Human basal ganglia recordings from implanted deep brain stimulation electrodes and the microlesion effect

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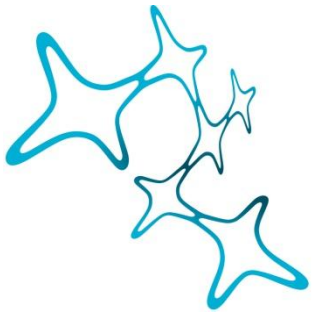

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Declaration of originality

I, Arun Singh, declare that this submission is my own work and to the best of my knowledge it contains no materials previously written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma at the Ludwig Maximilian University (LMU) or any other educational institution, except where due acknowledgement is made in this thesis. Any contribution made to the research by others, with whom I have worked at LMU or elsewhere, is explicitly acknowledged in the thesis.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Signature ……..……..

Summary

There is a lot of evidence from neurophysiological studies in patients undergoing functional neurosurgery that the basal ganglia play a major role in the preparation or regulation of movement. It is possible to record local field potentials (LFPs) from the subthalamic nucleus (STN) and globus pallidus internum (GPi) via the electrodes implanted for deep brain stimulation (DBS) in patients with Parkinson's disease (PD) and dystonia respectively. LFPs in PD patients have shown exaggerated synchronization of neuronal activity in the 8-30 Hz band in the STN and the GPi. This activity can be suppressed by voluntary movement, levodopa medication and DBS therapy. LFPs in patients with generalized dystonia as well as in treated advanced PD patients have revealed higher neuronal oscillatory activities in the GPi below 10 Hz. At the other end of the frequency spectrum, high-frequency LFP oscillations (60-90 Hz) are further enhanced by voluntary movement in PD and dystonia and in parkinsonian patients receiving medication. Exaggerated oscillatory activity in the basal ganglia in patients with PD and dystonia suggests the existence of a relationship or link with movement impairment.

The movements performed in the aforementioned studies were mostly simple movements executed with low velocity. Therefore, in our first study, we examined LFPs in PD and dystonic patients during repetitive passive, active and ballistic fast extensions and flexions of the elbow joint. In our second study, we investigated lower limb movements in dystonic patients. In this study, we analyzed LFPs recorded from the GPi of dystonic patients during walking on a treadmill machine. None of the dystonic patients who participated in this study showed gait disturbances. Therefore, LFP recordings were mainly determined by limb movement and less by disease process.

In the first study, we observed that the power of the alpha frequency band was higher during ballistic movements compared with rest, passive and active movements in both PD and dystonic patients. This study suggests that enhanced alpha frequency synchronization in the STN and GPi is caused by specific movement, not disease.

In the following study, we observed that LFP power in the 4-12 Hz and 60-90 Hz frequency bands was higher during walking than during the resting condition, but the power of the 15-25 Hz frequency band was decreased during walking. In the same study, modulation of 6-11 Hz

oscillation during a gait cycle confirms that basal ganglia also have information about individual gait cycles. This study proposes that, during gait, basal ganglia show synchronized activity in several bands, not in a specific frequency band.

In the last study, we investigated the effect of microlesions on the basis of a kinematic parameter (velocity of the movements) in patients with PD and dystonia. In this study, we recorded the movement parameter pre- and post-operatively during the execution of distal movements (finger tapping and pronation-supination movements) and proximal movement (ballistic arm movement (boxing) with touch). We observed that due to the 'microlesion effect', PD patients executed all motor tasks with improved velocity while dystonic patients were slower. This study suggests that a GPi lesion in dystonic patients can induce the bradykinesia.

In summary, this thesis clearly shows that specific movements (fast, slow, and walking) are associated with distinct frequency bands which can be recorded from the basal ganglia. These bands may constitute information channels by which the basal ganglia communicate with downstream structures (i.e. tegmental nuclei for gait, cortex). This knowledge has implications for basic scientific concepts as well as for therapy (deep brain stimulation).

Contents

1 Introduction

Neurophysiology is the study of the functions of the nervous system, including the brain, brain stem, spinal cord and the peripheral nervous system. Neurophysiological methods enable us to investigate the physiology and pathophysiology of the motor system. Movement, which is controlled by the motor system, is the result of a complex interaction between the central nervous system, nerves, and muscle fibres. The execution of movements is a complex process because it requires not only the activation of muscles but also control of unwanted interferences (passive forces i.e. inertia and gravity). Cortical and subcortical regions are involved in excitatory and inhibitory circuits, functioning simultaneously to execute a movement, and dysfunctions in these circuits cause motor disorders. Cortical and subcortical structures have been studied to understand the mechanism of the human motor system.

1.1 Anatomy of the human motor system

The spinal cord, medulla, pons, midbrain, diencephalon, and telencephalon contain the major components of the human motor system. Two parts of the telencephalon play main roles in motor control: the cerebral cortex and the basal ganglia (BG).

1.1.1 Cerebral cortex

The number of functionally distinct motor cortical structures remains uncertain. The modern view of the frontal cortex differentiates it into the primary motor cortex, nonprimary motor cortex and the prefrontal cortex (Fig. 1.1). The primary motor cortex (M1) can be considered as corresponding to Brodmann's area 4. M1 lies in the anterior bank of the central sulcus. Its medial part represents the leg, the lateral part contains the arm representation, and the more lateral part includes the face, tongue and mouth representation. There are many nonprimary motor cortical areas that occupy parts of Brodmann's area 6, 8 and 24. The medial group of areas divides into the supplementary motor area (SMA) and pre-SMA and cingulate motor areas. The lateral group of areas includes the premotor cortex (PMC). The SMA influences the planning and initiation of motor tasks on the basis of experience. Both the medial and lateral

areas of PMC seem to help in selecting a specific movement or sequence of movements from the repertoire of possible movements.

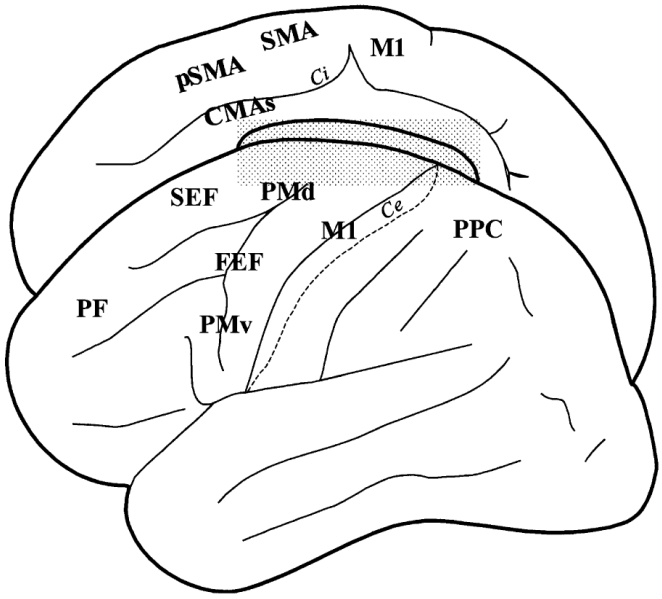

Figure 1.1: Motor areas of the human brain. The lateral surface of the left hemisphere is shown below the medial surface of the right hemisphere. The rostral surface is to the left; the dorsal surface is up. The dashed line indicates the fundus of the central sulcus. The stippled area on the medial surface represents the corpus callosum. Ce, central sulcus; CMAs, cingulate motor areas; FEF, frontal eye field; PF, prefrontal cortex; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; PPC, posterior parietal cortex; SEF, supplementary eye field; pSMA, presupplementary motor area. Adopted from (Ramachandran, 2003).

The primary and nonprimary motor cortical areas project to other major components of the motor system. The corticofugal system represents the cortical output system, projecting directly to the spinal cord and brainstem. Further outputs from the motor cortex comprise projections to the basal ganglia, the cerebellum, and the red nucleus.

The cerebellum is another brain region that plays a role in the coordination of limb and eye movements and is also important for maintaining balance and muscle tone. The cerebellum and cerebral motor cortex are not directly interrelated to each other, but output from both regions reach their target through intermediates (pontine nuclei, red nucleus, inferior olive, and brainstem nuclei) (Voogd, 2003).

1.1.2 Basal ganglia

Over the last decades, it has become evident that the basal ganglia are important structures of the brain for programming, selecting and initiation of movements (Alexander and Crutcher, 1990; Brown et al., 2006). Pathological neuronal activities recorded from the basal ganglia-thalamocortical network have been revealed in movement disorders (Gatev et al., 2006; Hutchison et al., 2004) and were related to the pathophysiology of the disturbed movements. The basal ganglia are an assembly of subcortical interconnected nuclei in the forebrain, diencephalon, and midbrain or can be divided into functionally distinct groups of nuclei (Fig. 1.2)

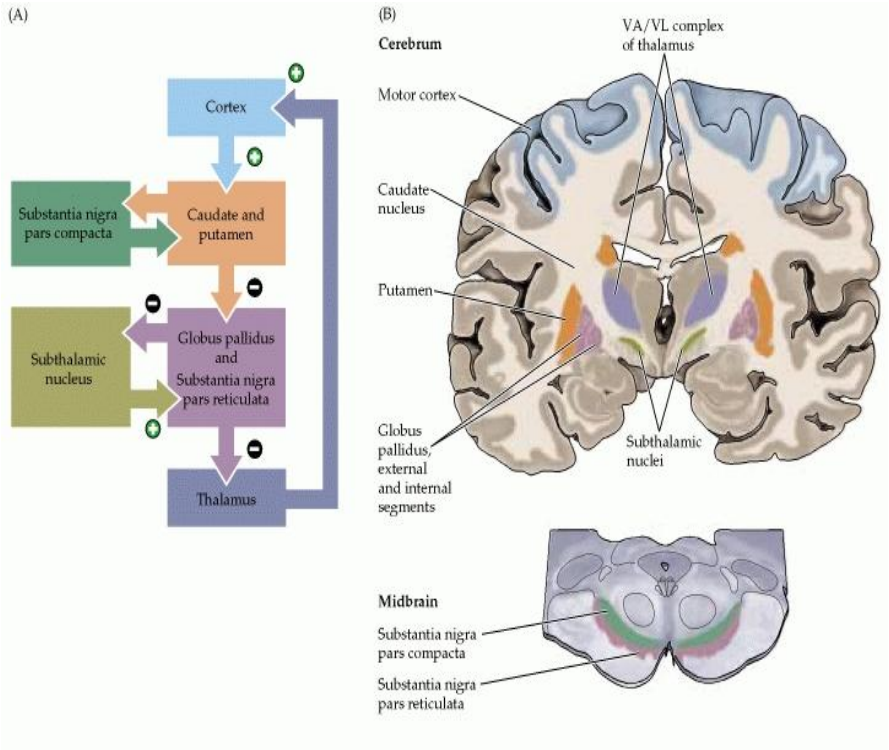

Figure 1.2: Motor components of the human basal ganglia: (A) Basic circuits of the basal ganglia pathway: (+) and (-) denote excitatory and inhibitory connections. (B) Idealized coronal section through the brain showing anatomical locations of structures involved in the basal ganglia pathway. The ventral anterior and ventral lateral thalamic nuclei (VA/VL complex) are the targets of the basal ganglia, relaying the modulatory effects of the basal ganglia to upper motor neurons in the cortex. Adopted from (Purves, 2001)

The striatum (caudate nucleus and putamen) is the primary afferent structure of the basal ganglia. The main output structures of the basal ganglia are the globus pallidus, composed of

globus pallidus externum (GPe) and globus pallidus internum (GPi), and the substantia nigra pars reticulata (SNr). Another part of the substantia nigra (substantia nigra pars compacta (SNc) is densely packed with melanin granules and is the origin of one of the two dopaminergic pathways of the brain. It can be seen above and behind the cerebral peduncles. Another important structure of the basal ganglia is the subthalamic nucleus (STN). STN and substantia nigra lie in the midbrain. STN is a small lens-shaped nucleus positioned below the thalamus on the dorsomedial surface of the internal capsule (Rothwell, 1994).

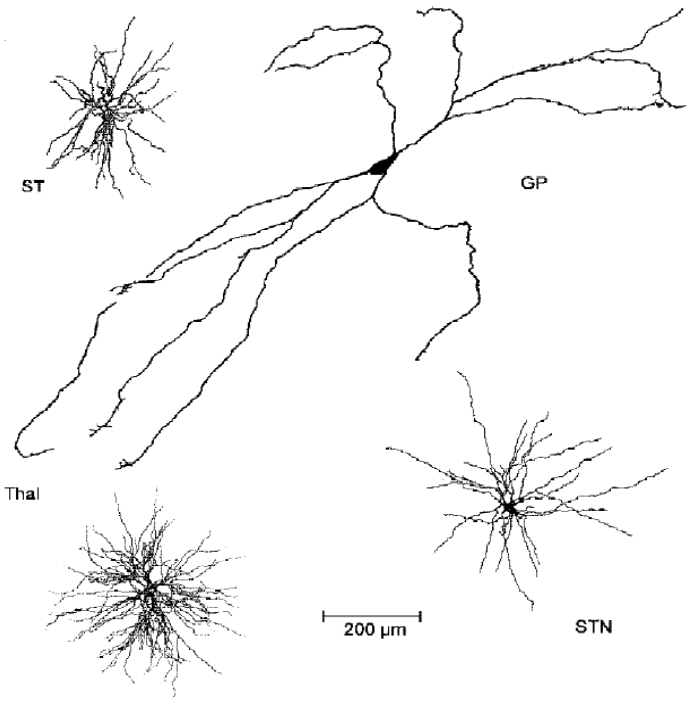

Figure 1.3: Four main neuronal types of the basal ganglia as they appear after reconstruction from serial sections and camera lucida drawing: All neurons are shown at the same magnification. Note the long and sparsely ramified dendrites of pallidal neurons (GP) compared with the short but densely ramified dendrites of spiny striatal (ST), subthalamic (STN) and thalamocortical (Thal) neurons. Adopted from (Yelnik, 2002).

Neuronal morphology gives evidence about the functional properties of the basal ganglia structures (Fig. 1.3) (Yelnik, 2002). The large number of synaptic connections suggests that these nuclei act as a programmable (implicit) memory storing structure.

Anatomical and physiological studies have tried to elucidate the functions of the basal ganglia. There is a clear segregation throughout these interconnected nuclei into three functional parts: the motor part (lateroposterior putamen), the associative part (cognitive function, anterior putamen and caudate nucleus) and the limbic part (ventral putamen with Nc. accumbens). Basal ganglia motor circuits not only control limb movements but also eye movements (saccades). Eye movement is normally controlled by the superior colliculus (SC) network. A basal ganglia nucleus, especially SNr, sends strong inhibitory projections to the SC. Many regions of the frontal cortex and basal ganglia might be involved in top-down control of the saccade-generating circuit. Neural circuitry, controlling eye movements, has been elucidated elsewhere (Munoz and Everling, 2004). The limbic part of the basal ganglia plays an important role in motivation and this part includes the nucleus accumbens (NA), ventral pallidum, and ventral tegmental area (VTA). It has been demonstrated that dopaminergic projection from the VTA to the NA plays a central role in the brain's reward system. Animal and human studies have also investigated spatially segregated functional territories in the basal ganglia in the control of goal-directed and habitual actions (Redgrave et al., 2010).

1.2 Movement disorders

Movement disorders include weakness or paralysis, abnormal reflexes and abnormal movements. They can result from the abnormal functioning of the motor pathways in the nervous system or from malfunctioning of the muscles. Movement disorders associated with basal ganglia disorders can be classified into a hypokinetic/bradykinetic and a hyperkinetic group. In both kinds of movement disorders, abnormal pathophysiological mechanisms of basal ganglia circuits are suspected to be the origin of the problem. Hypokinesia is characterized by a reduction in the amplitude and bradykinesia is characterized by slowness of movement with respect to velocity, while akinesia describes an impairment of movement initiation. Patients with hypokinetic disorders also show muscular rigidity and frequently also tremor. These three symptoms constitute the main features of the Parkinsonian complex. Bradykinesia results from abnormal speed of movements due to lack of the generation of adequate initial muscle agonist activation (Hallett and Khoshbin, 1980). Parkinson's disease (PD) is the most classic example of a hypokinetic movement disorder (Albin et al., 1989; DeLong, 1990).

Hyperkinetic movements are characterized by excess involuntary movements with high speed (dyskinesias). In humans, diseases like Huntington’s chorea, tics and dystonia (Albin et al.,

1989; DeLong, 1990) can be associated with dyskinesias. In the non-human primate, blocking the activity of the STN or its output to globus pallidus produces similar hyperkinetic movement disorders (Crossman, 1987; Robertson et al., 1989).

1.2.1 Parkinson's disease (PD)

PD is a neurodegenerative disorder characterized by motor symptoms such as tremor, muscular rigidity, akinesia, bradykinesia, freezing of gait, and non-motor symptoms such as cognitive dysfunction, depression, sleep disorders and autonomic dysfunctions. Dopamine deficiency is the pathophysiological hallmark of this symptom complex. Sequential or simultaneous joint movements are badly performed in PD, adding to the symptoms of deficient motor control. As the output of the basal ganglia is directed primarily to the SMA, it has been suggested that underactivity of this region is crucial for PD (Dick et al., 1986). Neuroimaging techniques (transcranial ultrasound, fMRI, CT and PET) have also demonstrated functional and structural abnormalities in the motor system in non-manifesting PD patients who have a mutant allele in the *Parkin* gene (van Eimeren and Siebner, 2006).

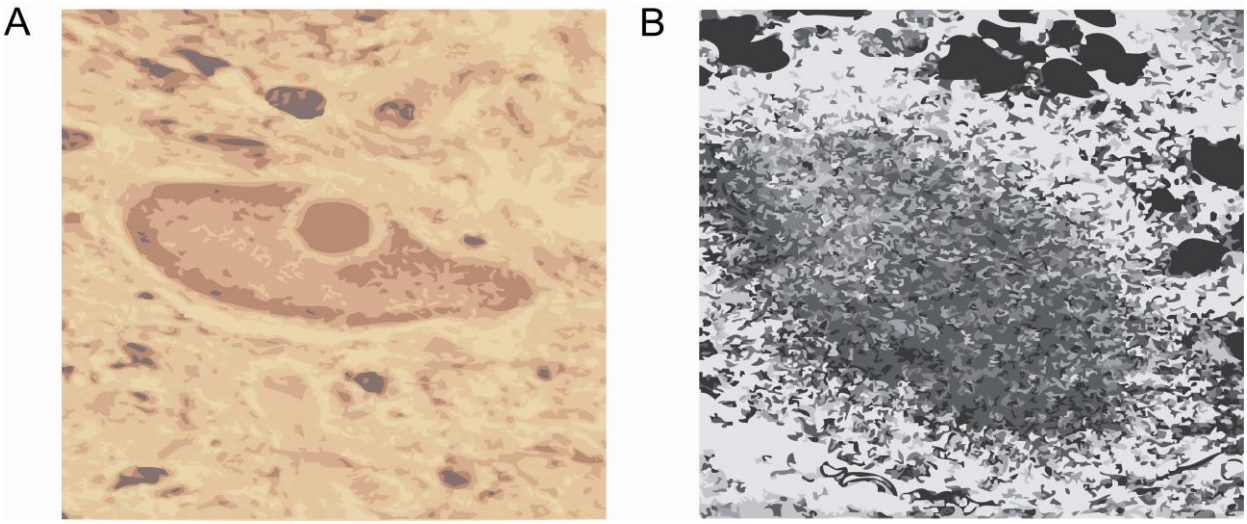

Figure 1.4: Lewy Body: (A) Lewy body in the cytoplasm of a pigmented dopaminergic neuron in the substantia nigra. (B) Ultrastructural examination shows an accumulation of filaments and granular material with a dense core and loose radiating peripheral filaments. Modified from (Lang and Lozano, 1998a).

As for other neurodegenerative diseases, aging is the major risk factor for PD. It results from the progressive death of neuromelanin-laden dopaminergic neurons of the pars compacta of the substantia nigra. Whereas the vast majority of PD patients have no genetic cause, genetic studies have found seven genes which are associated with L-dopa responsive parkinsonism. Mutations in parkin, PINK1, Dj-1 and ATP13A2 cause recessive early Parkinson symptoms. PINK1 and parkin create dysfunction in the mitochondrial pathway (Schapira, 1994). Many mutations in alpha-synuclein and parkin gene lead to aggregation of cytotoxic proteins due to the defects in the ubiquitin proteasome system (Olanow and McNaught, 2006). Alpha-synuclein, LRRK-2 and GBA mutations disturb a common biochemical pathway which is crucial in the pathogenic process. Normally, pathology of the PD is diagnosed by accumulation of alpha-synuclein protein into inclusions called Lewy bodies in nerve cells (Fig. 1.4) (Lang and Lozano, 1998a).

1.2.2 Dystonia

Dystonia comprises an assorted group of disorders, in which involuntary muscle contractions cause twisting or repetitive movements and abnormal postures (Fahn, 1988). It can be classified into two types, generalized (affecting the entire body) or segmental (affecting one or a few parts of the body) dystonia, and primary (idiopathic: develops spontaneously in the absence of any associated disease) or secondary (symptoms result from another disease or brain injury). Cervical dystonia (torticollis) is an example of primary segmental dystonia, characterized by sustained cervical muscle contraction causing abnormal neck twisting (Krauss et al., 1999). Primary focal dystonia occurs in adults and may involve the face, neck, arms and legs (rarely) (Table 1.1). In a seminal study, it was shown that abnormal postures in dystonia are generated by long epochs of continuous electromyography (EMG) activity. (Fig. 1.5) (Berardelli et al., 1998).

Primary generalized dystonia can be inherited as an autosomal dominant condition with reduced penetrance (Breakefield et al., 2008). The DYT1 variant, the most common inherited form of dystonia, is caused by the GAG deletion on the DYT1 gene which encodes torsin A (Ozelius et al., 1997a; Ozelius et al., 1997b). Many genetic loci codified with DYT1-DYT15 have also been identified which contribute to familial dystonia (Breakefield et al., 2008). By means of in vivo imaging, structural and functional changes in brain sensorimotor circuitry can be monitored in dystonic patients (Ceballos-Baumann et al., 1995).

Type of Dystonia	Main Clinical Features	Common Misdiagnoses
Cervical dystonia (spasmodic torticollis)	Abnormal head posture Head tremor Neck pain	Muscle strain Cervical disk disease Osteoarthritis
Blepharospasm	Increased blink rate Forced eye closure Difficulty opening eyes	Myasthenia gravis Dry eyes
Oromandibular dystonia	Jaw clenching (bruxism) Jaw in open position Lateral jaw shift	Temporomandibular joint syndrome Myasthenia gravis Dental malocclusion Edentulous movements
Orofacial dystonia	Action dystonias involving lips, tongue, or pharynx	Tic disorders
Spasmodic dysphonia		Chronic laryngitis, vocal-cord polyps, voice tremor, psychogenic causes
Adductor type	Voice breaks and strain	
Abductor type	Breathy voice	
Mixed type	Features of both	
Limb dystonia	Action dystonias affecting writing, playing musical instruments, handling tools, walking	Nerve entrapment Overuse syndromes Muscle cramps
Axial dystonia	Movements of shoulders, back, or abdomen	Myoclonus Motor tics Psychogenic causes

Table 1.1: Classification of primary adult-onset focal dystonias. Adopted from (Tarsy and Simon, 2006).

