Aus der Klinik für Neurologie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

The effect of GPi-DBS on automatic and controlled movement in dystonia

zur Erlangung des akademischen Grades
Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät
Charité – Universitätsmedizin Berlin

von

Moaz Al Ajia

aus Damaskus/Syrien

Datum der Promotion: 17.09.2021

Index

List of Figures

List of Tables

Abbreviations

ACC: anterior cingulate cortex

BG: basal ganglia

CM: centromedian nucleus

D1: D1 dopamine receptor

D2: D2 dopamine receptor

DBS: deep brain stimulation

GPe: globus pallidus externa

GPi: globus pallidus interna

H: healthy

ImpV: impulsive velocity

OFF: off stimulation

ON: on stimulation

PD: Parkinson’s disease

Pre-SMA: pre-supplementary motor area

Put: putamen

PV: peak velocity

RT: reaction time

MT: movement time

MC: motor cortex

PT: performance time

SNc: substantia nigra pars compacta

SNr: substantia nigra pars reticulari

STN: subthalamic nucleus

VL: nucleus ventralis lateralis

Abstract

Dystonia is a disabling movement disorder characterized by involuntary sustained or intermittent muscle contractions and abnormal posture. The classification system for dystonia is based on clinical characteristics (axis I) including the anatomical distribution of the affected body part, the etiology, and the age of onset (axis II). The pathophysiology of dystonia is not fully understood yet. However, a growing body of empirical evidence suggests that it is not attributed to one brain region, but rather that it could arise from abnormal sensorimotor network activity. Although its mechanism of action is not fully understood, deep brain stimulation (DBS) of the Globus pallidus interna (GPi) is a successful treatment for dystonia. The aim of our behavioral study is to explore the effect of GPi-DBS on the cognitive and kinematic aspects of automatic and controlled movements in dystonia. Furthermore, we intended to explore the role of the GPi as the main output of the basal ganglia (BG) in the different movement phases (initiation and execution) and to gain more insight on the pathophysiology of dystonia. Sixteen patients with dystonia undergoing pallidal deep brain stimulation and 16 age-matched healthy controls participated in a visuomotor tracking task requiring normal (automatic) and inverted (controlled) reaching movements. We found that GPi-DBS does not affect proactive inhibition and does not exert an instantaneous effect on the reaction time in the automatic and controlled conditions. GPi-DBS may decrease the average error and improve the movement efficiency in the controlled condition. However, it negatively influences the efficiency of automatic movement performance. Our results suggest that GPi-DBS may exert its effect by interfering with the output signal of the GPi. Furthermore, this study showed that GPi-DBS induces bradykinesia in the automatic condition, quantified by decreasing the peak velocity, which is a common clinical side-effect of GPi-DBS in dystonia.

Abstract in German

Dystonie ist eine behindernde Bewegungsstörung, die durch unwillkürlich anhaltende oder intermittierende Muskelkontraktionen und abnormale Körperhaltung gekennzeichnet ist. Das Klassifizierungssystem für Dystonie basiert für die klinische Achse I auf der anatomischen Verteilung des betroffenen Körperteils, dem zeitlichen Auftreten und dem Erkrankungsalter (Achse II). Die Pathophysiologie der Dystonie ist nicht vollständig verstanden. Studien der letzten Jahre haben gezeigt, dass abnorme Netzwerkaktivität mit pathologischen Oszillationen, abnormer sensomotorischer Integration und erhöhter Plastizität beteiligt sind. Obwohl der Wirkungsmechanismus nicht vollständig verstanden ist, ist die Tiefe Hirnstimulation (THS) des Globus pallidus internus (GPi) eine erfolgreiche Behandlungsmethode für die Dystonie. Ziel unserer Verhaltensstudie ist es, die Wirkung von pallidaler THS auf die kognitiven und kinematischen Aspekte automatischer und kontrollierter Bewegungen bei Dystonie zu untersuchen. Darüber hinaus wollen wir die Rolle des GPi als Hauptausgangsstation der Basalganglien (BG) in den verschiedenen Bewegungsphasen (Initiierung und Ausführung) untersuchen und mehr Einblick in die Pathophysiologie der Dystonie gewinnen. 16 Patienten mit Dystonie, die sich einer pallidalen Tiefen Hirnstimulation unterzogen, und 16 altersentsprechende gesunde Kontrollpersonen nahmen an einer visuomotorischen Aufgabe teil, die normale (automatische) und invertierte (kontrollierte) Reichweitenbewegungen erforderte. Wir fanden heraus, dass GPi-THS die proaktive Hemmung nicht beeinflusst und keinen sofortigen Einfluss auf die Reaktionszeit in automatischen und kontrollierten Zuständen hat. Im kontrollierten Zustand kann GPi-THS den durchschnittlichen Fehler verringern und die Bewegungseffizienz verbessern. Jedoch beeinflusst GPi-THS die Effizienz der automatischen Bewegungsleistung negativ. Unsere Ergebnisse legen nahe, dass GPi-THS seine Wirkung durch Störung des Ausgangssignals des GPi ausüben kann. Darüber hinaus zeigte diese Studie, dass GPi-THS im automatischen Zustand eine Bradykinesie induziert, die durch Verringern der Spitzengeschwindigkeit quantifiziert wird, was eine häufige klinische Nebenwirkung von GPi-THS bei Dystonie ist.

Introduction

1. Anatomical Pathways of the Basal Ganglia

Before we further illustrate the suggested models of the Basal Ganglia (BG) in dystonia, we will briefly demonstrate the functional anatomy of the BG. The cortico-basal ganglia-thalamic system is comprised of parallel circuits that are divided into motor, oculomotor, prefrontal and limbic circuits reflecting their functions (Thomas Wichmann 2016). The motor cortex (MC), premotor cortex, cingulate motor area, and the supplementary motor area project to the putamen and STN. (Monakow, Akert, and Künzle 1978; Inase et al. 1999). From the striatum, two pathways are formed, the so called "direct" and "indirect" pathways (Albin, Young, and Penney 1989; Alexander and Crutcher 1990). A GABAergic population of striatal neurons will form monosynaptic connection with the internal segment of the Globus Pallidus (GPi) and the substantia nigra pars reticulata (SNr), forming the direct pathway. The indirect pathway is formed from other GABAergic striatal neurons which project polysynaptically with GPi/SNr through the external segment of the Globus Pallidus (GPe) and the Subthalamic nucleus (STN) (Mink and Thach 1993; Nambu et al. 2000). Conversely, "the hyperdirect pathway" connects areas in the frontal cortex directly to the GPi through STN bypassing the striatum (Nambu, Tokuno, and Takada 2002).

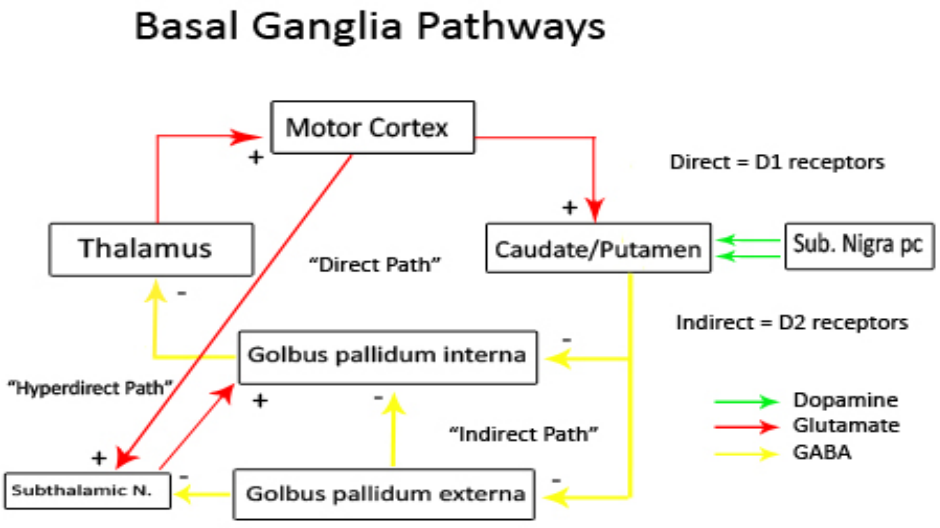

Figure 1: Illustration of the basal ganglia pathways.

Role of the Basal Ganglia in Movement Execution

Although it is well known that the final signal of movement originates from the upper motor neurons in the MC, movement accuracy cannot be achieved without the rigorous influence of the BG. To this end, the role of the BG in action selection has been suggested as the following. Movement initiation elicits corollary signals. First, a stop signal by the cortico-subthalamo-pallidal hyperdirect pathway activates the GPi and leads to an inhibition of basal ganglia-receiving areas of the thalamus and cortex, which are related to both the selected motor program and other competing programs. This is followed by disinhibition of the GPi through the direct pathway, which facilitates a selected program. Finally, further activation of the GPi by the indirect pathway (Nambu, Tokuno, and Takada 2002) takes place causing an inhibition of the motor cortex, a dynamic 'center-surround model' proposed by Nambu and colleagues (Nambu et al. 2000) that explains the initiation of an action.

2. Automatic and Controlled Movement and the Role of Basal Ganglia in Motor Control

Two types of motoric actions can be distinguished, habitual and controlled. An action is considered habitual (automatic) when it is performed automatically alongside another demanding task, and it is acquired slowly over time, so that the action becomes inflexible and insensitive to reinforcers and can be executed unconsciously without high cognitive demand like short term memory and selective attention. (Seger and Spiering 2011). Oppositely to automatic movement, which is also known as implicit control, a controlled movement (explicit control) is executed with more cognitive demand when a learning process takes place. However, the same motor action could be performed habitually or controlled. (Mazzoni and Wexler 2009). Whether the movement will be performed in a habitual or in a controlled manner is determined by many factors like overtraining, predictability, reward reinforcement, and urgency. (Redgrave et al. 2010). To unite the terminologies in the study, we will henceforth refer to the movement conditions as automatic or controlled.

At BG level, the movement initiation phase, which precedes the action selection, may involve concurrent tandem activation of both direct and indirect pathways - that is to say, a race between pathways to cancel the undesired action takes place, rather than sequential facilitatory starting and inhibitory stopping signals of the movement (Cui et al. 2013; Schmidt et al. 2013; Surmeier 2013). The direct pathway is probably the dominant pathway in the automatic movement, where its prior activation, contrary to the indirect pathway, may predict habit and its weakening may predict the suppression of the same habit (O'Hare et al. 2016).

Along with their role in selecting between two competing actions, BG are also important in the learning process, and therefore habit formation, when facing reward conditions. BG may act as a tutor to the cortex, possibly through its dopaminergic innervation (Frank 2011b), although the long-term retention of well-learned movements takes place in the motor cortices. (Turner and Desmurget 2010).

Cockburn and Frank proposed a "reinforcement learning and conflict monitoring" model. (Frank 2011a). In their model, Cockburn and Frank unified the two dominant theories about Error-related negativity (ERN) (a component of an event-related potential (ERP), time-locked to an external event or a response); one relates the ERN to reinforcement learning processes, while the other links the ERN to performance monitoring. In another relevant work, Holroyd and Cloes proposed that the ERN is generated when a negative reinforcement learning signal is conveyed to the Anterior cingulate cortex (ACC) via the mesencephalic dopamine system and that this signal is used by ACC to learn which action should be executed. (Holroyd and Coles 2002). Moreover, Botvinick et al. suggested that the ERN is a product of conflict monitoring processes in the ACC, where an ERN-like signature should be observed when a prepotent response must be overridden, when one of the several equally permissible responses must be selected, or when errors are made. (Botvinick et al. 2001). Frank and Cockburn linked the conflict in the ACC with striatal activation dynamics following reinforcement learning signals that encode reward feedback. (Frank 2011a):

During stimulus presentation in an unlearned trial, an action will randomly be selected with the Go/NoGo BG pathways. When feedback of the chosen action is given, a reinforcement learning signal will be elected by the SNc encoded as a phasic drop or burst of dopamine. The burst from the SNc simultaneously strengthens the Go signal and weakens the NoGo signal projected to the thalamus, and vice versa. According to the model the ACC receives excitatory input from the pre-SMA layer encoding the equivalent response. The ACC monitors the activity in the pre-SMA layer, as the pre-SMA is incapable of inducing an action selection without prior cortico-cortical learning.

When positive feedback is given, the Go signal gains the priority facilitated by the dopamine effect on the D1 receptors afterwards, the initially selected correct response in the pre-SMA is facilitated, the corresponding activity in the ACC comes to uniquely represent the biased response, and the conflict activity is reduced. When negative feedback is given, the dip in dopamine facilitates the activity in the NoGo pathway, the selected response in the pre-SMA is reduced, and the conflict in the ACC is increased. An increase in ACC conflict provides an

account of the fERN. This links the fERN to a conflict-detection mechanism in the ACC with the reinforcement learning signals.

The authors suggested that as cortical projections to the pre-SMA are strengthened, the conflict in the ACC will be progressively less sensitive to influences of the BG. This suggestion falls in line with observations stating that pharmacologically impairing the output of the BG (GPi) to the thalamus, and thence to the cortex, did not influence the automatic overlearned sequence production or the automatic motor choosing. (Piron et al. 2016; Desmurget and Turner 2010). This model also supports the view that the BG may act as a tutor of the cortex, and are therefore essential to the learning phase, but may not be crucial in retaining the overlearned movement. (Turner and Desmurget 2010).

Other researchers proposed a model, in which the storage of the automatic sequence is in the SMA, and its production is cortical. The BG activate the appropriate motor plan in SMA, which triggers Hebbian learning mechanisms between cortical areas that allow sequence learning and eventual automatic response production (Helie et al. 2015; Helie, Ell, and Ashby 2015).

Furthermore, many studies have shown an influence of BG on movement kinematics (Turner 2003; Desmurget and Turner 2008) (Summarized in Table 3). The strong relationship between the neuronal activity in BG and movement velocity and amplitude was also described in pathological movement conditions like dystonia. (Singh and Bötzel 2013; Brucke et al. 2012).

3. Clinical Characteristics of Dystonia

"Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation." (Albanese et al. 2013).

