# ENHANCING MOTOR PERFORMANCE IN THE HEALTHY AND PARKINSONIAN BRAIN:

# ADAPTATION, OSCILLATIONS, AND ELECTRICAL STIMULATION


*A thesis submitted for the degree of*
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This thesis is dedicated to my mother, Rima Joundi

This could not have been possible without your unending love and support

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*Raed Joundi, Magdalen College, Oxford University*
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**-Abstract-**

Parkinson's disease (PD) is characterized by debilitating impairments in motor control arising from pathophysiological alterations in basal ganglia circuitry and function. In this research thesis two main approaches, namely electrical recording and stimulation, are combined in order to better understand motor performance in Parkinson's disease and ways it might be improved. Three main types of motor behaviors are studied: discrete ballistic movement, repetitive movement, and motor adaptation.

- First, deep brain stimulation (DBS) of the subthalamic nucleus (STN) was shown to improve the velocity of discrete, ballistic movements in PD. The neural correlates of ballistic movements were then studied by recording from the STN of PD patients, revealing onset of beta-range desynchronization prior to, and gamma-range frequency synchronization during, performance activity of fast arm reaches. To determine a causal role for these oscillatory frequencies in motor behavior, the motor cortex of healthy humans was stimulated at either beta or gamma frequency during a 'go/no-go' grip force task. Beta stimulation resulted in slower force generation on 'go' trials but

enhanced inhibition during 'no-go' trials, whereas gamma stimulation resulted in faster force generation on 'go' trials.

- Second, STN DBS resulted in improved repetitive tapping performance in PD patients through a reduction in variability. Recordings from the STN demonstrated that repetitive movement was accompanied by a substantial and persistent suppression of beta oscillatory activity.
- Third, Parkinson's patients were tested on a motor adaptation task, revealing intact learning but impaired retention of a visuomotor rotation. Application of direct current stimulation of the motor cortex resulted in enhanced adaptation during both learning and retention in PD patients and healthy controls.
- These results causally implicate the basal ganglia and oscillatory activity in motor control, provide insight into the neuronal mechanisms of motor performance and adaptation, and demonstrate promising new avenues for enhancing motor control in Parkinson's disease.

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## II. ABBREVIATIONS

| | |
|---|---|
| ANOVA | Analysis of Variance |
| AC-PC | Anterior commissure – Posterior commissure |
| BG | Basal ganglia |
| CT | Computed tomography |
| CMpf | Centromedian and parafascicularis |
| D1 | D1 striatal dopamine receptor |
| D2 | D2 striatal dopamine receptor |
| DBS | Deep brain stimulation |
| DLPFC | Dorsolateral prefrontal cortex |
| EEG | Electroencephalography |
| FMR | Frequency of maximal rebound |
| FMS | Frequency of maximal synchronization |
| FSR | Force-sensitive resistor |
| GPe | Globus Pallidus externus |
| GPi | Globus Pallidus internus |
| HC | Healthy control |
| HFS | High-frequency stimulation |
| Hz | Hertz |
| IRI | Inter-response interval |
| ISI | Inter-stimulus interval |
| ITI | Inter-tap interval |
| L-DOPA | Levodopa |
| LFP | Local field potential |
| M1 | Primary motor cortex |
| MCP | Metacarpophalangeal joint |
| MEG | Magnetoencephalography |
| MPTP | 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine |

| | |
|---|---|
| MRI | Magnetic resonance imaging |
| mg | Milligrams |
| mm | Millimetres |
| ms | Milliseconds |
| OFC | Orbitofrontal cortex |
| PCA | Principal components analysis |
| PD | Parkinson’s disease |
| PET | Positron emission tomography |
| PMC | Premotor cortex |
| PPN | Pedunculopontine nucleus |
| REC | Research ethics committee |
| rTMS | Repetitive transcranial magnetic stimulation |
| S1 | Primary somatosensory cortex |
| SD | Standard deviation |
| SE | Standard error |
| SEM | Standard error of the mean |
| SMA | Supplementary motor area |
| SNpr | Substantia nigra pars reticulata |
| SNpc | Substantia nigra pars compacta |
| STN | Subthalamic nucleus |
| STNr | Subthalamic nucleus region |
| TDCS | Transcranial direct current stimulation |
| TACS | Transcranial alternating current stimulation |
| TMS | Transcranial magnetic stimulation |
| UPDRS | United Parkinson’s disease rating scale |
| VOR | Vestibulo-ocular reflex |

