.

2.1.3. Signal processing

Selected LFPs were processed offline using a custom-made script in MATLAB (ver. 2018b, Natick MA, USA), and the FieldTrip-toolbox (University Nijmegen, The Netherlands [9]). Bipolar recordings were filtered at 4–35 Hz. Segments of approximately 2 min were chosen from each condition. Jump artefacts were attenuated using a wavelet denoise filter, and contamination occurring at subharmonic frequencies of stimulation or line noise was removed using the DBSFILT-toolbox, by interpolation with neighboring frequencies (Université Lyon, France [10]).

Immediate changes in LFO-power were explored by obtaining periodograms for each LFP in the NoStim0, NoStim1, cDBS and aDBS conditions, using a multitaper window with 0.5Hz smoothing and 0.5Hz resolution. Each periodogram was normalized by dividing it by the root mean square (RMS) of its total beta power (13–30 Hz), in order to attenuate changes in noise floor due to stimulation, while allowing variations in LFO among conditions. By using the RMS of the beta power, we considered shifts in the whole beta spectrum as a consequence of stimulation changes in the noise floor, and changes in frequency peaks as a result of physiological effects of stimulation (Supplementary Figure 1). Mean low-frequency power was obtained from each periodogram.

2.2. New-implantation and battery-replacement recordings

LFP-recordings during the NoStim0 condition obtained from patients undergoing battery replacement (n=5) were compared to those measured during DBS-implantation (n=2). To complement the DBS-implantation cohort, LFP-recordings from a previous cohort of six dystonia patients obtained during DBS-implantation (described in Ref. [6]) were incorporated into the analysis (total n=8). Previous recordings were re-referenced from monopolar to bipolar, using the configuration 0–2 or 1–3. Channels per hemisphere were selected based on those used for stimulation in clinical practice. LFPs were normalized across subjects by transforming their amplitude into z-scores. Periodograms were derived from those LFPs, and their mean low-frequency power was calculated.

2.3. Statistical analysis

A repeated-measures ANOVA was performed using the mean low-frequency power calculated for the NoStim0, NoStim1, cDBS and aDBS conditions. Additionally, due to the exploratory nature of this study and the limited power of our pilot sample to detect differences at a group comparison level, additional pairwise comparisons were performed between conditions using permutation dependent t-tests. Mean low-frequency power between new-implantation and battery-replacement patients was compared using permutation independent t-tests. BFMDRS and TWSTRS scores were compared among conditions using repeated-measures ANOVA and additional explorative pairwise dependent t-tests between conditions were performed. All units are reported in means $\pm$ standard error of the mean (SEM).

3. Results

Patient information is presented in Table 1. Two GPi-LFP-recordings, each from a different patient, were discarded due to the presence of cardiac artefacts that interfered with aDBS. The group analysis (n=12) among stimulation conditions (NoStim0, NoStim1, cDBS and aDBS) did not reach significance [condition: $F(3,33)=2.27$; $p=0.097$]. Pairwise comparisons between conditions showed a mild but significant mean low-frequency power suppression during cDBS, compared to NoStim0 (Fig. 1B) [mean difference = -0.39 ± 0.17 a.u.; $t(11)=-2.2282$; $p=0.0477$]. The rest of the pairwise comparisons were not significant (Fig. 1C–D, Supplementary Table 1). All patients tolerated aDBS at similar voltages used for cDBS. The total amount of stimulation during aDBS was $43.05 \pm 16.8\%$ of that during cDBS. No acute changes in BFMDRS and TWSTRS scores were observed among conditions (Supplementary Table 2–4)

Figure. 1. Characteristics of low-frequency oscillations in dystonia patients across different conditions.

A) Schematic representation of the stimulation paradigm for aDBS: 1. The electrodes implanted in the internal globus pallidus are connected to the external amplifier (not represented here) through externalized extension wires. 2. In this example, recordings are obtained from contacts 0–2, while delivering stimulation from contact 1. a) LFP bandpass filtered at 3–37 Hz. b) LFP filtered around the low-frequency peak (7 Hz in this example). c) LFP is rectified and smoothed, and an arbitrary threshold is set. d) Stimulation is delivered according to the threshold established.

B) 1. Comparison of normalized PSDs obtained from LFP recordings of dystonia patients without stimulation, before pseudo-randomization (NoStim0) and during cDBS. 2. Comparison of mean low-frequency power between NoStim0 and cDBS.

C) 1. Comparison of normalized PSDs obtained from LFP recordings of dystonia patients without stimulation, before and after pseudo-randomization (NoStim0 and NoStim1 conditions). 2. Comparison of mean low-frequency power between NoStim0 and NoStim1.

D) 1. Comparison of normalized PSDs obtained from LFP recordings of dystonia patients without stimulation, before pseudo-randomization (NoStim0) and during aDBS. 2. Comparison of mean low-frequency power between NoStim0 and aDBS.

E) 1. Comparison of normalized PSDs obtained from LFP recordings of dystonia patients undergoing new DBS implantations (NoStimN) and patients undergoing battery replacements (NoStimB). 2. Comparison of mean low-frequency power of patients undergoing new DBS implantations (NoStimN) and battery replacements (NoStimB).

[BFMDRS-condition $F(2,8)=2.25$; $p=0.1678$; TWSTRS-condition $F(2,6)=1$; $p=0.421$], and pairwise comparisons were not significant. Mean low-frequency power in patients with chronic DBS ($5.73\text{--}4\pm 9.24 \times 10^{-5}$ z-scores) was significantly lower to that of DBS-naïve patients ($9.03 \times 10^{-4}\pm 9.24 \times 10^{-5}$ z-scores, Fig. 1D) [$t(22)=2.4635$, $p=0.0221$].

4. Discussion

In this study, we explored the effects of delivering stimulation at three different timescales in dystonia patients. Firstly, we observed that aDBS based on LFO-bursts did not lead to an acute change in either LFO-power or dystonic symptoms. Given the delayed response of dystonia to stimulation [1], it is possible that fast LFO-components are not able to directly reflect the clinical dystonic state. However, the long-term effects of targeting LFO-bursts still need to be explored. Secondly, we tested the acute effects of cDBS on LFO-power and dystonic symptoms. We confirmed that cDBS can swiftly suppress aberrant GPi-LFO [7]. This result supports the hypothesis that DBS modulates pathological hyper-synchronization in the motor network [5]. However, this acute LFO-suppression is initially subtle and might not be followed by a direct change in symptom severity. Lastly, we observed that the LFO of patients who had been chronically treated with cDBS were considerably lower than those of DBS-naïve patients, even when stimulation was suspended. From all the patients treated with chronic cDBS, most of them (4/5) presented more than the minimal clinically important improvement in dystonic symptoms [11] one year after DBS implantation. Since LFO are correlated with the severity of dystonic symptoms [4], it is possible that the LFO-suppression that takes place during cDBS occurs in a gradual manner, parallel to the gradual reduction in dystonic symptoms observed after cDBS is switched on.

The re-emergence of LFO after cDBS is suspended also occurs in a gradual manner [8]. Barow et al. showed that LFO remain suppressed shortly after stimulation is applied [7]. In our study, we observed that the OFF LFO-power of patients measured after pseudo-randomization (NoStim1) was slightly lower than before pseudo-randomization (NoStim0, Fig. 1C). This can be explained by the fact that in some patients the cDBS condition preceded the NoStim1 condition. This poststimulation effect becomes more apparent when chronic stimulation is suspended, since the LFO of dystonia patients increase only gradually over a period of several hours, if symptoms increase accordingly [8]. Therefore, stimulation algorithms designed to

track gradual changes in oscillatory power [12] can be tested in aDBS for dystonia (Supplementary Figure 2).

4.1. Limitations

The results obtained are preliminary, since a small patient sample was included, and only the acute effects of aDBS were explored. Similar to other studies involving LFP-recordings in dystonia, the patient group included is heterogeneous. Nevertheless, dystonic symptoms and prominent LFO were present in all patients. Prospective studies are required to explore the chronic within-subjects effect of both cDBS and aDBS on LFO and dystonic symptoms, in order to corroborate the claims provided here. However, the results obtained in this study are useful to generate data-driven hypotheses regarding the configuration of future aDBS systems for dystonia.

5. Conclusion

LFO-suppression in dystonia, similar to symptom response to cDBS, might be gradual, and remain after stimulation is suspended. Therefore, tracking gradual changes in LFO may be required for aDBS implementation. Future sensing aDBS devices will allow to explore the temporal relation between chronic LFO-suppression and dystonic symptoms [12].

Authors' roles

DPF: 1ABC, 2AB, 3A; MB: 1ABC, 2AC, 3B; JCvZ: 1C, 3B; MEvE: 1C, 3B; DLMO: 1BCE, 3A; JMCvD: 1ABC, 3B; MAJT: 1ABC, 3B.

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing of the first draft, B. Review and Critique.

Financial disclosures

None.

Funding statement

This study is publicly funded by grants received from the Dutch Brain Foundation ('Hersenstichting Nederland', grant F2015 (1)-04), the National Mexican Council of Science and Technology (CONACYT) grant number CVU 652927, and the University of Groningen/University Medical Centre Groningen (RuG/UMCG). This work is generated within the European Reference Network for Rare Neurological Diseases - Project ID No 739510.