The classification of dystonia can be categorized based on clinical characteristics (axis I) such as the anatomical distribution of the affected body regions, based on the age of onset and the etiology (axis II). In focal dystonia, one body region is affected, as in cervical dystonia, blepharospasm and spasmodic dysphonia. Segmental Dystonia, like craniocervical dystonia, affects two or more contiguous body parts, whereas multifocal dystonia consists of abnormalities in noncontiguous body parts. Hemidystonia, also called unilateral dystonia, involves dystonic contracture in one side of the body. On the other hand, generalized dystonia is characterized by abnormal movements in the legs and at least one other area of the body.

Additionally, dystonia is described as an isolated dystonia, or coexistent with other movement disorders as combined dystonia, or with other neurological manifestations as complex dystonia. Axis II describes the etiological classification, three types of dystonia have been identified; inherited, acquired and idiopathic. Isolated dystonia, where no abnormality other than dystonia is present, can present in a sporadic, autosomal dominant (i.e. DYT1), autosomal recessive or X-linked recessive manner (i.e. DYT3), and combined or complex dystonia are more often secondary to a hereditary complex neurological disorder (e.g. Huntington's disease and Wilson's disease) or acquired dystonia due to an exogenous insult that can be due to a variety of origins that have been identified, such as drug exposure, head trauma, encephalitis, perinatal hypoxia or inherited metabolic defects. It is of note that in isolated dystonia there are no structural brain abnormalities on radiographic studies.

The clinical features of dystonia can vary, and dystonic contractures can be broadly divided into *tonic* sustained co-contraction of the agonist and antagonist muscles or *phasic* with regular or irregular contraction patterns like tremor and myoclonus. (Yokochi et al. 2018).

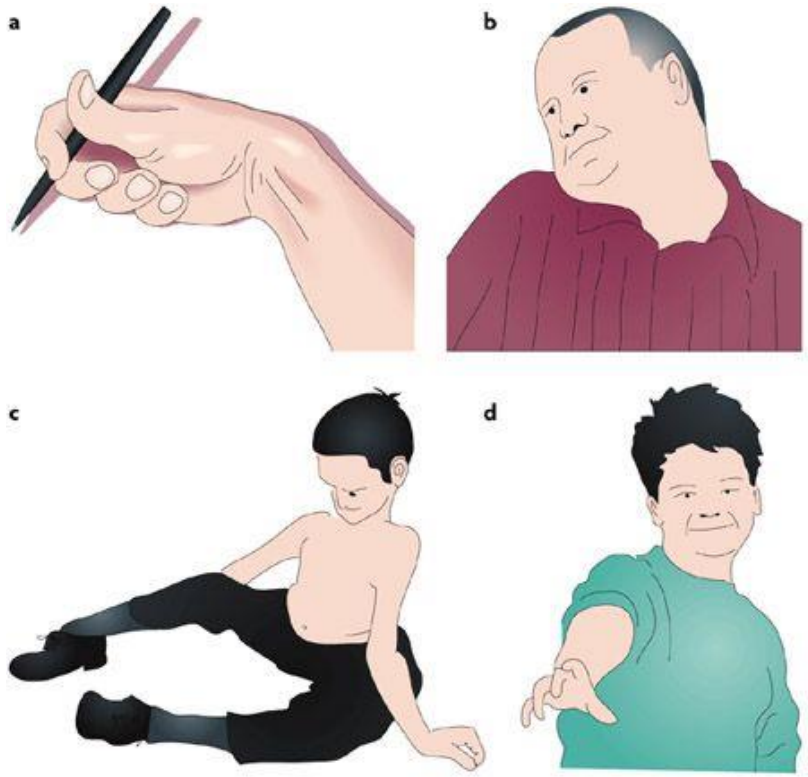

Figure 2: Forms of dystonia. **Writer's cramp (a). Torticollis (b). Generalized dystonia (c). Dystonic spasms in the upper limbs with facial grimacing (d).** Adapted from Breakefield et al. (2008).

4. Pathophysiological Role of Basal Ganglia in Dystonia

4.1 Proposed Pathophysiological Basal Ganglia Models in Dystonia

4.1.1 The Firing Rate and Firing Pattern Model

Electrophysiological studies in dystonia patients and animal models showed abnormal neuronal activity in GPi, with a low discharge rate of an irregular pattern instead of sustained tonic discharge (Vitek JL 1999; Gernert et al. 2002; Nambu et al. 2011). This neuronal activity was found distributed throughout the GPi in generalized dystonia, whereas it was found in focal areas of GPi in focal dystonia (Zhuang, Li, and Hallett 2004). Furthermore, the theta oscillation firing pattern in the GPi was associated with the dystonia severity symptoms (Neumann et al. 2017). Like the patterns of neuronal activity in the GPi, neurons in STN exhibited decreased tonic discharge rate and dystonia-related activity in STN is likely to be associated with symptom distribution. (Gernert et al. 2002).

In their dystonia model, Vitek and colleagues postulated that the striatal overactivity in both the direct and indirect pathways accounts for the observed changes in mean discharge rates, the altered patterns of neuronal activity, and the increased incidence of somatosensory responses of GPi neurons. However, the pathological changes in the level of corticostriatal activity were unclear.

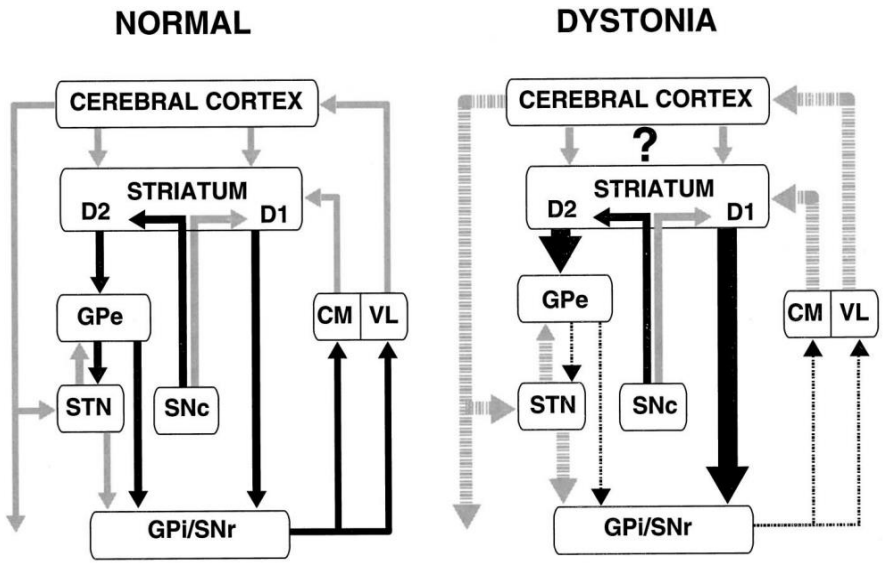

Figure 3: Rate model of Dystonia based on changes in neuronal discharge patterns in external and internal segment of the globus pallidus. Wide and thin lines represent increase and decrease in mean discharge rate, respectively. Interrupted lines highlight altered (abnormal) discharge patterns with increase in synchronization in the basal ganglia-thalamocortical loop leading to upregulated cortical output. Adapted from Vitek JL (1999).

4.1.2 The Dynamic Activity Model

Nambu and Chiken more recently proposed a model that could explain the role of BG in dystonia (Nambu, Tachibana and Chiken 2015). Based on their aforementioned 'center-surround' model, they presented a hypothetical novel model that could explain both hypokinetic and hyperkinetic movement disorders like Parkinson's disease and dystonia. Briefly, in the normal state, the 'center area' of GPi/SNr receives sequential inputs from the three pathways, hyperdirect, direct and indirect, whereas the 'surrounding' area continuously receives input from the inhibitory hyperdirect and indirect pathways, with a minimal projection of the excitatory direct pathway. The 'center' area initiates and terminates the selected motor program and the 'surrounding' area yields a continuous inhibition of the competing program. As a result, a normal movement is executed. In comparison, in a hyperkinetic disorder like dystonia, there is a dominancy of the direct pathway compared to the other pathways. Consequently, a 'wider' inhibition occurs in the center and surrounding areas, and an increased disinhibition in the thalamus and cortex which yields to involuntary movements (Figure 4).

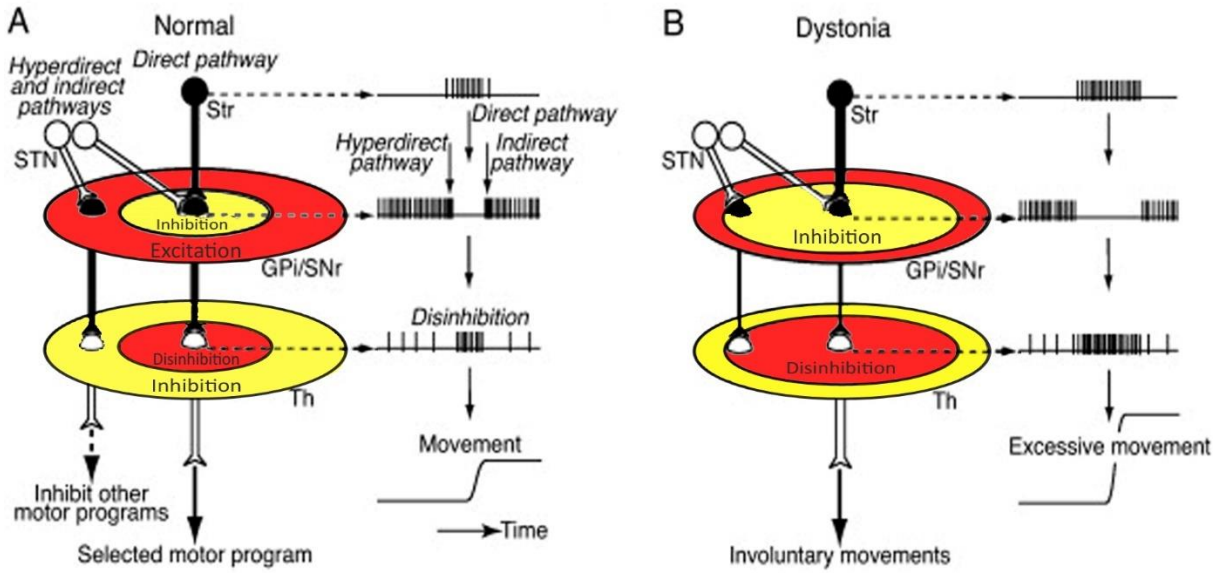

Figure 4: Dynamic activity model explaining the control of voluntary movements in the normal state (A) and dystonia (B). Spatial distributions (left in each panel) and temporal patterns (right in each panel) of neuronal activity in the striatum (Str), GPi/SNr and thalamus (Th) during movements are illustrated. Adapted and modified from Nambu, Tachibana, and Chiken (2015).

4.2 The Pathophysiology of Dystonia

The pathophysiology of dystonia is complex and not fully understood. Although dystonia has been traditionally regarded as a motor dysfunction of the BG loops, accumulating evidence

from experimental and clinical studies shows that dystonia is a network disorder. This means that dystonia is not only attributed to BG, but furthermore involves several other remote brain regions like the motor cortex (Lozeron et al. 2016) and the cerebellum (Prudente, Hess, and Jinnah 2014). The pathogenesis of dystonia is etiologically and phenomenologically heterogeneous. The identified abnormalities in the literature could be summarized as deficient inhibition, abnormal sensorimotor processing, and maladaptive plasticity at different levels of the nervous system. (Lin and Hallett 2009; Defazio, Berardelli and Hallett 2007). For example, in focal hand dystonia abnormal inhibition at the cortical level has been described in many studies using transcranial magnetic stimulation. Indeed, simultaneous inhibition of surrounding muscles is essential in the control of individual muscles and could play an important pathophysiological role in focal hand dystonia. With this said, failure of surround inhibition, due to deficient suppression by GABAergic interneurons, could mean abnormal inhibition at a cortical level and the subsequent stimulation of both target and neighboring non-target muscles, resulting in dystonic posturing (Lin and Hallett 2009). Furthermore, an endophenotype trait of abnormal sensory input is reported in writer's cramp, with both dystonic and non-dystonic hand expressing disorganized sensory cortical representation. This abnormality in somatosensory integration is a hallmark feature in focal dystonia and has been shown to correlate with symptom severity (Meunier et al. 2001). In line with this, using the paired associative stimulation paradigm (PAS), Quatraone et al. demonstrated that patients with writer's cramp and cervical dystonia had a stronger increase in corticospinal excitability than healthy subjects. (Quartarone et al. 2003; Quartarone et al. 2008). Furthermore, they reported a loss of topographical specificity of PAS-induced effects in the cervical dystonia. This suggests a maladaptive plasticity in dystonia which is not restricted to the symptomatic circuits, but rather may represent an endophenotypic trait.

A complex cerebral network composed of cortical areas, cerebellum, and BG are involved in sensorimotor integration, the process through which sensory information is used to plan, execute, and monitor movements. In regard to this, a growing body of evidence demonstrated sensory and sensorimotor dysfunctions in patients with focal dystonia and supported the hypothesis that abnormalities in dystonia extend beyond solely motor control, as they also involve the processing of sensory inputs and cognitive representation of movement (Avanzino et al. 2015; Hinkley et al. 2009). Based on many experimental studies, Avanzino et al. presented a new theoretical model of sensorimotor integration in which dystonic movement could emerge from dysfunctions at different levels of this network (Figure 5). Accordingly, the impairment of sensorimotor integration during movement could be the result of the drop of coherence

between the primary motor and sensory cortex in the gamma band, whose synchronization is an index of an efficient normal sensorimotor integration (Melgari et al. 2013). However, the relationship between the pathological somatosensory integration and the abnormal dystonic motor output is still debatable. One explanation is that repetitive non-physiologic motor behavior can cause changes in somatosensory representations. On the other hand, abnormal somatosensory representations may cause pathological motor output (Perruchoud et al. 2014).