## III. PUBLICATIONS AND ABSTRACTS

**Papers accepted for publication – incorporated in thesis**

**Joundi RA,** Brittain JS, Punt TD, Green AL, Jenkinson N, Aziz TZ. Stimulation of the subthalamic nucleus improves velocity of ballistic movements in Parkinson's disease. *Neuroreport – incorporated as Chapter 2*

**Joundi RA,** Brittain JS, Green AL, Aziz TZ, Brown P, Jenkinson N. Oscillatory activity in the subthalamic nucleus during arm reaching in Parkinson's disease. *Experimental Neurology* – incorporated as Chapter 3

**Joundi RA,** Jenkinson N, Brittain JS, Aziz TZ, Brown P. Driving Oscillatory activity in the human cortex enhances motor performance. *Current Biology. – incorporated as Chapter 4*

**Joundi RA,** Brittain JS, Green AL, Aziz TZ, Jenkinson N. High-frequency stimulation of the subthalamic nucleus selectively decreases central variance of rhythmic finger tapping in Parkinson's disease. *Neuropsychologia. – incorporated as chapter 5*

**Joundi RA,** Brittain JS, Green AL, Aziz TZ, Brown P, Jenkinson N. Persistent suppression of subthalamic beta-band activity during rhythmic finger tapping in Parkinson's disease. *Clinical Neurophysiology – incorporated as Chapter 6*

**Papers accepted for publication – not incorporated in thesis**

**Joundi RA**, Alonso V, Lago A, Brittain JS, del Olmo M, Brown P, Jenkinson N, Cheeran B. Effect of BDNF val/met polymorphism on visuomotor adaptation. *Experimental Brain Research – See Appendix*

**Joundi RA,** Brittain JS, Jenkinson N, Green AL, Aziz TZ. Rapid tremor frequency assessment with the iPhone accelerometer. *Parkinsonism and Related Disorders – see Appendix*

Little S, **Joundi RA**, Tan H, Green AL, Aziz TZ, Brown P. Low-Frequency stimulation of the subthalamic nucleus increases rigidity in Parkinson's disease. *Experiment Brain Research*

Brittain JS, Watkins K, **Joundi RA**, Ray N, Green AL, Aziz TZ, Jenkinson N. A role for the subthalamic nucleus in response inhibition during conflict. *Journal of Neuroscience.*

Ray NJ, Brittain JS, Holland P, **Joundi RA**, Stein JF, Aziz TZ, Jenkinson N. The role of the subthalamic nucleus in response inhibition: evidence from local field potential recordings in the human subthalamic nucleus. *Neuroimage*

Brittain JS, Jenkinson N, Holland P, **Joundi RA**, Green AL, Aziz TZ. Development of Holmes' tremor following hemi-cerebellar infarction. *Movement Disorders*

## Papers under review

**Joundi RA**, Brittain JS, Bogdanovic M, Aziz TZ, Brown P, Jenkinson N. Impaired motor memory retention and interference in Parkinson's disease. – *incorporated as Chapter 7*

## Conference abstracts

**Joundi RA,** Jenkinson N, Brittain JS, Aziz TZ, Brown P. Frequency-specific effects of transcranial alternating current stimulation on motor performance in healthy humans. *Nuffield Department of Clinical Neurosciences, Inaugural Symposium, 23rd November 2011 - Poster*

**Joundi RA**, Brittain JS, Bogdanovic M, Aziz TZ, Brown P, Jenkinson N. Motor adaptation, retention, and interference in Parkinson's disease. *16th International Congress of Parkinson's disease and Movement Disorders, Dublin, Ireland, June 17-21, 2012 – Poster*