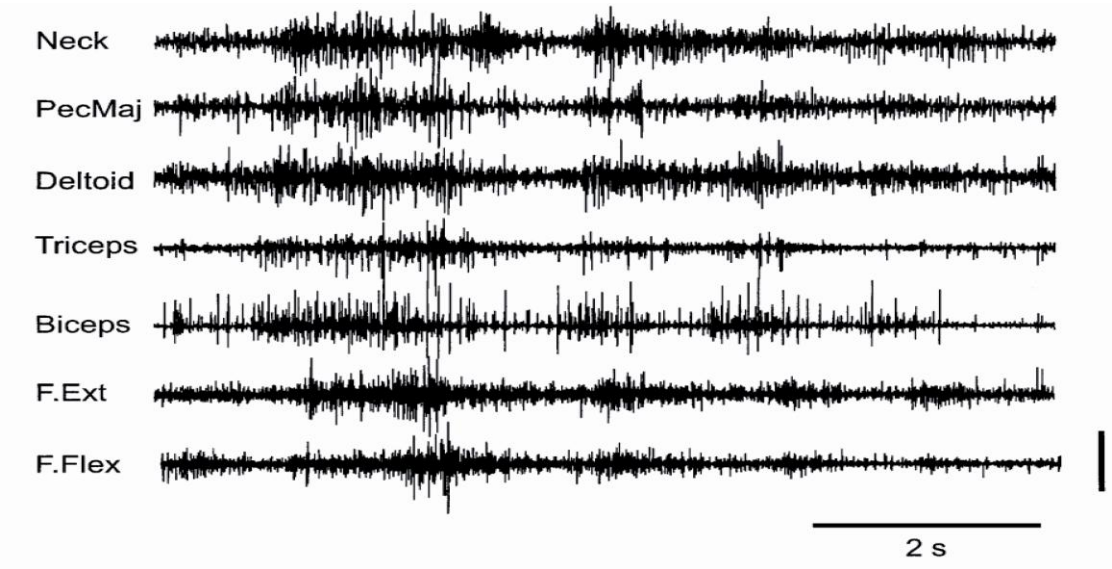

Figure 1.5: Electromyographic recordings of dystonic EMG activity in a patient with dystonia. Figure shows prolonged EMG bursts in a patient with segmental arm and neck dystonia. PecMaj = pectoralis major; F.Ext = forearm extensors; F.Flex = forearm flexors, modified from (Berardelli et al., 1998).

1.2.3 Tremor

Tremor is a rhythmic, involuntary oscillating movement with mostly constant amplitude and frequency. Tremor may be classified on the basis of its activation of antagonistic muscles (syncronus or alternating) and by its location, amplitude and frequency (4-7 Hz). In tremor, abnormal neuronal oscillations are relayed from the motor cortex through the corticospinal tracts to the anterior horn cells of the spinal cord to induce a distinctive pattern of contraction of agonist and antagonist muscles (Rohkamm, 2003). The most frequent types of tremors are parkinsonian and essential tremor. Parkinsonian tremor occurs due to rhythmic neuronal discharges in the basal ganglia and thalamus, which result from degeneration of the dopaminergic cells of the substantia nigra. Essential tremor is caused by excessive oscillations in olivocerebellar circuits, which travel to the motor cortex by passing through the thalamus. Chronic high-frequency stimulation of the thalamus (ventral intermediate nucleus (VIM)) with an implanted electrode has been shown to ameliorate parkinsonian and essential tremor (Koller et al., 1997).

1.3 Treatment of movement disorders

1.3.1 Pharmacological treatment

PD is still completely incurable but pharmacological and surgical treatment (see below) can improve the symptoms and thereby the quality of life. L-dopa in combination with a peripheral dopa-decarboxylase inhibitor is the most effective treatment for PD (Lang and Lozano, 1998b). Dopamine agonists (ropinirole, pramipexol, pergolide, piribedil) are also efficacious medicines. Type B monoamine oxidase inhibitors (selegiline and rasagiline) block the degradation of dopamine in the basal ganglia and can be used as disease-modifying agents (Lees et al., 2009). Side effects of these medications include dyskinesias and fluctuations. Dyskinesias have different clinical forms such as dystonic and choreic movements that occur in different stages after L-dopa intake. Fluctuations cause patients to be in a hyperkinetic or bradykinetic state at different times of the day. These side effects can be reduced or abolished by deep brain stimulation (DBS) (see below).

Different combinations of medicine, including anti-cholinergic, GABA agonist and dopaminergic agents, are used to treat dystonia (Jankovic, 2006). Focal dystonia can be treated by intramuscular injections of botulinum toxin (Curra et al., 2004). Implantation of DBS electrodes has become a successful therapy to alleviate the symptoms of generalized dystonia, where botulimum toxin cannot be applied and focal dystonia, when botulinumtoxin eventually can induce autoimmune resistance. (Kringelbach et al., 2007; Perlmutter and Mink, 2006).

1.3.2 Deep brain stimulation (DBS)

Since 1870, electrical stimulation of the brain has been used to investigate brain functions (Fritsch and Hitzig, 1870). From 1884, intraoperative electrical stimulation was applied as a tool to improve human neurosurgical procedures (Gildenberg, 2005). Movement disorders have been treated surgically since the invention of stereotaxy in the 1940s. First, thermocoagulations of the thalamus were performed for the treatment of tremor. During these operations it was noted that electrical stimulation of distinct basal ganglia nuclei or the thalamus can exert the same effect. DBS of the VIM of the thalamus was introduced to treat essential tremor (ET) or parkinsonian tremor (Benabid et al., 1987). Since then, the implantation of electrodes and subcutaneous pacemakers has become an efficient therapy to alleviate the symptoms of PD, dystonia and tremor. The precise mode of action of this therapy is yet unknown. Some modeling studies have explained that STN-DBS may suppress the somata of STN cells through activation of local GABA (gamma-aminobutyric acid) release from GPe afferents, while activating STN axons (McIntyre et al., 2004). STN stimulation has also been shown to evoke excitatory effects in the GPi, which is one of the primary receivers of the STN efferents and it may change neuronal oscillatory resonance characteristics of the STN-GPi network (Brown et al., 2004). GPi-DBS may directly activate the axons of GPi cells.

Recent data suggest that DBS therapy improves motor disabilities of PD in both young and elderly patients (Derost et al., 2007) but can also be associated with cognitive and affective side effects (Temel et al., 2006a). DBS is not only effective against tremor or PD but can also be used to treat dystonia as well as affective disorders such as depression (Jimenez et al., 2005), obsessive-compulsive disorders (Cosyns et al., 2003), Tourette's syndrome (Diederich et al., 2005), chronic pain and headache (Bittar et al., 2005). Targets for treating the motor symptoms of PD include the STN and the GPi (Bergman et al., 1990). High-frequency stimulation has been very effective against PD (Krack et al., 2003). The GPi is the main target for dystonic patients

(Kupsch et al., 2006; Vidailhet et al., 2005) but a thalamic target is also used for this disease (Lozano et al., 1997). Studying the mechanism of DBS may clarify fundamental issues such as the functional anatomy of brain circuits and the connection between activity in those circuits and behavior (Perlmutter and Mink, 2006). For a short period of time, the implanted electrodes allow the recording of electrical activity in the area of the electrode contacts (local field potentials, LFP). Improvement in motor abnormalities is correlated with the degree of suppression of synchronized beta frequency band activity in the motor cortical region (Silberstein et al., 2005) and suppression of beta oscillations in local field potential activity in the GPi or STN (Brown et al., 2004). This will be the main methodological approach in this thesis (see below).

1.3.3 Microlesion effect (MLE) after DBS implantation

Shortly after the implantation of DBS electrodes and even before electric current is applied, many patients show instant improvement of their symptoms. This has been named the 'microlesion effect' (MLE). MLE has been observed in both PD (Koop et al., 2006; Maltete et al., 2008) and dystonic patients (Cersosimo et al., 2009). The duration of this effect is usually in the order of one week.

The MLE is probably similar to the effect of the formerly applied stereotactic posteroventral pallidotomy (lesioning of the GPi) which was used as a treatment of the late stage of PD. Some studies reported that pallidotomy in PD can improve the kinematics of movements (Bastian et al., 2003; Kimber et al., 1999). Placement of the electrode in the GPi also makes a lesion that improves parkinsonism motor disability. To investigate the changes in regional brain metabolism after the insertion of DBS electrodes into the STN, a PET study was conducted. In this study, a significant reduction in glucose metabolism (the microlesion effect) was observed in the putamen/GP and thalamus, without stimulation (Fig. 1.6) (Pourfar et al., 2009).

Several reports demonstrate a marked improvement in dystonic patients following GPi lesion by the mere insertion of an electrode (Cersosimo et al., 2009; Ondo et al., 1998). Even slowing of movements after pallidum lesion has also been observed in many animal studies (Desmurget and Turner, 2008; Mink and Thach, 1991).

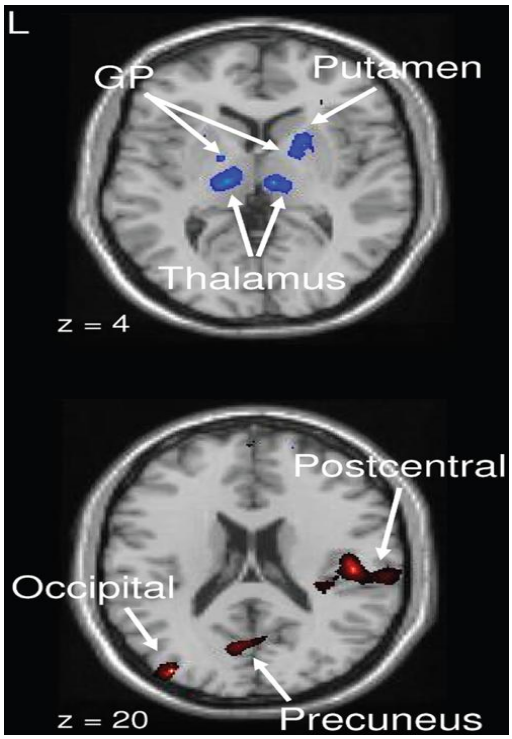

Figure 1.6: Voxel-based comparison of FDG PET images acquired at preoperative baseline and after STN DBS electrode placement. Statistical parametric maps are superimposed on a single-subject MR imaging brain template and thresholded at $t = 4.6$, $p < 0.005$. Metabolic increases (preoperative < postoperative) are color-coded from red to yellow, and metabolic decreases (preoperative > postoperative) are color-coded from blue to purple. These data show that the implantation alone is sufficient to change the activity of downstream centers in such a way that positive clinical effects can be explained. Adopted from (Pourfar et al., 2009).

1.4 Physiology of motor control

The most elementary movements are involuntary or reflexive movements which are controlled by the spinal cord. Most voluntary movements have a higher level of complexity and involve a more extensive underlying neural network. Voluntary movements are controlled by the immense network of the neuronal system comprising cortex, brain stem, and the spinal cord (Porter and Lemon, 1993). In addition, subcortical areas such as the basal ganglia and the cerebellum are also involved in the control of motor circuits. The primary motor cortex addresses the motor pathway directly via the corticospinal tract but, in addition, it also works indirectly via the interconnections with the basal ganglia, cerebellum, and brain stem (Fig. 1.7).

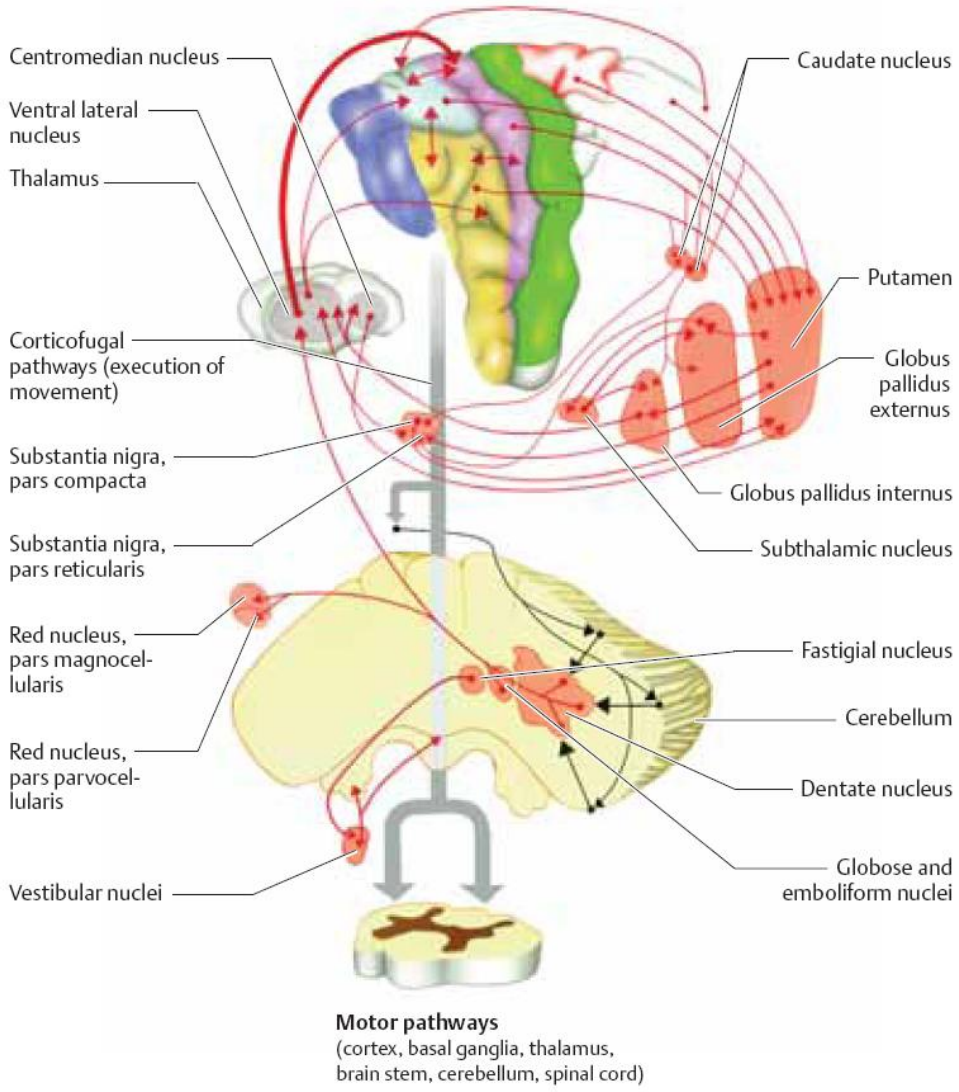

Figure 1.7: Circuitry of motor pathways. Adopted from (Rohkamm, 2003).

1.4.1 Pyramidal tract

The transmission of the motor signals to the periphery is done by the pyramidal system, which starts from the large pyramidal neurons of the motor cortex and passes through the pyramids of the brainstem, and finally ends at the motor neuron (Fig.1.8).

A motor unit is the functional unit consisting of a motor neuron and muscle fibers (Fig. 1.8). The motor neurons are located in the brain stem and spinal cord. The force of muscle contraction depends on the activation of the number of motor units and on the frequency of action potentials.

An earlier scheme of the motor system described an ‘extrapyramidal system’ as opposed to the pyramidal system. Whereas the pyramidal system was held responsible for voluntary actions, the ‘extrapyramidal system’ which consists of the basal ganglia, was thought to manage automatic and postural motor actions.

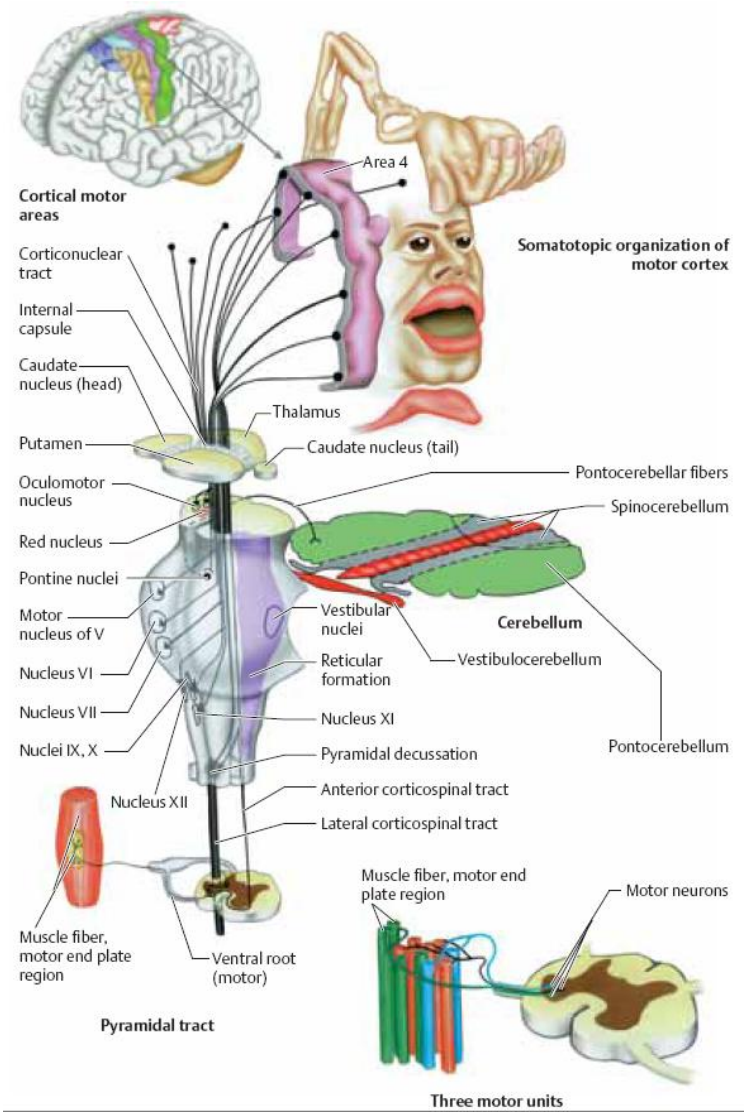

Figure 1.8: Diagram of the pyramidal corticospinal tract, somatotopic organization of motor cortex, cerebellum and its interconnections and motor units. Adapted from (Rohkamm, 2003).

1.4.2 Basal ganglia circuits

The basal ganglia are a group of nuclei that appear to manipulate motor, associative and emotional functions in a highly segregated way in normal condition. Information from almost all cortical areas arrives at the input nuclei of the basal ganglia, the striatum. This is also the main target for dopamine release from SNc. Information is conveyed between the striatum and the output nuclei of the BG GPi/SNr via a direct dopamine D1–receptor-mediated pathway and an indirect dopamine D2-receptor-mediated pathway which involves the GPe and STN. The information is the returned to the cortex via the thalamus. The direct pathway is supposed to facilitate the movements whereas the indirect pathway is thought to suppress movements. Dopamine D1 receptors help to excite the direct pathway and D2 receptors inhibit the indirect pathway (Wichmann and DeLong, 2006). In addition, STN also receives input from the cortex via the recently described 'hyperdirect' pathway (Nambu et al., 2000), (Fig. 1.9).

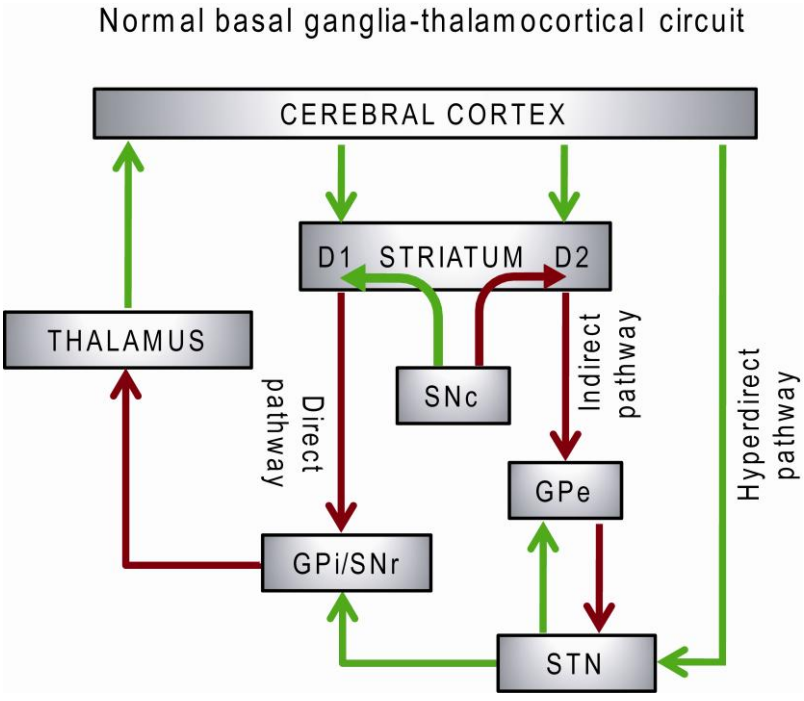

Figure 1.9: Schematic figure of the normal basal ganglia-thalamocortical circuit: Green arrows and red arrows indicate the excitatory (glutamatergic) and inhibitory (GABAergic) pathways respectively, modified from (Nambu et al., 2000; Wichmann and DeLong, 2006).

The basal ganglia nuclei are organized anatomically and physiologically in such a way that the striatum provides a specific, focused, context-dependent inhibition, whereas the STN provides less specific, divergent excitation. The output from the GPi/SNr is inhibitory in nature; therefore this functional center-surround organization contributes to the selection of motor programs which are appropriate in a specific context. (Mink, 1996) (Fig. 1.10).

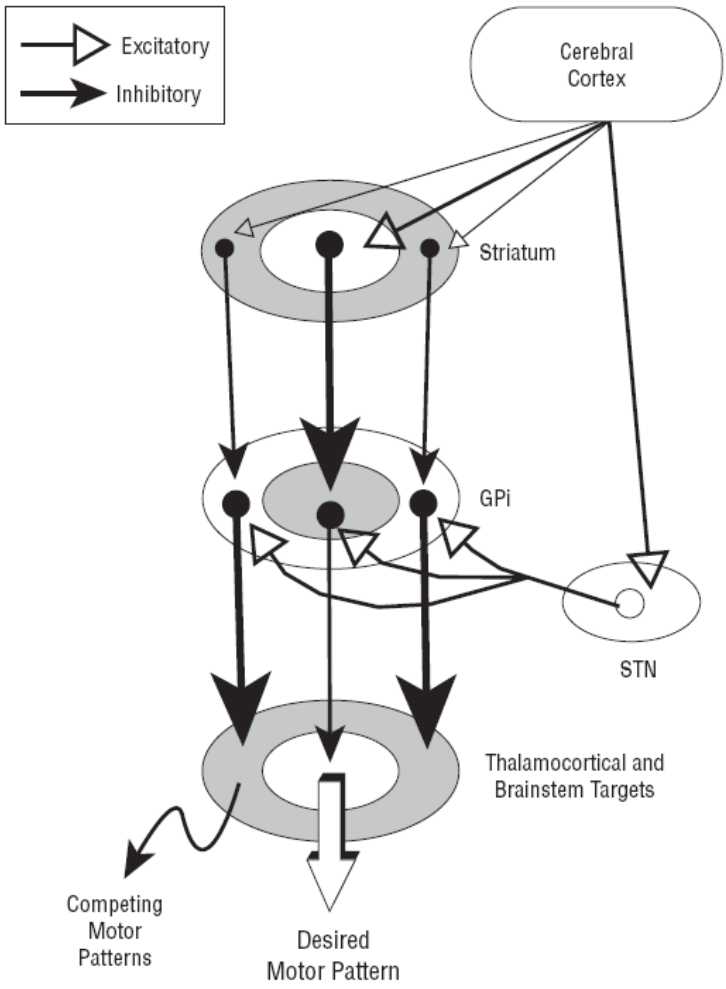

Figure 1.10: Functional organization of basal ganglia output for facilitation of desired motor programs and inhibition of competing motor programs. Open arrows indicate excitatory projections; filled arrows, inhibitory projections. Relative magnitude of activity is represented by line thickness. Adopted from (Mink, 2003).