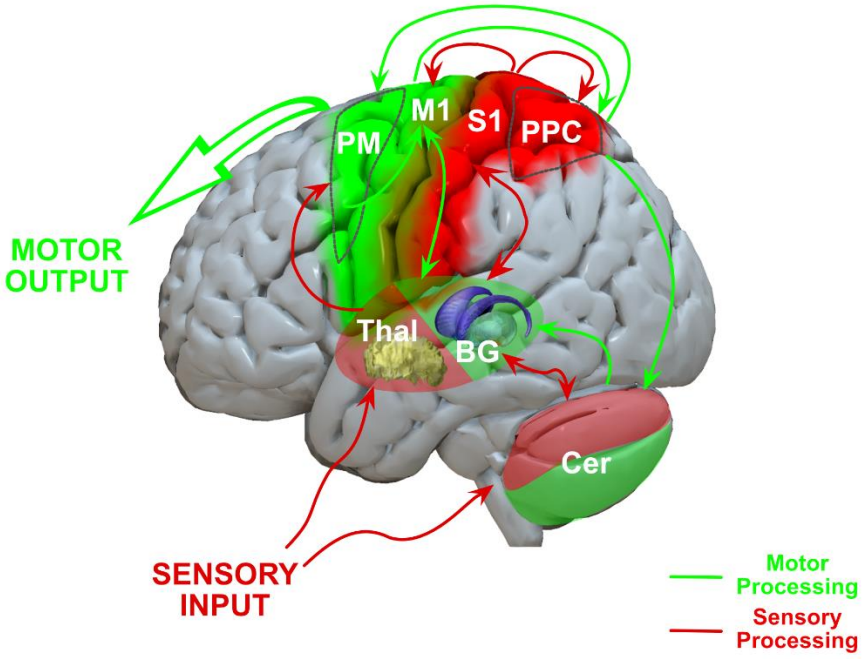

Figure 5: Schematic representation of the complex brain network involved in sensorimotor integration. Sensory input (red) is elaborated by subcortical (firstly Thal, Cer and then BG) and cortical (SI) regions and integrated within the motor plan (green) through associative areas (PPC and PM). Deficits of sensorimotor integration in dystonia could arise from dysfunctions at different levels of this network. BG: basal ganglia; Thal: thalamus; Cer: cerebellum; SI: primary somatosensory cortex; PM: premotor cortex; PPC: posterior parietal cortex; M1: primary motor cortex. Adapted and modified from Avanzino et al. (2015).

5. Treatment of Dystonia

The treatment of dystonia comprises mainly symptomatic control and rehabilitative measures (Jinnah and Factor 2015). Nonetheless, multiple oral medications do exist and have been used to treat dystonia, such as anticholinergic medicaments like trihexyphenidyl, benzodiazepines like clonazepam, and dopamine-related drugs like levodopa, which are particularly effective with dopa-responsive dystonia. (Cloud and Jinnah 2010). Furthermore, botulinum toxin injection is recommended in focal dystonia. Patients with generalized or complex cervical dystonia who do not respond to the medical treatment are considered for surgical treatment with

lesion surgeries or deep brain stimulation (Albanese et al. 2006). Deep Brain Stimulation (DBS) of the Globus pallidus interna (GPi) has achieved great success as a therapeutic method in dystonia and is now established as a class I evidence treatment for isolated generalized dystonia (Kupsch et al. 2005; Volkmann et al. 2014; Moro et al. 2017; Elkaim et al. 2019; Hale et al. 2020).

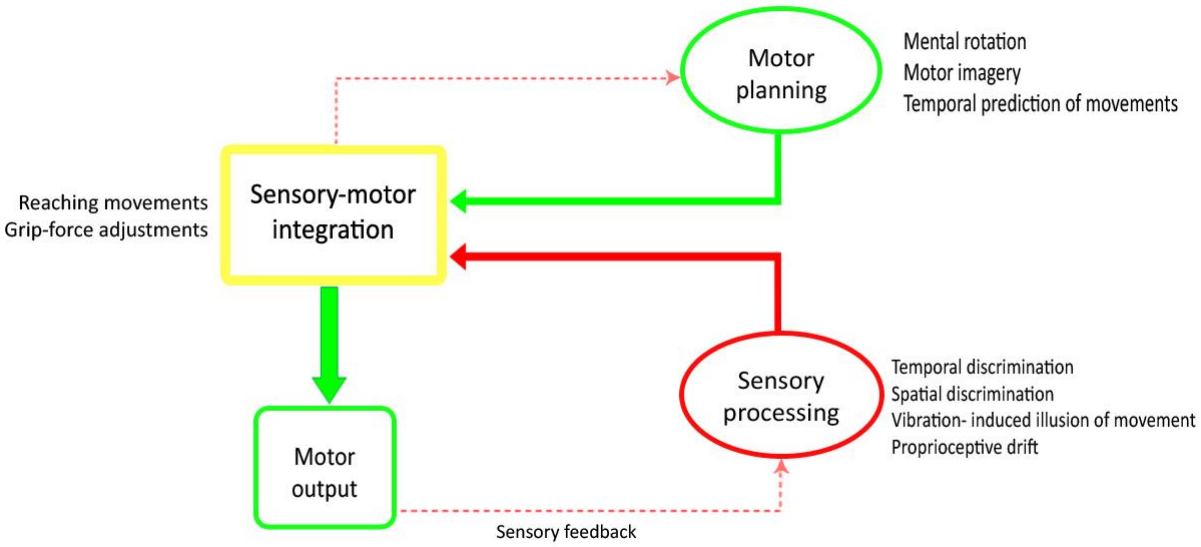

Figure 6: Simplified model of the interaction between sensory information (red) and motor elaboration (green). The tasks in which dysfunctions have been found in dystonic patients are indicated in the figure text. Adapted and modified from Avanzino et al. (2015).

6. GPi-DBS Mechanism of Action

Early studies suggested that DBS acts by inhibiting the neuronal activity in the targeted area, a model that is supported by the observations that DBS of the STN or GPi has similar clinical results to lesioning these nuclei (Limousin et al. 1995; Hashimoto T 2000; Filali et al. 2004; Lafreniere-Roula et al. 2010). Although the GPi receives both GABAergic inhibitory output from the striatum and GPe and glutamatergic excitatory inputs from the STN, the net effect of GPi-DBS is mediated by exciting the afferent inhibitory axons. This inhibitory effect of GPi-DBS can be explained by the activation of GABA receptors in the pallidum; high-frequency stimulation disrupts information flow through the GPi by completely inhibiting cortically evoked potentials, as well as spontaneous discharges of GPi neurons (Chiken and Nambu 2013, 2016).

DBS therapeutic effect in hypo- and hyperkinetic movement disorders is achieved by inducing frequency-dependent modulation of neuronal output, creating ‘informational lesion’ at the stimulated nucleus (Grill WM 2004). This DBS lesion-like effect disrupts the pathological synchronization of BG circuits and consequently releases downstream areas from the abnormal BG output, allowing restoration of functionality in the long-term (Wichmann T 2016). Additionally, high-frequency stimulation may achieve the optimal desynchronization of pathological theta and beta oscillations by imposing a time-locked high-frequency regular discharge pattern on the pathologically firing axons, which may prevent them from passing their pathological oscillations in the inter-pulse intervals. Alternatively, high-frequency stimulation may resonate with the average physiological oscillation frequencies of the basal ganglia–thalamus–cortex system. (Herrington, Cheng, and Eskandar 2016; Ashkan et al. 2017).

Furthermore, DBS may exert its therapeutic effect not only locally, but rather by modulating cortical plasticity. This can be deduced from the fact that the timing between DBS and symptom improvement varies between diseases. This is particularly relevant in dystonia, where underactivity of inhibitory cortical interneurons and excessive plasticity of the cortex are of pathophysiological importance. GPi-DBS can induce an early improvement in phasic dystonic movements, whereas tonic symptoms require months of DBS treatment to be relieved, indicating a possible involvement of DBS-induced plastic changes (Ashkan et al. 2017). This non-local effect of BG-DBS can be confirmed and explained in terms of it modulating the activity in the cortex and the cortico-basal ganglia connectivity. For example, STN-DBS reduces the pathological cortical beta phase-amplitude coupling in Parkinson's disease (de Hemptinne et al. 2015), while in dystonia, GPi-DBS reduces the abnormal inhibitory cortical activity (A.A. Kühn2003). This effect can be mediated by excitation of both afferent and efferent axons in the targeted nucleus, where the total net effects may vary according to dominant neuronal element (for example, exciting the afferent inhibitory axons in the GPi vicinity) (Chiken and Nambu 2016).

All DBS candidates need to be evaluated by a DBS neurologist for assessment of the severity of dystonia and disability level. To be considered a DBS candidate, dystonic patients should be disabled and have failed medical management (Hu and Stead 2014). The stimulation parameters consist of amplitude, pulse width, and frequency. In dystonia, therapeutic amplitudes typically range between 1.0 and 3.5 V. With a pulse width of 60–120 μs, and lower rates of stimulation (60– 80 Hz), symptomatic control can be as effective as higher frequencies (Marks Jr, William

J. 2015). The mechanism of action of DBS is not fully understood. However, many hypotheses can explain its effects on neurological conditions.

Aims of the Study

The main goal of our study is to explore the role of GPi as the output node of BG in a simple (automatic) and in a cognitively demanding (controlled) visuomotor tracking task. Moreover, we intend to explore the role of GPi in different movement phases (initiation and execution). Specifically, GPi participation in the temporal aspects of the movement, such as reaction time and proactive inhibition, as well as in the kinemetric aspects, such as movement velocity and trajectory error rate, is still an unexplored area.

To explore the above-mentioned parameters, stimulation of the GPi through DBS is conducted in dystonia patients, in which the temporal and kinematics parameters is compared in two stimulation conditions (On vs. Off) in the automatic and controlled motor tasks. This allows us to investigate the effect of GPi-DBS in dystonia at the subclinical level. The degree to which movement parameters are correlated with the clinical score will additionally be tested. Finally, the results will be compared between dystonia patients (On and Off DBS) and healthy subjects to investigate the pathological manifestation of dystonia.

Materials and Methods

1. Cohorts' Demographic and Clinical Characteristics

We included 16 patients (12 females) with primary dystonia (57.42 ± 9.50 years old) from the Movement Disorder Outpatient Clinic of the Department of Neurology, Charité University Medicine Berlin, and 16 age-matched healthy control subjects (62.97 ± 7.50 years old). All demographics and phenotypic dystonia classes are demonstrated in Table 1. In general, most of the patients and healthy subjects were right-handed (87.5 %).

All patients had isolated dystonia with variable body distribution (7 cervical dystonia, 1 segmental oromandibular dystonia, 1 multifocal dystonia, 7 generalized dystonia). All patients were evaluated in ON and OFF DBS with the respective dystonia rating scales. Cervical dystonia severity was evaluated using the movement scale of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Generalized and multifocal dystonia severity was evaluated with the movement scale of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). The average clinical scores in the DBS-ON condition for the cervical dystonia patients and the generalized and segmental dystonia patients were 2.57 ± 2.70 and 10.11 ± 11.50, respectively, while in DBS-OFF condition they were 16.57 ± 4.11 and 15.83 ± 12.10, respectively.

The ethical approval was acquired from the local ethics committee of Charité University Medicine Berlin. All participants signed an informed consent before conducting the study.

Table 1: Summary of the cohorts' demographics and clinical characteristics. TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale.

Patient N°	**Sex**	**Dystonia Type**	**BFMDRS/TWSTRS ON**	**BFMDRS/TWSTRS OFF**	**Age (years)**	**Age of the healthy control**
1	f	multifocal	BFMDRS = 1.5	BFMDRS = 8	59.32	66.29
2	m	generalized	BFMDRS = 6	BFMDRS = 8	55.26	59.56
3	f	cervical	TWSTRS = 0	TWSTRS = 21	53.76	59.53
4	f	generalized	BFMDRS = 9	BFMDRS = 28	50.28	55.16
5	f	cervical	TWSTRS = 7	TWSTRS = 13	57.94	63.34
6	f	cervical	TWSTRS = 0	TWSTRS = 18	69.67	73.22
7	f	cervical	TWSTRS = 4	TWSTRS = 18	75.11	74.04
8	f	generalized	BFMDRS = 12	BFMDRS = 13	56.04	66.66
9	f	cervical	TWSTRS = 0	TWSTRS = 10	67.04	72.55
10	f	cervical	TWSTRS = 4	TWSTRS = 15	65.38	69.85
11	f	cervical	TWSTRS = 3	TWSTRS = 21	63.14	68.72
12	f	generalized	BFMDRS = 3.5	BFMDRS = 10	52.65	58.57
13	m	generalized	BFMDRS = 2	BFMDRS = 4	35.45	51.12
14	m	segmental oromandibular	BFMDRS = 1	BFMDRS = 7.5	57.94	61.24
15	f	generalized	BFMDRS = 36	BFMDRS = 40	52.3	55.49
16	m	generalized	BFMDRS = 20	BFMDRS = 24	47.58	52.19

2. Surgery and DBS-Placement

Patients underwent bilateral implantation of DBS electrodes into the GPi. Surgery was performed under general anesthesia. The surgical targeting procedure of the posteroventral GPi was informed by stereotactic 2-mm-thick contiguous proton density magnetic resonance imaging (MRI) slices preoperatively and by intraoperative recording of the distinct local field potentials of the GPi. Confirmation of electrode placement in the GPi was obtained in all patients with immediate post-implantation stereotactic MRI or computed tomography.

3. Paradigm

We used a well-established paradigm which was previously used in patients with Parkinson's disease in Neumann et al. (2018). Briefly, participants were asked to perform a visuomotor task which entails moving a cursor on a computer screen by using a pen on a digitizing tablet. Cursor movement was initiated when a target (dot) appears in one of eight pseudo-randomized circularly arranged positions on the screen. The goal is to reach the dots as precisely as possible. To avoid visual distractions, a cross sign was displayed in the center of the screen, which was the starting point in the reaching movement and where participants had to focus on before the presentation of the target.

The task was programmed in MATLAB 2016b (The Mathworks, Natick, MA, USA). Trials started when the cursor position was moved to a central fixation cross. After 3 s without movement, a warning cue appeared for 500ms as a yellow circle surrounding the fixation cross and 500ms later the target appeared. The subjects could respond immediately after the target appeared.

The task included two pen-to-cursor mapping conditions. In the automatic condition (green target) the pen-to-cursor mapping was congruent, while in the controlled condition (red target), the pen-to-cursor mapping was inverted (see Figure 7 for an illustration).