Akwnowledgements

We would like to thank all the patients for their participation in this study. We would also like to thank prof. Peter Brown for his suggestions, Sebastian Balart-Sanchez for his help with the figure, Cor Kliphuis for his assistance during patient inclusion, and the OR staff for their help during the recordings.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.parkreldis.2020.08.030>.

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Condition 1	Condition 2	Difference	Std. Error	T value	P value
NoStim0	NoStim1	0.590	0.394	1.493	0.181
NoStim0	aDBS	-0.114	0.267	-0.435	0.668
NoStim1	cDBS	-0.198	0.262	-0.754	0.493
NoStim1	aDBS	-0.705	0.435	-1.619	0.163
aDBS	cDBS	-0.507	0.242	-2.086	0.061

Supplementary table 1. Results of the pairwise dependent t-tests of the comparison between NoStim0, NoStim1, cDBS and aDBS conditions.

Pt.	Channels used for recording	DBS parameters cDBS/aDBS	No Stimulation				cDBS				aDBS			
			BFMDRS		TWSTRS		BFMDRS		TWSTRS		BFMDRS		TWSTRS	
Dys	L: 0-2	1V 60µs 130Hz												
aDBS-		1V 60µs 130Hz												
GPI 1	R: 1-3													
Dys	L: 1-3	2.9V 60µs 130Hz												
aDBS-		2.9V 60µs 130Hz												
GPI 2	R: 1-3													
Dys	L: 0-2	3.1V 60µs 130Hz	8		17		8		17		8		16.5	
aDBS-		3.6V 60µs 130Hz												
GPI 3	R: 0-2													
Dys	L: 0-2	4V 60µs 130Hz	2				2				4			
aDBS-														
GPI 4														
Dys	L: 1-3	2.7V 60µs 130Hz	5.5		14		5.5		14		5.5		14	
aDBS-		2.7V 60µs 130Hz												
GPI 5	R: 1-3													
Dys	R: 1-3	3V 60µs 130Hz	21.5		7		21.5		7		25.5		7	
aDBS-														
GPI 6														
Dys	L: 1-3	3V 60µs 130Hz	3.5		13		3.5		13		3.5		13	
aDBS-		3V 60µs 130Hz												
GPI 7	R: 0-2													

Supplementary table 2. Clinical and stimulation details of the aDBS pilot-study patients.

Condition 1	Condition 2	Difference	Std. Error	T value	P value
NoStim	cDBS	0	0	0	1
NoStim	aDBS	-1.20	0.799	-1.500	0.500
cDBS	aDBS	-1.20	0.799	-1.500	0.500

Supplementary table 3. Results of the pairwise dependent t-tests of the comparison of BFMDRS in the NoStim, cDBS and aDBS conditions.

Condition 1	Condition 2	Difference	Std. Error	T value	P value
NoStim	cDBS	0	0	0	1
NoStim	aDBS	0.125	0.125	1	1
cDBS	aDBS	0.125	0.125	1	1

Supplementary table 4. Results of the pairwise dependent t-tests of the comparison of TWSTRS in the NoStim, cDBS and aDBS conditions.

Pt.	% of change BFMDRS after one year	% of change TWSTRS after one year	Pt.	Dystonia Type (phasic/ tonic) based on the preoperative videos	% of acute LFO change during cDBS compared to OFF (averaged between hemispheres)
DysaDBS-GPi 1	-38.6	-35.7	DysaDBS-GPi 1	Phasic	-16.4
DysaDBS-GPi 2	-37.5	-5.2	DysaDBS-GPi 2	Tonic	-18.3
DysaDBS-GPi 3	-36.9		DysaDBS-GPi 3	Phasic = Tonic	+0.08
DysaDBS-GPi 4	0	-5.8	DysaDBS-GPi 4	Phasic > Tonic	-21.5
DysaDBS-GPi 5	-27.7	-15.7	DysaDBS-GPi 5	Tonic > Phasic	-4.3
DysaDBS-GPi 6	+7.3		DysaDBS-GPi 6	Phasic	-0.7
DysaDBS-GPi 7	-29.8		DysaDBS-GPi 7	Tonic	-6.0

Supplementary table 5 (left). Percentage of change after one year of chronic cDBS, for the patients who underwent the pseudorandomized clinical trial.

Supplementary table 6 (right). Type of dystonia of the patients who underwent the pseudorandomized clinical trial. This classification was made based on the video recordings obtained before DBS implantation.

Supplementary figure 1. Power spectral density estimate of a dystonia patient during no stimulation and cDBS, before (left) and after (right) normalization.

Supplementary figure 2 (next page). Schematic representation of a tentative algorithm for aDBS in dystonia. When chronic stimulation is suspended, a decrease is observed in both the therapeutic effect of stimulation, and the severity of stimulation-related side-effects. In parallel, the power of low-frequency oscillations increases according to the return of dystonic symptoms. However, the presence of a strong poststimulation therapeutic effect is present in dystonia, in which symptoms do not instantly reappear, but they do it in a gradual manner [8]. In contrast, stimulation-dependent side-effects seem to appear only when stimulation is present, and to swiftly disappear once stimulation is switched off [2]. This indicates that the decay of DBS efficacy and stimulation-dependent side-effects might follow different time courses, where the decay of the former could be slower than the latter. If this is the case, stimulation could be maintained between threshold margins based on the optimal LFO-power suppression, in order to preserve the beneficial effects of stimulation, while reducing the presence of stimulation-dependent side-effects. A.1) Time-course representation of events in dystonia patients after cDBS is switched off. The maximum clinical benefit, and the presence of stimulation-dependent side-effects slowly decrease as a result of switching stimulation off. In parallel, the power of low-frequency oscillations increases according to the return of dystonic symptoms. A.2) Graphic representing the moment in which stimulation is switched off. B.1) Prospective time-course of events in dystonia during aDBS. Once stimulation goes off, the maximum clinical benefit slowly decreases as symptom severity slowly increases. In parallel, the power of low-frequency oscillations increases according to the return of dystonic symptoms. In this moment, stimulation is triggered on again when low-frequency oscillations cross a predefined threshold. Stimulation then continues until low-frequency oscillations are again successfully suppressed. The intervals in which low-frequency oscillations are processed could go from minutes (m) to hours (h), or even days (d). As stimulation is not continuously delivered, it is likely that the probability of presenting stimulation-dependent side effects also decrease. Due to the long-lasting poststimulation effect, the benefit of stimulation will be maintained until next stimulation delivery. A.2) Graphic representing the moments in which stimulation is titrated up or down.

10

SUMMARY AND GENERAL DISCUSSION

Adaptive DBS for Parkinson's Disease and Dystonia

Deep brain stimulation (DBS) is an effective treatment for patients with movement disorders, in whom medication alone is not satisfactory.¹ It has been successfully applied for more than 30 years in patients with Parkinson's disease (PD),² and for more than 20 years in patients with dystonia.³ Although the mechanism of action of DBS was initially largely unknown, it is becoming increasingly clear how DBS modulates different neural oscillatory circuits in charge of movement control.⁴ However, these new insights have barely made their way into the clinical DBS practice, where the current trial-and-error method used to program DBS is roughly similar to the one used when DBS was first implemented. In this one-size-fits-all approach, DBS is programmed by a trained clinician during a consultation, in which several parameter combinations are tested.⁵ After the optimal parameters have been found, DBS is set to deliver stimulation in a continuous way, using a fixed amplitude, frequency and pulse width. For that reason, current DBS has been also denominated continuous DBS (cDBS). In this continuous approach, clinical fluctuations are not taken into account, which can lead to DBS not only suppressing pathological, but also physiological rhythms that are required for normal motor or cognitive functions. The objective of this thesis was to translate novel insights on the mechanisms of action of stimulation into the development of smart devices, which are able to tackle the limitations currently observed with cDBS. The premise of these new devices is to adapt the amount of stimulation delivered, in order to target only specific elements of the neural activity that are aberrant in patients with movement disorders, such as PD or dystonia, while sparing the rest of the neural activity. For that reason, this new form of stimulation is called adaptive DBS (aDBS).

I. The role of pathological oscillations in movement disorders

In order to determine when and how stimulation should be delivered, future (a)DBS devices can make use of different electrophysiological biomarkers (physiomarkers) as feedback signals. In the first part of this thesis (**chapter one**), we discussed the fundamental concepts related to those physiomarkers. Ideally, the signals used as feedback for aDBS should be able to reflect the clinical state of the patients at each moment. Although several physiomarkers have been proposed for PD and dystonia,⁶ those that are embedded in the same local field potential (LFP) activity of the nuclei in which the DBS leads are implanted, seem to be the most promising to date. In patients with PD, prominent beta (13-35 Hz) oscillations, detected either in the subthalamic nucleus (STN)⁷ or in the internal globus pallidus (GPi),⁸ correlate with the severity of bradykinesia and rigidity, and are attenuated when stimulation⁹ or levodopa¹⁰ is administered. In patients with dystonia, prominent low-

frequency (LF, 4-12Hz) oscillations detected in the GPi correlate with the severity of dystonic symptoms,^{11,12} and are also attenuated when stimulation¹³ or antidystonic medication¹⁴ is administered. For those reasons, beta and LF oscillations are currently the best candidates for aDBS in PD and dystonia, respectively. However, although such oscillations are prominent in affected patients, it is up to now unclear to which extent these oscillations can be considered aberrant. Since electroencephalography has taught us that prominent oscillations in different frequency bands can be a characteristic of the healthy brain,¹⁵ it is possible that prominent oscillations are also a part of the normal physiology of the basal ganglia. Due to their deep localization in the skull, it is at present not possible to explore how those oscillations behave in healthy subjects, and animal research is not completely translatable to human physiology.