Now there is a lot of evidence explaining that alterations in the relationship between direct and indirect pathways or in GPi/SNr output may result in hypo- and hyperkinetic symptoms of basal ganglia disorders. Figure 1.11 shows that an increased pallidothalamic inhibition causes higher activity in the indirect pathway which promotes hypokinetic movements (parkinsonian), whereas figure 1.12 explains that reduced pallidothalamic inhibition results in reduced activity in the direct pathway which leads to hyperkinetic features (dystonia or hemiballism) (DeLong, 1990).

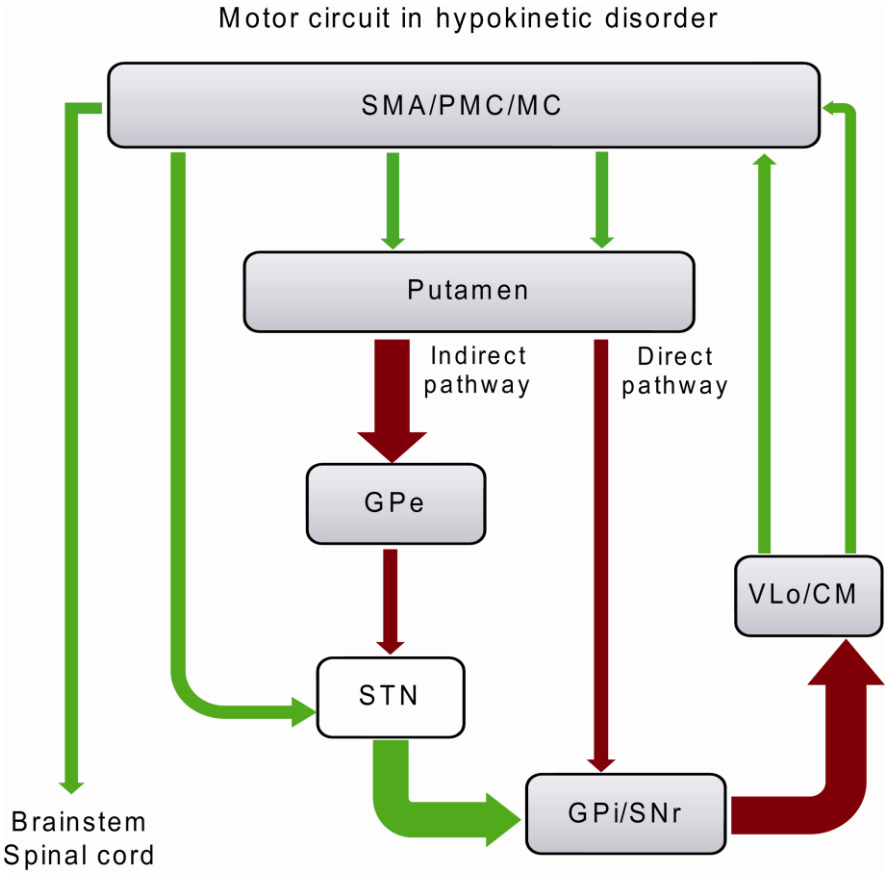

Figure 1.11: Schematic illustration of neuronal activity in the motor circuit in hypokinetic disorders (PD). Excessive inhibition of GPe within the indirect pathway directs disinhibition of the STN, which causes excessive excitatory activity in the basal ganglia output nuclei (GPI/SNr), thus resulting in higher thalamic inhibition. This is reinforced by lower inhibitory input to GPi/SNr via the direct pathway. Overall, these effects are assumed to result in a reduction in the usual reinforcing influence of the motor circuit upon cortically initiated movements. In this figure and figure 1.12, inhibitory neurons are represented by red arrows and excitatory neurons by green arrows. SMA, supplementary motor area; PMC, premotor cortex; MC, primary motor cortex; VLo, nucleus ventralis lateralis pars orlis; CM, centromedian nucleus, modified from (DeLong, 1990).

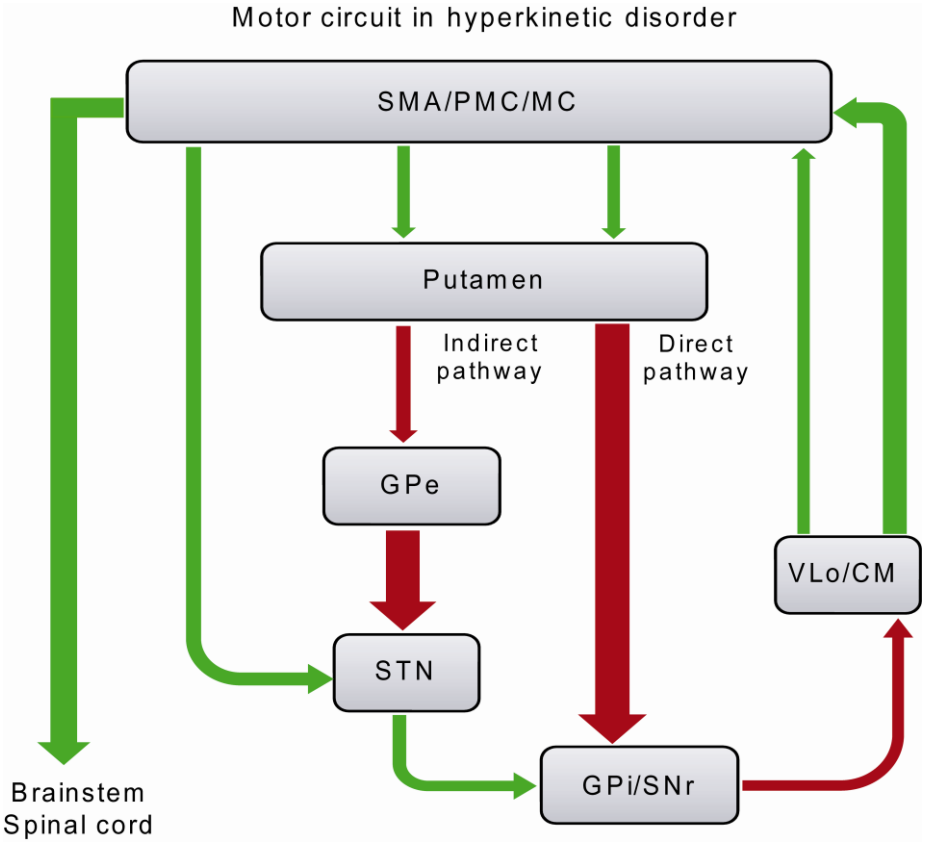

Figure 1.12: Schematic representation of neuronal activity in the motor circuit in hyperkinetic disorders (dystonia, hemiballism). STN lesions or lower striatopallidal inhibitory activities in the indirect pathway lead to reduced excitatory projections from the STN to GPi which in turn cause lower inhibitory outflow from GPi/SNr and excessive disinhibition of the thalamus. In general, it shows excessive positive feedback to the precentral motor fields connected through the motor circuit (SMA, PMC, MC), which results in hyperkinetic movements. Modified from (DeLong, 1990).

1.5 Neuronal oscillations: recordings from the basal ganglia

It is still not entirely known how populations of neurons communicate with each other. In the vicinity of active neuronal populations, oscillations of extracellular potentials can be recorded. In the case of cortical activity, these oscillations are well known as the electroencephalogram. In deep brain nuclei, similar oscillations can also be recorded and are called local field potentials (LFP). LFPs are extracellularly-recorded voltage fluctuations in the membrane potentials of neurons which are related to the net sum of actual depolarization in that region. Mainly, LFPs are the extracellular representatives of excitatory and inhibitory postsynaptic potentials (EPSP/IPSP) due to the action potentials.

The relationship between LFPs and neuronal discharge in the STN was demonstrated by a recording from a tetrode in a PD patient. This confirmed coupling between 15 Hz LFP oscillations and the discharges of local neurons, leading to elevated coherence between both signals at 15 Hz (Fig. 1.13) (Brown and Williams, 2005; Kühn et al., 2005).

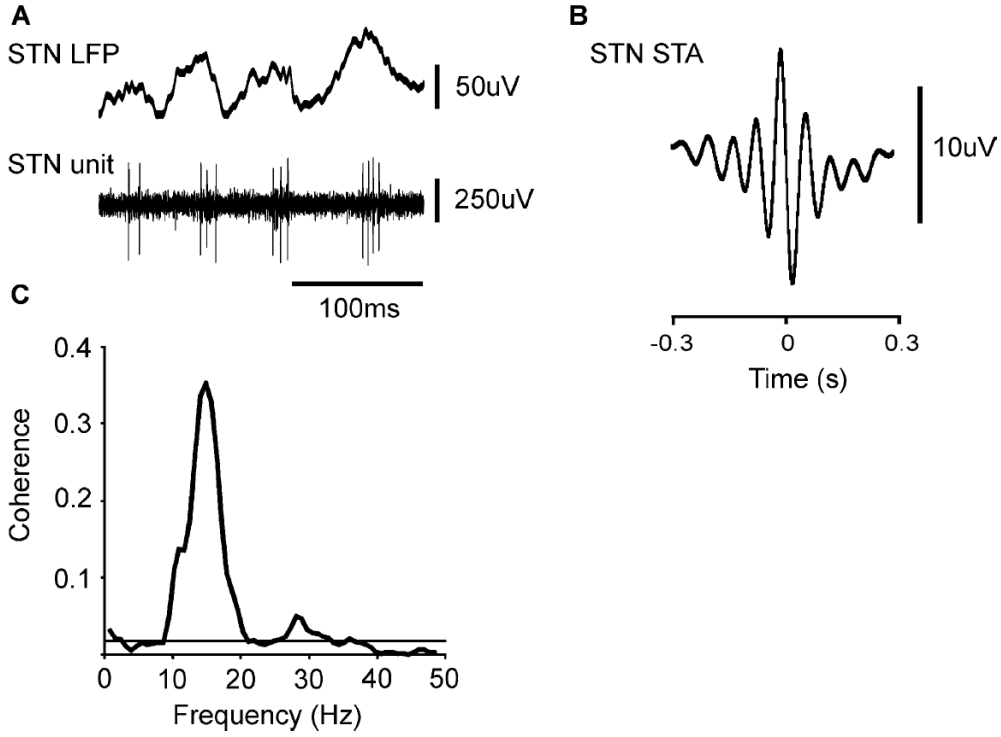

Figure 1.13: Relationship between LFPs and neuronal discharge in the STN of a PD patient. (A) raw data. (B) Spike triggered average of STN LFP. (C) Coherence between STN LFP and single cell activity. Adopted from (Brown and Williams, 2005).

Neural oscillations are, in addition to depolarization (‘spikes’) of single neurons, a fundamental mechanism for enabling coordinated communication of near or distant neurons during normal brain functioning and therefore they have attracted the interest of movement disorder researchers (Buzsaki and Draguhn, 2004).

These LFP oscillations can be subdivided on the basis of their characteristic frequency, such as delta (1-4), theta (5–8 Hz), alpha (7–12 Hz), beta (13–30 Hz), and gamma (30–90 Hz). LFPs can

also be subdivided into higher frequencies (90-200 Hz and 200-600 Hz) but the exact borders of these frequency bands have not been precisely defined.

Figure 1.14 shows the system of brain oscillators of the cerebral cortex. Discrete frequency bands (0.02 Hz to 600 Hz) can be ordered linearly on a logarithmic frequency scale. All brain oscillators have definable relationships between them and cover more than four orders of magnitude of frequency (Buzsáki, 2006).

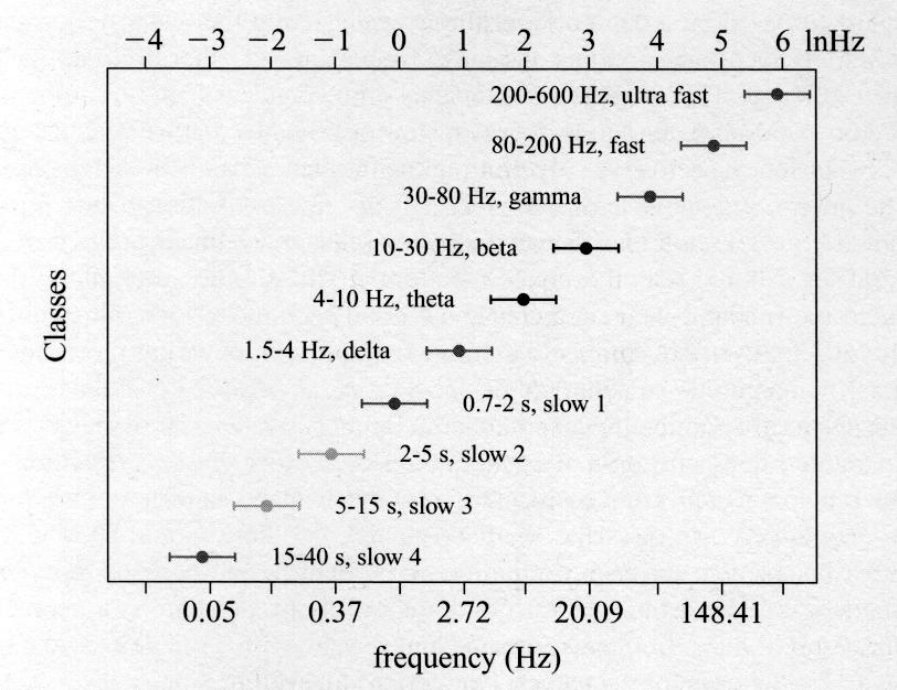

Figure 1.14: Oscillatory classes show a linear progression on the log scale. Adopted from (Buzsáki, 2006).

Invasive technology is used to record basal ganglia neuronal oscillations for the study of movement as well as to study the pathophysiology of movement disorders. The study of these neurophysiological recordings is exemplified in Figure 1.15. Current findings in humans and animals have shown the existence of different types of oscillatory activity in various nuclei of the basal ganglia.

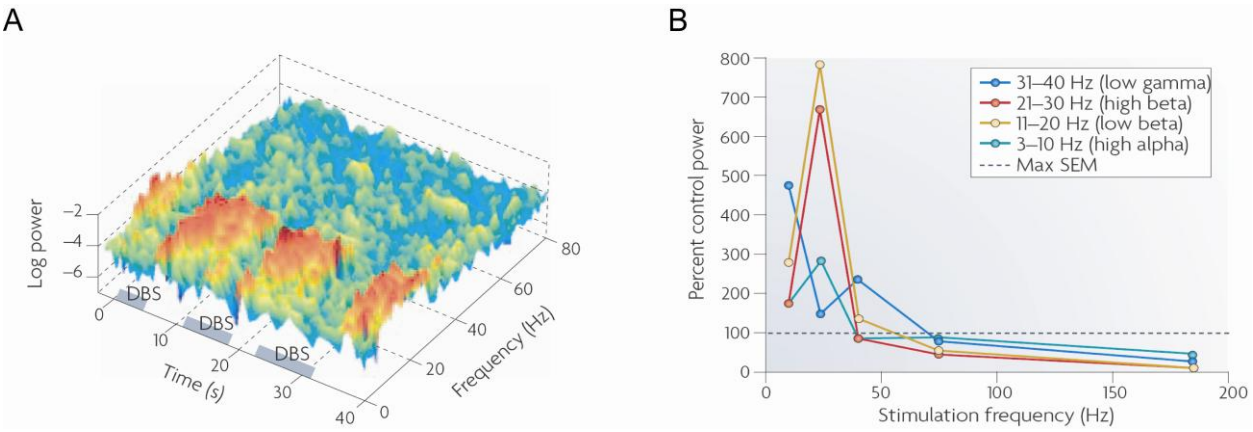

Figure 1.15: Neurophysiological recordings: (A) A time–frequency representation of LFPs recorded in the GPi during and between three periods of effective high-frequency DBS of the ipsilateral STN. DBS suppressed the prominent LFP power over 8–30 Hz. (B) The change in LFP power represented as percent changes. LFP power frequencies below 30 Hz are maximally potentiated by low-frequency DBS (25 Hz) in the STN, whereas all activities below 40 Hz are suppressed by high-frequency DBS (greater than 75 Hz). Adopted from (Kringelbach et al., 2007).

Abnormal patterns of oscillatory activity in STN and GPi have been observed in the 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated primate model of Parkinsonism (Bergman et al., 1994) (for more details, see below).

1.5.1 Current technologies for recording electrical brain activity

EEG and magnetoencephalography (MEG) are non-invasive methods to record oscillatory activity from scalp electrodes or magnetometers. EEG recording is obtained by placing electrodes on the scalp with a conductive gel (Fig. 1.16 (A)).

Recordings from the basal ganglia can be made from patients with implanted DBS electrodes after the operation, when an externalisation of the electrode is available for purposes of clinical testing (usually for 2 or 3 days). Thereafter, when the stimulator is implanted usually into the subclavicular region, these cables are not accessible any more. In Parkinsonian and dystonic patients, DBS electrodes (Medtronic Neurological Division, Minnesota, USA) with four platinum-iridium cylindrical contacts are implanted into the target nuclei (Mehrkens et al., 2009) (Fig. 1.16 (B)).

To record many neurons simultaneously, multielectrode arrays (the Utah electrode array) have been developed but have not been used in humans. In patients with epilepsy, electrocorticographic recordings can be done through subdural grids which consist of platinum-iridium or steel electrodes (Fig. 1.16 (C)).

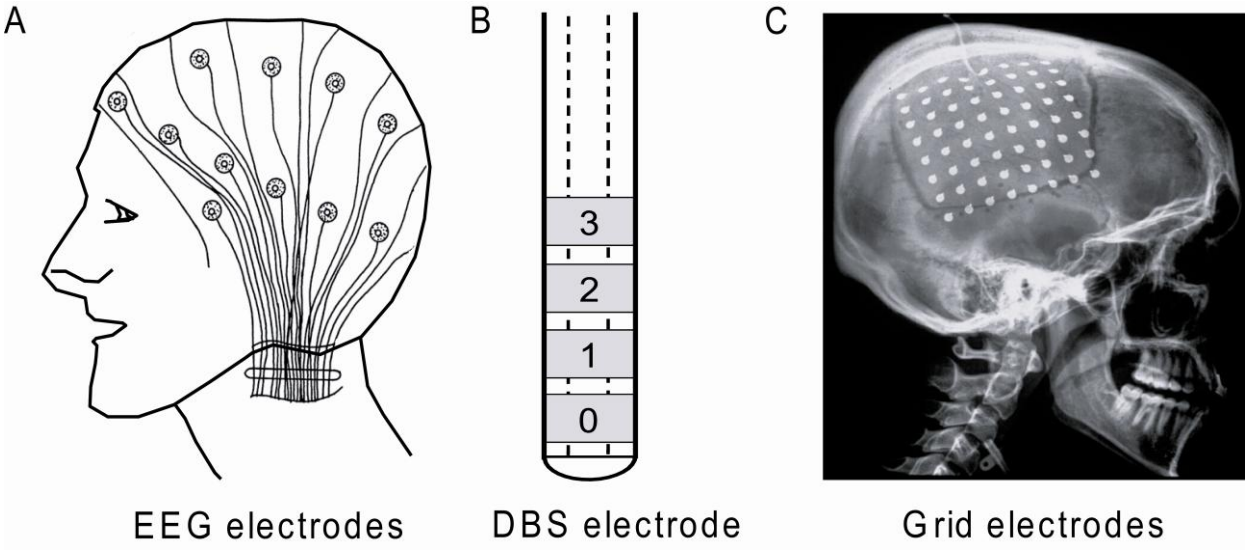

Figure 1.16: Electrodes used to record brain potentials. (A) EEG electrodes are used to record scalp brain potentials in normal subjects and in patients to diagnose brain disorder. (B) Deep brain stimulation electrodes can be used to record LFPs from the basal ganglia in movement disorders before the actual stimulation therapy begins. (C) Subdural grid electrodes are placed directly on the cortex and are used to record brain potentials in patients with epilepsy.

1.5.2 Aberrant LFP oscillations recorded from the basal ganglia

Studies in a primate model of PD first demonstrated abnormal single cell activity (i.e. increased synchronization of neuronal depolarization) in the basal ganglia (Bergman et al., 1994; Nini et al., 1995). Another study using the same model showed that 'pathological' neuronal bursting of cells in GPe, GPi and STN occurred in two frequency bands, 3-8 Hz and 8-15 Hz (Soares et al., 2004). Prominent slow oscillations in the basal ganglia neurons were also found in dopamine-depleted rats and were correlated with the LFPs of the cortex. In contrast, dopaminergic stimulation enhanced the ultraslow oscillations and increases the correlations within and between the basal ganglia nuclei (Ruskin et al., 2003). Further studies also found that the extracellular potential changes of patients with PD show specific properties which were related

to the pathophysiology of the disease. (Brown et al., 2001; Levy et al., 2002). LFP studies in humans have confirmed that there is prominent synchronized oscillatory activity in the STN in PD, and this activity can be transmitted to the GPi in parkinsonism (Brown et al., 2004). LFPs in the PD patients have shown exaggerated synchronized neuronal activity at 8-30 Hz in the STN and GPi (Brown et al., 2001; Williams et al., 2002). LFPs oscillations below 10 Hz are also observed in the GPi of dystonic and PD patients (Silberstein et al., 2003). Synchronized discharges predominantly occur at 3-10 Hz during the rest and action tremor in the untreated parkinsonism condition. Discharge pattern analysis of tremor-related cells revealed that thalamic cells are involved in the generation of 3-6 Hz tremor frequencies (Pare et al., 1990). So, slow oscillations at tremor frequencies or in the 13-30 Hz frequency band, following dopamine depletion, seem to disrupt the normal basal ganglia-thalamocortical function. However, gamma band oscillations seem to play a role in the execution of voluntary motor tasks (Kempf et al., 2009). The common explanation for these findings holds that the beta frequency range is related to bradykinetic states because it is enhanced in PD and generally reduced before and during a movement (Brown, 2003; Kühn et al., 2004).

1.5.3 Medication / DBS effects on basal ganglia oscillations in PD

Surprisingly, the dopamine precursor levodopa reduced low frequency activity in the beta range and resulted in a new peak at 70 Hz and 300 Hz in the gamma frequency band (Brown et al., 2001; Foffani et al., 2003). A similar effect was seen during STN inactivation (STN-DBS) and with dopaminergic treatment in a primate model of PD when irregular and oscillatory bursts of 8-20 Hz were diminished (Hammond et al., 2007). In addition, ‘pathological’ higher beta synchronized activity seen in the basal ganglia of PD patients is largely suppressed by therapy with dopamine replacement (Brown et al., 2001; Williams et al., 2002) (Fig. 1.17). In dystonic patients, the power of the GPi beta band oscillations is reduced even more than in Parkinsonian patients after levodopa intake (Silberstein et al., 2003). Like dopamine, DBS may also work to disrupt the pathophysiological oscillations in the basal ganglia and alleviate the symptoms (Brown et al., 2004). In a recent study, high frequency stimulation of STN in PD caused a reduction in the ‘pathological’ beta band activity and a decrease of cortico-BG synchrony in this frequency band for up to 25s after cessation of stimulation (Kühn et al., 2008).