All participants completed 60 trials of each condition, split into blocks of 30 trials (ordered block: 4 X 30 trials). The condition was announced before each block, so that the patients could prepare for the pen-to-cursor mapping. The condition of the first block (automatic versus controlled) was randomized across patients and healthy controls.

A separate block was presented after the first two ordered blocks. This block contains 60 trials with pseudo-randomly appearing conditions. The subjects had no prior knowledge of the upcoming trials within this block (random block: 1 X 60 trials). The reason for adding this extra block was to preserve the automaticity in executing the green targets (compared to the red targets) in the last ordered group, as it was considered "Semi-Controlled" in the extra block,

and to decrease the possible “learning” effect of the trial progression regarding the controlled condition in the last ordered group. In another words, this extra block helped in preserving the contrast between the automatic and the controlled condition for the last ordered group (for an illustration, see Figures 7 and 8).

Dystonia patients completed 180 trials twice, once with GPi stimulation turned on for at least 30 minutes and once after GPi stimulation was switched off for at least 30 minutes. Again, the starting stimulation condition was pseudo-randomized across patients (9 started on stimulation, 7 started off stimulation). Cursor movement traces were saved for offline analysis by converting the concurrent cursor positions in the x- and y-axes to analogue signals (using a National Instruments digital analogue converter: NI-USB 6212, National Instruments) that were recorded on a separate computer (using Spike2 software with a 1401 Power Mk2 (CED) A-D converter and a sampling rate of 1000Hz for offline analysis). All movement traces were analyzed using custom MATLAB code.

Visuomotor-task Parameters Description:

As for each task consisted of movement, the motor response initiation represented by the reaction time (RT), while the execution of the movement was represented by the movement time (MT). The latter is defined as the time between movement onset and the time the cursor reaches the target in each trial. The peak velocity (PV) was calculated as the peak of the first derivative of movement traces. To quantify a measure of accuracy in conflict (controlled) condition, trajectory error was calculated. In brief, the average difference between the optimal movement trajectory (straight line) connecting the fixation cross and the target entrance of the cursor interpolated for the length of the movement has been taken as trajectory error. Deviation from a straight trajectory leads to increased distance that needs to be covered and is therefore considered less optimal. Another parameter of interest is performance time PT, which was defined as the sum of the reaction time and the movement time of each trial. Finally, proactive inhibition (or the action restrain in dystonia), which is the preparatory latency to stop an upcoming response tendency (Aron 2011), was quantified by the difference between reaction time of the learned automatic movement and the new conflict controlled movement, a well-established indicator of the inhibition (Kohl et al. 2015; Pan et al. 2018).

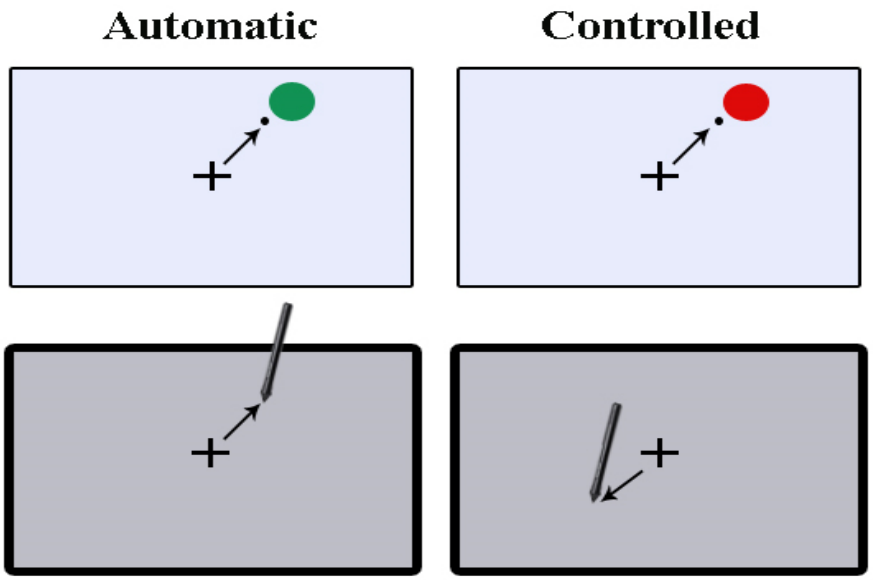

Figure 7: Visuomotor-task: automatic and controlled movement. In the automatic condition (green target) the cognitive demand is low, where the pen-to-cursor mapping is congruent, while in the controlled condition (red target) the cognitive demand is high, where the pen-to-cursor mapping is inverted.

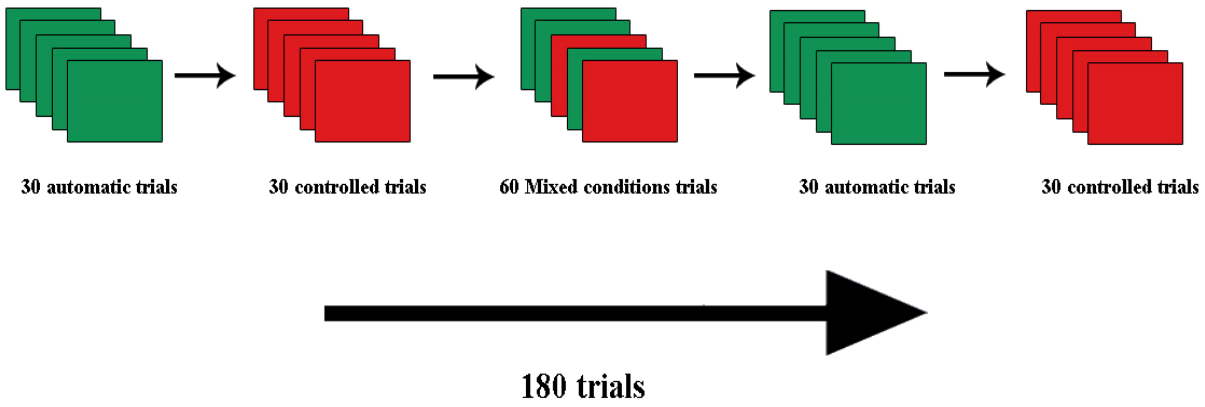

Figure 8: Visuomotor-task trial presenting order. Each session consists of 180 trials divided into 5 blocks. The first block is 30 trials with the same movement condition (either automatic=green or controlled=red). The second block is 30 trials with the same condition, which is opposite to that in the first block. The third block contains 60 trials of mixed conditions, which are presented randomly. The fourth and fifth blocks are equal to the first and second blocks, respectively.

4. Statistical analysis

All statistical analyses were carried out in Excel and MATLAB 2017. To avoid the violation of necessary assumptions such as normality, linearity, and equality of variance, we implemented a permutation test with 10,000 permutations, which also has the advantage of detecting the significance between groups independently from their randomization status.

The correlation analysis was conducted using a non-parametric rank-based Spearman's correlations, which is robust for outliers. All data are presented as mean and two-sided standard deviation.

Briefly, the off-line analysis of the parameters averages was conducted after extracting the average values for each subject for each movement condition (for patients also for each stimulation condition) from the already saved session-wise acquired average tables in the 4 ordered blocks. Outliers, defined by values above twice the value of standard deviation were already omitted, this being conducted by another MATLAB code written for this purpose. The significant difference between groups and stimulation conditions was calculated using the permutation test. The average values were saved intermediately in Excel sheets for backup purposes and further verification.

The correlation between the impulsive velocity and the trajectory error was carried out using Spearman's correlation, and testing its significance was carried out by the premutation test, after extracting all trial values of these parameters for each study condition in the ordered blocks from the saved session-wise MATLAB files.

Results

1. Effects of Pallidal Stimulation on Movement Initiation

1.1 Reaction Time

Broadly speaking, there was no effect of GPi-DBS on reaction time, regardless of the movement/task condition. However, healthy subjects reacted faster than dystonic patients in both stimulation conditions (ON/OFF) during the automatic task, with a trend towards significance (RT healthy = 466.72 ms, *P* (H-OFF) = 0.09, *P* (H-ON) = 0.07). On the other hand, GPi-DBS did not bring a significant difference in RT between DBS-ON and DBS-OFF conditions in the patient cohort (RT ON = 561.61 ms, RT OFF = 563.29 ms. *P* (ON-OFF) = 0.48). Additionally, healthy subjects did not show difference from the patient group under the influence of the more cognitively demanding (controlled movement) task (RT healthy = 681.73 ms, RT ON = 638.49 ms, RT OFF = 645.16 ms. *P* (ON-OFF) = 0.30, *P* (H-OFF) = 0.18, *P* (H-ON) = 0.16).

Table 2: Movement parameters during automatic and controlled movement tasks of healthy and patient cohorts. SD=standard-deviation. All values are statistical means. Values between brackets represent standard deviations.

Parameters	**Automatic Movement**			**Controlled Movement**		
	DBS-ON	**DBS-OFF**	**Healthy**	**DBS-ON**	**DBS-OFF**	**Healthy**
RT (ms)	561.61 (227.62)	563.29 (258.80)	466.72 (71.74)	638.49 (121.56)	645.16 (104.40)	681.73 (134.52)
MT (ms)	671.21 (244.57)	639.10 (210.77)	512.80 (161.76)	777.38 (200.36)	785.56 (214.94)	750.22 (300.57)
ImpV (au)	0.19 (0.09)	0.20 (0.09)	0.22 (0.06)	0.17 (0.06)	0.16 (0.09)	0.17 (0.08)
PV (au)	0.30 (0.05)	0.32 (0.06)	0.35 (0.09)	0.26 (0.06)	0.28 (0.06)	0.29 (0.10)
Trajectory Error (au)	16.66 (6.26)	18.30 (8.46)	13.38 (2.98)	17.36 (4.21)	18.83 (5.70)	15.25 (3.74)

1.2 Proactive Inhibition (PI) Time

The current study also aimed to elucidate how pallidal stimulation could affect PI time as an index of the action restrain quantified by the difference between reaction time of the learned automatic movement and the new controlled movement. With regard to this, the permutation test did actually demonstrate a significantly longer PI time in healthy subjects in comparison to dystonic patients during DBS-ON and DBS-OFF conditions (H-PI = 215.00 ms, DBS-ON = 76.88 ms, *P* (H-ON) < 0.01; DBS-OFF = 81.86 ms, *P* (H-OFF)= 0.021). Nonetheless, the current analysis indicated no change in PI time when DBS was turned ON in dystonic patients (*P* = 0.446).

2. Effects of Pallidal Stimulation on Movement Execution

2.1 Movement Time (MT)

Similar to the results of RT, healthy subjects took a shorter time to execute the automatic movement task than dystonic patients in both DBS conditions (MT healthy = 512.80 ms, MT DBS-OFF = 639.10 ms, *P* (H-OFF) = 0.018; MT DBS-ON = 671.21 ms, P(H-ON) = 0.011). In contrast, MT was not significantly different between DBS conditions in dystonic patients (*P* (ON-OFF) = 0.1861).

Furthermore, we did not observe a significant difference between the healthy participants and patients in either DBS condition (MT healthy = 750.21 ms, MT DBS-ON = 777.38 ms, *P* (H-ON) = 0.35; MT DBS-OFF = 785.56 ms, *P* (H-OFF) = 0.3458; *P* (ON-OFF) = 0.441).

2.2 Impulsive velocity (ImpV)

In another step, we aimed to explore the effect of pallidal stimulation on the initial segment of the movement task, namely ImpV. In the automatic condition, there was no significant difference between the dystonia patients and the healthy subjects. Furthermore, GPi-DBS did not change this parameter in dystonia (ImpV healthy = 0.22 au, ImpV OFF = 0.20 au, ImpV ON = 0.19 au, *P* (H-OFF) = 0.2734, *P* (H-ON) = 0.1379, *P* (ON-OFF) = 0.1683). In the case of controlled task performance, there was no statistically significant difference between healthy and patient groups irrespective of DBS state (ImpV healthy = 0.17 au, ImpV ON = 0.17 au, ImpV OFF = 0.16 au. *P* (ON-OFF) = 0.3541, *P* (H-OFF) = 0.3664, *P* (H-ON) = 0.4179).

2.3 Peak Velocity (PV)

In order to dissect movement velocity changes in relation to DBS effect, we further investigated how stimulating the pallidum could affect PV as a velocity substrate occurring later in mid-

movement. On average, healthy subjects showed a higher PV value compared to dystonic patients in ON stimulation (PV healthy = 0.35 au, PV DBS-ON = 0.30 au, *P* (H-ON) = 0.019). Interestingly, with an inverse effect of the impulsive velocity, GPi-DBS induced a slower peak velocity in the dystonia group (PV DBS-OFF = 0.32 au. *P* (ON-OFF) = 0.038). We did not detect a statistically significant difference between the healthy subjects and patients in OFF stimulation (*P* (H-OFF) = 0.15). Dystonic patients (DBS-OFF and DBS-ON) and healthy subjects showed similar peak velocity in the cognitively demanding (controlled-movement) task (PV healthy = 0.17 au, PV DBS-ON = 0.17 au, *P* (H-ON) = 0.16; mean PV DBS-OFF = 0.16 au, *P* (H-OFF) = 0.32; *P* (ON-OFF) = 0.17).

3. Effects of Pallidal Stimulation on Trajectory Error

Another aspect of task performance is how many errors the performer would make. As a further goal, we aimed to get insight on this aspect through measuring the effect of DBS on trajectory error. In the automatic movement task, there was significantly less trajectory error in healthy subjects than dystonic patients in DBS-OFF (Error healthy = 13.38 au, Error OFF = 18.30 au. *P* (H-OFF) = 0.0362) and a trend towards significance in DBS-ON (Error ON = 16.66 au, *P* (H-ON) = 0.0632), while patients performed indifferently during both DBS states (*P* (ON-OFF) = 0.112).

Furthermore, healthy subjects demonstrated less trajectory error compared to the dystonic patients' OFF stimulation (Error healthy = 15.25 au, Error DBS-OFF = 18.83 au, *P* (H-OFF) = 0.046) during controlled movement task performance. However, there was no significant difference between healthy subjects and patients' ON stimulation (*P* (H-ON) = 0.108). GPi-DBS decreased trajectory error average in patient group with a trend towards significance (Error ON = 17.36 au, *P* (ON-OFF) = 0.0637).