In order to circumvent these limitations, the power of basal ganglia oscillations can be compared between patients with different diseases who are treated with DBS, under similar conditions. If certain oscillations are prominent in patients with one of the diseases, but not in patients with the other disease, it becomes more likely that the prominent oscillations found in the former are indeed increased. Furthermore, when combining this finding with the fact that prominent oscillations correlate with the severity of clinical symptoms, and are decreased by medication or stimulation, it can be inferred that those oscillations are aberrant. Given that DBS has been used for many years to treat PD and dystonia in similar targets (namely the GPi and the STN),¹⁶ they seem to be the best candidates to be used as a control for each other. A few studies have directly compared the power of low-frequency and beta oscillations between PD and dystonia patients, using intracerebral recordings of each other as baseline for the comparison. However, the statistical power of individual articles that performed this comparison has been limited by the small number of patients that have been included in each study. For that reason, the focus of **chapter two** was to systematically describe the results found in all of the aforementioned articles, and to pool these results into a meta-analysis, in order to increase their statistical power. The results of this meta-analysis indicate that LF and beta oscillations are present in both diseases, but the power distribution of those oscillations is different in each disease. In this meta-analysis, it was confirmed that LF-power is increased in the internal globus pallidus (GPi) and the subthalamic nucleus (STN) of dystonia patients, in comparison to that of PD patients. Similarly, it was corroborated that beta power is increased in the GPi of PD patients, when compared to that of dystonia patients. This suggests that the pathological role of beta oscillations in PD, and LF oscillations in dystonia, is dependent on the magnitude of these oscillations,^{17,18} and not on their pure presence in the basal ganglia.

Finally, the comparisons of beta oscillations in the STN between PD and dystonia were inconclusive, as only two articles were included, which reported opposite results. In one article, subthalamic beta oscillations were found to be significantly increased in PD patients, while the other reported no differences. A third article that did not meet the inclusion criteria for the meta-analysis also reported increased beta oscillations in the STN of PD patients.¹⁹ After the publication of this meta-analysis, a new case report performed the same comparison, which also found that beta oscillations are increased in the STN of PD patients.²⁰ This brings the total number of articles reporting increased subthalamic beta oscillations in PD patients compared to dystonia patients to three, in contrast with only one reporting no differences between both diseases. For that reason, it seems that subthalamic beta oscillations are indeed increased in PD patients. However, more studies are needed that compare recordings of PD patients with a larger number of dystonia patients implanted in the STN, in order to provide a definite answer. Although increased subcortical oscillations were first described in PD and dystonia, recent evidence indicates that such oscillations are not only prominent in these movement disorders. Prominent LF-power has also been found in the basal ganglia of patients with hyperkinetic disorders other than dystonia, such as Tourette's syndrome²¹ and tremor,²² and in patients with PD during levodopa-induced dyskinesias.²³ Similarly, prominent beta oscillations have been detected in the basal ganglia of patients with neurodegeneration with brain iron accumulation (NBIA) type I, who have a bradykinetic phenotype.²⁴ Therefore, it is likely that increased LF-power indicates the presence of a hyperkinetic state, and increased beta-power the presence of a hypokinetic state.

Traditionally, the extent of basal ganglia oscillations in PD and dystonia has been studied in the frequency domain, by estimating their spectral power density. This analysis provides an overview of the average power of LF or beta oscillations within a time interval that can range from one or several seconds to minutes or more for the estimation. However, this technique is not able to reflect the rapid power fluctuations that occur within that interval. Other techniques that are performed in the time domain, or in a combination of time and frequency domains, can reveal rapid fluctuations in oscillatory activity that occur in the order of milliseconds. Recently, the importance for patients with PD of these fast temporal fluctuations has been highlighted,²⁵ since it has been observed that subthalamic beta oscillations occur in the form of 'bursts',²⁶ and that the relationship between beta oscillations and clinical symptoms is dependent on the amplitude and duration of these bursts.²⁶ Beta bursts with a long duration (>600ms) and a high amplitude are predominant in patients with PD during the OFF state. In contrast, the amplitude and duration of these bursts are reduced when stimulation or levodopa is administered. For that reason,

it has been proposed that beta bursts that have a high amplitude and duration are pathological, while beta bursts with short amplitude and duration are physiological. However, it is currently not known how these basal ganglia bursts behave in the healthy brain, due to the limitations related to the intracerebral nature of the LFP recordings. As mentioned earlier, one alternative to address this limitation consists in performing comparisons of LFP recordings from patients with PD and dystonia, with DBS electrodes implanted in the same target. The first aim of **chapter three**, was to investigate the characteristics of beta bursts that occur in the GPi of patients with PD, and to compare these characteristics with the beta bursts measured in the GPi of patients with dystonia. In addition to this, a second aim of this chapter was to describe the temporal characteristics of LF bursts in dystonia for the first time, and compare this to the characteristics of LF bursts detected in PD patients. The results of this study showed that the amplitude of beta bursts was increased in the GPi of PD patients, when compared to the beta bursts measured in the GPi of patients with dystonia. This observation confirms previous findings that indicated that the amplitude of beta bursts is increased in the GPi of patients with PD.¹⁷ In contrast, when the beta bursts detected in the GPi of PD patients were compared to those of patients with the same disease, but with DBS electrodes implanted in the STN, no differences were found. Therefore, there is a possibility that pallidal and subthalamic oscillations reflect the characteristics not only of the nuclei self, but of the whole basal ganglia network.^{27,28} Regarding pallidal LF oscillations, the amplitude of LF bursts was found to be increased in patients with dystonia, compared to the amplitude of LF bursts found in the GPi of patients with PD. Although this findings were described in a small patient cohort, they suggest that the amplitude of LF bursts is increased in the GPi of patients with dystonia.

In summary, the basal ganglia oscillations of patients with PD and dystonia present distinctive characteristics in the LF and beta frequency range. Beta oscillations are increased in the STN and GPi of patients with PD, correlate with the severity of bradykinesia and rigidity,²⁹ and are suppressed by both stimulation⁹ and medication.¹⁰ LF oscillations are increased in the GPi and STN of patients with dystonia, correlate with the severity of dystonic symptoms,¹² and are suppressed by either stimulation¹³ or medication.¹⁴ In the next sections the implementation of those oscillations as feedback signals in aDBS systems for PD and dystonia will be discussed.

II. Adaptive Deep Brain Stimulation in Parkinson's Disease

Closed-loop paradigms for PD were initially trialed in non-human primate PD models, showing the efficacy of aDBS in controlling bradykinesia.³⁰ A few years afterwards, the first aDBS trials were carried out in PD patients with DBS electrodes implanted in the STN, since the STN is up to now the preferred target for this patient group.³¹ The trials were performed during the immediate postoperative phase, in which the extension wires that are connected to the DBS electrodes are still externalized. In these trials, beta oscillations recorded from the implanted electrodes were used as a physiomaer to titrate aDBS, using different control algorithms. The base of these control algorithms is to track the temporal fluctuations of beta oscillations, by processing LFPs in the time domain, or by combining time and frequency analysis. When trials used a time domain approach,^{32,33} the original LFP signal is real-time filtered in a narrow frequency band around the frequency where the beta peak is found, in order to track the fast changes observed in beta bursts. Alternatively, when using a time-frequency approach, consecutive power spectral density (PSD) estimates are obtained at regular intervals (800-1500 ms), which are able to reveal gradual changes in the background beta power.^{34,35} This approach can be used to trace changes in beta oscillations related to medication. Regardless of the approach, it was observed in the first aDBS trials that beta-based aDBS is effective in controlling parkinsonian symptoms,³⁶ and that aDBS could even be more effective than cDBS,³² at least in the acute phase. Furthermore, it was observed that side effects due to excessive stimulation, such as dysarthria³³ or stimulation-dependent dyskinesias,³⁴ are not present during aDBS. However, the maximum effects of aDBS were limited in these by the presence of a microlesion effect. The microlesion effect is a temporary improvement of parkinsonian symptoms that occurs at the moment the electrodes are inserted.³⁷ Given that the LFPs had to be measured directly after implantation, the microlesion effect potentially interfered with the results of aDBS studies carried out in this phase. A way to measure LFPs when the patients are in a steady state is to perform the recordings when the DBS batteries are replaced. This usually takes place several years after the electrodes are implanted. In **chapter four**, a proof-of-principle was conducted in a PD patient during battery replacement. In this trial, beta-based aDBS was tested for the first time outside the perioperative period. It was confirmed here that aDBS can be effective in patients with chronically implanted electrodes.