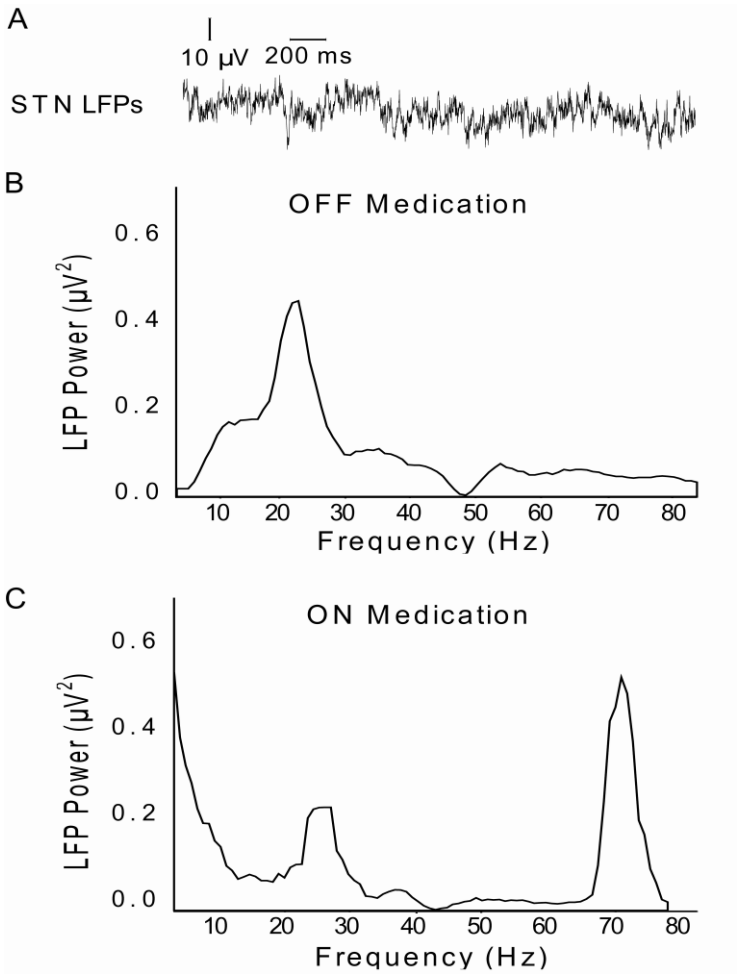

Figure 1.17: LFPs recorded from the STN of a patient with PD. (A) Raw data after withdrawal of medication. (B) Power spectrum of the LFP data in 'off medication' state (C) Power spectrum of LFP data after subsequent levodopa treatment. It is noticeable that during 'off medication' state there was a peak in the beta frequency band which was not seen in 'on medication' state when a peak in the gamma frequency band was observed.

1.5.4 Synchronized neuronal activity in other movement disorders

Synchronization of neuronal activity in humans has also been seen in other movement disorders, such as Wilson disease, essential tremor and physiological tremor (Chou et al., 2005). Other movement disorders, such as dystonia, drug-induced dyskinesia and Tourette's syndrome, differ in terms of the degree of synchronization of neural activity in the basal ganglia (Obeso et al., 2007; Schnitzler and Gross, 2005). The pathophysiological oscillations of Tourette's syndrome have not been very well investigated, but lesion or high-frequency electrical stimulation can reduce motor or vocal tics. This improvement was seen due to the modulation of synchronized oscillations (Diederich et al., 2005).

1.5.5 Oscillations during motor tasks

Peter Brown's group established a model of the relationship between beta frequency oscillations and motor tasks. They observed a reduced beta band amplitude prior to and during the self-paced voluntary movements (Cassidy et al., 2002). Another study, where a warning cue was followed by 'go' or 'nogo' signals to execute/inhibit movements, suggests that increased beta activity is related to movement inhibition (Kühn et al., 2004). So, the above studies showed that oscillations in the beta band have antikinetic effects (Fig. 1.18). Even during motor imagery, beta synchronization in the STN was also observed in PD patients (Kühn et al., 2006). This beta frequency modulation may also depend on bradykinesia and fatigue. One recent study found that the modulation of beta frequency diminished as finger tapping became more bradykinetic (Androulidakis et al., 2008). These findings indicate that higher oscillations in the beta frequency band interfere with the brain's circuits for the execution of motor tasks, causing the akinesia and bradykinesia that are associated with PD.

Modulation of beta oscillations not only happens during the execution of motor tasks but it can also be seen during the observations of action. Marceglia explained that in Parkinson patients desynchronized activity in the low beta band (10-80 Hz) was present only during action-observation, while synchronized activity was observed in the high beta band (20-30 Hz) both during observation of actions and of static objects. So, the dynamics of beta oscillations in the basal ganglia can also provide the information about the motor system in relation to the motor context (Marceglia et al., 2009).

A recent study investigated beta frequency synchronization in basal ganglia (substantia nigra pars reticulata) of the rat during gait. 12-25 Hz band frequency power values were reduced in all hemispheres during walking, while 25-40 Hz activity was increased only in the dopamine cell lesioned hemisphere (Avila et al., 2010).

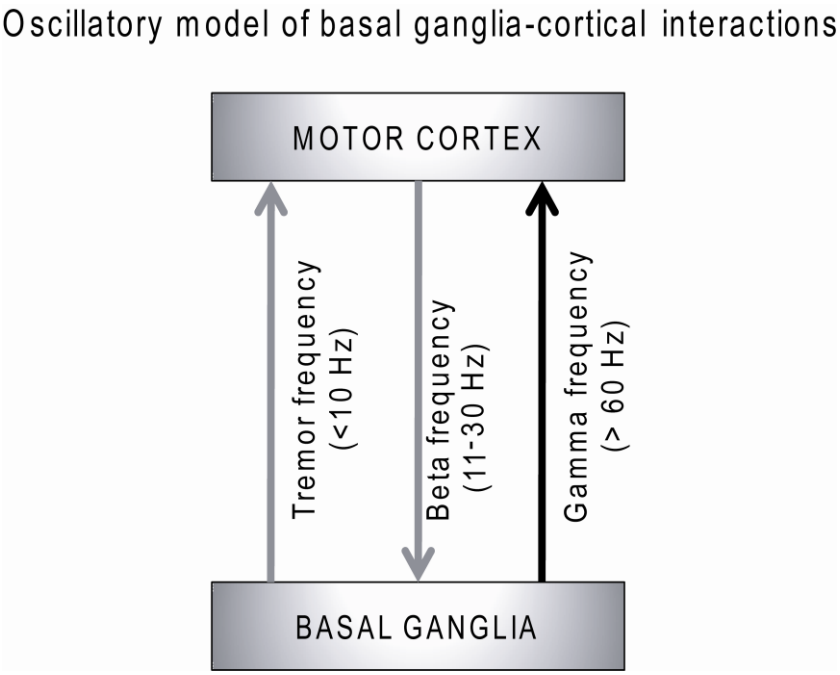

Figure 1.18: Schematic figure of the oscillations in different frequency bands in the basal ganglia-cortical loop of PD: Loss of dopamine in the striatum enhances pathophysiological oscillations in the basal ganglia which drive to the other brain region. The grey arrow shows the antikinetic effect whereas the black arrow shows the prokinetic effect, modified from (Brown, 2003).

Synchronized activity in the gamma frequency band was observed during the motor tasks in the STN-LFPs of PD patients (Kempf et al., 2009) and also in dystonic patients (Liu et al., 2008). These results suggest that higher frequencies have a prokinetic effect (enabling or supporting normal movement). 70 Hz oscillations have also been seen during movement in the normal rodent STN (Brown et al., 2002). In PD patients, gamma activity also increases during movements and dopaminergic treatment, confirming the prokinetic function of this frequency band. Recordings from the motor cortex of epileptic patients also show higher gamma band activity on the contralateral side during the movement. As we know that STN receives direct excitatory input from the primary motor cortex and the supplementary motor area, it might be possible that motor tasks which modulate cortical oscillations might affect the synchronized activity in the STN.

Pre-movement potentials to saccades recorded via STN-DBS electrodes are observed similarly to the so-called readiness potential before limb movement and can also be recorded from cortical

areas. This finding indicates that the basal ganglia have a common mechanism of motor preparation for both limb and eye movements (Fawcett et al., 2007). The physiology of basal ganglia function related to saccades can be understood by studying the basal ganglia-superior colliculus circuit.

In dystonia, other frequency bands (mainly theta) have been related to pathological dystonic movements (Silberstein et al., 2003). Lower LFP synchronization at 8-20 Hz was observed during voluntary or passive movement or vibration in dystonia, while the higher LFP synchronization in 3-20 Hz band was correlated with the strength of muscle spasms (Liu et al., 2008).

1.5.6 Oscillations during cognitive functions

Basal ganglia disorders can also be accompanied by deficits in cognitive function (e.g. Huntington's disease). Oscillatory activity in the gamma band recorded using non-invasive and invasive methods has been shown during many cognitive functions like attention, arousal, object recognition, and language perception. STN stimulation can also improve the reaction time motor performances after desynchronizing neuronal activity in the beta band (Temel et al., 2006b).

1.6 Aim of the thesis

The precise role and function of the basal ganglia are still unknown. The studies mentioned above leave many questions unanswered. Some of these questions were addressed in the work on which this thesis is based: In the first project (Chapter 1), we investigated LFP oscillations during repetitive elbow flexion/extension which were either performed in a passive, slow active or fast ballistic fast fashion. The question was whether specific activity of the BG can be recorded during these movements, e.g. is the activity dependent on the velocity of the movement? Do active and passive movements elicit the same pattern of BG activity?

In our second project (Chapter 2) we studied LFPs during the repetitive movements of lower limbs, i.e. during walking on a treadmill machine. In this project, LFP signals were collected via DBS macroelectrodes inserted into the GPi of dystonic subjects. These patients did not show gait impairment and therefore the analyzed LFPs were assumed to be more related to the task than to

the disease. Such recordings have not yet been reported in the literature and are only possible in primates with bipedal gait (humans).

It is known that many PD and dystonic patients show instant motor improvement after DBS surgery without stimulation of the target due to the MLE. In project 3 (Chapter 3), we investigated the MLE in both PD and dystonia by analyzing kinematic parameters of proximal and distal arm movements. We collected data from PD and dystonic subjects pre and postoperatively and explained the effect of basal ganglia lesions. In this study, velocity was selected as a kinematic parameter to show the results. We also compared the kinematic results within and between the groups.

2 Cumulative thesis

This cumulative thesis is based on 3 publications. In the following chapters, the abstracts of these publications and the contribution of the author to the relevant publication are indicated. The full articles are included in the appendix section of this thesis. The full list of publications is also mentioned in another section of the contents.

2.1 Alpha frequency modulation in the human basal ganglia is dependent on motor task

Singh, A., Levin, J., Mehrkens, J. H., and Bötzel, K., 2011. Alpha frequency modulation in the human basal ganglia is dependent on motor task. Eur. J. Neurosci. 33, 960-967.

Depth recordings from the basal ganglia of patients suffering from Parkinson's disease (PD) or dystonia have revealed local field potential (LFP) activity in specific frequency bands. Depth recordings also allow us to study LFP power spectra during different types of limb movements, thus helping to elucidate the role of the basal ganglia in specific motor tasks. Accordingly, we recorded bilateral LFP activity from the subthalamic nucleus (STN) of patients with PD (n = 9) and from the globus pallidus internum (GPi) of patients with dystonia (n = 8). Recordings were taken during the performance of repetitive passive, active and ballistic fast extensions and flexions of the elbow joint and during rest. The first result was that the frequency spectra varied task-specifically in a similar fashion in GPi and STN. The amplitude of the alpha frequency on the contralateral side was significantly higher in ballistic fast movements compared with rest, passive and active performance in both STN and GPi. In conclusion, ballistic fast movements cause synchronized basal ganglia activity in the alpha range. Because this was seen in both patient groups (PD and dystonia) we consider this activity as task-specific rather than disease-related.

The author of this doctoral thesis contributed to this work (Singh et al., 2011a) by organizing the recording sessions, preparing the experimental setup, instructing the patients, performing LFP recordings, analysing the data and by writing the manuscript.

2.2 Pattern of local field potential activity in the globus pallidus internum of dystonic patients during walking on a treadmill

Singh, A., Kammermeier, S., Plate, A., Mehrkens, J. H., Ilmberger, J., and Bötzel, K., 2011. Pattern of local field potential activity in the globus pallidus internum of dystonic patients during walking on a treadmill. Exp. Neurol. doi:10.1016/j.expneurol.2011.08.019.

The basal ganglia (BG) are involved in gait. This notion is exemplified by observations that gait is disturbed by most diseases that affect the BG. However, it is unclear in what way the BG are activated during gait. One method to investigate the activity of the BG is to record local field potentials (LFPs) from electrodes placed in the BG for therapeutic purposes. Nowadays, the globus pallidus internum (GPi) represents the target for deep brain stimulation (DBS) in dystonia. LFPs recorded from this area have been shown to delineate activity associated with dystonic cramps but also activity which may be relevant for certain types of movement. In this study we recorded LFPs from DBS electrodes implanted into the GPi of eight patients with dystonia during walking on a treadmill machine and compared these data with data acquired during rest (sitting and standing). There was no difference in the power of frequency bands during the sitting and standing conditions. LFP power in the theta (4-8 Hz), alpha (8-12 Hz) and gamma (60-90 Hz) frequency bands was higher during walking than during the resting conditions. Beta (15-25 Hz) frequencies were the only frequencies that were down-regulated during walking. The amplitude of the theta and alpha frequency bands was modulated during the gait cycle. These data shed light on the function of the BG in patients with dystonia and demonstrate that, during gait, their overall activity increases in a specific way without showing increases of narrow frequency bands.

The author of this doctoral thesis contributed to (Singh et al., 2011b) by performing LFP recordings during walking, including data analysis, and by writing the manuscript.

2.3 Opposite effects of microlesions of the globus pallidus internum and subthalamic nucleus after DBS electrode implantation

Singh, A., Kammermeier, S., Mehrkens, J. H., and Bötzel, K., 2011. Opposite effects of microlesions of the globus pallidus internum and subthalamic nucleus after DBS electrode implantation. (Submitted to Neuropsychologia)

Deep brain stimulation is widely used for the treatment of movement disorders such as Parkinson's disease or dystonia. The precise mechanism by which this therapy achieves clinical improvement is unclear. To gain further insight into these mechanisms, we studied movement velocity preoperatively and immediately after the implantation of deep brain stimulation electrodes without stimulation in patients with Parkinson's disease and dystonia. There was a clear clinical improvement of symptoms in both groups, which has been described previously as a 'microlesion effect' (MLE). However, movement parameters were affected differently, i.e. PD patients experienced increased movement velocity due to the MLE, whereas dystonic patients were significantly slower after electrode implantation. We suggest that the improvement of dystonia is achieved by inducing bradykinesia in patients with dystonia undergoing DBS.

The author of this doctoral thesis contributed to (Singh et al., 2011c) by performing kinematic recordings before and after the surgery, data analysis, and by writing the manuscript.

3 Discussion

LFPs, recorded from the basal ganglia via DBS electrodes, can provide information on the pathophysiology of movement disorders. In particular, it has been shown that beta frequency (8-30 Hz) oscillations are prominent in untreated PD patients and can be suppressed by voluntary movement, medication and surgical therapy. However, low frequency (< 10 Hz) LFPs in the pallidum may be correlated with the pathophysiology of dystonia. Higher oscillations in the gamma frequency band were seen during movements in PD and dystonia and after dopamine therapy in PD patients. Further, synchrony below 10 Hz or at lower frequencies and in the higher gamma band could also be detected during motor and other tasks.

Most studies describe synchronized activity in the beta and lower frequency bands as an indicator of movement disorders. Comparison of the STN neurons between PD patients and the normal monkey shows that PD patients have lower response variability and suggests that basal ganglia disorders have diminished information-carrying capacity (Gale et al., 2009). It has also been suggested that oscillations at different frequency bands may help to sustain the segregation of neuronal information processing in the basal ganglia.

3.1 Frequency modulation during motor performances in the basal ganglia

Basal ganglia oscillations which occur during movement were explained in the introduction section (see the contents). From these findings it became clear that most of the studies have been performed using simple movements. Therefore it was not known whether complexity or speed of the movement may be reflected in the basal ganglia activity. Thus we studied basal ganglia oscillations during simple and complex (repetitive ballistic fast) arm movements in PD and dystonia and lower limb movements in dystonia. We also investigated whether STN and GPi behave differently during such tasks. PD and dystonic patients executed passive, active flexion and extension of the arm and ballistic fast movement. The new finding was that we observed synchronized activity in the basal ganglia in the alpha frequency band during the ballistic motor tasks. We also found movement-related higher gamma frequency band activity during simple and ballistic tasks as compared to rest, but the power of the gamma activity was the highest during ballistic task (Singh et al., 2011a). We observed that power value in the gamma frequency

band increased with movement velocity in the basal ganglia. Previous findings on magnetoencephalographic (MEG) recordings in normal subjects have shown oscillations in the cortex similar to those we found in the BG (Muthukumaraswamy, 2010). This can be seen as an indicator of a direct exchange of information between the motor cortex and BG in the basal ganglia –cortical circuit during motor tasks.

We know that STN, GPi and GPe are interconnected in the basal ganglia-thalamocortical circuit and neuronal activity in the STN can affect the GPi activity. It has been shown that GPi or GPe have similar oscillatory features in PD and dystonia (Silberstein et al., 2003). Ballistic movements, which were associated with higher activity in the lower frequency band, differ from simple movements in terms of force and speed (Inase et al., 1996). Study on non-primates demonstrated that the neuronal discharge rate in GPi during arm movements depends on the amplitude, speed and direction of movements. Therefore, we suggested for the first time that fast arm movement with higher force can evoke synchronized low-frequency band activities of the LFP in the STN and GPi and that this type of oscillation may be typical for this type of movement. Other studies have reported that this type of oscillation may be related to dystonia (Liu et al., 2008). Our results suggest that the movement performed is the crucial factor, i.e. dystonic fast movements can evoke similar potentials which are correlated with the movement but not with dystonia.

In our second study, we investigated for the first time changes in the GPi LFP activity of dystonic patients during walking on a treadmill machine. Imaging techniques such as fMRI and PET have revealed the involvement of the supplementary motor area, somatosensory cortex as well as cerebellar areas and brainstem during real and imagined locomotory tasks (Jahn et al., 2008; la Fougere et al., 2010). An EEG study in normal subjects during stepping movements showed the activation of SMA, PMC, and somatosensory cortical regions (Raethjen et al., 2008). While walking on a treadmill, the power of alpha and beta bands was more pronounced in the sensorimotor cortical area when the contralateral leg was pushed off (Gwin et al., 2011). Thus, previous findings have investigated the involvement of cortical regions in steady-speed human gait. However, there was no study concerning the active engagement of the basal ganglia region during walking.

We observed higher spectral power in the theta, alpha and gamma bands, while lower power was seen in the beta frequency band during walking. Thus walking is associated with a distinct activity of the BG which can be described with this frequency pattern. Furthermore, modulation

in the theta-alpha band was noticed during a gait cycle at the early stance phase and swing phase of the contralateral leg. Overall higher spectral group activities were observed during walking in the dystonic patient group. As in our study, all patients had no gait disturbances, so we concluded that the results were mainly influenced by lower limb motor tasks and less by disease. This notion is supported by other studies (Liu et al., 2006; Singh et al., 2011a).

3.2 Effect of microlesions of the basal ganglia

In the last study, we studied the effect of microlesions in PD and dystonic patients. We know that the precise mechanism of the MLE is uncertain but it may be caused by the local edema which can deactivate the neuronal activity and may last up to several weeks. To this end, we recorded movement parameters during proximal and distal movements (finger tapping, pronation and supination movement) and ballistic (boxing) movement before and after the insertion of DBS electrodes.

A previous study has described clinical improvements of the symptoms that were the reason for the operation (Cersosimo et al., 2009; Derrey et al., 2010). Our study is the first study of movement parameters in these situations in two groups of patients. After surgery and without stimulation, clinical improvements have been seen in PD (Maltete et al., 2008) and dystonic patients (Cersosimo et al., 2009). Our aim was to explain the MLE on the basis of kinematic parameters (velocity of the movements). This study revealed that postoperative PD patients executed the motor tasks with increased velocity. On the contrary, dystonic patients performed with reduced velocity after the surgery due to the MLE. This study supports the previous findings that MLE can improve bradykinesia in PD patients (Maltete et al., 2008) and as a new finding we suggest that this type of surgery may induce bradykinesia in dystonic patients (Berman et al., 2009). Studies on primates have also discussed the slowing of movements after GPi lesions (Desmurget and Turner, 2008; Mink and Thach, 1991). It has been shown that, in the basal ganglia motor loop circuit, GPi sends inhibitory input to the supplementary motor area (SMA) via the thalamus. In PD patients, reduced activity in SMA can be related to the bradykinetic feature and SMA activity can be increased by medications and pallidotomy (Rascol et al., 1992). However, in dystonia, increased activity in SMA and the primary motor cortex (PMC) has been observed and basal ganglia lesions can reduce activity in the PMC (Ceballos-Baumann et al., 1995). Therefore, microlesions may improve the bradykinetic feature in PD by lessening the association of excessive tonic and phasic inhibitory output from the basal ganglia

to the thalamus and can improve the hyperkinetic feature of dystonia by decreasing the abnormally low level of the basal ganglia outflow (DeLong, 1990). In the same study, results of the quotient of fatigue (QF) showed improvement in fatigue after lesioning of the basal ganglia. Therefore, an alteration in the striato-thalamo-cortical loop by insertion of an electrode (MLE) may also be associated with lower levels of fatigue in movement disorders.

3.3 Future directions

From single cell neuronal recordings and local field potential studies, it is clear that the basal ganglia communicate with the cortex and other brainstem centers to influence or select appropriate movements. Decoding this communication might allow us to influence movement execution in patients with basal ganglia disorders. State-of-the-art DBS uses one type of frequency and one type of amplitude 24 h per day. The studies presented here might lead to more refined stimulation protocols tailored to the needs of the individual patient.

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NEUROSYSTEMS

Alpha frequency modulation in the human basal ganglia is dependent on motor task

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Keywords: ballistic fast movements, globus pallidus internum, local field potentials, subthalamic nucleus

Abstract

Depth recordings from the basal ganglia of patients suffering from Parkinson's disease (PD) or dystonia have revealed local field potential (LFP) activity in specific frequency bands. Depth recordings also allow us to study LFP power spectra during different types of limb movements, thus helping to elucidate the role of the basal ganglia in specific motor tasks. Accordingly, we recorded bilateral LFP activity from the subthalamic nucleus (STN) of patients with PD (n = 9) and from the globus pallidus internum (GPi) of patients with dystonia (n = 8). Recordings were taken during the performance of repetitive passive, active and ballistic fast extensions and flexions of the elbow joint and during rest. The first result was that the frequency spectra varied task-specifically in a similar fashion in GPi and STN. The amplitude of the alpha frequency on the contralateral side was significantly higher in ballistic fast movements compared with rest, passive and active performance in both STN and GPi. In conclusion, ballistic fast movements cause synchronized basal ganglia activity in the alpha range. Because this was seen in both patient groups (PD and dystonia) we consider this activity as task-specific rather than disease-related.

Introduction

Diseases of the basal ganglia (BG) are known to alter the execution of limb movements in a disease-specific fashion. Neuronal coding in the BG occurs in the form of single cell depolarizations and local field potential (LFP) oscillations, which are inherently interconnected (Brown & Williams, 2005). Recordings from the human BG can be made from the subthalamic nucleus (STN) or the globus pallidus internum (GPi) which are targets for permanent deep brain stimulation (DBS) electrodes used as a therapy in Parkinson's disease (PD) (Bergman *et al.*, 1990; Aziz *et al.*, 1991; Limousin *et al.*, 1995; Krack *et al.*, 2003; Deuschl *et al.*, 2006) and dystonia (Bereznai *et al.*, 2002; Vidailhet *et al.*, 2005; Kupsch *et al.*, 2006). Using this approach, recordings from the BG of patients have previously revealed prominent and synchronized oscillations of the LFPs at different frequencies.