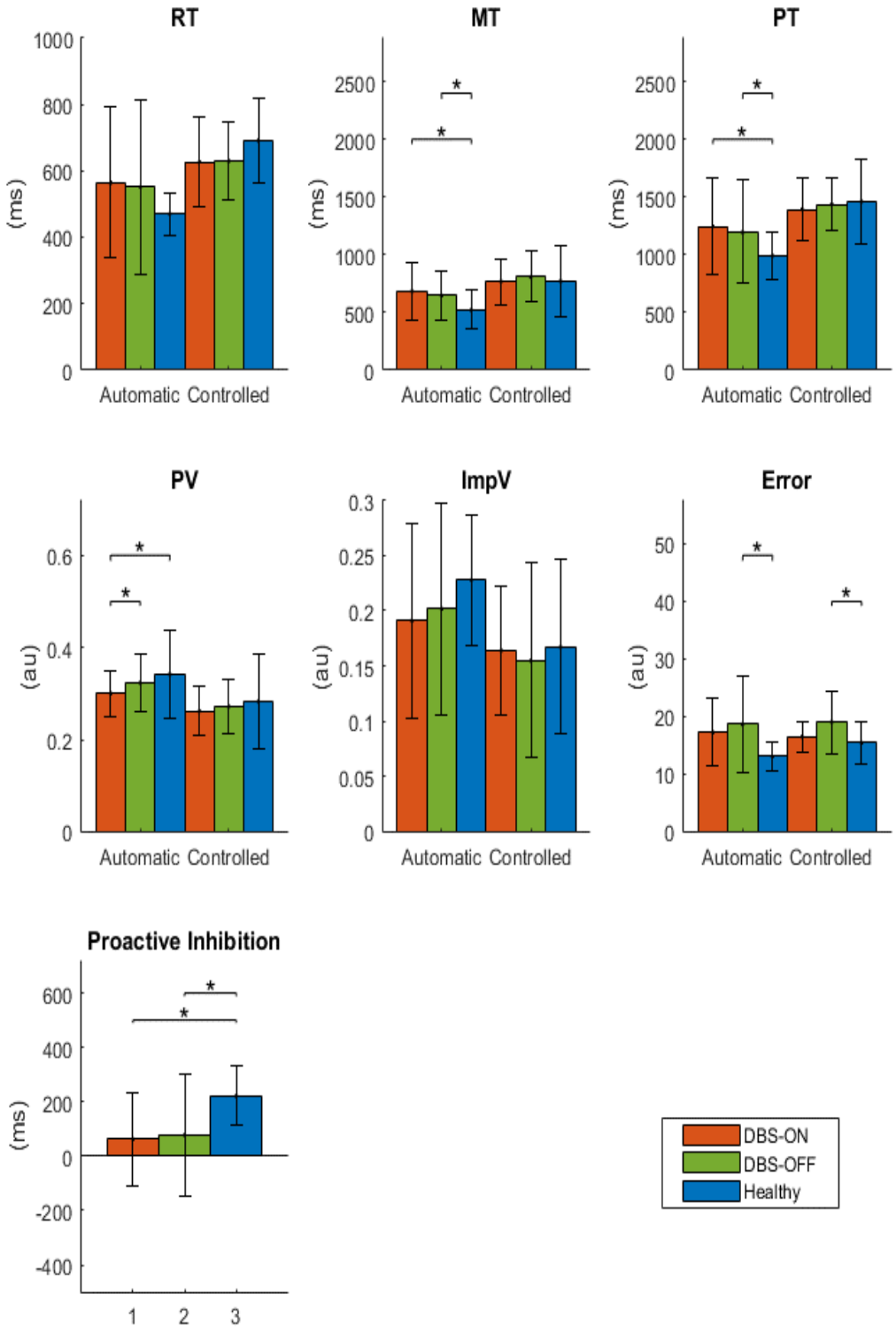

Figure 9: Illustration of the main results. Red = DBS-ON, green = DBS-OFF, blue = Healthy. RT = reaction time, MT = movement time, PT = performance time, PV = peak velocity. * indicates a significant *P* value < 0.05.

4. Effects of Pallidal Stimulation on Movement Efficiency

Movement efficiency, quantified by the Spearman correlation between the trajectory error and the initial velocity across the 60 trials averaged over subjects, showed that GPi-DBS ameliorated the negative correlation (Trade-off) between the aforementioned parameters during automatic task performance (Spearman's rho ON = -0.0242, P = 0.417; Spearman's rho OFF = -0.33, P = 0.0004; Spearman's rho H = -0.526, P = 0).

In contrast to this, DBS caused a trade-off between the initial velocity and trajectory error in the controlled task (Spearman's rho ON = -0.452, P = 0), whereas dystonia patients without GPi stimulation did not execute the uncontrolled task efficiently (Spearman's rho OFF = -0.065, P = 0.3). The healthy subjects showed a negative correlation; hence, there was movement efficiency in both conditions (Spearman's rho H = -0.424, P = 0).

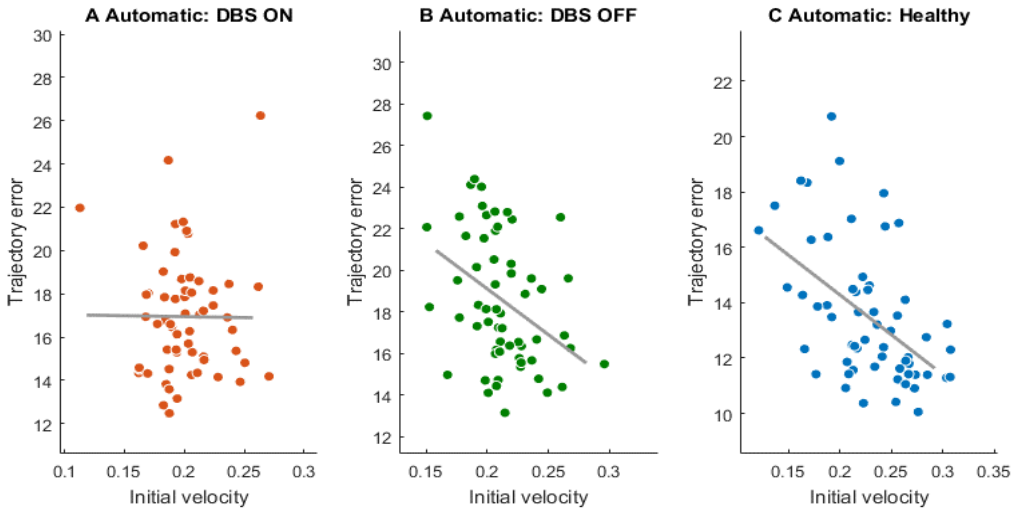

Figure 10: Spearman's correlation between the trajectory error and the impulsive velocity in the automatic condition. Red = DBS-ON, green = DBS-OFF, blue = healthy (rho ON = -0.0242, P = 0.417; rho OFF = -0.33, P = 0.0004; rho H = -0.526, P = 0).

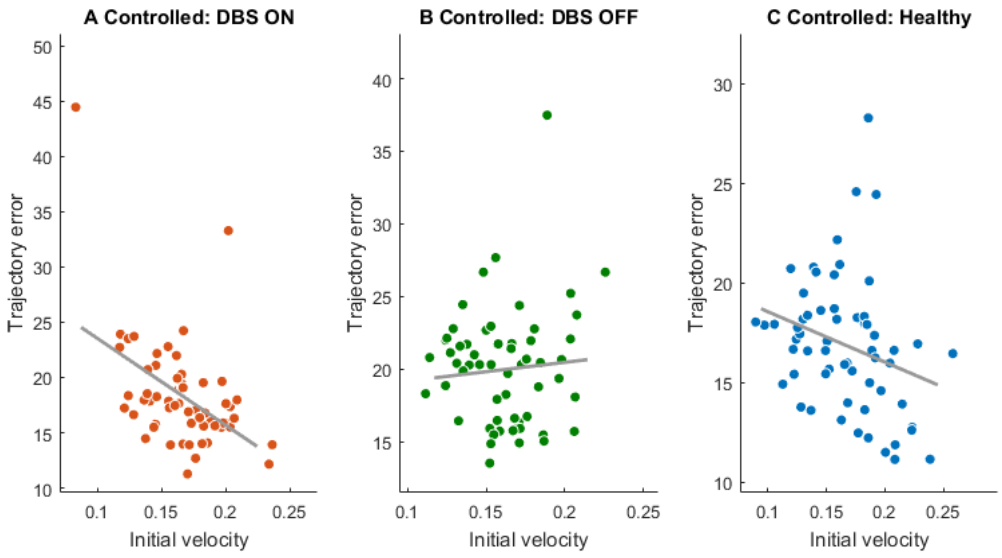

Figure 11: Spearman's correlation between the trajectory error and the impulsive velocity in the controlled condition. Red = DBS-ON, green = DBS-OFF, blue = healthy (rho ON = -0.452, *P* = 0, rho OFF = -0.065, *P* = 0.3, rho H = -0.424, P = 0).

5. Correlation between the Clinical Score and the Behavioral Parameters

There was no correlation between the clinical score and the behavioral parameters except for a negative correlation between the peak velocity and the clinical score in the automatic movement condition when GPi-DBS is turned Off (Spearman's rho = -0. 469, *P* = 0.0306). Furthermore, there was a negative correlation between the impulsive velocity and the clinical score in the automatic condition with DBS-OFF (Spearman's rho = -0. 471, *P* = 0.0274). This indicates that at their neutral state (DBS-OFF) the more severely clinically affected dystonia patients had slower impulsive and peak velocity in the automatic condition. Finally, the impulsive velocity was negatively correlated with the clinical score in the controlled condition when DBS was turned on (Spearman's rho = -0. 494, P = 0.0222).

Discussion

In this study we used pallidal DBS to explore the role of the Globus pallidus internus as the main output station of the basal ganglia on the cognitive and kinematic aspects of automatic and controlled movements in dystonia. Our main finding is that pallidal DBS may not exert an instantaneous effect on the movement initiation in dystonia in the automatic or in the controlled condition. Overall, GPi-DBS decreased the average error and improved the movement efficiency in the controlled condition. Our results suggest that GPi-DBS may interfere with the output signal of the GPi, thereby influencing movement execution. Before we discuss our results in more detail, we will highlight the related behavioral studies in the literature on GPi-DBS in PD, and those on pallidotomy and the pharmacological lesioning of GPi.

1. Suggested Role of GPi in Movement Kinematics: Evidence from Previous Studies

Schubert et al. showed that DBS of the posteroventrolateral of GPi in Parkinson's disease might improve performance by shortening the reaction time in simple and choice RT motor tasks (Schubert et al. 2002). In another study, Kohl et al. utilized a Go/NoGo motor task with two trial-types, one with a higher-conflict, cognitively demanding (controlled) condition and the other with lower cognitive demand (automatic). They demonstrated that GPi-DBS speeded up the response initiation, with significantly faster Go RTs in DBS On state, while the error rate was not significantly altered. In the same study, proactive inhibition, quantified by the RT difference between cognitively demanding and lower conflict Go trials, was only significantly lower in patients with the GPi-DBS On vs. healthy controls. Furthermore, GPi-DBS had no significant effect on reactive inhibition measured by the reaction time of the NoGo controlled trials. From these observations, one can conclude that the GPi is essential in the direct Go pathway, and thus could be facilitated by DBS to reach the required threshold to initiate an action, but does not alter the indirect NoGo pathway (Kohl et al. 2015). In line with these findings, Pan et al. used a stop-signal paradigm and showed that the effect of GPi-DBS on response initiation and reactive inhibition was in accord with the previous study. However, in contrast to Kohl et al, they concluded that GPi-DBS could improve the dysfunctional proactive inhibition in PD toward a healthy state by causing more latency in the action-preparation in a conflict situation. They suggested that GPi-DBS acts as an amplifier, activating the afferent pathways in the GPi, on the assumption that GPi-DBS reduces the inhibitory output to thalamo-cortical areas when an inhibitory signal reaches the GPi from the direct pathway. Similarly, when excitatory signals arrive from the hyperdirect and indirect pathways, GPi-DBS increases

the inhibitory output (Pan et al. 2018). Conversely, a study of pallidal pharmacological lesioning in primates interestingly demonstrated the increased probability of executing the controlled (not learned) motor task erroneously, but not the learned (automatic) task, during a choice motor task. This implies a critical role of the BG in learning, but not in expression of automatic movement (Piron et al. 2016). Furthermore, in a motor sequence task, GPi lesioning caused similar kinematic negative effects with dysmetria and motor slowing in both the overlearned (automatic) and random (controlled) conditions. On the other hand, the fluid automatized integration of these movements into a learned sequence was preserved, suggesting that GPi is not essential in motor sequencing or the storage of overlearned sequences, but is crucial in motor execution (Desmurget and Turner 2010). After all, pallidotomy and GPi lesioning caused a different outcome at the temporal level (Table 3).

Table 3: Summary of the studies on GPi-DBS and pallidotomy in automatic and controlled movements. * similar in both conditions. ** Reaction time in the GO trials.

Intervention on GPi	Reaction Time	Correct decision in controlled (not learned/high conflict) condition	Correct decision in automatic (learned/low conflict) condition	Reactive inhibition	Proactive inhibition (RT controlled minus RT automatic)	References
Pharmacological lesioning GPi vs. healthy in primates	Increases both in automatic and controlled conditions	Impairs success rate	No effect	-	-	(Piron et al. 2016)
	Little or no change in automatic. Increases movement time in the automatic condition	-	-	-	-	(Horak and Anderson 1984)
	Decrease slightly in both conditions *	Increases execution errors and decreases velocity *	Increases execution errors and decreases velocity *	-	-	(Desmurget and Turner 2010)
Pallidotomy in Parkinson's Before vs. after	Decreases in simple (automatic) and in choice (controlled)	-	-	-	No difference	(Hayashi et al 2003) (Jankovic et al. 1999)
GPi-DBS Parkinson's On vs. Off	Decreases in On in automatic and controlled**	No effect	No effect (omission errors)	No difference	No difference	(Kohl et al. 2015).
	Decreases in On in automatic (no effect in the controlled) **	No effect	No effect	No difference	More in On vs. Off	(Pan et al. 2018)
	Decreases in On in both conditions	-	-	-	-	(Schubert et al. 2002)
GPi-DBS Parkinson's vs. healthy	Increases in Off vs. healthy only in controlled**	Healthy make fewer errors	Healthy make fewer errors	No difference	Less in On vs. healthy	(Kohl et al. 2015)
	Decreases in On vs. healthy only in automatic**	Healthy are more accurate	Healthy are more accurate	No difference	No effect	(Pan et al. 2018)

2. Movement Initiation (Reaction Time and Impulsive Velocity)

2.1 GPi-DBS does not Improve the RT Instantly in the Automatic Condition

Our results showed no statistically significant difference in the average RT in dystonia patients between On-DBS/Off-DBS states and compared to the healthy subjects in both automatic and controlled conditions. However, there was a trend toward significance where the healthy subjects reacted relativity faster than the patients in the automatic condition, suggesting a pathological movement initiation in the automatic movement in dystonia.