The next step was to test the acute effects of aDBS in a group of patients without the microlesion effect. This is a fundamental step before aDBS can be explored in a chronic setting. Clinical trials testing cDBS have mostly focused on the chronic efficacy of stimulation, by comparing the clinical scores of patients with PD before cDBS and

after several months or years of treatment.³¹ Since stimulation during cDBS remains fixed, the acute effect of cDBS might be of less relevance. This is not the case with aDBS, in which stimulation is dynamically modulated according to a physiomarker. For this reason, it is possible that when comparing aDBS and cDBS at a single endpoint, the clinical scores are similar between these two approaches, whereas symptoms in-between phases present a large variation because of fluctuations in stimulation amplitudes. In order to fully implement aDBS, it is relevant to investigate not only what the chronic effects of aDBS are, but also the acute response that patients show to this dynamic form of stimulation. In **chapter five**, a research protocol aimed to investigate the acute effects of aDBS was presented. This protocol describes the objective and design of the study, which is the comparison between the acute effects of cDBS and aDBS, in PD patients undergoing battery replacement surgery. The tests included in the protocol were aimed at evaluating both motor symptoms and the presence of stimulation-induced side effects. The two main motor symptoms evaluated in this study were bradykinesia and tremor. These symptoms were chosen for two reasons: a) they can be evaluated on both hands, which are one of the few body parts that can be tested intraoperatively, and evaluated afterwards in a video by a blinded rater; b) bradykinesia is correlated with beta oscillations,³⁸ while tremor is not;²⁹ therefore, it was possible to explore whether these symptoms would respond differently to beta-based aDBS. The side effects evaluated were stimulation-induced dysarthria, and impaired response inhibition. The results of this study are presented in **chapter six**. The patient group included had the DBS electrodes implanted for 7 years on average. The results of this study showed that aDBS is effective in controlling bradykinesia, at least in the acute setting, despite aDBS having alternating ON/OFF periods. This can be explained by the fact that only pathological beta bursts were targeted.²⁶ In our study, bradykinesia scores were significantly better during aDBS compared to no stimulation, although no differences were present between cDBS and aDBS. In contrast, the response of tremor to beta-based aDBS was dichotomous. In most of the patients, both cDBS and aDBS were able to induce a sustained tremor suppression. Nevertheless, two patients presented re-emergent tremor in one of the hands, which was dependent on the fluctuations in stimulation delivery that take place during aDBS. In this study, tremor re-emergence was only seen in patients in whom even cDBS could not fully suppress tremor. As mentioned before, the severity of tremor is not correlated with the amount of beta oscillations present in the STN. However, it has been observed that the presence of tremor is able to suppress beta oscillations.³⁹ For that reason, it is possible that the continuous presence of tremor interacted with beta oscillations, causing the erratic behavior observed during aDBS. In summary, our study demonstrated that aDBS is effective in controlling bradykinesia, at least in the acute setting, after the microlesion effect has disappeared. Next to this, this study

showed that tremor can be successfully suppressed using beta-based aDBS, but this might not be the case for all the patients with tremor. Further research is required, in which only tremor patients with different degrees of tremor and responses to stimulation are included.

aDBS was effective not only in controlling PD symptoms, but it also had a positive effect on the side-effect profile of stimulation. In our trial, aDBS did not induce stimulation-induced dysarthria, which is observed during cDBS therapy.³³ If this is confirmed in long-term studies, it could be one of the best advantages of aDBS. Stimulation-induced dysarthria is a troublesome side effect, which can prevent programmers to use the most optimal settings for stimulation. Programming strategies aimed at reducing this side effect include changing the active contact to a more dorsal position and reducing the voltage delivered.⁴⁰ However, these interventions can have deleterious consequences in the therapeutic effect already achieved with cDBS. By reducing the amount of stimulation delivered, aDBS might allow to continue stimulating through the most optimal contact, without fearing the emergence of stimulation-induced dysarthria. Regarding response inhibition, no differences were found between no stimulation, cDBS and aDBS. As disease progression itself has been associated with impaired response inhibition,⁴¹ it is possible that the impairments in response inhibition caused by the long PD duration observed in this patient cohort (mean disease duration of 16 years) have masked any effects caused by stimulation.

Although the STN remains the preferred target for DBS in PD, recently the GPi is re-emerging as a viable target for DBS.⁴² In **chapter three**, aDBS was tested for the first time in the GPi of a patient with PD, undergoing battery replacement, using beta oscillations as a feedback signal. To the best of our knowledge, this is the first time that prominent beta oscillations in the GPi of a PD patient, are reported outside the perioperative period. Therefore, it can be confirmed that prominent pallidal oscillations are preserved in the GPi after the microlesion effect has disappeared. This is also the first time beta-based aDBS is tested in the GPi for PD. aDBS was well tolerated in this proof-of-principle study. Therefore, it can be concluded that performing aDBS in the GPi is feasible, which opens the possibility to perform larger clinical trials using aDBS systems in the GPi for patients with PD.

To summarize, the areas in which beta-based aDBS has potential to overcome cDBS in the clinical practice include a potential improved therapeutic effect, and the reduction of stimulation-induced side effects. To clarify the relationship of beta oscillations and tremor will be one of the challenges that aDBS will need to tackle in order to be

implemented in the chronic setting. Therefore, the results presented here could work as a blueprint for the design of chronic aDBS trials.

III. Adaptive Deep Brain Stimulation in Dystonia

Although aDBS has been primarily studied in PD, it has the potential to be translated to other diseases in which aberrant oscillations are present. In the last part of the thesis, the use of aDBS in dystonia was explored. As mentioned before, the presence of prominent LF oscillations in the GPi has the potential to be used as a physiomarker in aDBS for dystonia.¹² In **chapter eight**, a review of all the publications that provide evidence of the link between LF oscillations and dystonic symptoms, and how these oscillations could be used in future aDBS systems, was performed. The potential benefits of limiting the amount of stimulation delivered in dystonia patients could include an improved efficacy of stimulation, by only targeting the neural elements that are aberrant in patients with dystonia, and the reduction of stimulation-induced side effects, such as parkinsonism^{43–45} and dysarthria.^{46,47}

In **chapter three**, aDBS based on a physiomarker specific for dystonia (LF bursts) was tested for the first time in a dystonia patient with DBS electrodes implanted in the GPi, during a battery replacement operation. This is also the first time that LF oscillations in the GPi of a patient with dystonia are reported outside the immediate post-implantation phase. This proof of principle showed that LF-burst based aDBS is feasible and well tolerated. In **chapter nine**, this protocol was extended by testing aDBS based on LF bursts in a group of patients with dystonia. In this pilot study, the LFPs of patients with dystonia who underwent either DBS implantation or battery replacement surgery were recorded, and stimulation was delivered both continuously, and based on the magnitude of LFO-bursts. The aim of this study was to confirm that cDBS can induce an instant LF-oscillation suppression,¹³ and to explore the acute relation of this suppression with clinical symptoms; additionally, the acute effects of aDBS for dystonia based on LF-bursts were also tested. In this study it was confirmed that cDBS induced a LF-oscillation suppression immediately after stimulation was switched on. However, this suppression is modest, and immediate changes in clinical symptoms might not be observed. This indicates that cDBS produces a physiological effect from the moment that stimulation is delivered, but that it takes more time before this can be translated into an improvement on clinical symptoms. Remarkably, it was observed that the patients with dystonia who had been effectively treated with chronic cDBS, presented a much lower GPi-LF power than those patients in whom the DBS electrodes had just been implanted. Therefore, it might be possible that LF

power becomes gradually suppressed after cDBS is switched on. This implies that the time course of LF-oscillation suppression could mirror the response of dystonic symptoms to stimulation, which also takes place on a gradual manner.⁴⁸ Since no changes were observed during LF-burst based aDBS in the acute setting, it might be possible that the fast LF oscillation components are not able to directly reflect the gradual changes in dystonic symptoms. However, at present it is not possible to establish whether aDBS based on LF-bursts could also be effective when chronically applied. A logic next step would be to establish the temporal influence of stimulation on LF oscillations, similarly to how it has been established for beta oscillations in PD.⁴⁹ Chronic LFP-recordings are therefore required to further test the utility of LF oscillations as physiomarkers for dystonia, and to check whether LF-based aDBS can induce a symptom reduction, when applied for longer periods. Moreover, different approaches to deliver aDBS than those used in PD can be tested in dystonia patients.