Low-frequency oscillations have been observed in patients with primary dystonia where LFPs have prominent power in the 3–12 Hz band within the GPi (Chen *et al.*, 2006). This is in accordance with low-frequency neuronal burst discharge single-cell recordings in dystonia (Starr *et al.*, 2005). In another study it was reported that temporal coupling between the pallidal oscillations and muscle activity was synchronized in the range 3–20 Hz during hypertonic cramps caused by dystonia (Liu *et al.*, 2008). Beta frequency oscillations have been associated with the bradykinetic state of PD patients (Brown & Williams, 2005) as the power in this band is decreased when patients are under dopaminergic medication (Brown *et al.*, 2001; Levy *et al.*, 2002) and the degree of beta-suppression is correlated with a reduction of rigidity and bradykinesia (Kuhn *et al.*, 2009). Higher frequency oscillations (70-Hz band) have been recorded during movements (Gatev *et al.*, 2006; Kempf *et al.*, 2009). The same LFP oscillations have also been confirmed to take place in the rodent STN related to movement (Brown *et al.*, 2002). Subcortical gamma activity may be functionally related to motor cortical gamma activity, as they are phase-coupled (Cassidy *et al.*, 2002; Williams *et al.*, 2002), and both increase with movement (Androulidakis *et al.*, 2007; Ball *et al.*, 2008; Cheyne *et al.*, 2008). In parkinsonism, gamma activity is also increased with dopaminegic therapy along with improvement in motor performance, so it was suggested that synchronized activity of the gamma band in basal ganglia may smooth the progress of motor processing (Brown *et al.*, 2001; Brown, 2003).

The movements investigated in the aforementioned studies were mostly finger or joystick movements of similar type. The objective of the current study was therefore to investigate LFPs occurring during repetitive elbow movements involving different velocities, complexity and rate of force production. Furthermore, we wished to investigate whether STN and GPi exhibit similar or different activity during these tasks.

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TABLE 1. Clinical characteristics of the patients

Case	Sex/age (years)	Disease	Disease duration (years)	Hand movement	Analysed bipolar electrodes		Postoperative motor scores* UPDRS/H & Y stage or GDS	Medication (daily dose)
					Right side	Left side		
1	M/56	PD	12	R	1–2	0–1	32/1.5	Clozapin 12.5 mg
2	F/54	PD	12	R, L	0–1	1–2	26/2.5	Pramipexol 1.5 mg
3	M/71	PD	22	R, L	0–1	1–2	37/3.0	Levodopa LT 100/25 mg
4	F/68	PD	9	R, L	0–1	0–1	55/2.5	None
5	M/56	PD	11	R, L	1–2	0–1	32/2.0	Levodopa 200 mg, Cabergolin 2 mg
6	M/53	PD	15	R	1–2	1–2	43/2.5	Levodopa LT 100 mg
7	M/70	PD	10	R, L	1–2	2–3	73/3.0	Levodopa 300 mg
8	M/62	PD	13	R, L	1–2	0–1	50/2.5	Quetiapin 25 mg, Levodopa 200/50 mg
9	M/68	PD	14	R, L	0–1	0–1	61/3.0	None
10	F/50	Dystonia	5	R	0–1	2–3	15	Clonazepam 1.5 mg
11	M/65	Dystonia	14	R, L	1–2	0–1	5	Clonazepam 2 mg, Mirtazapin 22.5 mg
12	F/43	Dystonia	5	R, L	0–1	2–3	7	Tetrazepam, 1.5 mg
13	F/47	Dystonia	25	R, L	0–1	0–1	22	Tetrabenazin 100 mg
14	F/67	Dystonia	5	R, L	1–2	0–1	22	Tetrabenazin 100 mg
15	F/56	Dystonia	32	R	0–1	1–2	10	Pramipexol 0.35 mg Mirtazapin 30 mg, Perazin 25 mg
16	F/22	Dystonia	11	R	1–2	0–1	35	Biperiden 4 mg, Tetrabenazin 50 mg
17	F/64	Dystonia	30	R, L	1–2	1–2	16	None

*Unified Parkinson's Disease Rating Scale (UPDRS)/Hoehn and Yahr staging (H & Y) scores for PD patients and Global Dystonia Scale (GDS) for dystonic patients. Scaling is done during off-medication state.

Materials and methods

Patients and surgery

Seventeen patients who underwent bilateral implantation of DBS electrodes in the STN for the treatment of PD (n = 9) and in the GPi (n = 8) for the treatment of cervical dystonia were studied. Their clinical details are summarized in Table 1. All patients gave their written informed consent, as approved by the local university's ethics committee and in accordance with the Declaration of Helsinki (1964). The STN-DBS electrodes used were model 3389 (Medtronic Neurological Division, Minneapolis, MN, USA) with four platinum-iridium cylindrical connections (1.27 mm in diameter and 1.5 mm in length) and an edge to edge separation of 0.5 mm, while GPi-DBS electrodes (model 3387) had contacts spaced 1.5 mm apart. Contact 0 of the inserted DBS electrodes was the most inferior and contact 3 the most superior. DBS electrodes were targeted using T1- and T2-weighted magnetic resonance imaging (MRI). The initial coordinates for the STN were 12 mm lateral, 3 mm posterior and 3 mm inferior to the midpoint of the anterior and posterior commissures. The corresponding coordinates for the GPi were 20 mm lateral, 3 mm anterior and 4 mm inferior to the midpoint of the commissures. The intended STN and GPi coordinates were adjusted through direct visualization of the target on the individual stereotactic magnetic resonance images. The exact position of the electrodes was refined based on intraoperative recordings of single unit activity, which were made with the Inomed system (Inomed, Teningen, Germany) using up to three simultaneously introduced microelectrodes. Intraoperative macrostimulation was performed to determine the effect on Parkinsonian symptoms and to evaluate the threshold for stimulation-induced side-effects. Patients suffering from PD were operated with local anaesthesia, and dystonic patients were operated under general anaesthesia (propofol). Implantations of stimulators occurred usually 2–4 days after electrode placement. Recordings were performed during this epoch. Postoperative MRI scans confirmed correct electrode placement in all patients.

Postoperatively, the mean (±SD) motor Unified Parkinson's Disease Rating Scale (UPDRS III) for Parkinson's patients off medication was 45.44 (±15.53) and Hoehn and Yahr staging of PD was 2.5 (±0.5). For dystonic patients the Global Dystonia Scale (GDS) was studied after surgery and the average score was 16.5 (±9.8).

Paradigm

All patients were in the off-drugs state for at least 6 h. They were seated in a comfortable chair with a backrest and performed two self-paced active movements and one passive movement with the right and left arm on different trials. Five subjects were not able to perform with the left arm due to intravenous lines (antibiotics) (Table 1). Active movements consisted of a repetitive active extension and flexion of the arm at the elbow joint (about 90°, 1/s) and a self-paced fast boxing movement in which subjects hit a punch-bag with the fist while seated. The passive movement resembled task one with the difference that the experimenter moved the forearm at a comparable pace as in task one. In addition, LFPs were also recorded in a resting condition (without any movement) and in some patients also during passive shaking of the upper body (n = 5) to control for movement artefacts in the LFP recordings. All movements were performed for 60 s. The subjects performed a short exercise run before the recordings were started to get used to the experimental setting.

Recordings

STN and GPi LFPs were recorded from all contacts of both DBS electrodes with contact 3 on the right side as a reference. In addition, we recorded arm movements with a goniometer and the electromyogram of the triceps brachii muscle of the moving arm with a pair of gold electrodes. Bioelectric signals were amplified (filter 0.1 Hz–1 kHz) and stored (2.5 kHz per channel) using Brain Amp hardware and Brain Vision Recorder software (Brain Products GmbH, Gilching, Germany). The signal of the goniometer was recorded with no filters.

Analysis

Initially, data were resampled to 2048 Hz. All analyses were performed off-line using BrainVision Analyzer 2.0 (Brain Products GmbH) and Matlab 7.7.0 (The Mathworks, Lowell, MA, USA). Intracranial LFP traces were re-referenced to yield three traces per electrode (0–1, 1–2 and 2–3). LFP data were filtered (Butterworth zero phase 2–100 Hz, 12 db/oct). We also used a 2- to 4-Hz band rejection filter with lower order ($n = 2$) because 2–4 Hz artefacts were sometimes seen during movements. EMG data were also filtered (20–300 Hz). A 50-Hz notch filter was used. Analysis of the movement parameters (mean interval, angular amplitude and maximum angular velocity) was done automatically by a Matlab program which evaluated the goniometer trace. A movement was detected when the angular velocity was above 20°/s. By visual inspection, only those movements that were regular and larger than 60° were accepted. For these accepted movements only, a marker was set at the peak of the goniometer trace (maximum elbow extension), which was then used to segment the recordings. Segments were centred at these markers and ranged from −500 to + 500 ms. Data recorded during rest were similarly marked by placing a marker after blocks of 2048 data points. Spectra were estimated using a fast Fourier transform (with Hanning window) with a frequency resolution of 1 Hz. The power spectra of all segments were averaged. We analysed the data in the following frequency bands: alpha (8–12 Hz), low beta (13–20 Hz), high beta (21–30 Hz) and gamma (60–90 Hz). For statistical evaluation we selected traces of one electrode pair per side which yielded the highest amplitudes in the alpha band and included at least one of the DBS electrode contacts likely to be in STN or GPi as determined from postoperative MRI. For statistical analysis, the amplitudes in the specified frequency bands of the averaged spectra were used.

Stereotactic coordinates of the active therapeutic electrodes were calculated from the postoperative MRI scans using a Matlab program and are depicted in Table 2. For time–frequency analysis, a continuous wavelet transformation (CWT) was applied to the LFP segments. Power values were computed with the Morlet complex wavelet. Minimal and maximal frequency limits were selected from 1 to 90 Hz. The Gabor normalization method was used to normalize the wavelet function, which is almost equivalent to the Gabor transform. CWT data of the segments were averaged.

Statistics

All statistical analyses were carried out using SPSS v17 (SPSS, Chicago, IL, USA). Amplitudes of the three frequency bands in the three movement tasks were normalized with reference to the resting condition. Differences in these data between single movement tasks and rest were evaluated by *t*-tests with the Bonferroni correction method. Separate ANOVAs for repeated measures were calculated for GPi and STN data and for every frequency band to detect differences between movement tasks. Factors were ipsilateral and contralateral recording side and movement task ($n = 3$). In ANOVAs, pairwise comparisons were performed with Bonferroni correction. Mauchly's test was used to confirm the sphericity of the data and when it was violated the Box adjustment procedure for degree of freedom was carried out. The Greenhouse–Geisser method was used for sphericity corrections. *Post-hoc* paired *t*-tests were performed to determine relevant differences of power changes between the motor tasks. Differences were considered statistically significant at $P < 0.05$. All error bars in figures represent standard errors of the mean (SEM).

Results

Modulation of LFP oscillation in the alpha frequency band

The main difference between the LFP spectra during rest and movements was observed within the alpha frequency band in both STN and GPi recordings (Fig. 1). In ballistic fast movements a significant bilateral power increment was seen compared with rest in the alpha frequency band ($P < 0.0167$; *t*-test with the Bonferroni correction) in both the Parkinsonian and the dystonic group. The differences between tasks (active, passive, fast ballistic) and recording side were established in two-way repeated-measures ANOVAs. In the alpha frequency band, significant differences were found in both STN and GPi groups (STN – $F_{1.3,18.9} = 15.03$, $P = 0.0001$; GPi – $F_{1.4,16.3} = 8.63$, $P = 0.006$). Furthermore there was no main effect of recording side (STN – $F_{1.0,14.0} = 0.89$, $P = 0.360$; GPi – $F_{1,12} = 1.83$, $P = 0.20$). Also, no significant interaction of side and task was observed in either group (STN – $F_{1.2,16.6} = 2.19$, $P = 0.156$; GPi – $F_{2,24} = 2.33$, $P = 0.118$). Paired *t*-tests revealed significantly higher differences between passive and ballistic fast movements in the contralateral side compare with the ipsilateral side (Ipsilateral STN – $t_{14} = -2.24$, $P = 0.042$; Contralateral STN – $t_{14} = -2.64$, $P = 0.02$; Ipsilateral GPi – $t_{12} = -2.22$, $P = 0.046$; Contralateral GPi – $t_{12} = -3.01$, $P = 0.01$) and between active and ballistic fast movements, but only in the contralateral side (Ipsilateral STN – $t_{14} = -2.01$, $P = 0.06$; Contralateral STN – $t_{14} = -3.52$, $P = 0.003$; Ipsilateral GPi – $t_{12} = -2.09$, $P = 0.06$; Contralateral GPi – $t_{12} = -2.73$, $P = 0.02$; Fig. 2). A CWT analysis revealed that synchronization in the alpha range was found at around the time of higher acceleration in the fast ballistic movement (Fig. 3). To study whether alpha band activity is related to movement artefacts, we recorded LFP data from DBS electrodes during passive shaking of the upper body ($n = 5$). We found only 2- to 4-Hz artefacts in the LFP data, which may come from the movements of the electrode wires (Fig. 4).

Low beta, high beta and gamma frequency band oscillations

No clearly discernible peaks in the low beta and high beta frequency bands were seen during any of the tasks (Fig. 1) but a small peak in

TABLE 2. Averaged stereotactic coordinates of the active electrode

	Parkinson patients			Dystonic Patients		
	x	*y*	*z*	*x*	*y*	*z*
Right side	13.4 ± 0.9	0.22 ± 1.9	2.1 ± 1.0	20.4 ± 1.7	3.5 ± 0.9	3.0 ± 2.5
Left side	12.5 ± 1.0	0.78 ± 1.5	3.0 ± 2.3	19.4 ± 1.9	3.9 ± 1.7	2.9 ± 2.3

Coordinates are shown in mm as mean ± SD: *x*, laterality from midline; *y*, anterior distance from anterior–posterior commissure midpoint; *z*, inferior distance from anterior–posterior commissure plane.

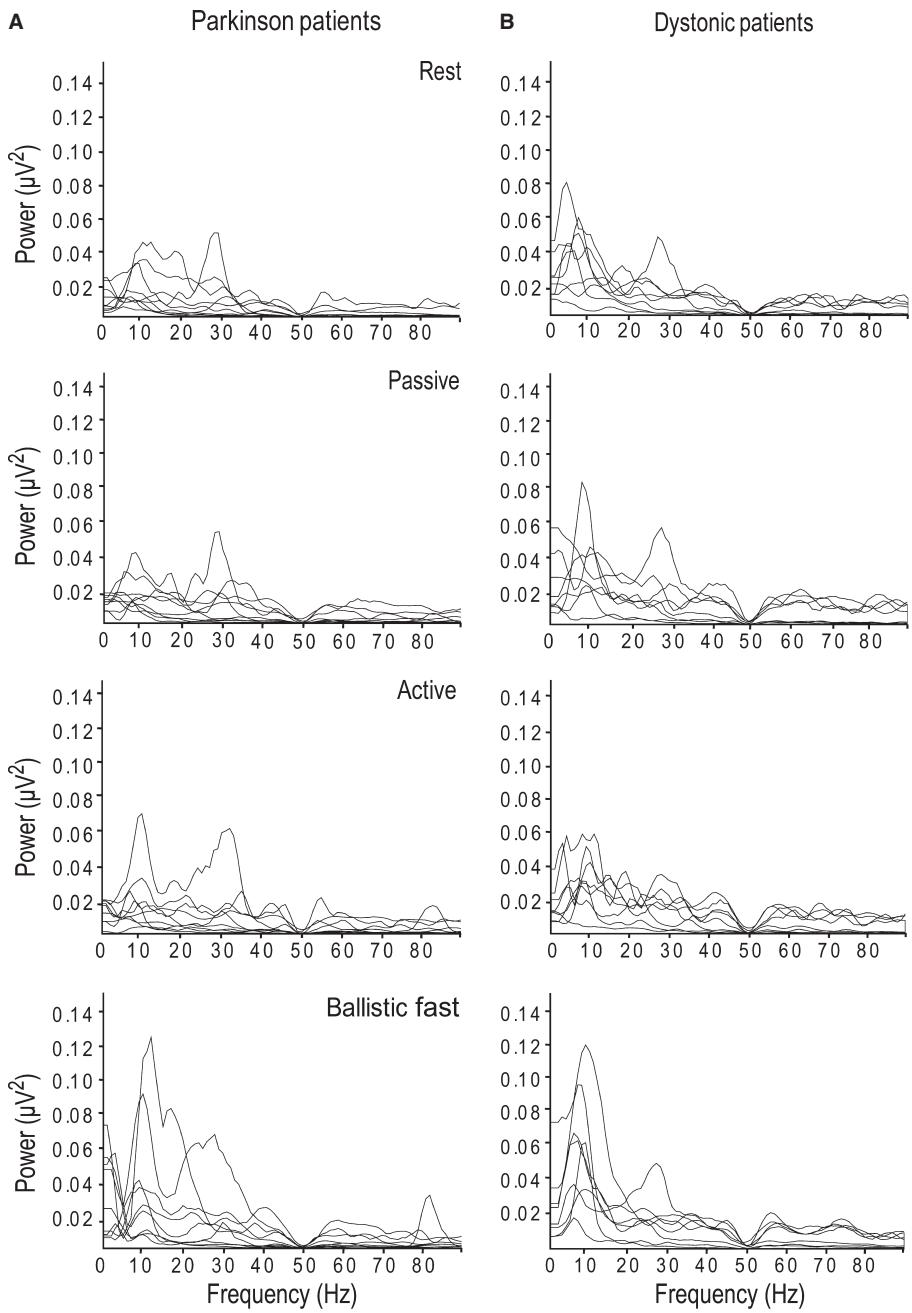

FIG. 1. Power spectra of LFP data acquired during rest, passive, active and ballistic fast activities from all subjects. LFP data were demonstrated from the contralateral side of the basal ganglia while movements were performed with the right arm. Frequency range is selected from 0 to 90 Hz. (A) All Parkinson patients; (B) all dystonic patients. In both groups of subjects the power spectra show higher power values in the alpha frequency range during ballistic fast movement.

gamma frequency band was seen during the ballistic task. There was no significant difference in normalized power in the low beta frequency band during motor tasks as compared with the resting condition ($P > 0.017$). In the ballistic fast motor task only, a significant increase in normalized power in the high beta band was found bilaterally ($P < 0.017$) in PD subjects when compared with the resting condition. In dystonic subjects the normalized power in the high beta band was significantly higher bilaterally in active and ballistic motor tasks ($P < 0.017$; Fig. 2) as compared with rest. ANOVA revealed no significant differences in the low beta frequency band between motor tasks in either group of subjects (STN – $F_{2.0,28} = 2.20$, $P = 0.129$; GPi – $F_{2,24} = 0.31$, $P = 0.737$).

There was a significant difference between tasks in the high beta frequency band in both subject groups (STN – $F_{2.0,28} = 7.07$, $P = 0.003$; GPi – $F_{2,24} = 3.68$, $P = 0.04$). Paired t-tests revealed significant changes between the passive and ballistic task ($t_{14} = -3.41$, $P = 0.004$) and the active and ballistic task ($t_{14} = -3.18$, $P = 0.007$) in PD subjects only in the contralateral side. Pairwise comparison did not show significant changes among the tasks ($P > 0.05$) in dystonic subjects.

In the gamma band, after comparison with the resting condition significant synchronization ($P < 0.017$) was seen bilaterally during all motor tasks in both PD and dystonic patients. In this frequency band, lower statistical differences between the tasks were found in both PD

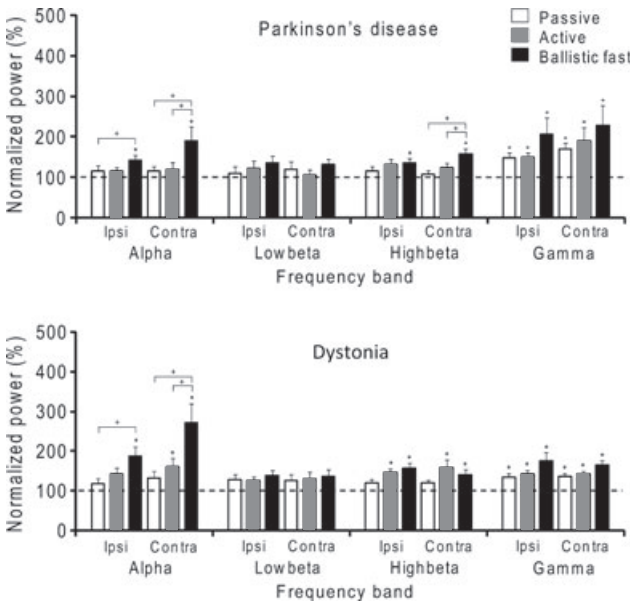

FIG. 2. Comparison of the mean changes in normalized power of LFP signals across alpha, low beta, high beta and gamma frequency bands in ipsilateral and contralateral sides of patients with Parkinson's disease and dystonia. Changes were shown over motor conditions, i.e. during passive, active and ballistic fast motor tasks. Data are presented as mean ± SE; $^{*}P < 0.017$ test against resting condition (100%); $^{+}P < 0.05$ between motor tasks; Ipsi, ipsilateral side; Contra, contralateral side.

(STN – $F_{1.3,18.4} = 3.88$, $P = 0.054$) and dystonic subjects (GPi – $F_{2,24} = 3.56$, $P = 0.044$). However, pairwise comparison did not show a significant difference between the tasks in both groups ($P > 0.05$).

ANOVA revealed that in the low beta, high beta and gamma frequency bands there was no significant effect of side ($P > 0.05$) in either subject group. No significant interaction effect of task and side was observed in the low beta, high beta and gamma frequency bands ($P > 0.05$).

Movement parameters

An automated analysis of the goniometer traces revealed the parameters of all movements (amplitude, velocity and frequency). Surprisingly, fast ballistic boxing movements were apparently performed faster by the PD patients; details of the results are given in Table 3.