**Joundi RA**, Brittain JS, Bogdanovic M, Aziz TZ, Brown P, Jenkinson N. Impaired motor adaptation retention in Parkinson's disease, improved with cortical stimulation. *Neural Control of Movement Annual Conference, Venice, Italy, April 23-28, 2012 – Oral presentation*

## IV. TABLE OF CONTENTS

# 1. INTRODUCTION:

# PARKINSON'S DISEASE, THE BASAL GANGLIA, AND MOTOR CONTROL

## 1.1 PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The overall incidence of PD in the general population is 13.4 per 100,000, which increases dramatically over the age of 60 and is higher for men than women (Van Den Eeden et al. 2003). The first detailed description of Parkinson's disease was written by James Parkinson in 1817 in a paper entitled 'An Essay on the Shaking Palsy'. PD is associated with four main cardinal symptoms – bradykinesia (slowness of movement), akinesia (difficulty initiating movement), resting tremor, and postural instability (Hughes et al. 1992).

Several stages of degeneration have been identified in PD, progressing from olfactory and vagal nuclei, to the substantia nigra, and finally to the cortex (Braak et al. 2003). However, the substantia nigra and basal ganglia remain the foremost areas of degeneration and contributors to symptomatology. The primary pathology in PD is the degeneration of dopamine-containing neurones in the substantia nigra pars compacta (SNpc), thereby depriving the striatum from dopaminergic input and resulting in widespread aberrant activity in the basal ganglia. A common feature in PD seen at autopsy is the presence of large amount of alpha-synuclein collections. Alpha-synuclein is an otherwise normal protein that undergoes a conformational change and

becomes insoluble, thereby aggregating in large amounts (Spillantini et al. 1998). These deposits are termed Lewy bodies (Lewy, 1912) – and are thought to ultimately contribute to the degeneration and death of neurones.

The causes of the degeneration are yet unknown. The largest risk factor is age (de Rijk et al. 1995). Many genes have been identified as conferring higher susceptibility to acquiring PD, although the contribution is small (Lees, et al., 2009). Lastly, other risk factors such as organophosphate exposure have been identified (Lees et al., 2009). Such chemical environmental risk was further supported by the induction of parkinsonian state in a cohort of intravenous drug users in San Franscisco who accidentally synthesized and injected MPTP (1-4-phenyl-1,2,3,6-tetrahydropyridine). This led to parkinsonian-like symptoms and degeneration of the substantia nigra on autopsy (Langston et al. 1983). MPTP was subsequently used experimentally in primate models to simulate and study PD (Burns et al., 1983; Bergman et al.; 1990, Aziz et al., 1991).

The main treatment for PD is dopamine replacement therapy (Birkmayer & Hornykiewicz, 1961). For many individuals this dramatically ameliorates the motor symptoms of bradykinsia and akinesia, although tremor, gait freezing, and postural instability are less responsive (Bloem 1992; Hughes et al. 1993). Spurred by success in animal models (Bergman et al., 1990; Aziz et al., 1991; Wichmann et al., 1994), lesioning of the subthalamic nucleus (STN) and globus pallidus internus (GPi) were shown to ameliorate motor signs in PD (Alvarez et al., 2009). More recently, deep brain stimulation of

the STN and GPi has emerged as a therapeutic option for individuals with dopamine-induced motor fluctuations, tremor, or reduction in effectiveness of dopamine agonists over time (Deuschl et al. 2006). Figure 1.1 shows an example of a patient with implanted electrodes in the STN, as well as the typical electrode model. Both dopaminergic therapy and deep brain stimulation are thought to regularize aberrant activity in the pathological basal ganglia, which will be explored further in the following sections. As PD is a basal ganglia disorder, knowledge of BG anatomy, physiology, and pathophysiology has contributed a great deal to our understanding and approach to the disorder.