Future perspectives

When I started working on this thesis, it was only possible to record LFPs either intraoperatively or in the immediate postoperative phase, when the DBS electrodes were still externalized. While several tests can be performed during this setting, it is not possible to observe what the chronical LFP fluctuations are, when patients perform their daily activities. By the time of writing this chapter, a new generation of implantable pulse generators which are able to perform chronic aDBS has become widely available,⁵⁰ and the first long-term aDBS clinical trials are about to start. Therefore, an exponential increment of research articles testing new forms of closed-loop stimulation is expected to take place in the upcoming years. This will ultimately result in the development of patient-specific stimulation algorithms, designed to provide a more effective, efficient and better-tolerated DBS therapy. The findings described in this thesis can be used as a base for these trials, in which aDBS will have to be tested in real-life situations. In **chapter seven**, the first aDBS trial using an implantable pulse generator to record and stimulate was discussed, together with aspects in which aDBS has shown promising results, and that will likely be the focus of upcoming aDBS studies. Furthermore, the challenges that aDBS will have to face on its transition into the clinical care were also highlighted. The main questions that need to be answered before aDBS can be implemented in the clinical practice are discussed in **chapter six**. Some of those questions include:

- What is the chronic interaction of oscillations with medication? Are LF or beta oscillations able to chronically reflect the clinical state changes caused by medication?
- What is the influence of voluntary movements throughout the day on LF and beta oscillations? Are instinctive movements such as gait, and physiological fluctuations, such as circadian rhythms, able to influence the way in which LF and beta oscillations represent the clinical state of the patients?
- Is aDBS able to provide a sustained benefit in terms of increased efficacy or reduced side effects, compared to cDBS?

It is expected that these, and many more questions can be answered with the help of the new generation of sensing DBS devices. Additionally, advanced classification techniques based on machine learning algorithms can be explored,⁵¹ in order to refine the accuracy in which basal ganglia oscillations predict the severity of parkinsonian or dystonic symptoms. Once the chronic effectivity and safety of aDBS is established, it will be possible to incorporate this therapy into the clinical practice.

Final thoughts

The results described here represent early explorations in the new field of closed-loop deep brain stimulation. Extensive progress has been made in understanding how oscillations relate to clinical symptoms, and how this knowledge can be incorporated into the development of prospective aDBS devices that can be used in the clinical setting. The main advantage of aDBS is that aDBS itself can be adapted to new insights of the neurophysiology of the motor networks. Ultimately, aDBS will increase the therapeutic options available to treat patients with movement disorders (and beyond). There are exciting times for aDBS ahead.

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Acknowledgements
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Adaptieve Diepe Hersenstimulatie voor de ziekte van Parkinson en dystonie

Diepe hersenstimulatie (*Deep Brain Stimulation*, DBS) is een geavanceerde behandeling voor bewegingsstoornissen, zoals bij de ziekte van Parkinson en dystonie. DBS is bij zorgvuldig geselecteerde patiënten een behandeloptie indien het effect van medicatie onvoldoende is, of wanneer de bijwerkingen hiervan overheersen. DBS betreft de implantatie van elektroden in diepe hersengebieden, zoals de basale kernen en de thalamus. Deze elektroden zijn aangesloten op een onder het sleutelbeen geïmplanteerde neurostimulator die elektrische pulsen afgeeft. Ondanks dat DBS al decennia met succes wordt toegepast, is het exacte mechanisme waarmee DBS kan leiden tot het verminderen van symptomen nog niet geheel opgehelderd. Mede vanwege dit gebrek aan kennis, heeft DBS momenteel nog een aantal beperkingen. De eerste beperking is dat DBS van oudsher continu wordt toegepast, zonder een terugkoppeling van het effect op de symptomen van de patiënt. Deze continue stimulatie houdt geen rekening met eventuele schommelingen van de symptomen of het effect van medicatie. Deze vorm van DBS wordt ook wel continue DBS (cDBS) genoemd. De tweede beperking is dat cDBS handmatig moet worden ingesteld door een daartoe geschoolde clinicus. Het programmeren is voornamelijk gebaseerd op de respons van de patiënt ten tijde van het instellen. Andere parameters met betrekking tot het effect van cDBS worden momenteel niet gebruikt. Het programmeren van het DBS-systeem is daarom nog altijd een tijdrovende zaak. Een derde beperking is dat er bijwerkingen van cDBS kunnen optreden, die alleen kunnen worden verminderd door de instellingen op de motoriek aan te passen. Vaak leiden deze aanpassingen tot suboptimale cDBS-instellingen, bijvoorbeeld als gevolg van het gebruik van DBS-electrode contactpunten die verder van het ideale doelgebied af liggen.

Zoals gezegd is er meer kennis over het werkingsmechanisme van DBS nodig om deze behandeling te verbeteren. Dit kan door via de geïmplanteerde DBS-elektroden lokale metingen te verrichten. Deze metingen helpen om te begrijpen hoe DBS verschillende hersennetwerken beïnvloedt. Het doel van dit promotieonderzoek is via deze metingen tot nieuwe inzichten te komen over het werkingsmechanisme van DBS en deze inzichten te vertalen naar de ontwikkeling van 'slimme' DBS-systemen die de eerder genoemde beperkingen van cDBS kunnen overwinnen. Het uitgangspunt van deze innovatieve DBS-systemen is dat de stimulatie alleen is gericht op de afwijkende (pathologische) aspecten van de lokale hersenactiviteit. Zo kan de normale

(fysiologische) hersenactiviteit bij patiënten met Parkinson of dystonie ongemoeid worden gelaten. Deze nieuwe vorm van stimulatie heet adaptieve DBS (aDBS).

Dit proefschrift bestaat uit drie delen: het eerst deel bespreekt de pathologische hersenactiviteit (oscillaties) bij bewegingsstoornissen, en hoe deze oscillaties kunnen worden gebruikt in aDBS-systemen. Het tweede deel geeft weer wat de effectiviteit van aDBS is bij Parkinson, en het derde deel de toepassing van aDBS bij dystonie.

I. De rol van pathologische oscillaties bij bewegingsstoornissen

Het eerste deel van het proefschrift beschrijft de kenmerken van de oscillaties die bij Parkinson en dystonie in de basale hersenkernen *nucleus subthalamicus (STN)* en *globus pallidus internus (GPI)* worden waargenomen. Dit deel beschrijft bèta-oscillaties (Parkinson) en laagfrequente oscillaties (dystonie), aangezien deze oscillaties bij de respectievelijke aandoeningen verstoord zijn.

De centrale vraag hierbij is op welk tijdstip en op welke wijze stimulatie via DBS-systemen moeten worden geleverd. Toekomstige (a)DBS-systemen kunnen feedback ontvangen en aanwenden om dat te bepalen, waarbij gebruik gemaakt kan worden van verschillende elektrofysiologische biomarkers (zogenaamde 'fysiomarkers').

Hoofdstuk 1 van dit proefschrift bespreekt de fundamentele concepten die verband houden met fysiomarkers. Idealiter geven zij de exacte klinische toestand van patiënt op elk gewenst moment weer. Voor Parkinson en dystonie kunnen verschillende fysiomarkers gebruikt worden, waarvan de meest veelbelovende markers zijn ingebed in hetzelfde lokale veldpotential (local field potential – LFP) van de kernen waarin de DBS-elektroden zijn geïmplant. Bij patiënten met Parkinson zijn prominente bèta-oscillaties (13-35 Hz) in de STN of GPI waar te nemen. Deze komen overeen met de ernst van traagheid (bradykinesie) en stijfheid (rigiditeit). Het toedienen van stimulatie of levodopa verzwakt de oscillaties. Bij patiënten met dystonie zijn prominente laagfrequente (4-12Hz) oscillaties in de GPI waarneembaar. Deze staan eveneens in verhouding tot de ernst van de dystonie. Bèta- en laagfrequente oscillaties zijn daarom momenteel de meest veelbelovende fysiomarkers voor aDBS bij Parkinson en dystonie.

De diepe locatie in de hersenen van de STN en GPI maakt het onmogelijk om hier bij gezonde proefpersonen onderzoek naar te doen. Wel is het mogelijk om de fysiomarkers te vergelijken bij patiënten met verschillende ziekten die onder vergelijkbare omstandigheden met DBS worden behandeld. Bij de ziekte van Parkinson en dystonie wordt al vele jaren DBS in zowel de GPI als de STN toegepast. Het ligt daarom voor de hand om deze ziekten als controle voor elkaar te gebruiken. Enkele

studies hebben de mate van laagfrequente en bèta-oscillaties tussen Parkinson en dystonie rechtstreeks vergeleken. Het betrof in elk onderzoek maar weinig patiënten, waardoor de statistische waarde beperkt is. **Hoofdstuk 2** beschrijft derhalve een meta-analyse van de samengestelde resultaten van deze onderzoeken. Het betreft acht artikelen met in totaal 127 meetgegevens van patiënten met dystonie, en 144 meetgegevens van patiënten met Parkinson. Uit deze meta-analyse blijkt dat laagfrequente en bèta-oscillaties voorkomen bij beide aandoeningen, maar in een verschillende verhouding. De meta-analyse bevestigt dat laagfrequente oscillaties meer voorkomen in de GPi en STN bij dystonie dan bij Parkinson. Daarnaast bevestigt deze analyse dat de bèta-oscillaties in de GPi meer optreden bij Parkinson dan bij dystonie. Niet de aanwezigheid van deze oscillaties in de basale ganglia, maar de mate van voorkomen lijkt dus bepalend voor hun pathologische rol. De vergelijking van bèta-oscillaties in de STN bij Parkinson en dystonie leverde geen sluitende conclusie op.