The lack of effect of GPi-DBS on RT in patients performing the automatic condition trials could be explained by the following. Due to the lack of a conflict in the automatic condition, we did not expect a race between the direct and the indirect pathways (Cui et al. 2013; Schmidt et al. 2013; Surmeier 2013), but rather a dominancy of the "GO" direct pathway. (O'Hare et al. 2016). In the three previously mentioned GPi-DBS studies on Parkinson's disease (Schubert et al. 2002; Kohl et al. 2015; Pan et al. 2018), stimulating the GPi decreased the reaction time of the learned movement. These consistent findings suggested that GPi-DBS facilitates reaching the required threshold to initiate an action by enhancing the activity of the dominant GO direct pathway at the GPi. The lack of an instantaneous effect of GPi-DBS on RT in dystonia compared with idiopathic PD may be dependent on the disease-related pathophysiology; according to the "dynamic activity model" (Nambu, Tachibana, and Chiken 2015), the degenerative loss of pigmented dopaminergic neurons of the substantia nigra pars compacta in PD reduces movement-related inhibition through the direct pathway in the center area and facilitates movement-related GPi excitation through the hyperdirect and indirect pathways in the center and surrounding areas, which causes a shorter and narrower movement-related GPi inhibition "center", whereas in dystonia the GPi inhibition center is wider and the direct pathway is more dominant (Nambu, Tachibana, and Chiken 2015). The discrepancy in the pathophysiology at this level could be the reason that there was a different effect of GPi-DBS on RT between dystonia and PD. Moreover, the facilitatory role of DBS could be more prominent and instantaneous on the "narrower" direct pathway in PD.

Furthermore, it cannot be excluded that GPi-DBS could accelerate the automatic movement initiation - not necessarily immediately by its local modulation, but by its delayed (hours) plastic effects on remote motor network hubs (Herrington, Cheng, and Eskandar 2016). Modulating the pathological circuitry at the premovement level may require a more remote plastic effect - an effect that could not be measured in our paradigm. This modulation does not mean that the network is reorganized to produce the correct trajectory movement.

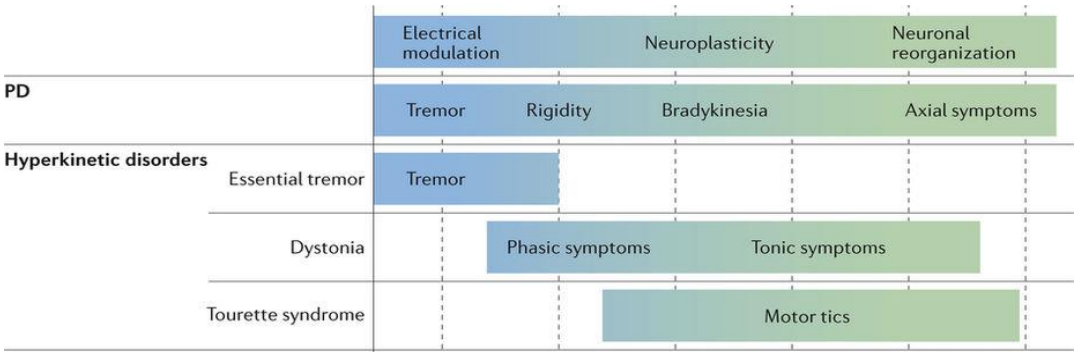

Figure 12: Logarithmic scale showing patterns of symptom improvement following the switching on of deep brain stimulation electrodes in patients to treat a range of disorders. Adapted from Ashkan et al. (2017).

2.2 Lack of Effect of GPi-DBS on RT and Impulsive Velocity in the Controlled Condition

Under conflict condition the time needed to initiate a motor response, as well as the impulsive velocity did not differ across the groups (On vs. Off vs. Healthy). The lack of effect of DBS could be explained by the following.

We designed the controlled condition to be executed with a higher cognitive strain, whereby the participants should overcome the habitual movement to react as quickly as possible toward the target. Although our experiment was not designed as a target-choice motor task, we expected a decision-making process in choosing between the automatic and the controlled movement program in the controlled trials block.

Switching to a controlled movement from an automatic movement requires inhibiting the outputs of the automatic process that proceed more quickly than the controlled process. The fast hyperdirect pathway involving the STN may play a role in the switch (Isoda and Hikosaka 2011). We assume that the proactive inhibition process of the pre-potent habitual movement, mediated by the hyperdirect pathway, may play an essential role as a first step in choosing an action, then the race between the direct and the indirect pathway takes place for the controlled movement to be performed.

Our findings suggest that GPi-DBS in dystonia may not play a role in canceling an action in the controlled movement. The two following factors could explain this.

First, as in the Kohl el al. study, our results showed that stimulating the GPi did not affect the hyperdirect pathway quantified by the proactive inhibition, the process needed in choosing

between two actions (see center-surround model). Furthermore, the proactive inhibition in dystonia seems to be pathological, as the healthy subjects implemented more proactive inhibition compared with the dystonia patients, regardless of DBS condition. This indicates that abnormal proactive inhibition is a prevalent feature in dystonia that was not altered by stimulating the GPi.

Second, the race between the direct and the indirect pathways in dystonia may not be altered by DBS. This comes in line with the findings of other studies (Kohl et al. 2015; Pan et al. 2018) that showed a lack of GPi-DBS influence on the reactive inhibition process mediated by the indirect pathway, which, with its D2 receptors, may mediate the signaling processes needed for switching to the target with the higher value (Ueda et al. 2017). However, except for the Pan et al. study, GPi-DBS speeded up the response initiation not only in the learned condition, but also in the conflict condition in Parkinson's disease, which was still mediated by an instantaneous effect on the Go direct pathway rather than the NoGo indirect pathway.

To summarize, GPi-DBS probably does not affect the proactive and reactive inhibition in dystonia.

3. Trajectory Error

Both trajectory error and peak velocity are indicators of the performance strategy. Since they are related to the movement direction, we assume that the trajectory error and the initial velocity correspond to the early stage of the movement execution, and are thus the earliest outcome of the cognitive process.

3.1 GPi-DBS may Negatively Influence the Efficiency of the Automatic Movement Performance

In the automatic movement, healthy subjects had a tendency towards performing the task with fewer errors compared with dystonic patients regardless of DBS state. This indicates a pathological release of a movement that is supposed to be habitual. Furthermore, GPi-DBS did not decrease the average trajectory error in dystonia. Our findings come in line with the findings from previous studies in PD (Table 3), where GPi-DBS also failed to enhance the error rate in the low-conflict habitual movement (Pan et al. 2018; Kohl et al. 2015). Furthermore, decision-making motor task experiments on primates showed that pharmacological inactivation of the GPi did not impair target choice, with the higher reward being in well-learned automatic behavior and the automatized integration of the movement into a learned sequence (Desmurget and Turner 2010; Piron et al. 2016). Although there was no consistent role of the GPi in

producing the automatic decision and sequences at the kinematic level, the aforementioned findings could still be true. Taking this into consideration, our results suggest that either GPi, as the main BG output node, does not have an essential role in inhibiting errors in the automatic movement, or that GPi-DBS failed to decrease the average error in dystonia as in PD.

To address this question, we analyzed the correlation between the impulsive velocity and the trajectory error, as they are the earlieist kinementic outcomes of the movement. We found a negative trade-off between the impulsive velocity and the trajectory error was present when DBS is turned off, which was also the case in healthy subjects. On the other hand, GPi-DBS caused no trade-off between these two parameters.

This suggests that GPi-DBS may have a negative effect on the efficiency of the automatic movement performance. Specifically, GPi-DBS can "uncouple" the trading-off between the trajectory error and the impulsive velocity, a point that we will revisit. Moreover, GPi may have a role in executing the automatic motor task, which could be modulated by DBS.

3.2 GPi-DBS Decreases the Average Error and Improves the Movement Efficiency in the Controlled Condition

In the controlled condition, the healthy group performed the task with a lower average error compared with dystonic patients with DBS-OFF. Furthermore, GPi-DBS might enhance the controlled movement performance in dystonia by reducing the trajectory error (*P* ON-OFF with a trend towards significance 0.0637). Our results contradict the findings from GPi-DBS studies in PD, where stimulating the GPi did not reduce the error rate when facing a new, not learned, high conflict condition (Table 3). GPi-DBS did not worsen the efficiency, as seen in the automatic movement. Instead, there was a trade-off between the impulsive velocity and the trajectory error in the healthy subjects and in DBS-ON. This negative correlation was not detected in the DBS-OFF condition.

We will try to interpret our findings based on the aforementioned "reinforcement learning and conflict monitoring" model proposed by Cockburn and Frank that considers the dynamic interaction between cortex-basal ganglia loops (Figure 13).

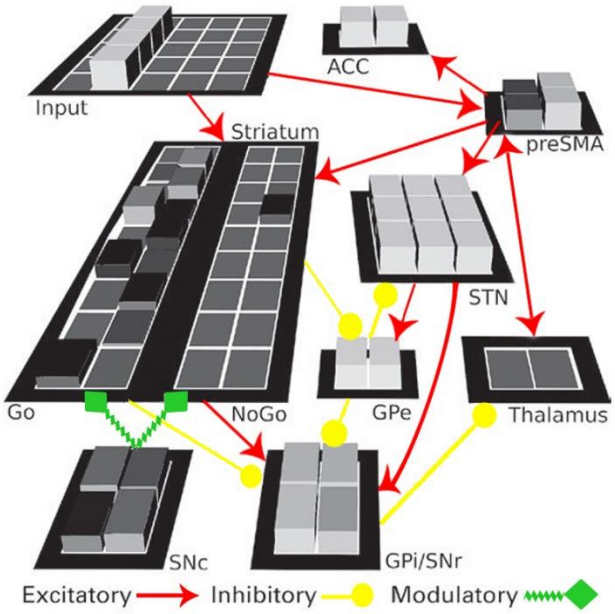

Figure 13: Neural network model of the BG circuit, with two different responses represented by two columns of units in each of the Go, No-Go, GPe, GPi/SNr, thalamus, pre-SMA, and ACC layers. Adapted and modified from Frank (2011a).

The healthy subjects started with a higher trajectory error compared to the end of the controlled block (Spearman's correlation coefficient between the trajectory error across the 60 trials averaged over the subjects and the trials order rho = -0.546, $P = 0$). Applying this model on our study, it could be assumed that healthy subjects initially reacted using the automatic pre-potent pattern (as if the cursor moves in the direction of the pad-pen) (Isoda and Hikosaka 2011), which is mediated by the input Pre-SMA Go pathway, then a negative feedback is given, which is cued with the subject's internal conscious signal instead of the externally given signal. As a result, the dopamine dip faciliates the NoGo pathway and the pre-potent (former automatic) initial response in the pre-SMA is reduced. Additionally, the conflict in the ACC would be suspected to increase. Another correcting movement program would be then chosen by the pre-SMA and executed by the Go pathway. During the progression, the correct Go response would be learned by this dopamine-dependent system and would be adopted at the end by the pre-SMA as an automated movement, which could be executed independently from dopamine secretion with no conflict in the ACC. In other words, we suggest the following learning sequence in the controlled block toward movement consolidation/automatization.

In the first trial: Incorrect Go (pre-SMA old automatic movement) - No Go (high ACC conflict) - correct Go (in pre-SMA)

In progress: correct Go - NoGo (lower ACC conflict) - correct Go

In the final trial: correct Go (pre-SMA new automatic movement, no conflict in ACC)

According to the defective sensorimotor learning hypothesis, the different types of dystonia would be characterized by functional alterations in the sensorimotor circuit supposed to integrate sensory input and motor output (Breakefield et al. 2008; Perruchoud et al. 2014).

Based on this model, we could interpret our findings by assuming that GPi-DBS enhances this network at its input and output level without influencing the indirect NoGo pathway, but rather by modulating the activity at the pre-SMA level by modulating the abnormal sensorimotor integration, making it more efficient at integrating the sensory (input) with the motor execution (output). This notion harmonizes with the GPi kinematic role stated in the aforementioned pallidal lesioning study (Desmurget and Turner 2010), suggesting that GPi is not essential in the storage of overlearned sequences, but that it is crucial in the motor execution (Desmurget and Turner 2010), and it comes in line with the electrophysiological findings of Herrojo et al. in idiopathic dystonia patients, who demonstrated that error-related pallidal activity, characterized by theta oscillations, may predictively influence the cortical ENR, which might be independent of explicit response conflict.

The influence of GPi-DBS in modulating the activity of the motor cortex has been demonstrated by other studies in dystonia (A.A. Kühn 2003) and in Parkinson's disease (Valálik et al. 2009).

Our assumption was further supported by the efficiency factor represented by the correlation between the trajectory error and the impulsive velocity, which are the earliest kinematic manifestations (output) of this network. We found that performance efficiency is abnormal in dystonia patients in comparison with the healthy subjects being represented by a negative trade-off. GPi-DBS normalized the efficiency, whereby the patients executed the reaching movement with a higher initial speed at lower trajectory error trials. This may reflect more efficiency at the cortical level, where the sensory input is integrated with the best motor program.

Putting this all together, GPi-DBS in dystonia may enhance the efficiency of the motor execution in the controlled reaching movement by modulation of the GPi activity and by enhancing the abnormal sensorimotor integration at the cortical level.