Discussion

The major finding of the current study is that complex fast arm movements cause synchronized activity in the BG in the alpha frequency range. Slow repetitive active or passive elbow flexions were not accompanied by these oscillations. No clear frequency peaks were observed in the low beta and high beta frequency bands but a small gamma peak was noted in the ballistic task. Recordings from the BG have, to our knowledge, not been reported for a comparable motor task. Our study was not designed to detect disease-specific LFP

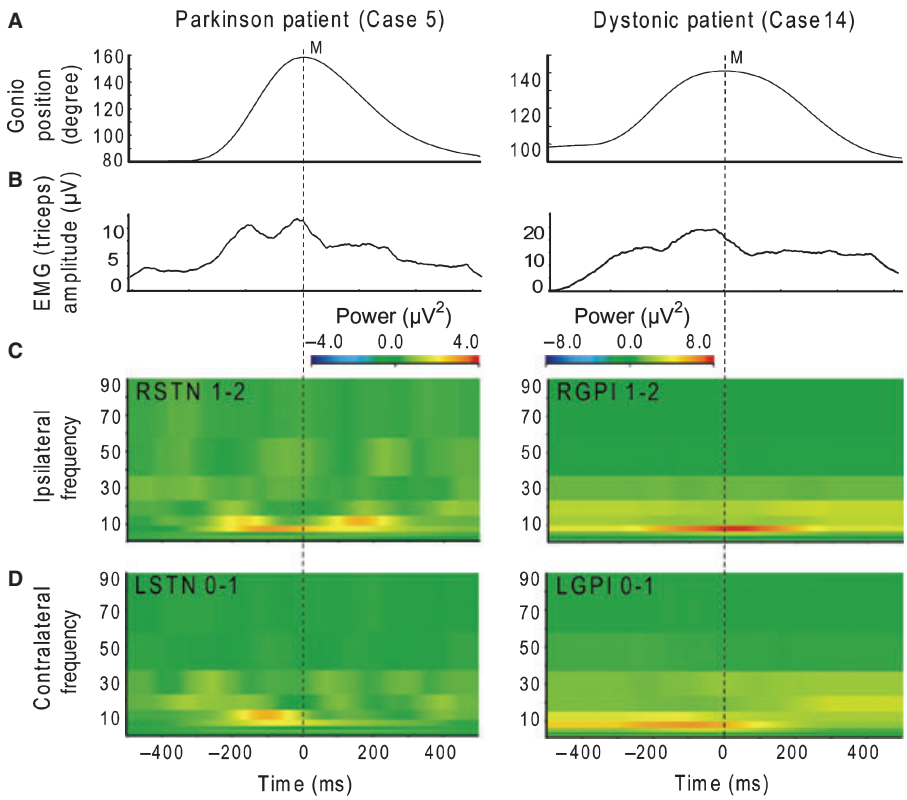

FIG. 3. Oscillatory power as measured by wavelet analysis during ballistic fast movements in a PD patient (left) and a dystonic patient (right) – joint angle was recorded with a goniometer (A) while muscle activities were picked up through gold electrodes. Rectified averaged bipolar EMG signal recorded from triceps brachii muscle (B) and power frequency spectrum from the ipsilateral (C) and contralateral side (D) show synchronized activities in the alpha frequency range. Vertical dotted lines and M marker denote complete extension of the arm.

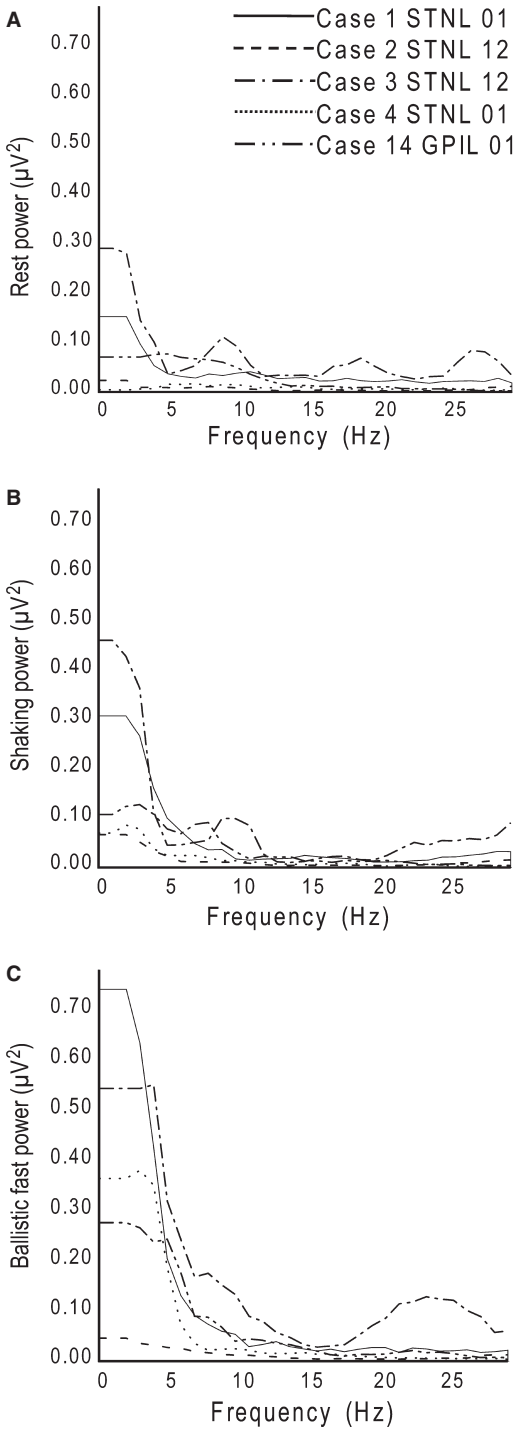

FIG. 4. Power spectra of STN-LFP recorded through contralateral DBS electrodes in five PD patients and one dystonic patient during (A) rest, (B) passive shaking of the upper body and (C) during right arm ballistic fast performance. Movement artefacts (during shaking and ballistic movements) are clearly seen in the frequency band below 5 Hz. This prompted use of a 2- to 4-Hz band rejection filter for all analyses.

modulations but rather to study whether different types of movement cause different LFP changes in STN and GPi. Thus, we suggest that enhanced alpha rhythm synchronization in STN and GPi during complex fast movements is caused by this specific movement. This is supported by the following findings: both patient groups showed the same characteristic LFP differences for different movements and the performance of the patients with respect to movement parameters was comparable. In fact, Parkinsonian patients performed faster boxing movements. This may be due to micro-lesion effects, which facilitate movements in the case of STN lesions and alleviate dystonia immediately after electrode implantation in the GPi (Cersosimo *et al.*, 2009) possibly by inducing a bradykinetic effect (Berman *et al.*, 2009).

TABLE 3. Results of kinematic analysis

Movement	Parameter	Parkinson's patients	Dystonic patients
Passive	Mean interval between movements (s)	1.53 ± 0.37	1.68 ± 0.31
	Mean amplitude of movements (°)	77.67 ± 5.38	84.71 ± 20.42
	Mean max. velocity of movements (°/s)	206.75 ± 44.39	195.0 ± 62.85
Active	Mean interval between movements (s)	1.33 ± 0.44	2.05 ± 1.16
	Mean amplitude of movements (°)	60.56 ± 9.39	78.83 ± 18.46
	Mean max. velocity of movements (°/s)	194.12 ± 73.19	200.74 ± 68.95
Ballistic Fast	Mean interval between movements (s)	1.41 ± 0.63	1.73 ± 0.85
	Mean amplitude of movements (°)	56.04 ± 11.51	56.42 ± 15.54
	Mean max. velocity of movements (°/s)	466.7 ± 99.58	327.9 ± 133.04

Data are shown as mean ± SD.

It is not surprising that STN and GP showed comparable LFP changes in our recordings. These two structures are mutually connected and the connections between STN and globus pallidus externum (GPe) are the major candidate for a BG pacemaker (Gatev *et al.*, 2006), although in an isolated preparation no coherent activity could be seen (Loucif *et al.*, 2005). Connections between STN and GPi are excitatory and there is strong evidence that STN neurons strongly affect neuronal discharge in GPi (Nambu *et al.*, 2000). Although the electrode tip in this study was in the GPi, it cannot precisely be determined whether the particular electrode contacts that we recorded from were in the GPi or GPe. However, GPi and GPe seem to exhibit similar LFP characteristics in PD and dystonia and react comparably on dopaminergic therapy in PD (Silberstein *et al.*, 2003). Also, in a study using functional MRI in healthy subjects, GPi and GPe showed the same differential activation with respect to different movement tasks (Vaillancourt *et al.*, 2004). The latter authors found the lowest activation of both STN and GPi during fast ballistic finger movements in comparison with finger movements with a slow rate of force increase. Their findings are congruent with our data, which show specific patterns of low-frequency LFP synchronicity during ballistic movements. Low-frequency synchronizations of BG LFPs as reported here have been seen in other instances, which were related to abnormal movements of the extremities. In a PD patient, low-frequency oscillations at around 4 Hz were predominant during dyskinesias after STN electrode implantation (simultaneous recordings from GPi and STN) (Foffani *et al.*, 2005). In dystonia, this low-frequency band (4–10 Hz) showed increased activity (Silberstein *et al.*, 2003; Chen *et al.*, 2006). Temporal coupling between dystonic muscle activity and pallidal oscillation in the range 3–20 Hz has been reported for primary

dystonia (Liu *et al.*, 2008). Single cell recordings from humans suggest that the discharge rate of GPi neurons is reduced in dystonia and that oscillatory activity in the 2- to 10-Hz band is increased (Starr *et al.*, 2005). Taking these findings together, it emerges that lower frequency synchronization (below 10 Hz) is seen in hyperkinetic states (dystonia and Parkinsonism with dyskinesias), whereas it seems that 8- to 30-Hz oscillations are associated with akinetic states in PD (Brown *et al.*, 2001; Levy *et al.*, 2002). In our data, low-frequency oscillations were seen during fast but not slow or passive arm movements. The fast boxing movements differed from the other two movements with regard to rate of force production and velocity. When similar arm movements were investigated with single cell recordings of the GPi in non-human primates, neuronal discharge rates were found to correlate with amplitude, velocity and direction of movement (Georgopoulos *et al.*, 1983; Inase *et al.*, 1996).

In contrast to other studies, we found no prominent 20-Hz peak, as has been described in the Parkinsonian off-medication state, in the recordings of our PD patients. Furthermore, a decrease of power in the 13–30 Hz band during movement, as reported by Kuhn *et al.* (2009), was not found. On the contrary, we found an increase of power in the high beta band on the contralateral side in both groups during active tasks. This has been reported by Androulidakis *et al.* (2008), who found that beta frequency may be increased by ongoing movements. Additionally, it is by no means clear that movement-related desynchronization of beta power, as described in PD patients, is only related to this disease, as the same observations were also manifest in the striatum of healthy monkeys (Courtemanche *et al.*, 2003) and in the putamen of epileptic patients (Sochurkova & Rektor, 2003).

We could not find a clear lateralization of the reported frequency changes. This is in accordance with other reports (Kuhn *et al.*, 2004; Doyle *et al.*, 2005; Williams *et al.*, 2005). It seems that frequency changes in the BG are indicators for different types of possibly bilateral 'movement states' but are not indicative of specific movement parameters.

We revealed significant power activity in the gamma range during motor tasks, consistent with the idea that synchronized gamma oscillations are related to movement activities in both PD and dystonic patients (Brucke *et al.*, 2008; Liu *et al.*, 2008; Kempf *et al.*, 2009). This is in agreement with earlier findings that movement-related synchronized activity in the gamma band is a feature of BG activity that can be seen in different disorders and has also been studied in the cortical area (Crone *et al.*, 1998).

In summary, we found that fast movements with a high rate of force production induce low-frequency synchronicity of the LFP in the BG. Together with observations during dystonic movements or dyskinesias in PD it seems evident that these low-frequency LFP modulations indicate a state of ongoing forceful or generalized movements.

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Abbreviations

BG, basal ganglia; CWT, continuous wavelet transform; DBS, deep brain stimulation; GPe, globus pallidus externum; GPi, globus pallidus internum; LFPs, local field potentials; MRI, magnetic resonance imaging; PD, Parkinson's disease; STN, subthalamic nucleus.

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Pattern of local field potential activity in the globus pallidus internum of dystonic patients during walking on a treadmill

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Pattern of local field potential activity in the globus pallidus internum of dystonic patients during walking on a treadmill

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ABSTRACT

The basal ganglia (BG) are involved in gait. This notion is exemplified by observations that gait is disturbed by most diseases that affect the BG. However, it is unclear in what way the BG are activated during gait. One method to investigate the activity of the BG is to record local field potentials (LFPs) from electrodes placed in the BG for therapeutic purposes. Nowadays, the globus pallidus internum (GPi) represents the target for deep brain stimulation (DBS) in dystonia. LFPs recorded from this area have been shown to delineate activity associated with dystonic cramps but also activity that may be relevant for certain types of movement. In this study we recorded LFPs from DBS electrodes implanted into the GPi of eight patients with dystonia during walking on a treadmill machine and compared these data with data acquired during rest (sitting and standing). There was no difference in the power of frequency bands during the sitting and standing conditions. LFP power in the theta (4–8 Hz), alpha (8–12 Hz) and gamma (60–90 Hz) frequency bands was higher during walking than during the resting conditions. Beta (15–25 Hz) frequencies were the only frequencies that were down-regulated during walking. The amplitude of the theta and alpha frequency bands was modulated during the gait cycle. These data shed light on the function of the BG in patients with dystonia and demonstrate that, during gait, their overall activity increases in a specific way without showing increases of narrow frequency bands.

Introduction

The neurophysiology of gait has been studied extensively in the cat and the rat but bipedal human gait is difficult to study. Human bipedal gait can be disturbed by neurological diseases, namely those involving the basal ganglia (BG). Animal studies have revealed several supraspinal locomotor centers that send efferent signals to the pontomedullary reticular formation and the spinal central pattern generators (Grillner, 2006; Jahn and Zwergal, 2010). One of these centers, the mesencephalic locomotor region has received attention recently as a target for deep brain stimulation (DBS) for patients with advanced Parkinson's disease (PD) with predominant gait problems (Ferraye et al., 2010; Mazzone et al., 2005). Imaging studies of human locomotion using functional magnetic resonance imaging (fMRI) have taken advantage of the fact that imagined movement can activate the same areas as real movement (Jahn et al., 2008). In the Positron emission tomography scanner, areas activated previously by specific activities (i.e. walking) can be recognized using [^{18}F]-FDG as a tracer (la Fougere et al., 2010). These imaging studies revealed gait-related activations of cortical (supplementary motor area, somatosensory cortices) as well as cerebellar areas (vermis, paravermis) and brainstem involvement (pontine tegmentum). BG activities were sparse in these studies (subthalamic nucleus, caudate nucleus and putamen in fMRI only). Furthermore, the mesencephalic locomotor region was activated only during imagined walking in the magnetic resonance imaging (MRI) scanner. This area was shown to be more activated in Parkinsonian patients with freezing of gait than in non-freezers (Snijders et al., 2011). Electroencephalography (EEG) investigations in humans have been conducted during stepping movements (Raethjen et al., 2008; Wieser et al., 2010). These investigations revealed modulation of electrocortical activity mainly in the supplementary motor area, primary motor cortex, cingulate cortex and somatosensory association cortex. Compared to rest, there was a suppression of alpha and beta power during stepping by 68 and 35% (Wieser et al., 2010). Intra-stride variation of these frequency bands during treadmill-walking was investigated (Gwin et al., 2011) and a small increase of alpha and beta band power was observed in the

Abbreviations: BG, basal ganglia; DBS, deep brain stimulation; PD, Parkinson's disease; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; EEG, electroencephalography; LFPs, local field potentials; GPi, globus pallidus internum; CWT, continuous wavelet transformation; SEM, standard errors of the mean

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sensorimotor cortical areas at the times of contralateral push-off. High gamma spectral fluctuations during the gait cycle were prominent in several cortical areas. A significant coherence of muscular and cortical electrical activities was found between the tibialis anterior muscle and midline scalp electrode potentials at the first harmonic of the stepping frequency (Raethjen et al., 2008).

DBS of the BG for treatment of movement disorders offers the opportunity to record local field potentials (LFPs) from the BG during the epoch between electrode implantation and stimulator implantation. These recordings have revealed that pathological movement states may be accompanied by specific frequencies of the BG LFPs, e.g. increased lower beta rhythms in Parkinsonian akinesia (Kühn et al., 2004). For dystonia, lower frequency oscillations in the 4–10 Hz range seem to be pathognomonic (Chen et al., 2006; Liu et al., 2002). In addition, certain movement types seem to be correlated with specific frequency components (Singh et al., 2011). BG activity recorded from DBS electrodes during treadmill-walking is the subject of this paper and has, to our knowledge, not been reported previously. Recordings were performed from eight patients who had DBS electrodes located in the globus pallidus internum (GPi) for treatment of focal or segmental dystonia of the neck and upper trunk. None of our patients had gait disturbances. Therefore, we assume that the recordings presented here were mainly determined by the motor task (i.e. walking) and less by the disease process.

Material and methods

Patients and surgery

Eight patients (5 m, 3f, age 30–63 years) were recruited after having given written informed consent for this study that had been approved by the local university ethics committee and is in accordance with the Declaration of Helsinki. Five patients had adult-onset cervical dystonia without generalization and had been treated with botulinum toxin for several years until this failed to cause improvement (Table 1). Two patients had a severe form of Meige Syndrome that was not treatable otherwise (Opherk et al., 2006). One patient (case 3) had a form of segmental dystonia resembling Rapid-Onset Dystonia–Parkinsonism (Deutschlander et al., 2005) with sudden onset at age 15 with predominant involvement of face and arms but without leg involvement. Parkinsonian features were absent. The patient had no genetic evidence for this or any other juvenile-onset dystonia syndrome. All patients had undergone bilateral implantation of DBS electrodes (model 3387, Medtronic Neurological Division, Minnesota, USA) in the GPi for the treatment of dystonia (Bereznai et al., 2002) at the Department of Neurosurgery in our institution. In brief, the stereotactic coordinates in the posteroventral GPi were referred to the midpoint of the anterior and posterior commissures and were 20 mm lateral, 3 mm below and 3 mm anterior. The preoperative visualization of the target and surrounding structures (especially the optic tract) was done by obtaining T1- and T2-weighted MRI while the stereotactic frame was mounted on the head. If necessary, the coordinates were corrected through direct visualization of the target and the optic tract. Intraoperative microrecordings confirmed the positions of the electrode within the target nucleus. Electrode leads were externalized for 3 days to allow for testing of possible stimulation-induced side effects. Postoperatively, correct electrode placement was confirmed in all patients by MRI. Pre- and postoperatively, standardized dystonia assessments were performed (Toronto Western Spasmodic Torticollis Rating Scale; Global Dystonia Rating Scale) and scores are reported with all other clinical details in Table 1.

Experimental protocol

Recordings were performed on the first or second postoperative day under three conditions: sitting (3 min), standing (3 min) and walking (two times 3 min) on a force-measuring treadmill machine (FDM-T Treadmill, Zebris Medical GmbH, Germany), as shown in Fig. 1. Walking velocity was adjusted to the subject's preferred speed (on average: 22 m/min see Table 1). From the treadmill, signals were transmitted to a computer with appropriate software allowing for the calculation of gait parameters. LFPs of the GPi were recorded from the four contacts of the implanted stimulation electrodes in a bipolar fashion using the Brain Vision Recorder (Brain Products GmbH, Gilching, Germany). This resulted in three traces per electrode. Only the trace containing the electrodes with the highest clinical efficiency was chosen for further evaluation (see Table 1). In addition, the knee angles of both legs were recorded with goniometers mounted to both legs of the patient. The subject carried the battery-driven amplifier in a small backpack. The amplifier was connected to the recording computer via optical fibers. LFPs were filtered (0.1 Hz–1 kHz) and LFP and goniometer signals were sampled at 2.5 kHz and monitored online. Any medication was withdrawn at least 8–10 h before recording.

Data analysis

All processing and analysis was performed in Brain Vision Analyzer 2.0 (Brain Products GmbH, Gilching, Germany) and MATLAB R2008b (The Mathworks, Lowell, MA, USA). Data were resampled to 2048 Hz and filtered through Butterworth zero phase filters (slope 12 db/oct; 1 Hz–90 Hz).

Power spectral analysis was performed with the LFP recordings acquired from one electrode pair per hemisphere. These traces were divided into segments of 8 s duration and spectra were calculated using the fast Fourier transform (maximum resolution ~0.125 Hz) with the Hanning window. The spectra of the segments were averaged. LFP spectra were analyzed in the 4–8 Hz (theta), 8–12 Hz (alpha), 15–25 Hz (beta) and 60–90 Hz (gamma) frequency ranges. For statistical evaluation, mean spectral power values from right and left electrodes were averaged because there is evidence of bilateral involvement of the BG during locomotion tasks (Grasso et al., 1999; Manca et al.,

Table 1
Summary of dystonic patients' clinical and recording demographics.

Case/gender	Age/disease duration (years)	Disease	Analyzed bipolar electrodes		Pre/postop TWSTR scales	Pre/postop GDS scales	Speed of walking (m/min) on treadmill	Medications (daily dose)
			Left side	Right side				
1/M	48/20	Cervical dystonia	0–1	0–1	22/7	6/4	21.7	No medication
2/M	57/7	Cervical dystonia	0–1	0–1	25/16	21/8	25	Metformin 500 mg
3/F	30/15	Segmental dystonia	1–2	1–2	18/13	35/30	25	Tetrabenazine 25 mg
4/F	63/13	Cervical dystonia	0–1	0–1	38/16	20/10	20	No medication
5/M	40/8	Meige Syndrome	0–1	0–1	10/7	17/10	25	No medication
6/M	59/8	Cervical dystonia	0–1	1–2	24/20	12/9	25	No medication
7/F	52/11	Cervical dystonia	0–1	0–1	23/11	10/4	15	Tiotropiumbromid
8/M	42/5	Meige Syndrome	0–1	1–2	15/10	26/16	20	Mirtazapine 30 mg

M = male; F = female; TWSTR = Toronto Western Spasmodic Torticollis Rating Scale; GDS = Global Dystonia Rating Scale.
Scaling is done during off-medication and off-DBS states.

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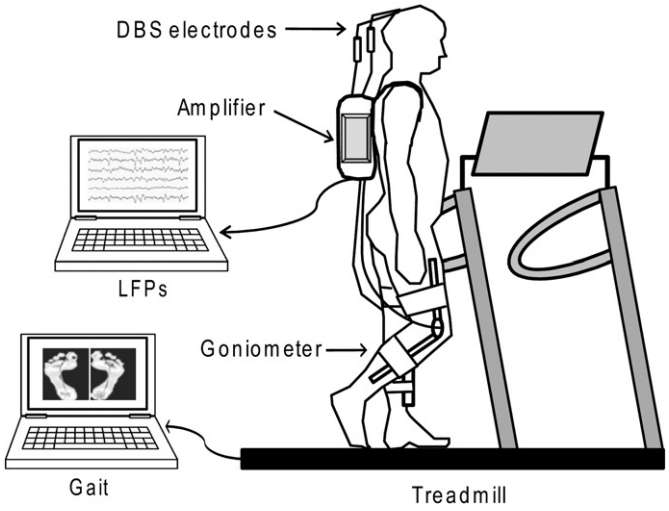

Fig. 1. Schematic illustration of the experimental setup. Subjects walked two times for 3 min on the treadmill and rested on the stationary treadmill for 1 min in between.

2010). The mean spectral power values in the above frequency ranges were calculated for further analysis. To reduce the inter-recording variation, data of the standing and walking conditions were normalized with respect to the sitting condition and specified as a percentage increase or decrease in power. These normalized data were used for the statistical analysis.

The time–frequency spectrograms of the LFP for both hemispheres were plotted (continuous wavelet transformation (CWT) using the complex Morlet wavelet, see the supplement) to visualize the spectral power modulations during one gait cycle. Before this, data were band-pass filtered (3–90 Hz). The spectrum between 3 Hz and 45 Hz was selected for visualization. Data for each gait cycle for 8 patients and 2 hemispheres were computed and averaged. Thereafter, grand mean averages for the whole group were computed using a time window of 1200 ms before through 300 ms after maximum flexion of the right knee. This event indicates the middle of the swing phase of the right leg. Because no time-warping of the data with respect to gait cycle is performed, this procedure may cause blurring of the plots at the outer limits. However, it has the advantage that the frequency of the LFPs is not subjected to change as would have been the case if data had been time-warped.

Statistical analysis

Non parametric tests (Wilcoxon signed ranks) were performed for all frequency bands using SPSS 18 (SPSS, Chicago, IL, USA) to detect statistical differences between conditions (sitting–standing, sitting–walking and standing–walking). The decisive factor of significance was $P<0.05$.