Oorspronkelijk werd de mate van oscillaties in de basale kernen bij Parkinson en dystonie bestudeerd op basis van een spectrale analyse in het frequentiedomein. Deze techniek kan echter niet de snelle fluctuaties weergeven die binnen een interval van milliseconden optreden. Analyse in het zogenaamde temporele domein, of het temporele en frequentiedomein tezamen, onthullen deze fluctuaties wel. Onlangs is waargenomen dat bèta-oscillaties in de STN optreden in de vorm van '*bursts*', en dat de klinische symptomen van Parkinson samenhangen met de amplitude en duur van deze *bursts*. Of deze *bursts* voorkomen in gezonde hersenen is niet bekend, vanwege de eerder genoemde beperkingen van het meten van LFP's diep in de hersenen bij gezonde personen. Het uitvoeren van vergelijkingen van LFP-metingen bij patiënten met Parkinson en dystonie, via DBS-elektroden geïmplanteerd in hetzelfde doelgebied, biedt ook hier een uitkomst.

Hoofdstuk 3 biedt een weergave van onderzoek naar de kenmerken van bèta-*bursts*, waarbij het voorkomen in de GPi bij Parkinson en dystonie wordt vergeleken. *Bursts* in de GPi en STN bij Parkinson worden tevens met elkaar vergeleken. Daarna wordt in dit hoofdstuk gekeken naar de temporele kenmerken van laagfrequente *bursts* bij Parkinson en dystonie. Bij vijf patiënten met Parkinson en zeven patiënten met dystonie worden de LFP's van GPi-elektroden vergeleken, alsmede bij zes Parkinsonpatiënten met in de STN geïmplanteerde DBS-elektroden (totaal 34 elektroden). Deze vergelijking toont aan dat de amplitude van bèta-*bursts* in de GPi verhoogd is bij Parkinson. De *bursts* in de GPi en STN bij Parkinson lieten daarentegen geen onderlinge verschillen zien. De amplitude van laagfrequente *bursts* in de GPi is verhoogd bij patiënten met dystonie.

Samengevat: bèta-oscillaties zijn toegenomen bij de ziekte van Parkinson en correleren met symptomen daarvan. Deze oscillaties kunnen daarom worden gebruikt als terugkoppeling in aDBS bij Parkinson. Op dezelfde manier zijn laagfrequente oscillaties toegenomen bij dystonie en correleren ze met dystone symptomen. Deze oscillaties kunnen derhalve worden gebruikt in aDBS voor dystonie.

II. Adaptieve diepe hersenstimulatie bij de ziekte van Parkinson

Dit deel beschrijft de experimenten waarin aDBS wordt getest bij patiënten met Parkinson. De eerste aDBS-onderzoeken met in de STN geïmplanteerde DBS-elektroden werden direct na de implantatie van de elektroden uitgevoerd. De belangrijkste bevindingen uit deze onderzoeken waren dat: bèta-gebaseerde aDBS effectief is bij het beheersen van Parkinson symptomen; aDBS zelfs effectiever zou kunnen zijn dan cDBS; en dat bijwerkingen als gevolg van overmatige stimulatie, zoals dysartrie, niet aanwezig zijn tijdens aDBS. Het inbrengen van de DBS-elektroden tijdens de operatie maakt echter een klein tijdelijk letsel wat Parkinson symptomen eveneens tijdelijk kan verbeteren. Dit letsel-effect maakt het lastig te beoordelen of de verbetering van symptomen door aDBS komt. Eén manier om LFP's te meten met uitsluiting van dit letsel-effect is door opnames uit te voeren wanneer de DBS-batterijen worden vervangen. Dit gebeurt meestal enkele jaren nadat de elektroden zijn geïmplantéerd.

Hoofdstuk 4 beschrijft een *proof-of-principle* studie bij een patiënt met Parkinson tijdens de batterij-vervangingsoperatie. In dit onderzoek is bèta-gebaseerde aDBS voor het eerst buiten de perioperatieve periode getest. Deze studie toonde aan dat aDBS effectief kan zijn bij patiënten met langdurig geïmplanteerde elektroden.

Hoofdstuk 5 beschrijft een onderzoeksprotocol met daarin het doel en de opzet van een vergelijking tussen de acute effecten van cDBS en aDBS bij patiënten met Parkinson die een batterij-vervangingsoperatie ondergaan. De in het protocol opgenomen testen zijn gericht op het evalueren van zowel motorische symptomen als de aanwezigheid van door stimulatie veroorzaakte bijwerkingen.

Hoofdstuk 6 beschrijft de resultaten van de studie aan de hand van dit protocol. De twee belangrijkste motorische symptomen die werden geëvalueerd zijn bradykinesie en tremor. Bradykinesie is gecorreleerd met bèta-oscillaties, terwijl tremor dat niet is. Daarom was het belangrijk om te onderzoeken of beide symptomen zouden reageren op bèta-gebaseerde aDBS. De geëvalueerde bijwerkingen zijn stimulatie-geïnduceerde dysartrie en verminderde responsremming. Aan deze studie hebben 11 patiënten met Parkinson deelgenomen die een batterij-vervanging ondergingen.

Deze patiënten zijn op een zogenaamde cross-over manier pseudo-gerandomiseerd in drie condities (geen stimulatie, aDBS, of cDBS). Bij elke conditie werd een korte versie van de Unified Parkinson's Disease Rating Scale en de Speech Intelligibility Test afgenomen. In de opgenomen patiëntengroep waren de DBS-elektroden gemiddeld 7 jaar geleden geïmplantéerd.

Deze studie toont aan dat aDBS effectief is bij het beheersen van bradykinesie, althans op korte termijn, ondanks het feit dat aDBS afwisselende AAN/UIT-perioden heeft. Dit kan worden verklaard doordat niet de fysiologische, maar alleen de pathologische bèta-**bursts** het doel van aDBS zijn. In onze studie waren bradykinesie-scores significant beter tijdens aDBS. Daarnaast kon zowel cDBS als aDBS bij de meeste patiënten de tremor onderdrukken. Verder was aDBS niet alleen effectief bij het beheersen van de Parkinson-symptomen, maar had het ook een positief effect op het bijwerkenprofiel van stimulatie. In onze studie veroorzaakte aDBS geen stimulatie-geïnduceerde dysartrie, hetgeen wel aanwezig kan zijn tijdens cDBS-therapie. Een andere test die gericht was op de evaluatie van responsremming is afgenomen in de drie condities van geen stimulatie, cDBS, en aDBS liet geen verschillen tussen de condities zien.

Sinds kort is er een nieuwe generatie implanteerbare pulsgeneratoren verkrijgbaar die tegelijkertijd signalen opneemt en stimulatie toedient. Deze pulsgeneratoren zijn in staat om aDBS langdurig uit te voeren. **Hoofdstuk 7** bespreekt de eerste aDBS-studie met zo een pulsgenerator. Daarnaast benoemt dit hoofdstuk de aspecten waarin aDBS veelbelovende resultaten heeft laten zien. Deze zullen waarschijnlijk de focus zijn van toekomstige aDBS-studies. Verder wijst deze studie op de uitdagingen waarmee aDBS zal worden geconfronteerd bij de overgang naar de klinische zorg, zoals het aanpassen van stimulatie tijdens dagelijkse activiteiten.

Uit de hierboven beschreven experimenten blijkt dat aDBS effectief is bij de ziekte van Parkinson in een experimentele setting. Het volgende onderdeel beschrijft testen voor aDBS verricht in dystonie patiënten.

III. Adaptieve diepe hersenstimulatie bij dystonie

Het doel van dit deel van het onderzoek is het verkennen van de mogelijkheden voor aDBS bij dystonie. Hoewel aDBS hoofdzakelijk is bestudeerd bij Parkinson, kunnen de uitkomsten worden vertaald naar andere ziekten met afwijkende oscillaties.

Hoofdstuk 8 beschrijft de redenen waarom aDBS bij dystonie kan worden toegepast. Het geeft een overzicht van alle publicaties die het verband tussen laagfrequente

oscillaties en dystone symptomen beschrijven, en hoe laagfrequente oscillaties in toekomstige aDBS-systemen kunnen worden gebruikt. Er zijn zeker twee mogelijke voordelen van het beperken van de hoeveelheid stimulatie bij dystonie. Ten eerste kan het de stimulatie effectiever maken door enkel de pathologische oscillaties die afwijkend zijn bij dystonie te behandelen. Ten tweede kan het door stimulatie veroorzaakte bijwerkingen verminderen, zoals parkinsonisme en dysartrie.

Het eerste experiment van aDBS bij een patiënt met dystonie is beschreven in **hoofdstuk 3**. Dit hoofdstuk beschrijft de allereerste test van aDBS gebaseerd op een fysiomarker die specifiek is voor dystonie (laagfrequente **bursts**). Dit experiment is tijdens een batterij-vervanging uitgevoerd via in de GPI geïmplanteerde DBS-elektrodes. Dit is de eerste keer dat laagfrequente oscillaties in de GPI bij dystonie gebruikt worden voor aDBS. Dit **proof-of-principle** toont aan dat op laagfrequente **bursts** gebaseerde aDBS mogelijk is, en dat dit goed verdragen wordt.