In the automatic condition, based on this model, we assume that the correct reaching movement is already learned. Therefore, the transition toward the automatization, as seen in the controlled condition, is not as expected, but rather it adheres to the following program:

correct Go (pre-SMA automatic movement, no conflict in ACC)

In other words, the correct automatic program is already stored in the SMA cortex and executed through the direct Go pathway independently from dopamine rewarding system, the BG here being only a "transition gate point" rather than a "tutor" (Turner and Desmurget 2010).

In this condition, through its output GPi, the BG may provide the urgency signal that controls the amount of sensory evidence needed before "committing" to the motor program already favored by the premotor and the primary motor cortex (Thura and Cisek 2016, 2014, 2017). When the cortical sensory input is big enough, the GPi "Gate" is opened confirming the commitment to that choice. This urgency signal grows over time and modulates the speed-accuracy trade-off - in our case, the efficiency (Thura and Cisek 2016, 2014, 2017). It is important to state that the reaching movement at the automatic condition was not 100% free of conflict, since the green dot was presented at any point in 360 degrees. However, the greater cognitively demanding task in our experiment was to adapt the new cursor-pen directionality motion, and secondarily to this, it was to move as quickly and as accurately as possible toward the target. Therefore, the essential part of improving the performance of the healthy subjects in the automatic condition was the urgency signal provided by the BG, rather than overcoming an incorrect Go program. Furthermore, Thura et. al have detected this signal in a highly trained movement. Whether this BG urgency signal plays a role in executing a new unlearned (controlled) movement needs to be elucidated in further studies.

Our dystonia patients with the DBS-Off condition made more errors than the healthy subjects. This could be attributed to the following. As demonstrated earlier, the acquisition of the saved automatic program in the dystonic cortex by the sensory integration is abnormal, therefore the "correct" Go program, the most suitable movement program in this case, is abnormal.

In the automatic movement, stimulating the GPi did not decrease the average error, or improve movement efficiency. Instead, it worsened the movement efficiency, where no more correlation between speed and trajectory errors was detected. This indicates that GPi-DBS may interfere with the basal ganglia urgency signal that modulates the relation between the speed (motor vigor) and the accuracy (error rate) in the automatic condition.

4. Movement Execution (Peak Velocity and Movement Time)

4.1. GPi-DBS Induces Bradykinesia in the Automatic Condition

In the automatic condition, dystonia patients with DBS-ON and DBS-OFF required more time to execute the motor task compared to the healthy subjects. This suggests a pathological

movement scaling in dystonia. GPi-DBS was not able to normalize the movement execution time in dystonia. However, stimulating GPi decreased the peak velocity in dystonia. The lack of a corresponding effect of GPi-DBS on these two parameters, which are supposed to mirror each other, may indicate a different movement strategy in dystonia patients, which could be manipulated by GPi-DBS at the velocity parameter as we will discuss later. This discrepancy between movement time and peak velocity has also been reported in dystonia patients without DBS treatment (Katschnig-Winter et al. 2014).

4.2. Movement Execution in the Controlled Condition is not Changed

In the controlled condition, we did not see a difference in these parameters between the dystonia patients with DBS-On and DBS-OFF and compared to the healthy subjects. The lack of effect of GPi-DBS on the peak velocity in this condition, unlike the automatic condition, may support the idea that GPi-DBS may exert its effect mainly by facilitating the direct pathway, which is dominant in the automatic condition (O'Hare et al. 2016).

4.3. A Possible Explanation of GPi-DBS-Induced Bradykinesia

Bradykinesia, quantified in our experiment by the peak velocity, is a common clinical side effect of pallidal stimulation in dystonia (Berman et al. 2009; Amtage et al. 2013; Mahlknecht et al. 2018; Hübl et al.). However, it is worth mentioning that there was no distinction between reaction times and movement times in the aforementioned cited clinical observations.

Amtage et al. proposed a possible explanation of GPi-DBS-induced bradykinesia. They argued that based on the underlining pathology of dystonia, there may be an exaggerated activation of the direct pathway with enhanced inhibition of the GPi, and based on the hypothesis that high frequency stimulation induces selective GABAergic axons release (Dostrovsky et al. 2000), GPi-DBS would increase the GABAergic output into the thalamus, resulting in a suppression of the hyperkinetic movements causing hypokinetic movement, an effect that is noticed more in the phasic symptoms than the tonic ones (Amtage et al. 2013). However, this hypothesis did not differentiate between the movement initiation/preparation phase and the movement execution phase.

In this respect, we noticed an inconsistent effect of GPi-DBS on the velocity in dystonia, where in our experiment, GPi-DBS decreased the peak velocity (movement execution) but not the impulsive velocity (movement initiation). Producing a plausible explanation is complicated, given the complexity of the cortico-basal ganglia-cortical networks as well as the unclear dystonia pathophysiology and DBS mechanism. However, the activity along the direct pathway

nodes (striatum, pallidum, thalamus) may differ between movement preparation and execution phases. (Neumann et al. 2018). Therefore, a corresponding difference of GPi-DBS effect during the task performance is expected.

In their recent work, Neumann et al. suggested a firing rate model of the cortex-basal ganglia-thalamus network during the performance of a reaching motor task. They proposed that during movement preparation, the activity of the GPi is increased, then it declines gradually as movement execution progresses (Neumann et al. 2018). The firing rate of the striatum, on the other hand, with its direct (D1) and indirect (D2) pathways, increases gradually in the motor execution (Neumann et al. 2018). Taking this into account, it is plausible to theorize that stimulating the pallidum in the execution phase may have a more prominent effect than in the preparation phase, whereby stimulating the GPi in the execution phase may excite the less active inhibitory efferent axons of the GPi projecting on the thalamus. This may release the GPi from the gradually increasing inhibitory striatal signal, which in turn induces a slowing of the movement.

5. Correlation between the Clinical Score and the Behavioral Parameters

The lack of correlation between the clinical score and most of the behavioral parameters in both stimulation conditions (automatic and controlled) could suggest that the tested behavioral parameter changes were at the subclinical level. The most clinically relevant parameter was the velocity in the automatic condition. Here, severely affected dystonia patients in their neutral state with the DBS turned off had slower impulsive and peak velocity in the automatic condition. This is an indication that these parameters would be clinically relevant, especially in terms of contributing towards answering the question: “Why can GPi DBS induce bradykinesia as a common side effect?”

Limitations

We acknowledge the following limitations:

- The small size of our patient sample. Dystonia is relatively a rare movement disorder, and placement of the DBS requires special neurosurgical training at advanced surgical centers. Although most of the studies conducted on human subjects with dystonia treated with GPi-DBS have included few patients, we managed to recruit 16 subjects. Future work on GPi-DBS in dystonia should be conducted with multicenter cooperation to avoid this issue.
- Out of ethical considerations, we were unable to switch off the stimulation for more than 30 minutes, whereas the duration needed to induce plastic changes in the tonic symptoms is hours to days.
- The role of the GPi was studied in a pathological state (dystonia), so it is not possible to segregate the normal "unmasked" contribution of the GPi in the movement from the pathophysiology of dystonia. Furthermore, it is hard to differentiate its role at the neutral state without prior modulation with DBS. Moreover, the healthy subjects were without DBS implantation. Therefore, the pure effect of GPi-DBS on our behavioral parameters without the interference of the dystonia pathology could not be studied.
- Because it was a behavioral study, we did not study the corresponding changes in the LFP. A combination of a behavioral and electrophysiological study would be essential to test our hypothesis that the GPi-DBS in dystonia may have different effects on the velocity depending on the movement phase.
- We acknowledge the heterogenicity of our dystonia group, which may affect the execution of the movement according to the affected part of the body. However, as we discussed above, the pathophysiology of dystonia appears to be an endophenotypic trait that affects the whole brain plastic circuitry and cannot be attributed to one part of the brain. Therefore, the electrical activity of the GPi, as the output node of the BG, is expected to always be pathological in all types of dystonia.

References

A.A. Kühn, MD; B.-U. Meyer, MD†; T. Trottenberg, MD; S.A. Brandt, MD; G.H. Schneider, MD; and A. Kupsch, MD. 2003. 'Modulation of motor cortex excitability by pallidal stimulation in patients with severe dystonia', NEUROLOGY.

Albanese, A., M. P. Barnes, K. P. Bhatia, E. Fernandez-Alvarez, G. Filippini, T. Gasser, J. K. Krauss, A. Newton, I. Rektor, M. Savoiardo, and J. Valls-Sole. 2006. 'A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and dystonia plus syndromes: report of an EFNS/MDS-ES Task Force', Eur J Neurol, 13: 433-44.

Albanese, A., K. Bhatia, S. B. Bressman, M. R. Delong, S. Fahn, V. S. Fung, M. Hallett, J. Jankovic, H. A. Jinnah, C. Klein, A. E. Lang, J. W. Mink, and J. K. Teller. 2013. 'Phenomenology and classification of dystonia: a consensus update', Mov Disord, 28: 863-73.

Albin, R. L., A. B. Young, and J. B. Penney. 1989. 'The functional anatomy of basal ganglia disorders', Trends Neurosci, 12: 366-75.

Alexander, G. E., and M. D. Crutcher. 1990. 'Functional architecture of basal ganglia circuits: neural substrates of parallel processing', Trends Neurosci, 13: 266-71.

Amtage, F., T. J. Feuerstein, S. Meier, T. Prokop, T. Piroth, and M. O. Pinsker. 2013. 'Hypokinesia upon Pallidal Deep Brain Stimulation of Dystonia: Support of a GABAergic Mechanism', Front Neurol, 4: 198.

Aron, A. R. 2011. 'From reactive to proactive and selective control: developing a richer model for stopping inappropriate responses', Biol Psychiatry, 69: e55-68.

Ashkan, K., P. Rogers, H. Bergman, and I. Ughratdar. 2017. 'Insights into the mechanisms of deep brain stimulation', Nat Rev Neurol, 13: 548-54.

Avanzino, L., M. Tinazzi, S. Ionta, and M. Fiorio. 2015. 'Sensory-motor integration in focal dystonia', Neuropsychologia, 79: 288-300.

Berman, B. D., P. A. Starr, W. J. Marks, Jr., and J. L. Ostrem. 2009. 'Induction of bradykinesia with pallidal deep brain stimulation in patients with cranial-cervical dystonia', Stereotact Funct Neurosurg, 87: 37-44.

Botvinick, M. M., T. S. Braver, D. M. Barch, C. S. Carter, and J. D. Cohen. 2001. 'Conflict monitoring and cognitive control', Psychol Rev, 108: 624-52.

Breakefield, X. O., A. J. Blood, Y. Li, M. Hallett, P. I. Hanson, and D. G. Standaert. 2008. 'The pathophysiological basis of dystonias', Nat Rev Neurosci, 9: 222-34.

Brucke, C., J. Huebl, T. Schonecker, W. J. Neumann, K. Yarrow, A. Kupsch, C. Blahak, G. Lutjens, P. Brown, J. K. Krauss, G. H. Schneider, and A. A. Kuhn. 2012. 'Scaling of movement is related to pallidal gamma oscillations in patients with dystonia', J Neurosci, 32: 1008-19.

Chiken, S., and A. Nambu. 2013. 'High-frequency pallidal stimulation disrupts information flow through the pallidum by GABAergic inhibition', J Neurosci, 33: 2268-80.

———. 2016. 'Mechanism of Deep Brain Stimulation: Inhibition, Excitation, or Disruption?', Neuroscientist, 22: 313-22.

Cloud, L. J., and H. A. Jinnah. 2010. 'Treatment strategies for dystonia', Expert Opin Pharmacother, 11: 5-15.

Colosimo, C., and A. Berardelli. 2011. 'Clinical phenomenology of dystonia', Int Rev Neurobiol, 98: 509-24.

Cui, Guohong, Sang Beom Jun, Xin Jin, Michael D. Pham, Steven S. Vogel, David M. Lovinger, and Rui M. Costa. 2013. 'Concurrent activation of striatal direct and indirect pathways during action initiation', Nature, 494: 238-42.

de Hemptinne, C., N. C. Swann, J. L. Ostrem, E. S. Ryapolova-Webb, M. San Luciano, N. B. Galifianakis, and P. A. Starr. 2015. 'Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease', Nat Neurosci, 18: 779-86.
Defazio, G., A. Berardelli, and M. Hallett. 2007. 'Do primary adult-onset focal dystonias share aetiological factors?', Brain, 130: 1183-93.
Desmurget, M., and R. S. Turner. 2008. 'Testing basal ganglia motor functions through reversible inactivations in the posterior internal globus pallidus', J Neurophysiol, 99: 1057-76.
———. 2010. 'Motor sequences and the basal ganglia: kinematics, not habits', J Neurosci, 30: 7685-90.
Dostrovsky, J. O., R. Levy, J. P. Wu, W. D. Hutchison, R. R. Tasker, and A. M. Lozano. 2000. 'Microstimulation-induced inhibition of neuronal firing in human globus pallidus', J Neurophysiol, 84: 570-4.
Elkaim, L. M., N. M. Alotaibi, A. Sigal, H. M. Alotaibi, N. Lipsman, S. K. Kalia, D. L. Fehlings, A. M. Lozano, and G. M. Ibrahim. 2019. 'Deep brain stimulation for pediatric dystonia: a meta-analysis with individual participant data', Dev Med Child Neurol, 61: 49-56.
Filali, M., W. D. Hutchison, V. N. Palter, A. M. Lozano, and J. O. Dostrovsky. 2004. 'Stimulation-induced inhibition of neuronal firing in human subthalamic nucleus', Exp Brain Res, 156: 274-81.
Frank, Jeffrey Cockburn and Michael. 2011a. 'Reinforcement Learning, Conflict Monitoring, and Cognitive Control: An Integrative Model of Cingulate-Striatal Interactions and the ERN', In: Mars RB, Sallet J, Rushworth MFS, Yeung N, editors. Neural basis of motivational and cognitive control. Vol. 9. Cambridge, MA: MIT Press, p. 311–331.
Frank, M. J. 2011b. 'Computational models of motivated action selection in corticostriatal circuits', Curr Opin Neurobiol, 21: 381-6.
Gernert, Manuela, Mustapha Bennay, Maren Fedrowitz, Jan H. Rehders, and Angelika Richter. 2002. 'Altered Discharge Pattern of Basal Ganglia Output Neurons in an Animal Model of Idiopathic Dystonia', The Journal of Neuroscience, 22: 7244-53.
Geyer, Howard L., and Susan B. Bressman. 2006. 'The diagnosis of dystonia', The Lancet Neurology, 5: 780-90.
Grill WM, Snyder AN, Miocinovic S. 2004. 'Deep brain stimulation creates an informational lesion of the stimulated nucleus.', Neuroreport.
Hale, A. T., M. A. Monsour, J. D. Rolston, R. P. Naftel, and D. J. Englot. 2020. 'Deep brain stimulation in pediatric dystonia: a systematic review', Neurosurg Rev, 43: 873-80.
Hashimoto, T. 2000. Neuronal activity in the globus pallidus in primary dystonia and off-period dystonia.
Helie, S., S. W. Ell, and F. G. Ashby. 2015. 'Learning robust cortico-cortical associations with the basal ganglia: an integrative review', Cortex, 64: 123-35.
Helie, S., J. L. Roeder, L. Vucovich, D. Runger, and F. G. Ashby. 2015. 'A neurocomputational model of automatic sequence production', J Cogn Neurosci, 27: 1412-26.
Herrington, T. M., J. J. Cheng, and E. N. Eskandar. 2016. 'Mechanisms of deep brain stimulation', J Neurophysiol, 115: 19-38.
Herrojo Ruiz, M., J. Huebl, T. Schonecker, A. Kupsch, K. Yarrow, J. K. Krauss, G. H. Schneider, and A. A. Kuhn. 2014. 'Involvement of human internal globus pallidus in the early modulation of cortical error-related activity', Cereb Cortex, 24: 1502-17.
Hinkley, L. B., R. L. Webster, N. N. Byl, and S. S. Nagarajan. 2009. 'Neuroimaging characteristics of patients with focal hand dystonia', J Hand Ther, 22: 125-34; quiz 35.