Results

Power spectral analysis of LFPs

During walking, the LFP spectra of GPi recordings showed significantly higher power values in the lower frequency bands (theta, alpha) and in the gamma band as compared to during sitting or standing. The opposite was seen in the beta band where the power was significantly reduced during walking (Figs. 2 and 4). Some small narrow-band peaks in the spectra were in the same frequency as the goniometer signal or its harmonics and were probably artefact-related (Fig. 3). No significant differences over all frequency bands were observed between the sitting and the standing conditions (see Table 2 and Fig. 4).

A statistical comparison of the theta band values between walking and sitting ($P=0.03$) as well as between walking and standing ($P=0.04$) showed significant differences. In the alpha frequency band power was higher during walking than during sitting ($P=0.01$) or standing ($P=0.01$). In the beta frequency band a significant depression of the values during walking was seen in comparison with sitting ($P=0.01$) but not when compared with standing ($P=0.17$). The gamma frequency band again was significantly enhanced during walking when compared with sitting ($P=0.01$) or standing ($P=0.01$) (Fig. 4).

Time–frequency analysis of LFPs related to gait cycle phases

The plots of individual subjects revealed considerable differences, but a modulation of the amplitudes in the theta-alpha (6–11 Hz) range was seen in all subjects. The grand average revealed a maximum

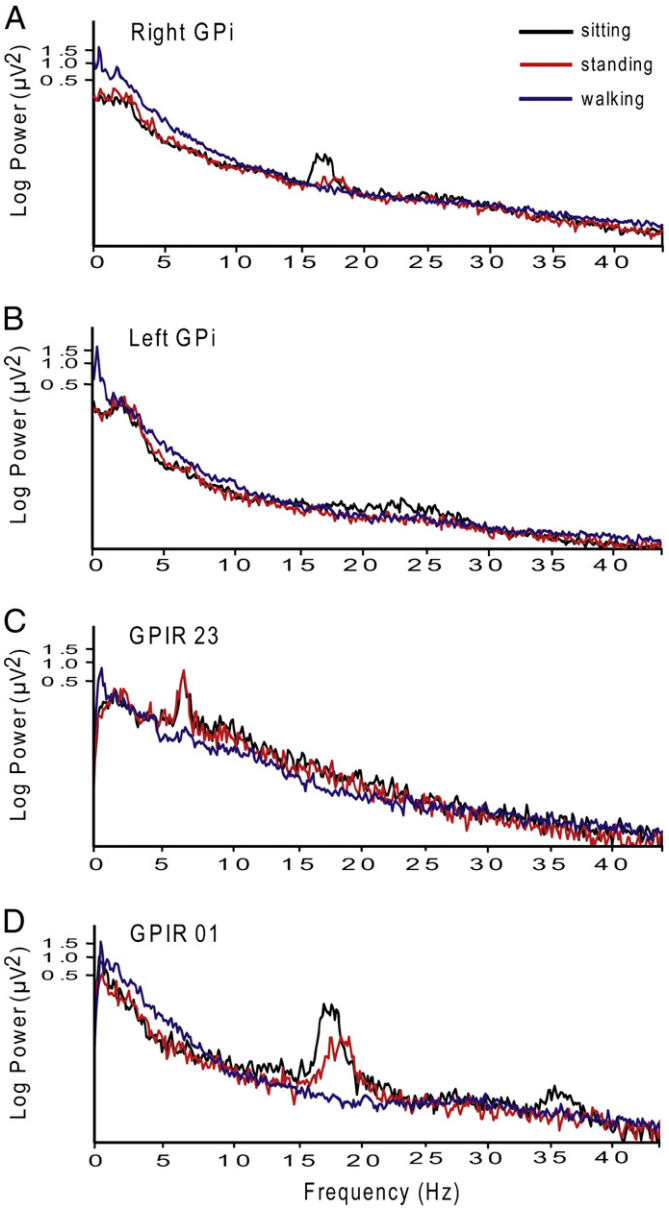

Fig. 2. LFP power spectra acquired during sitting, standing and walking conditions are overlaid. A: grand average LFP power spectra of all subjects obtained from the analyzed contact pair of DBS electrodes, inserted in the right hemisphere (Right GPi) and B: left hemisphere (Left GPi). C: power spectra from case 7 displaying narrowband oscillatory activity of 7 Hz. D: power spectra from case 8 displaying a frequency peak at 18 Hz.

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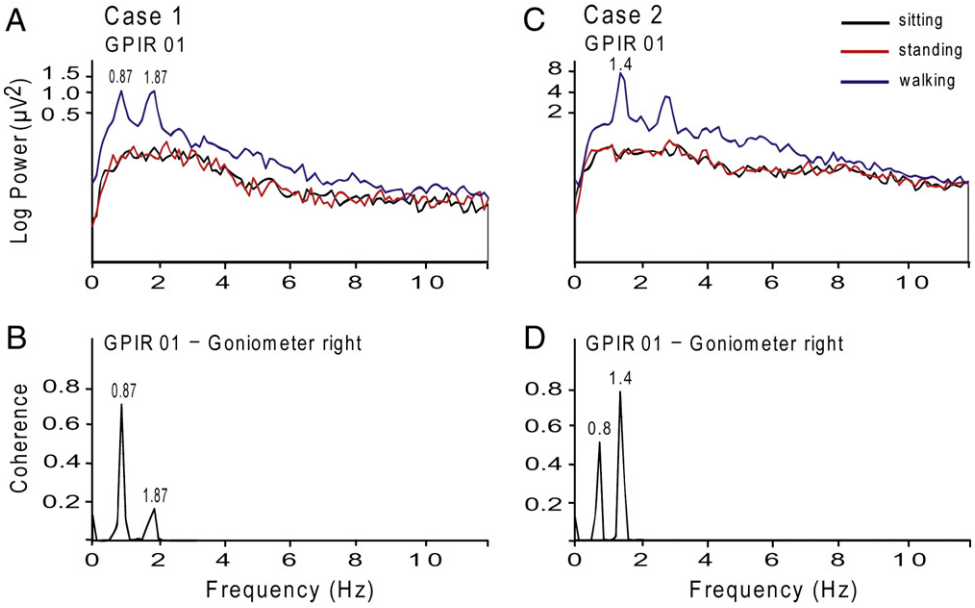

Fig. 3. Spectra of LFPs and coherence with the goniometer trace exemplified in two cases. In the frequency range between 1 and 2 Hz distinct peaks in the LFP spectrum show high coherence with the goniometer trace and can thus be judged as artifacts. Increment of the LFP spectrum in lower frequency bands during gait can clearly be seen (blue traces) and shows no correlation with goniometer data. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

of 6–11 Hz amplitude during the early stance phase of the left leg in the right hemisphere and symmetrically on the left during the early stance phase of the right leg (Fig. 5).

Individual LFP characteristics

Two patients showed interesting small band frequency peaks during sitting and standing but not walking. In case 7, this peak had a maximum at 7 Hz and was seen in the upper two traces on the left and on the uppermost trace on the right (Fig. 2C). In case 8, this peak was in the beta range (18 Hz) and only seen in the lower two traces on the right (Fig. 2D). This will be discussed below.

Discussion

The present study investigated the changes of pallidal oscillations during gait in patients with dystonia as compared to sitting and standing. We are aware of the fact that the results may not be generalized without further recordings from other patients not suffering from dystonia. We found that walking on a treadmill causes a significant increase of the LFP power in the theta, alpha and gamma bands and a depression of the beta band. Further analysis showed that oscillations in the theta-alpha range are modulated during the gait cycle.

The first conclusion from these results is that gait apparently is not associated with changes in a single frequency band. During gait, the BG change their activity in terms of an increase in several bands. This is in agreement with the observation that the appearance of single frequency peaks is indicative of abnormal synchronization, as observed in PD or corresponding animal models (Levy et al., 2002; Nini et al., 1995) or dystonia (Foncke et al., 2007). Furthermore, it is noteworthy that the only frequency band not increased but reduced during gait was the beta band (15–25 Hz). Antikinetic properties have been attributed to this part of the spectrum since it is elevated during rest in akinetic states of PD (Brown, 2003) and suppressed before and during an upcoming movement (Brown and Williams, 2005; Kühn et al., 2004). This reduction during action was also seen in recordings from the substantia nigra of rats whether in the dopamine-depleted or normal state (Avila et al., 2010). However, the dopamine depleted rats had clearly higher resting beta activity than normal. Oscillations in the high beta range (25–40 Hz) were only seen in the dopamine depleted rats during walking. As an endorsement of previous studies, our work seems to indicate that the division of the basal frequency bands into prokinetic and antikinetic is also applicable for walking (at least in patients with dystonia) and that in 'normal' walking the activation occurs in a diffuse rather than a focal increase of the specific frequency bands.

Table 2
Nonparametric tests result.

Frequency bands	Wilcoxon signed ranks test		
	Pair tasks	Z score	*P* values
Theta band	Sit–stand	−1.68	0.09
	Sit–walk	−2.1	0.03
	Stand–walk	−1.96	0.04
Alpha band	Sit–stand	−1.4	0.16
	Sit–walk	−2.52	0.01
	Stand–walk	−2.52	0.01
Beta band	Sit–stand	−1.4	0.16
	Sit–walk	−2.52	0.01
	Stand–walk	−1.35	0.17
Gamma band	Sit–stand	−1.63	0.10
	Sit–walk	−2.52	0.01
	Stand–walk	−2.52	0.01

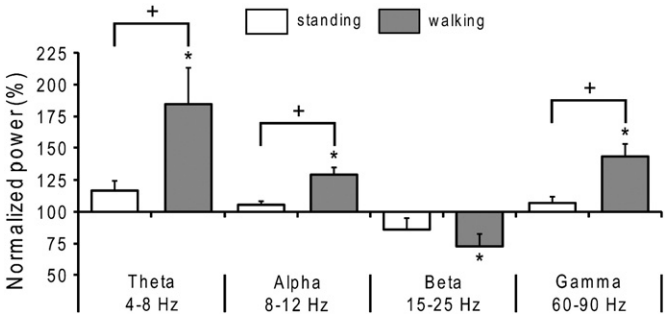

Fig. 4. Mean changes in normalized power values of the LFPs in theta, alpha, beta and gamma frequency bands. Changes were illustrated during standing and walking on a treadmill. Data are presented as mean ± SEM; statistical significance (*$p<0.05$) is shown against sitting condition (100%) and $^{+}p<0.05$ between standing and walking conditions.

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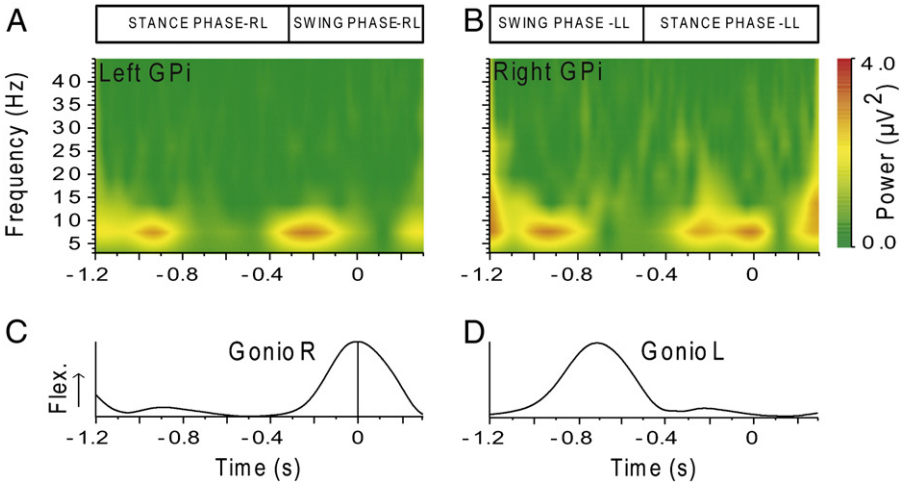

Fig. 5. Time–frequency plots (wavelet transformation) of LFP oscillations during gait cycle. Upper row (A and B): analyzed electrode pair. Right electrode pair is on the right side. C and D: goniometer traces. Modulation of LFPs occurs in the 6–11 Hz frequency range. In this frequency band, amplitudes are up-regulated during the early stance phase and swing phase of the contralateral leg. LL: left leg, RL: right leg, Gonio: goniometer. Flex: flexion.

What was the influence of the underlying disease of our patients on the frequency spectra we recorded? One limitation of our study might be that the diagnoses of our patients were heterogeneous, including distinct forms of focal and segmental dystonia. However, all patients had electrodes in the same anatomical area, and none of them showed any walking disability. With respect to the complex experimental procedure within a clinical setting, we consider this choice of patients as appropriate. Several authors have reported mostly indirect evidence for the notion that dystonia causes an enhanced increase of synchronized low frequency (4–10) activity (Chen et al., 2006) and BG oscillations of this band show a high coherence with the electromyogram of dystonic muscles (Foncke et al., 2007; Liu et al., 2006). Successfully executing the 'geste antagoniste' caused a desynchronization in this particular frequency band (Tang et al., 2007). It is therefore most likely that the spectra of our patients were also enhanced in the theta band or theta and alpha bands. A peculiar peak at 7 Hz during sitting and standing but not walking was seen in one patient only (cervical dystonia) (Fig. 2C). Since we have no video documentation of our experiment we cannot exclude the possibility that that patient may have had dystonic head movements accompanied by this LFP frequency during sitting and standing but not during walking (however, this would be unusual). On the other hand, this patient was undergoing treatment for obstructive lung disease with an anticholinergic (tiotropium bromide) that may be relevant as well. Another patient (case 8) showed narrowband synchronization in the lower beta frequency range during sitting, which was slightly reduced during standing and vanished while the subject walked (case 8, Meige Syndrome). The patient had been an in-patient in the psychiatric unit due to depression related to his severe disabilitating movement disorder and had been treated with tetrabenazine until 1 week before the operation. The appearance of spectral peaks in the lower beta band caused by dopamine blocking or depleting agents has been described (Kühn et al., 2008) in patients at rest and we consider this the reason for the individual differences in this patient's frequency spectrum during sitting and standing.

When walking, our patients showed an increase of the overall amplitudes of the spectral groups that have been reported to be enhanced in dystonia. Furthermore, in a recent study we showed that BG LFPs in the alpha band are increased in ballistic fast arm movements in patients with PD as well as dystonia (Singh et al., 2011). In PD, when the ability to move recurs after administration of levodopa, the 4–10 Hz band of GPi LFPs increases (Silberstein et al., 2003). Thus, involuntary dystonic cramps as well as voluntary proximal limb movements (i.e. ballistic arm movements, walking) can cause similar frequency changes, which raises the question of whether these are related to the movement itself or the pathophysiology of dystonia. The observation of Liu et al.(2006) may shed some light on this issue: they reported that the mobile component of dystonic movements but not sustained dystonic contractions was accompanied by low-frequency synchronization in the BG; this may be taken as evidence that this part of the spectrum is related to ongoing movement whether it is dystonic or voluntary. Thus we see more evidence for the notion that our findings were 'gait-related' rather than 'disease-related'.

Scalp-EEG has been recorded during walking in previous studies. An increase of spectral power in the 1.5–8.5 Hz frequency band was found during running as compared to walking and attributed to mechanical artifact (Gwin et al., 2010). In Fig. 3, the authors show that in frequency bands up to 30 Hz a significant increase of all bands also occurs during running, which may extend the interpretation of our findings in the direction that faster speed of walking, or even running, may accentuate the rather diffuse increase of BG activity. The same group investigated gait-phase related modulation of scalp-EEG (Gwin et al., 2011) and found a small increase of alpha and beta activities over the sensorimotor cortices and the cingulate cortex as the leading foot touched the ground. It can be assumed that, during this phase, this activity is coupled to the activity of the BG as reported here since we also found increased alpha activity during the early stance phase of the contralateral leg in the GPi. Since the cortex is connected to the BG via the hyperdirect path to the STN (Nambu et al., 2002), and the STN together with GPi are assumed to be the main oscillators in the BG, cortical rhythms are likely to be mirrored in the BG. Over the same cortical areas, multi-electrode EEG recordings showed a high coherence with leg muscle activity during stepping movements (Raethjen et al., 2008). On the contrary, a suppression of alpha and beta rhythms over midline EEG electrodes (Cz and Pz) has also been observed during stepping movements (Wieser et al., 2010). In contrast to our human data, animal experiments have revealed distinct spectral peaks of electric activity of locomotor structures during locomotion (Slawinska and Kasicki, 1995). In these experiments, hypothalamic locomotor areas of the rat showed low frequency peaks (1–6 Hz) during sitting that were not seen while walking, when a distinct theta peak emerged. This suggests that the dynamic association of the oscillatory activities in different frequency bands in the BG may provide a coordination of different processing streams. Other structures could be connected to the BG by using distinct frequency channels, thus being active preferably when the BG enhance oscillations at a frequency at which these structures can show resonance oscillations. This might be clarified by recordings from patients with tegmental DBS electrodes.

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Conclusions

The dynamic association of the oscillatory activities in different frequency bands may serve to activate or inhibit different processing streams in the BG and the structures they are connected with. In our study we were able to show that walking on a treadmill is associated with an increase of LFP oscillations in the 4–12 Hz and 60–90 Hz frequency bands and a decrease in 15–25 Hz. These changes may initiate or sustain gait-related activity in locomotor brainstem centers. A modulation of 6–11 Hz oscillation during the gait cycle was found and seems to indicate that information about individual gait cycles is also present in the BG.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.expneurol.2011.08.019.

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Opposite effects of microlesions of the globus pallidus internum and subthalamic nucleus after DBS electrode implantation

Opposite effects of microlesions of the globus pallidus internum and subthalamic nucleus after DBS electrode implantation

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Abstract

Deep brain stimulation is widely used for the treatment of movement disorders such as Parkinson's disease or dystonia. The precise mechanism by which this therapy achieves clinical improvement is unclear. To gain further insight into these mechanisms, we studied movement velocity preoperatively and immediately after the implantation of deep brain stimulation electrodes without stimulation in patients with Parkinson's disease and dystonia. There was a clear clinical improvement of symptoms in both groups, which has been described previously as a 'microlesion effect' (MLE). However, movement parameters were affected differently, i.e. PD patients experienced increased movement velocity due to the MLE, whereas dystonic patients were significantly slower after electrode implantation. We suggest that the improvement of dystonia is achieved by inducing bradykinesia in patients with dystonia undergoing DBS.

Keywords: Deep brain stimulation, Parkinson's disease, dystonia, movement, bradykinesia.

1. Introduction

Deep brain stimulation (DBS) with multipolar electrodes connected to a subcutaneous pacemaker has evolved into a standard technique, targeting the subthalamic nucleus (STN) in advanced idiopathic Parkinson´s disease (PD) with severe motor fluctuations (Aziz, Peggs, Sambrook, & Crossman, 1991; Deuschl, Schade-Brittinger, et al., 2006; Krack, et al., 2003) and the globus pallidus internum (GPi) in severely impairing dystonia resistant to or ineligible for botulinum toxin treatment (Bereznai, Steude, Seelos, & Bötzel, 2002; Kupsch, et al., 2006; Mehrkens, et al., 2009).

After DBS lead implantation and even before the actual electrical stimulation is initiated, many patients show an improvement of symptoms due to a so-called microlesion effect (MLE), the precise mechanism of which is so far unknown. This MLE has been observed in both PD patients (Koop, Andrzejewski, Hill, Heit, & Bronte-Stewart, 2006; Maltete, et al., 2008) and patients with dystonia in whom the improvement in symptom reduction 24 h after the implantation (due to the MLE) was significantly correlated with outcome after 6 months (Cersosimo, et al., 2009). Previous studies on the MLE in PD as well as in dystonia used motor scales taken by expert neurologists to assess clinical improvements (Cersosimo, et al., 2009; Cersosimo, et al., 2008; Derrey, et al., 2010; Maltete, et al., 2008), whereas kinematic data have not been reported in these circumstances. It seems most likely that the MLE is caused by inactivation of neurons surrounding the implanted electrode by a local edema. The time course of the MLE would be compatible with this notion, since the positive effect of the MLE on the parkinsonian or dystonic symptoms lasts for a few days only (Cersosimo, et al., 2009; Granziera, et al., 2008).

PD is a neurodegenerative disease which manifests clinically with the compulsory criteria of progressive bradykinesia (slowing of movements) (Berardelli, Rothwell, Thompson, & Hallett,

2001; Hughes, Daniel, Kilford, & Lees, 1992; Limousin, et al., 1999) and other motor symptoms like rigor, tremor and postural instability. PD subjects exhibit bradykinesia during ballistic mass movements of the arm (Flowers, 1975), movements with high spatial accuracy (Montgomery & Nuessen, 1990; Sanes, 1985) and during complex fine motor tasks (Berardelli, et al., 2001; Dafotakis, Fink, Allert, & Nowak, 2008; Schettino, et al., 2004; Schwab, Chafetz, & Walker, 1954). It is known that movement speed is increased by STN-DBS (Sturman, Vaillancourt, Verhagen Metman, Bakay, & Corcos, 2010; Vaillancourt, Prodoehl, Verhagen Metman, Bakay, & Corcos, 2004), GPi-DBS (Lang, et al., 1997) and by thermocoagulation of these nuclei (Kimber, Tsai, Semmler, Brophy, & Thompson, 1999; Maltete, et al., 2008).

Dystonia is characterized by abnormal muscle co-contractions of agonists and antagonists, forcing body parts into an abnormal posture (Fahn, 1988). Dystonia can be exacerbated by voluntary movements (Berardelli, et al., 1998). Beyond that, studies point to complex deficits in motor feedback circuits (Inzelberg, Flash, Schechtman, & Korczyn, 1995). Bradykinesia is normally not a symptom of dystonia in limbs which are not affected by the disease, although movement time may be prolonged due to a longer deceleration phase (Inzelberg, et al., 1995) and sequential arm movements were reported to be slow (Agostino, Berardelli, Formica, Accornero, & Manfredi, 1992). Therapeutic neurosurgical interventions concentrate on the GPi, the same structure which is also targeted for the relief of Parkinsonian symptoms (Follett, et al., 2010). Therefore one might expect that STN and GPi microlesions would have the same effect on kinematic parameters.

In the present study, the focus is not on MLE-induced clinical improvement but on kinematic parameters of limb movements and how they may be affected by the MLE. While the MLE in PD is expected to cause an increase of movement velocity, this has not been addressed in patients

with dystonia undergoing DBS. Animal experiments seem to point to slowing of movements after lesions of the pallidum (Desmurget & Turner, 2008; Mink & Thach, 1991). However, it seems worthwhile to investigate movement speed in PD and dystonia before implantation of electrodes and shortly afterwards (during the epoch of the presumed MLE) to address the following questions: Is movement velocity altered by the MLE in both groups? Is the effect similar in GPi and STN implantation? Are certain movements (proximal vs. distal, controlled vs. ballistic) specifically affected? The answers to these questions are relevant for the yet unknown mechanisms by which DBS causes symptom relief or may explain certain adverse symptoms caused by stimulation.

2. Methods

2.1. Subject selection and clinical assessment

Sixteen patients undergoing DBS were investigated. Seven had electrodes implanted bilaterally in the STN for advanced PD (mean ± SD age: 61 ± 5 years) and nine bilaterally into the GPi for cervical dystonia (mean ± SD age: 50 ± 13 years). All pre- and postoperative recordings were done while patients were in the off-drug state for at least 8 hours. The regular pre-operative levodopa equivalence of PD patients was calculated according to Krack (Table 1 (Krack, et al., 1998)).