Hoofdstuk 9 beschrijft hoe de bevinding van hoofdstuk drie uitgebreid wordt, om aDBS te testen op basis van de aanwezigheid van laagfrequente **bursts** in een groep patiënten met dystonie. In deze pilotstudie wordt de registratie beschreven van LFP's bij patiënten met dystonie tijdens DBS-implantatie of batterij-vervanging. De DBS-stimulatie is op twee verschillende manieren afgegeven: continu (cDBS), en gebaseerd op de omvang van laagfrequente **bursts** (aDBS). Deze studie bestaat uit twee delen. Het doel van het eerste deel is driedelig: in de eerste plaats een bevestiging dat cDBS een onmiddellijke onderdrukking van de laagfrequente oscillatie kan veroorzaken. Ten tweede: onderzoek naar de acute relatie tussen deze onderdrukking en klinische symptomen. Ten derde zijn de acute effecten van aDBS voor dystonie op basis van laagfrequente **bursts** getest. In deze studie zijn zeven patiënten onderzocht: twee tijdens de DBS-implantatie, en vijf tijdens een batterij-vervangende operatie. De patiënten met dystonie werden gepseudorandomiseerd onder drie condities: geen stimulatie, cDBS, en aDBS.

In het tweede deel van de studie zijn LFP's in rusttoestand van patiënten die een batterij-vervanging ondergingen vergeleken met die verkregen tijdens DBS-implantatie. Voor dit laatste onderdeel zijn LFP's van een eerder cohort van zes patiënten met dystonie, die DBS-implantatie ondergingen, meegenomen in de analyse.

Deze studie bevestigt dat cDBS onmiddellijk na inschakeling laagfrequente oscillaties onderdrukt. Deze onderdrukking is echter initieel niet uitgesproken, en onmiddellijke veranderingen in klinische symptomen kunnen mogelijk niet waargenomen worden. Ten opzichte van de matige eerste reactie van dystonie op DBS is het opvallend dat bij

patiënten met dystonie die effectief zijn behandeld met langdurige cDBS, de sterkte van de laagfrequente oscillaties lager is dan bij patiënten bij wie de DBS-elektroden net zijn geïmplant. Het is daarom mogelijk dat laagfrequente oscillaties geleidelijk worden onderdrukt nadat cDBS is ingeschakeld. De reactie van dystone symptomen is ook geleidelijk. Daarom is het mogelijk dat het tijdsverloop van laagfrequente oscillatie-onderdrukking de reactie van dystone symptomen op stimulatie weerspiegelt.

Een logische volgende stap zou zijn om de temporele invloed van stimulatie op laagfrequente oscillaties vast te stellen, vergelijkbaar met hoe het is vastgesteld voor bèta-oscillaties in Parkinson. Langdurige LFP-opnames zijn daarom nodig om het nut van laagfrequente oscillaties als fysiomarkers voor dystonie verder te testen, en om te controleren of op lage frequentie-gebaseerde aDBS de dystone symptomen kan verminderen, wanneer het gedurende langere perioden wordt toegepast. Bovendien kunnen verschillende algoritmes bij patiënten met dystonie voor het toedienen van aDBS dan worden getest.

IV. Conclusie

Dit proefschrift beschrijft in het eerste deel de oscillaties die aanwezig zijn in de STN en GPi bij Parkinson en dystonie, en hoe deze oscillaties gebruikt kunnen worden in aDBS-systemen. Het tweede deel beschrijft het testen van aDBS bij patiënten met Parkinson. Het laatste deel beschrijft het testen van aDBS bij patiënten met dystonie.

Tenslotte geeft **hoofdstuk 10** een algemene samenvatting en bespreking van de belangrijkste bevindingen van dit proefschrift. Samengevat kunnen deze als volgt worden beschreven: (1) de laagfrequente en bèta-oscillaties gevonden in de basale kernen van patiënten met Parkinson en dystonie vertonen verschillende kenmerken; (2) aDBS gebaseerd op beta-oscillaties is effectief en geeft mogelijk minder bijwerkingen dan cDBS bij patiënten met de ziekte van Parkinson, althans op korte termijn, nadat het letsel-effect is verdwenen; (3) laagfrequente oscillaties kunnen worden gebruikt als fysiomarker voor aDBS bij dystonie. Meer onderzoek is echter nodig om effectieve controle-algoritmen vast te stellen. De bevindingen die dit proefschrift presenteert, zijn bedoeld als basis voor lange-termijn onderzoeken. Hierbij dienen implanteerbare pulsgeneratoren te worden gebruikt die in staat zijn om langdurige aDBS uit te voeren en de klinische toepassingen te verkennen.

Acknowledgements

Many years ago, I decided to start this adventure, in which I keep discovering new things every day. Throughout this journey I have had the opportunity to learn a lot from my supervisors, colleagues, and friends. I would like to take this moment to express my gratitude to each of you. I also want to thank all the people back home for all the support I continue to receive from them. I would not be where I am today if it were not for their help. A special note of thanks goes to all the patients who decided to participate in the different studies of this thesis. I am confident this research will contribute to the improvement of the treatment they currently receive.

First of all, I would like to thank my supervisors for their guidance and patience.

Prof. dr. J. Marc C. van Dijk, dear Marc, thank you for believing in me. From helping me to get the grant for this PhD, all the way to the last part of this thesis, you always encouraged me to pursue my goals and to go the extra mile. I also want to thank you for always making me feel welcome. Whether it was by organizing borrels so I could get to know the staff, or by practicing Dutch with me during our meetings, you always made me feel I was part of the team. During my PhD you always knew when to keep me on track. You did not hesitate to tell me when I needed to wrap things up, but you also gave me the freedom to follow my research interests, and you allowed me to develop myself in the process. I admire everything you have achieved, and I am glad that I was able to witness some milestones in your academic career as well, like your oratie. Hopefully I will be able to follow that path one day.

Prof. dr. Marina de Koning-Tijssen, dear Marina, thank you for guiding me during my PhD. It has been amazing to be part of your research group, and to share experiences not only inside the hospital, but in the many conferences and retreats all around the world. I admire your passion for studying movement disorders and how, despite your busy agenda, you always have time for your students. I am glad to see that we were able to take our research project to a successful end. But not everything was work, I am happy I was also able to take part in the many social activities you organized for us. The work-life balance was always present in the group. During all these years I have learned a lot from you, not only about dystonia and many movement disorders more, but I have also learned that I need to break out of my shell and speak up my mind. Those are teachings that I will always carry on with me.

Dr. Martijn Beudel, dear Martijn, I still remember when we first discussed this project, and you said that it would be a good idea if I learned how to program. I did

not know back then how much of an impact that would have in my life, but now I realized that it was one of the best life advices someone has ever given me. Thank you for your supervision and support in this project and afterwards. I admire your passion about DBS and everything around it. It is safe to say you have been able to successfully transfer that enthusiasm to me. Thank you for always finding a way to help me out, and to support me in achieving my academic and personal goals. During this project we have developed a great work dynamic, and I am very grateful that you made it possible for us to continue working together in this new academic phase. Let's make a success of this new project too.

Dear **Prof. Peter Brown**, thank you for welcoming me in your lab at the John Radcliffe Hospital, in Oxford. I had an amazing time there. A large part of this thesis is based on research coming from your lab, so having the opportunity to be there and see at first-hand how this research is being performed was a unique experience for me. Many thanks as well for the supervision and feedback in the parts of the thesis in which we worked together. Also many thanks to all the members of the lab for the great moments I had during my stay.

In addition to my supervisors, I would like to thank all the co-authors from the UMCG and Oxford that contributed to this thesis: from the UMCG I would like to thank **dr. G. Drost, dr. M.E. van Egmond, dr. J.-W. Elting, Prof. dr. T. van Laar, drs. H. R. Moes, drs. D.L.M. Oterdoom**, and **drs. J.C. van Zijl**, for all the clinical and technical input provided in the chapters of this thesis. From the co-authors in Oxford, I would like to thank **Dr. S. Little, Dr. G. Tinkhauser** and **Dr. A. Pogosyan** for their contribution in one or more of the chapters of this thesis, and the advice I received from them. Also thanks to the co-authors from other centres who contributed to this thesis.

Many thanks to **Prof. dr. P. van Dijk, Prof. dr. P.R. Schuurman** and **Prof. dr. Y. Temel** for the assessment and approval of this thesis.

To all the NCHIR (PhD) students: thank you for making my PhD much more pleasant. To the ones I shared the office with: **Peter**, you and I started at the same time, and we have gone through all the stages of the PhD together... inclusions, failures, articles accepted, rejections, just to name a few. It has been great to share this journey with you, and I do miss all the lunches, borrels, and nights out we had in Groningen. **Yuanyuan**, as the other non-Dutch in our group, we have had the same struggles, so we could understand each other very well. We always brought a nice variation to the group. **Sebastiaan**, you always have a story to tell, and it was really fun to have shared the office with you. Thanks also for all the times you helped me with the inclusions.