Holroyd, C. B., and M. G. H. Coles. 2002. 'The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity', Psychol Rev, 109: 679-709.
Horak, F. B., and M. E. Anderson. 1984. 'Influence of globus pallidus on arm movements in monkeys. I. Effects of kainic acid-induced lesions', J Neurophysiol, 52: 290-304.
Hu, Wei, and Matt Stead. 2014. 'Deep brain stimulation for dystonia', Translational Neurodegeneration, 3: 2-2.
Inase, M., H. Tokuno, A. Nambu, T. Akazawa, and M. Takada. 1999. 'Corticostriatal and corticosubthalamic input zones from the presupplementary motor area in the macaque monkey: comparison with the input zones from the supplementary motor area', Brain Res, 833: 191-201.
Isoda, M., and O. Hikosaka. 2011. 'Cortico-basal ganglia mechanisms for overcoming innate, habitual and motivational behaviors', Eur J Neurosci, 33: 2058-69.
Jankovic, J., L. Ben-Arie, K. Schwartz, K. Chen, M. Khan, E. C. Lai, J. K. Krauss, and R. Grossman. 1999. 'Movement and reaction times and fine coordination tasks following pallidotomy', Mov Disord, 14: 57-62.
Jinnah, H. A., and S. A. Factor. 2015. 'Diagnosis and treatment of dystonia', Neurol Clin, 33: 77-100.
Katschnig-Winter, P., P. Schwingenschuh, M. Davare, A. Sadnicka, R. Schmidt, J. C. Rothwell, K. P. Bhatia, and M. J. Edwards. 2014. 'Motor sequence learning and motor adaptation in primary cervical dystonia', J Clin Neurosci, 21: 934-8.
Kohl, S., K. Aggeli, I. Obeso, M. Speekenbrink, P. Limousin, J. Kuhn, and M. Jahanshahi. 2015. 'In Parkinson's disease pallidal deep brain stimulation speeds up response initiation but has no effect on reactive inhibition', J Neurol, 262: 1741-50.
Lafreniere-Roula, M., E. Kim, W. D. Hutchison, A. M. Lozano, M. Hodaie, and J. O. Dostrovsky. 2010. 'High-frequency microstimulation in human globus pallidus and substantia nigra', Exp Brain Res, 205: 251-61.
limousin, P. et al. 1995. 'Bilateral Subthalamic Nucleus Stimulation for Severe Parkinson’s Disease', Movement disorders : official journal of the Movement Disorder Society.
Lin, Peter T., and Mark Hallett. 2009. 'The pathophysiology of focal hand dystonia', Journal of hand therapy : official journal of the American Society of Hand Therapists, 22: 109-14.
Lozeron, P., A. Poujois, A. Richard, S. Masmoudi, E. Meppiel, F. Woimant, and N. Kubis. 2016. 'Contribution of TMS and rTMS in the Understanding of the Pathophysiology and in the Treatment of Dystonia', Front Neural Circuits, 10: 90.
Mahlknecht, P., D. Georgiev, H. Akram, F. Brugger, S. Vinke, L. Zrinzo, M. Hariz, K. P. Bhatia, G. M. Hariz, P. Willeit, J. C. Rothwell, T. Foltynie, and P. Limousin. 2018. 'Parkinsonian signs in patients with cervical dystonia treated with pallidal deep brain stimulation', Brain.
Mazzoni, P., and N. S. Wexler. 2009. 'Parallel explicit and implicit control of reaching', PloS one, 4: e7557.
Melgari, J. M., F. Zappasodi, C. Porcaro, L. Tomasevic, E. Cassetta, P. M. Rossini, and F. Tecchio. 2013. 'Movement-induced uncoupling of primary sensory and motor areas in focal task-specific hand dystonia', Neuroscience, 250: 434-45.
Meunier, S., L. Garnero, A. Ducorps, L. Mazieres, S. Lehericy, S. T. du Montcel, B. Renault, and M. Vidailhet. 2001. 'Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganization', Ann Neurol, 50: 521-7.
Mink, J. W., and W. T. Thach. 1993. 'Basal ganglia intrinsic circuits and their role in behavior', Curr Opin Neurobiol, 3: 950-7.

Monakow, K. Hartmann-von, K. Akert, and H. Künzle. 1978. 'Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey', Experimental Brain Research, 33: 395-403.

Moro, E., C. LeReun, J. K. Krauss, A. Albanese, J. P. Lin, S. Walleser Autiero, T. C. Brionne, and M. Vidailhet. 2017. 'Efficacy of pallidal stimulation in isolated dystonia: a systematic review and meta-analysis', Eur J Neurol, 24: 552-60.

Nambu, A., S. Chiken, P. Shashidharan, H. Nishibayashi, M. Ogura, K. Kakishita, S. Tanaka, Y. Tachibana, H. Kita, and T. Itakura. 2011. 'Reduced pallidal output causes dystonia', Front Syst Neurosci, 5: 89.

Nambu, A., H. Tokuno, I. Hamada, H. Kita, M. Imanishi, T. Akazawa, Y. Ikeuchi, and N. Hasegawa. 2000. 'Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey', J Neurophysiol, 84: 289-300.

Nambu, A., H. Tokuno, and M. Takada. 2002. 'Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway', Neurosci Res 43: 111-7.

Nambu, Atsushi, Yoshihisa Tachibana, and Satomi Chiken. 2015. 'Cause of parkinsonian symptoms: Firing rate, firing pattern or dynamic activity changes?', Basal Ganglia, 5: 1-6.

Neumann, W. J., A. Horn, S. Ewert, J. Huebl, C. Brücke, C. Slentz, G. H. Schneider, and A. A. Kühn. 2017. 'A localized pallidal physiomarker in cervical dystonia', Ann Neurol, 82: 912-24.

Neumann, W. J., H. Schroll, A. L. de Almeida Marcelino, A. Horn, S. Ewert, F. Irmen, P. Krause, G. H. Schneider, F. Hamker, and A. A. Kuhn. 2018. 'Functional segregation of basal ganglia pathways in Parkinson's disease', Brain.

O'Hare, Justin K, Kristen K Ade, Tatyana Sukharnikova, Stephen D Van Hooser, Mark L Palmeri, Henry H Yin, and Nicole Calakos. 2016. 'Pathway-Specific Striatal Substrates for Habitual Behavior', Neuron, 89: 472-79.

Pan, Y., L. Wang, Y. Zhang, C. Zhang, X. Qiu, Y. Tan, H. Zhou, B. Sun, and D. Li. 2018. 'Deep Brain Stimulation of the Internal Globus Pallidus Improves Response Initiation and Proactive Inhibition in Patients With Parkinson's Disease', Front Psychol, 9: 351.

Perruchoud, D., M. M. Murray, J. Lefebvre, and S. Ionta. 2014. 'Focal dystonia and the Sensory-Motor Integrative Loop for Enacting (SMILE)', Front Hum Neurosci, 8: 458.

Piron, C., D. Kase, M. Topalidou, M. Goillandeau, H. Orignac, T. H. N'Guyen, N. Rougier, and T. Boraud. 2016. 'The globus pallidus pars interna in goal-oriented and routine behaviors: Resolving a long-standing paradox', Mov Disord, 31: 1146-54.

Prudente, C. N., E. J. Hess, and H. A. Jinnah. 2014. 'Dystonia as a network disorder: what is the role of the cerebellum?', Neuroscience, 260: 23-35.

Quartarone, A., S. Bagnato, V. Rizzo, H. R. Siebner, V. Dattola, A. Scalfari, F. Morgante, F. Battaglia, M. Romano, and P. Girlanda. 2003. 'Abnormal associative plasticity of the human motor cortex in writer's cramp', Brain, 126: 2586-96.

Quartarone, A., F. Morgante, A. Sant'angelo, V. Rizzo, S. Bagnato, C. Terranova, H. R. Siebner, A. Berardelli, and P. Girlanda. 2008. 'Abnormal plasticity of sensorimotor circuits extends beyond the affected body part in focal dystonia', J Neurol Neurosurg Psychiatry, 79: 985-90.

Redgrave, P., M. Rodriguez, Y. Smith, M. C. Rodriguez-Oroz, S. Lehericy, H. Bergman, Y. Agid, M. R. DeLong, and J. A. Obeso. 2010. 'Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease', Nat Rev Neurosci, 11: 760-72.

Schmidt, Robert, Daniel K. Leventhal, Nicolas Mallet, Fujun Chen, and Joshua D. Berke. 2013. 'Canceling actions involves a race between basal ganglia pathways', Nature neuroscience, 16: 1118-24.

Schubert, T., J. Volkmann, U. Müller, V. Sturm, J. Voges, H. J. Freund, and D. Y. von Cramon. 2002. 'Effects of pallidal deep brain stimulation and levodopa treatment on reaction-time performance in Parkinson's disease', Experimental Brain Research, 144: 8-16.

Seger, C. A., and B. J. Spiering. 2011. 'A critical review of habit learning and the Basal Ganglia', Front Syst Neurosci, 5: 66.

Singh, Arun, and Kai Bötzel. 2013. 'Globus pallidus internus oscillatory activity is related to movement speed', European Journal of Neuroscience, 38: 3644-49.

Surmeier, D. James. 2013. 'To go or not to go', Nature, 494: 178-79.

Thomas Wichmann, Mahlon R. DeLong. 2016. 'Deep Brain Stimulation forMovement Disorders ofBasal Ganglia Origin: Restoring Function or Functionality?', Neurotherapeutics

Thura, D., and P. Cisek. 2014. 'Deliberation and commitment in the premotor and primary motor cortex during dynamic decision making', Neuron, 81: 1401-16.

———. 2016. 'Modulation of Premotor and Primary Motor Cortical Activity during Volitional Adjustments of Speed-Accuracy Trade-Offs', J Neurosci, 36: 938-56.

———. 2017. 'The Basal Ganglia Do Not Select Reach Targets but Control the Urgency of Commitment', Neuron, 95: 1160-70 e5.

Turner, R. S., and M. Desmurget. 2010. 'Basal ganglia contributions to motor control: a vigorous tutor', Curr Opin Neurobiol, 20: 704-16.

Turner, R. S. et al. 2003;. 'Motor Subcircuits Mediating the Control of Movement Extent and Speed', J Neurophysiol.

Ueda, Y., K. Yamanaka, A. Noritake, K. Enomoto, N. Matsumoto, H. Yamada, K. Samejima, H. Inokawa, Y. Hori, K. Nakamura, and M. Kimura. 2017. 'Distinct Functions of the Primate Putamen Direct and Indirect Pathways in Adaptive Outcome-Based Action Selection', Front Neuroanat, 11: 66.

Valálik, István, Miklós Emri, Zsolt Lengyel, Pál Mikecz, Lajos Trón, András Csókay, and Teréz Márián. 2009. 'Pallidal Deep Brain Stimulation and L-Dopa Effect on PET Motor Activation in Advanced Parkinson's Disease', Journal of Neuroimaging, 19: 253-58.

Vitek JL, Chockkan V, Zhang JY, Kaneoke Y, Evatt M, DeLong MR, and others. 1999. 'Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus.', Ann Neurol.

Yokochi, Fusako, Kenji Kato, Hirokazu Iwamuro, Tsutomu Kamiyama, Katsuo Kimura, Akihiro Yugeta, Ryoichi Okiyama, Makoto Taniguchi, Satoko Kumada, and Junichi Ushiba. 2018. 'Resting-State Pallidal-Cortical Oscillatory Couplings in Patients With Predominant Phasic and Tonic Dystonia', Frontiers in Neurology, 9: 375.

Zhuang, P., Y. Li, and M. Hallett. 2004. 'Neuronal activity in the basal ganglia and thalamus in patients with dystonia', Clin Neurophysiol, 115: 2542-57.

Eidesstattliche Versicherung

„Ich, Moaz Al Ajia, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: [The effect of GPi-DBS on automatic and controlled movement in dystonia] selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

[Für den Fall, dass Sie die Forschung für Ihre Promotion ganz oder teilweise in Gruppenarbeit durchgeführt haben:] Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection

Acknowledgements

I would like to thank all those without whose assistance this thesis would not exist.

Thanks to my supervisors Prof. Dr. Andrea Kühn and Dr. Wolf-Julian Neumann for giving me the opportunity to conduct this experiment in their department and for guiding me in my first academic work.

Thanks to Dr. Gregor Wenzel for helping in recruiting the patients. Thanks to the entire research team of the movement disorders unit at the Charité.

Special thanks to the patients, who agreed to temporarily dispense the DBS treatment with the intention of contributing for a better understanding of dystonia.