Clinical rating was performed before and after surgery without medication and with stimulation off, using the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores and the modified Hoehn and Yahr (H & Y) scale for PD; the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) and the Global Dystonia Rating Scale (GDS) were used for dystonic patients. The study was approved by the ethics committee of the medical faculty of the Ludwig-Maximilian

University, Munich. All subjects gave their written informed consent prior to participation. Clinical information for PD and dystonic patients is given in Table 1.

2.2. Surgical intervention

DBS electrode implantation was performed according to good clinical practice and local center procedure guidelines, as reported previously (Bereznai, et al., 2002; Singh, Levin, Mehrkens, & Bötzel, 2011). Electrodes were implanted by MRI-guided stereotaxy in the STN for PD (model 3389, Medtronic Neurological Division, Minnesota, USA) and GPi for dystonia (model 3387, Medtronic). PD patients were operated on under local anesthesia and patients with dystonia under general anesthesia. Initial target coordinates were 20 mm lateral, 4 mm below and 3 mm anterior to the midpoint of the anterior and posterior commissures for dystonia and 11 mm lateral, 3 mm posterior and 3 mm below for the STN. These standard target coordinates were then adjusted based on individual anatomical MRI-landmarks (e.g. third ventricle/optical tract) if necessary. Microelectrode recordings (usually 3 tracks per side) were used to detect target-specific neuronal discharges. Correct electrode placement was verified for all cases by postoperative 1.5T MRI.

2.3. Experimental set-up

All tests were conducted preoperatively and on the first or second day after the implantation of DBS electrodes. We applied a test battery of arm, hand and finger movements as specified below. Subjects were seated in a comfortable chair with a backrest for tapping and pronation tasks and stood for boxing tasks. Tasks were performed with both sides sequentially for each task, if possible (see below). All tasks were first demonstrated by the investigator and a brief practice trial was performed to familiarize subjects with the tasks. No external pacing or starting cues were given. Subjects were instructed to perform the movements as fast as possible. In the PD group one subject could not perform any motor task with the left hand because of severe tremor,

in three patients with dystonia left-sided movements were not possible postoperatively due to i.v. catheters for antibiotics (Table 1).

2.3.1. Distal movements: finger tapping (FT), pronation-supination movements (PSM)

Fig. 1 (A & B) illustrates the experimental set-up for repetitive finger tapping (FT) and repetitive alternating forearm pronation and supination movements. Finger tapping was performed with the index finger against the thumb. Two ultrasound emitters were placed on the index finger and the thumb, and their distance was continuously monitored with an ultrasound measurement system (CMS20S, Zebris, Isny, Germany), which calculated three-dimensional spatial positions of ultrasonic markers (diameter: 10 mm), based on the transmission time of ultrasound pulses emitted from markers and received by the three microphones built into a sensor board. Spatial coordinates of the each marker were sampled with 50 Hz in three dimensions. Forearm pronation and supination movements (PSM) were performed with the subjects holding a cardboard tube in their fist (4 cm diameter, 15 cm length) with one ultrasound marker mounted on each end of the tube. Subjects were allowed to hold their hands in the most comfortable position; the ultrasound sensor board was then adjusted to reliably record the movements in that comfortable position (see Fig.1). FT and PSM tasks were each recorded for 25 seconds, starting 5 seconds after movement onset.

2.3.2. Proximal movements: ballistic arm movements (boxing) with touch (BT)

The experimental set-up is illustrated in Fig. 1 (C). Subjects executed repetitive fast ballistic boxing movements against a punching bag. Subjects were instructed to hit a designated area as fast as they could. Subjects stood at arm's length from the bag; before surgery some PD patients had to be seated in front of the bag. Patients performed 30-45 strokes with pauses after every 10 to 15 actions to prevent fatigue. A calibrated goniometer was used to record elbow joint position.

2.4 Data analysis and statistics

Data were analyzed off-line with MATLAB R2008b (The Mathworks, Lowell, MA, USA). From the three-dimensional datasets of the FT movements the distance between the two markers was calculated, and amplitude, frequency, and peak velocity of each individual movement were determined. We evaluated peak velocity only, since amplitude is a redundant parameter in this setting and frequency does not reflect bradykinesia (Keresztenyi, et al., 2007). For PSM, the three-dimensional data sets were transformed so that the variance was maximized in the x–y plane of rotation and minimized in the z-dimension (main axis transformation after eigenvector-determination). In this way, the plane of the microphones and the movement plane were aligned. Thereafter the angle between a line connecting the two markers and the horizontal was determined, and the angular amplitude, frequency, and peak velocity were calculated for each cycle. Peak angular velocity of the movements was used as the criterion for evaluation.

In the boxing task, the angular velocity of the elbow movements was computed for movements which exceeded a minimum angular velocity of 20deg/s.

Kinematic data were pooled for both arms of an individual (see table 1) after the exclusion of differences between the dominant versus non-dominant hand with the t-test (see Results).

Only for the analysis of fatigue all trials were analyzed. For pre- and postopertive velocity comparison, only the fastest 30% of all trials were taken. The mean was calculated from these data, resulting in one value per test for each subject and test session. Further statistical analyses were carried out with SPSS v18 (SPSS, Chicago, IL, USA). The differences between pre- and postoperative values were determined with an analysis of variance for repeated measures (ANOVA) and a general linear model of two-factor mixed design for each of the four motor tasks. Between-group variable factors were “PD” and “dystonia”; within-subject variables were

"pre-operative" and "post-operative". Non-spherical data was corrected for by the Greenhouse-Geisser method. A post-hoc paired t-test identified within-group differences between "pre-operative" and "post-operative". A percentage change in mean (angular) velocities was calculated separately. An *alpha error* <0.05 was taken for statistically significant differences; error bars in the figures show the standard error of the mean.

3. Results

3.1. Clinical ratings pre-operatively and during MLE

PD patients improved significantly in motor UPDRS score and H & Y scale (during the off-medication and off-stimulation state) compared to before surgery (mean improvement - motor UPDRS: -39.0 % $p < 0.001$, paired t-test; H & Y scale: -38.8 % $p < 0.001$), as did dystonia patients in both TWSTRS and GDS (mean improvement - TWSTRS -41.1 % $p < 0.004$, paired t-test; GDS: -36.6 % $p < 0.001$).

3.2. Dominant versus non-dominant arm

There was no significant difference in mean (angular) velocity between both arms across all four motor tasks (each $p > 0.05$), in accordance with another study (Dafotakis, et al., 2008). Therefore, data from both arms was pooled for further analysis.

3.3. Finger tapping (FT)

ANOVA revealed a significant effect of interaction between pre- and post-operative performance and group ($F(1,26) = 7.36$; $p = 0.012$). Effects of group and pre- and post-operative performance within-group were not significant (group effect: $F(1,26) = 0.013$; $p = 0.91$; pre- versus post-operative within group: $F(1,26) = 0.028$; $p = 0.87$).

Paired t-tests revealed a significant postoperative decrease of velocity by 31% in the dystonic group (t(14) = 3.08; p = 0.008), whereas finger tapping velocity in PD patients increased postoperatively by 51% (t(12) = -1.5; p = 0.16) (Fig. 2 A).

3.4. Pronation-supination movement (PSM)

ANOVA of PSM peak angular velocity showed significant effects of the factor group (F(1,26) = 21.56; p = 0.001) and interaction between group vs. within-group (F(1,26) = 17.20; p = 0.001). No significant effects were seen for the within-group factor by itself (F(1,26) = 2.73; p = 0.11). The paired t-test revealed a significant increase in angular velocity for PD patients (t(12) = -2.45; p = 0.03, 22.78%) and a significant decrease in dystonia (t(14) = 3.54; p = 0.003, -26.07%) (Fig. 2 B).

3.5. Boxing with touch (BT)

ANOVA results revealed significant differences between groups and significant effects of interaction (group: F(1,26) = 22.36; p = 0.001; group*within-group interaction: F(1,26) = 9.74; p = 0.004). No significant differences were observed for the within-group factor by itself (F(1,26) = 2.71; p = 0.11). PD patients were significantly faster after DBS surgery (t(12) = -2.20; p = 0.04, 25.82 %), while dystonic subjects performed this task with significantly lower angular speed after surgery (t(14) = 2.70; p = 0.017, -28.97 %) (Fig. 2 C).

3.6. Fatigue effects

To check whether there was an effect of fatigue during the tasks, a quotient of fatigue (QF) was calculated from the mean velocities of the last 30% versus the first 30% of all trials. Fatigue effects could be observed in the FT and PSM tasks, which were performed without pauses. QF

improved after surgery in both PD and dystonia, although only to a minor extent ($p > 0.05$) (Fig. 3).

4. Discussion

In this study, we investigated the MLE after the insertion of DBS electrodes in patients with PD and dystonia. While both groups showed a significant improvement of their clinical scores after electrode implantation (i.e. improvement of symptoms) without stimulation and thus caused by the MLE, movement velocity as investigated in our tests was unexpectedly reduced in dystonia but increased (as expected) in PD. This has several implications for the mechanism by which the basal ganglia influence movement.

4.1. MLE and DBS apparently have the same effect on clinical scores

We could confirm the observations made by others (Cersosimo, et al., 2008; Derrey, et al., 2010) that electrode implantation can cause partial symptomatic relief in dystonia. We assume that the implantation mimics (or acts like) thermocoagulation which has been used in the last century for the treatment of dystonia (Cooper, 1976; Lozano, et al., 1997). The time course of MLE-induced improvement was not investigated further but one study suggests that MLE may last up to 3 months (Deuschl, Herzog, et al., 2006; Granziera, et al., 2008). The immediate symptomatic improvement may be seen as contradicting several reports in which a sustained clinical improvement was only seen months after GPi DBS for dystonia (Kupsch, et al., 2006; Vidailhet, et al., 2005). However, in our clinical experience improvement usually begins within the first two weeks after initiation of stimulation but the final result may be delayed by the resolution of contractures of joints and ligaments (unpublished observations). Similarly, our PD patients showed a clear improvement of bradykinesia and rigidity during the MLE period (Cersosimo, et al., 2009; Maltete, et al., 2008). This is not surprising since a subthalamotomy can improve

parkinsonism (Obeso, et al., 2009) and a lesion of the STN can induce hemiballism in otherwise healthy individuals. With regard to the clinical data, these once more confirm that lesions and high-frequency stimulation of the basal ganglia can induce the same clinical effect, namely amelioration of symptoms.

4.2. Lesions of GPi and STN have opposite effects on movement velocity

The unambiguous finding that the group of dystonic patients showed reduced movement velocity after electrode implantation is our main result and has not yet been reported in this form. Proximal (boxing) and distal movements (finger tapping and pronation/supination) were equally affected. This finding is in line with reports that symptoms of bradykinesia have been reported by patients after GPi stimulation for treatment of dystonia (Berman, Starr, Marks, & Ostrem, 2009). The latter authors reported the results of a questionnaire aimed at detecting symptoms of bradykinesia and found that handwriting was the most frequently affected motor function. Furthermore, they found a tendency for higher ratings of the bradykinesia questionnaire score to be associated with more benefit from the treatment. On the other hand, pallidotomy in PD increases the speed of arm movements (Kimber, et al., 1999) and GPi stimulation is applied to reduce parkinsonian symptoms (Follett, et al., 2010; Schenk, Baur, Steude, & Bötzel, 2003). This contradiction is most likely explained by the anatomical proximity of GPi and globus pallidus externum (GPe) which have opposite functions in the basal ganglia circuitry: GPe has inhibitory connections to STN and its stimulation or lesion may lead to increased activity of the STN, thereby increasing movement. GPi mediates the output of the STN and a lesion can inhibit movement, as seen in our study or in the results of the questionnaire of Berman et al (Berman, et al., 2009). Confirmatory data come from a study in which different contacts of the multipolar DBS implanted into the GPi of PD patients were stimulated (Krack, et al., 1998). In this study the

authors could induce severe akinesia and a complete arrest of levodopa-induced dyskinesias by stimulation of the lowest contacts, whereas stimulation of the upper contacts (at the border between GPi and GPe) led to a moderate improvement of off-drug akinesia and could also induce dyskinesias in some patients. Surprisingly, the effect of fatigue was slightly reduced postoperatively in both groups, albeit not significantly. This may be interpreted as an interesting double dissociation between fatigue and movement parameters in both groups. However, an effect of training cannot be excluded. The following consequences arise from our findings: the MLE changes motor parameters of PD and dystonic patients. Recordings from stimulation electrodes during this phase undertaken to gain insight into basal ganglia physiology must account for altered movement parameters as well as local edema. Ideally these recordings should be done at least a week after the implantation; however this is in conflict with clinical and safety requirements.

4.3. GPi-DBS in dystonia works by introducing bradykinesia

There is increasing evidence that GPi lesions (as investigated in this study) and GPi stimulation cause bradykinesia (Berman, et al., 2009). This may be achieved by silencing aberrant discharge patterns of GPi neurons which are associated with pathophysiological oscillatory activity in the 3-10 Hz frequency band (Gatev, Darbin, & Wichmann, 2006). It seems conceivable that this is the main mechanism by which dystonic symptoms are reduced during stimulation. This question needs to be clarified in the future since some bradykinetic symptoms can cause severe disability (unpublished observations). Changes of stimulation frequency may offer a chance to alleviate dystonia without bradykinetic side effects but this has not yet been investigated. Age, type of dystonia and pre-operative movement parameters may be crucial as predictors for postoperative bradykinesia.

In conclusion, microlesions of the STN can accelerate movement in PD and lesions of the GPi can inhibit excessive movements in dystonia. Since these two movement disorders are at opposite ends of the spectrum, these opposite effects are therapeutic. However, it should be noted that not only excessive, but also normal movement is affected by microlesions and, in the case of dystonia, probably also by stimulation.

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Figure captions

Fig. 1. Schematic representation of experimental setup. (A) FT: finger tapping motor task (B) PSM: forearm pronation and supination movement task (C) BT: ballistic movement (boxing) with touch.

Fig. 2. Illustration of the mean (angular) velocity of executed (A) finger tapping (B) pronation and supination movement (C) ballistic movement with touch motor tasks before and after the insertion of electrodes in PD and dystonic patients. PD: Parkinson's disease; Dys: dystonia. Note the significant effect (paired t-test, $*p < 0.05$) between pre-operative and post-operative motor performance.

Fig.3. Histograms of quotient of fatigue (QF) in PD and dystonia pre- and postoperatively during finger tapping (FT) and pronation and supination movement (PSM) tasks. Mean value of QF shows the improvement (not significant) in fatigue after the basal ganglia lesion.

Table 1

Clinical details of PD and dystonic patients

Parkinson's Disease						Dystonia					
Case/ Gender	Age (years)	Disease duration (years)	Pre/post-op motor UPDRS scales	Pre/post-op H&Y staging	Pre-op Levodopa equivalent (mg/day)	Case/ Gender	Age (years)	Disease duration (years)	Pre/post-op TWSTRS scales	Pre/post-op GDS scales	Pre-op medication (daily dose)
1/M	56	12	25/9	3.5/1.5	1050	1/M	66	6	20/12	35/24	No medication
2/M	59	8	26/10	3.5/1.5	1630	2/F	63	13	38/16	20/10	No medication
3/M	69	10	16/11	2/1.5	980	3/M	30	18	6/4	15/8	Diazepam 5 mg
4/M	67	8	40/29	4/3	1400	4/M	40	8	10/7	17/10	No medication
5/M	57	8	14/10	3.5/1.5	1000	5/F	52	11	23/11	10/4	No medication
6/M	63	18	25/18	3/2	1100	6/M	50	34	16/7	18/13	No medication
7/F*	57	20	36/24	5/4	1620	7/M*	57	7	25/16	21/8	No medication
						8/F*	30	15	18/13	35/30	Tetrabenazine 25 mg
						9/M*	59	8	24/20	12/9	No medication

*Subject executed motor tasks only with right hand while other subjects performed with both hands.

M = male; F = female; UPDRS = Unified Parkinsons's Disease Rating Scale; H & Y = Hoehn and Yahr staging;

TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; GDS = Global Dystonia Rating Scale

All scalings were assessed during off-medication and off-DBS state.

Figure 1

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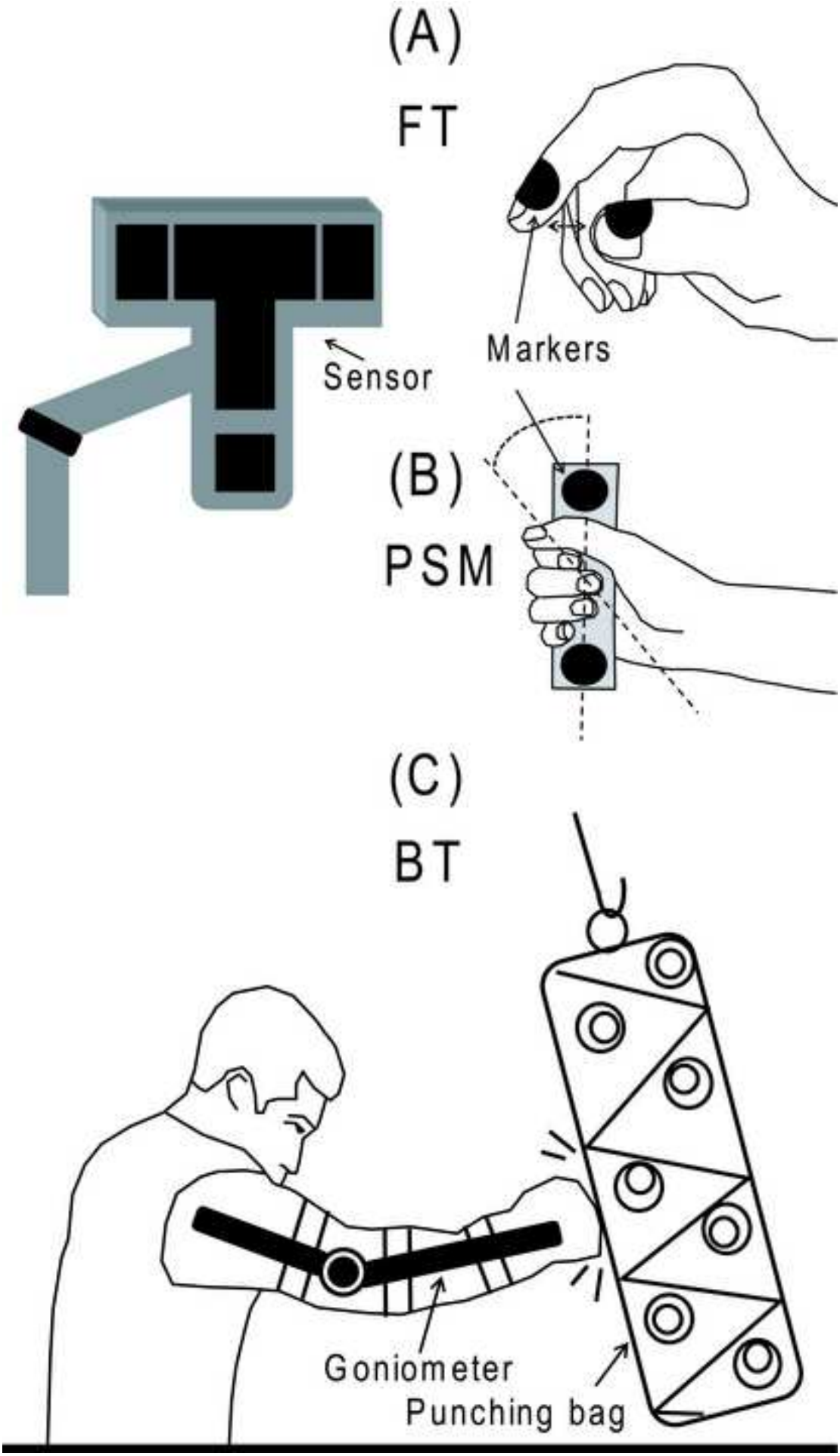

Figure 2

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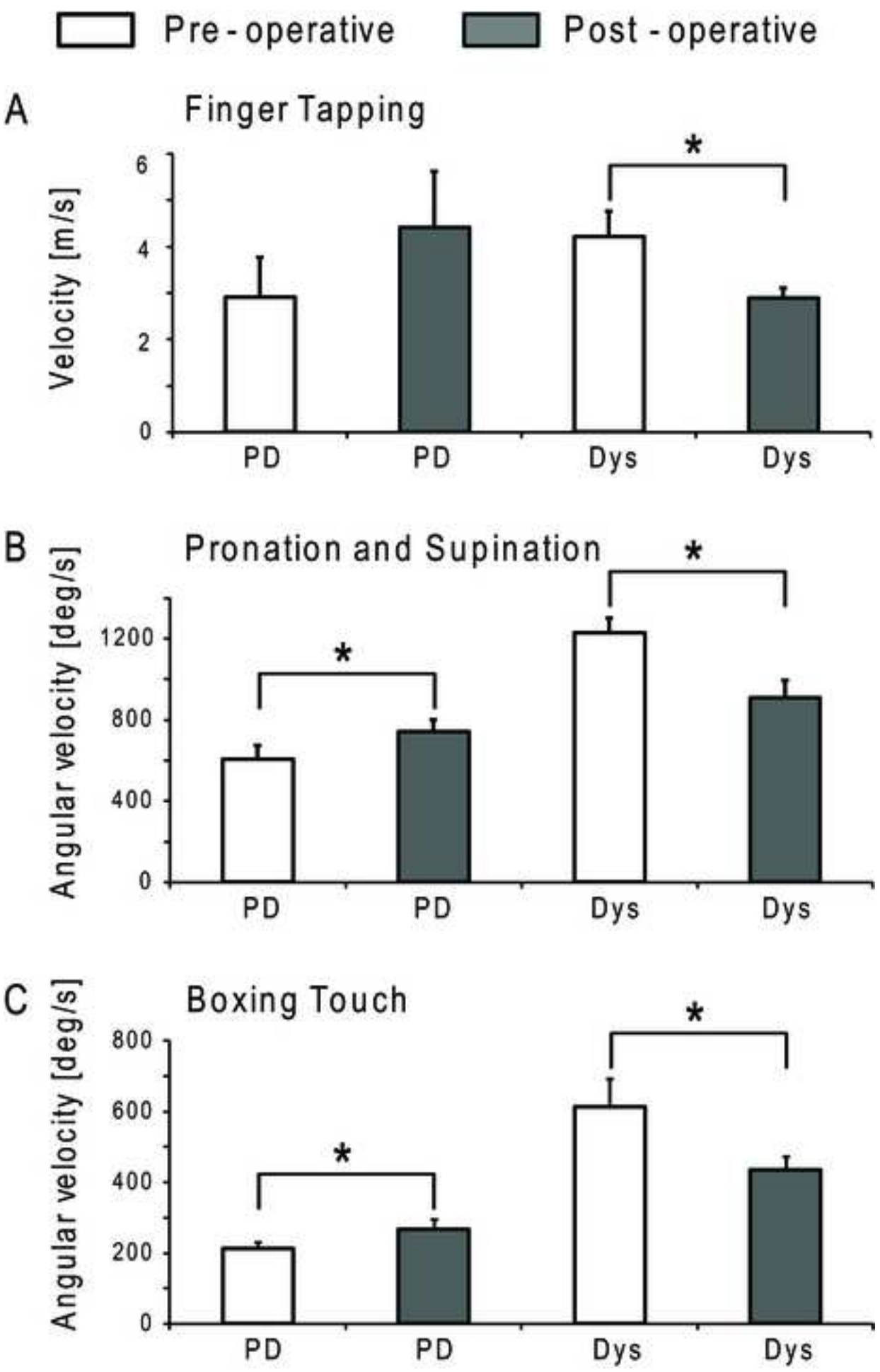

Figure 3

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