Lilian, even though we only shared the office in the last part of my PhD, we still have many memories together inside and outside the hospital, like all the dinners and borrels with the group. To my office neighbours: **Rik**, although we did not share the office, we were technically roommates for a couple of days in Dublin. You are another DBS enthusiast and I am glad to hear we will share more time together in Amsterdam. **Naomi**, it was great to organize the borrels of the Department together. As you are also from the DBS team visiting Amsterdam, I hope to see you there. **Bianca**, it is very motivating to see the dedication that you have to your work. Also thanks to the other NCHIR (PhD) students with whom I shared some time in Groningen: **Anne, Asmara, Brandt, Carola, Daria, Liesanne, Rob, Stefan** and many more. Also **Joost**, what a nice surprise to have met you again in Amsterdam.

Thanks to **Peter** and **Rik** for being the paranymphs during my ceremony.

Jonathan, I would like to thank you for all the help during this project. From beginning to end our research projects were intertwined, and we had many chances to support each other. You are an excellent clinician, and I learned a lot just by seeing you perform all those UPDRS and BFMDRS.

I would like to thank to all the current and former (PhD) students from the Department of Neurology, with whom I had the chance to share rooms, meetings, ideas and experiences: **Anouk, Arnoud, Asterios, Beorn, Cheryl, Danique, Didin, Elisa, Elze, Franka, Gerrit, Harmen, Hanna, Hans, Inge, Jaime, Jeannette, Jeffrey, Jelle, Jolien, Jonathan, Joyce, Lenny, Lisette, Maartje, Madelein, Marja, Maraike, Marenka, Marieke, Marouska, Mariano, Marlous, Marrit, Mayra, Miaozen, Myrthe de K, Myrthe S, Nick, Octavio, Omar, Rahul, Roald, Robbert, Saar, Sabine, Sandra, Sanne, Sebastian, Sjoukje, Sterre, Sygrid, Tinka, Wieke, Zeus**, and many more of course. I have a lot of good memories from the V4, but with some of you I had the chance to share several congresses, retreats, and borrels at the Hooghoudt. I will fondly remember all the fun moments that had together. And for sure there were many of those.

Because doing research also involves a lot of planning and organization, I would like to thank all the people who helped me arranging all the practical things related to this project: **Alida, Cor, Diane, Ivonne, Marga, Marga Yvonne**, all the staff from **OK9**, and everyone from the **planningbureau** and other sections from the Department.

Thanks to all the staff from the Department of Neurosurgery for letting me learn from you, either in the morning meetings, or during all the times I had the chance to attend a surgery.

Also thanks to the small Mexican community in the UMCG, **Jaime, Sebastian,** and **Zeus**. There are feelings you can only express in your mother tongue, so having you there was always an outlet for me. I am proud to see so many talent representing Mexico abroad.

Thanks to my new research team in Amsterdam (our **Percept** and **DBS database** groups), including all the neurologist, neurosurgeons, technical medicine specialists, psychiatrists, psychologists residents, nurse specialists, (PhD) students and technicians. It has not always been easy to carry out our research in the current circumstances. However, thanks to the enthusiasm of everyone involved, we have managed to keep all the projects going.

Beste **Adelbert, Cees, Cootje, Floor**, ik kan jullie niet genoeg bedanken voor al jullie tijd en hulp. Ik waardeer enorm wat jullie voor de groep van buitenlandse artsen hebben gedaan. Als ik (hopelijk binnenkort) weer als arts aan de slag mag, is het mede dankzij jullie.

I would also like to thank all the people I have met outside work. Although my family is not living here, thanks to you I have felt at home here as well.

Dear **Hannah, Manu, Mariel, Matthias and Mert**, thanks for making the very first part of my stay unforgettable. Although now we are spread around the world, I am glad we can still keep in touch and hopefully we can reunite again as soon as the current situation allows it.

Dear **Aldy, Irene, Johanna, Pam, Rodrigo,** and **Simon**. I miss you all. Thanks for being there during all of my stay in Groningen. I have learned my lesson. Next time there is an event in Utrecht or elsewhere, I will just say yes. You never know when the whole world is about to change. Also thanks to everyone that I have met through this group: **Anika, Bart, Daniel, Hector, Joost, Kristian, Marc, Roland, Rous, Sem,** and more.

To all my friends living in Groningen: **Adriaan, Leonard, Lorenzo, Maarten, Nienke, Tim**. I am glad to see that the distance has not stopped us to keep in touch. Thanks for being there for me all these years. **Thomas** and **Tim**, we had an amazing

time in Groningen, and life has reunited us again. Thanks for being there, especially in these times.

Also thanks to the people from the Café de las Lenguas (**Desy, Susan, Wout**), Korno (**Grant, Lukas K, Lukas S, Victor**), the Nuclear Department (**Kars, Menno, Rodrigo**), and my German friends (**Kilian, Lenny, Tim**, and more).

And to the Spanish speakers in these acknowledgements:

Uzz, a pesar de la distancia, cada que nos vemos es como si el tiempo nunca hubiera pasado. Ya es toda una vida de conocernos, y me alegra saber que estas triunfando y que eres feliz haciendo lo que más te gusta hacer. **Bety**, igual que con Uzz, es toda una vida la que llevamos de conocernos. Gracias por todos los momentos que hemos pasado juntos. Me alegra mucho verte feliz.

Para todos los del grupo de Uzz y sus amigos: **Adra, Bety, Chris, Dany, David, Diego, Elvia, Gabes, Guridi, Kike, Jordi, Luis, Nancy, Neto, Oscar, Perlita, Raul, Uzz, Vig**. Hemos pasado tantas cosas juntos que hasta podríamos escribir un libro de eso. Me da mucho gusto ver que a pesar de todos los años que han pasado ya, nuestro grupo sigue unido. Muchas gracias por su amistad. Espero verlos pronto. **Marco y Pam**, gracias por su apoyo y su amistad desde hace ya más de diez años. **Andrea, Andres, Karen**, siempre recordaré el tiempo juntos durante el servicio social. Qué bueno que aún seguimos en contacto en el grupo, también con **Monse**.

Por último, quiero agradecer a mi familia por todo lo que han hecho por mí. Hace mucho tiempo que estoy fuera de casa, y no hay día en que no piense en ustedes. A **mi papá, mamá**: siempre han hecho su mejor esfuerzo en brindarnos todo lo que necesitamos, muchas gracias por siempre cuidar de nosotros. A **Tanis**, estoy muy orgulloso de ti. Siempre he admirado todos tus logros, y como siempre has trabajado muy duro para poder ayudar a la familia. Gracias por ser la doctora de la casa y cuidar la salud de todos. A **Oli** y a mi tía **Rufi**, muchas gracias por ayudarme y siempre estar al pendiente de mí. A **Jona**, gracias por apoyar a todos en la familia estos años, sobre todo cuando no he podido estar ahí. A toda mi familia: gracias por todo el esfuerzo que han hecho para que yo pueda estar aquí.

Y por supuesto, **Tim Huiskes**. Durante varios años he hecho mi mejor esfuerzo por entender tu idioma, así que ahora es tu turno de descifrar este mensaje. Cuántos momentos no hemos pasado juntos estos años! Desde viajes alrededor del mundo, visitando ciudades hermosas, hasta quedarnos hasta tarde tratando de terminar

nuestro trabajo. Gracias por todo el apoyo que me has dado. Ahora que tú empiezas tu doctorado, espero también poderte apoyar en lo que necesites, incluso si solo es para dar una vuelta en bici por la ciudad para despejar la mente. Siempre saldremos adelante.

Curriculum Vitae

Dan Piña Fuentes was born on January 16th, 1989 in Mexico City, Mexico.

He finished high school at the Escuela Nacional Preparatoria 2 'Erasmus Castellanos Quinto', UNAM, in Mexico City (profile Economy and Social Sciences).

In 2008 he was admitted to the Medical School of the Universidad Nacional Autónoma de México (UNAM), Ciudad Universitaria. In 2013, he was granted a scholarship from the Carlos Slim Foundation to carry out a medical internship at the University Medical Center Groningen, the Netherlands. He graduated in 2015 with the project titled 'Prevalence of neuropsychiatric disorders in drug-naïve subjects with Parkinson's disease (PD)'.

In 2015, he was awarded a scholarship from the Consejo Nacional de Ciencia Tecnología (CONACYT) to pursue a PhD in the Department of Neurosurgery of the University Medical Center Groningen, the Netherlands, with the project titled 'Adaptive Deep Brain Stimulation for Parkinson's disease and dystonia,' under the supervision of Prof. J. Marc C. van Dijk and Prof. Marina de Koning-Tijssen (promotores), with Dr. Martijn Beudel as daily supervisor (co-promotor). In 2019, as part of his doctorate program, Dan did a research stay at the John Radcliffe Hospital in Oxford, UK, under the supervision of Prof. P. Brown.

Since January 2020, he carries out postdoctorate research at the Amsterdam University Medical Center, location AMC, supervised by Dr. M. Beudel. Besides this, he has been recently accepted at the Vrije Universiteit Amsterdam to complement his medical studies, in order to become a medical doctor in the Netherlands.

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