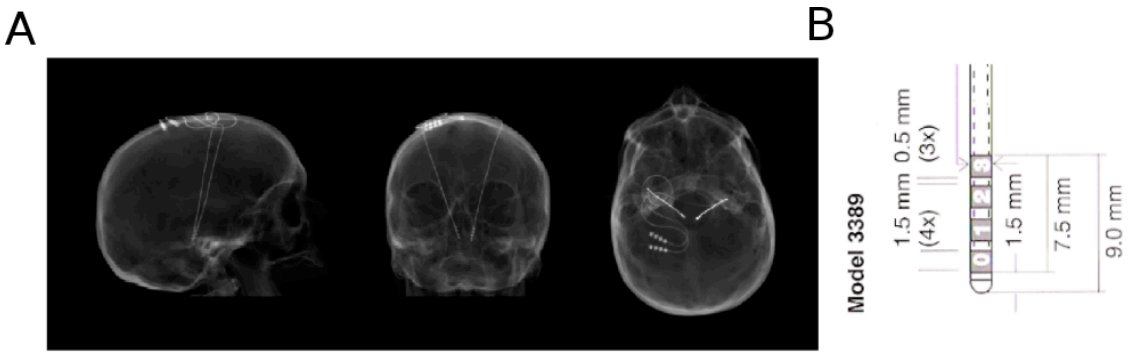


**Figure. 1.1.** Deep brain stimulation. A) X-ray of patient with implanted electrodes in the subthalamic nucleus. B) Typical electrode measurements.

## 1.2 MODELS OF BASAL GANGLIA PATHOPHYSIOLOGY

### 1.2.1 Rate model

*1.2.1.1 Characteristics*

The basal ganglia comprise a highly interconnected network of nuclei that serve a variety of functions (Alexander et al., 1990). This network includes

the striatum (subdivided into the caudate and putamen), subthalamic nucleus (STN), globus pallidus internus (GPi), globus pallidus externus (GPe), and substantia nigra (subdivided into the substantia nigra par compacta (SNpc) and substantia nigra pars reticulata (SNpr)).

The basal ganglia is thought to be involved with several segregated cortico-basal ganglia-thalamo-cortical circuits: motor, oculomotor, limbic, dorsolateral prefrontal and lateral-orbitofrontal (Alexander et al., 1990). In the case of the motor circuit, an early model of the BG and related nuclei was formed by Roger Albin and Marlon DeLong (Albin et al., 1989; DeLong 1990). They used anatomical, physiological, and neuropharmacological evidence to describe the basic set of dynamic interconnections within the nuclei of the basal ganglia. In this model, modifications in firing rate between these nuclei dictate the motor state. This general model can be sub-divided into three main pathways: The direct pathway, indirect pathway and hyperdirect pathway.

The direct pathway comprises excitatory (glutamatergic) connections from the cortex to the striatum, followed by inhibitory connections from the striatum to the BG output nuclei (GPi/SNpr), and from GPi/SNpr to the thalamus. The thalamus in turn excites the primary motor cortex. Thus, an increase in firing rate in the striatum would inhibit the GPi/SNpr, which would disinhibit the thalamus, thereby promoting activation of the cortex and facilitation of movement.

In contrast, the indirect pathway has a more complex route. Here again, the cortex projects to the striatum. Then, the striatum sends inhibitory projections to the GPe, which in turn inhibits STN, and finally the STN excites the GPi/SNpr complex. The output at this point is similar to the direct pathway, with inhibitory connections from the GPi/SNpr to the thalamus. Thus, more activity in the indirect pathway would result in disinhibition of the GPi/SNpr complex. This would ultimately inhibit the thalamus, thereby suppressing motor output.

Lastly, there is also a postulated 'hyperdirect' pathway, which bypasses the striatum and provides strong excitatory input from motor-related cortical areas to the pallidum and STN. A possible mechanism for movement might involve constant inhibition of motor areas in the thalamus and cortex through the indirect and hyperdirect pathway, followed by release of selected programs through the excitatory cortico-striato-pallidal direct pathway (Nambu et al., 2002).

In this model, the first two pathways - direct and indirect - are thought to be functionally segregated and differentially modulated by dopamine. Both pathways receive input from the cortex via the striatum; the striatum is modulated by dopaminergic projections from the SNpc. The striatum contains both D1 and D2 dopamine receptors; activation of D1 receptors promotes activity in the direct pathway, whereas activation of D2 receptors inhibits the indirect pathway (see Figure 1.1).

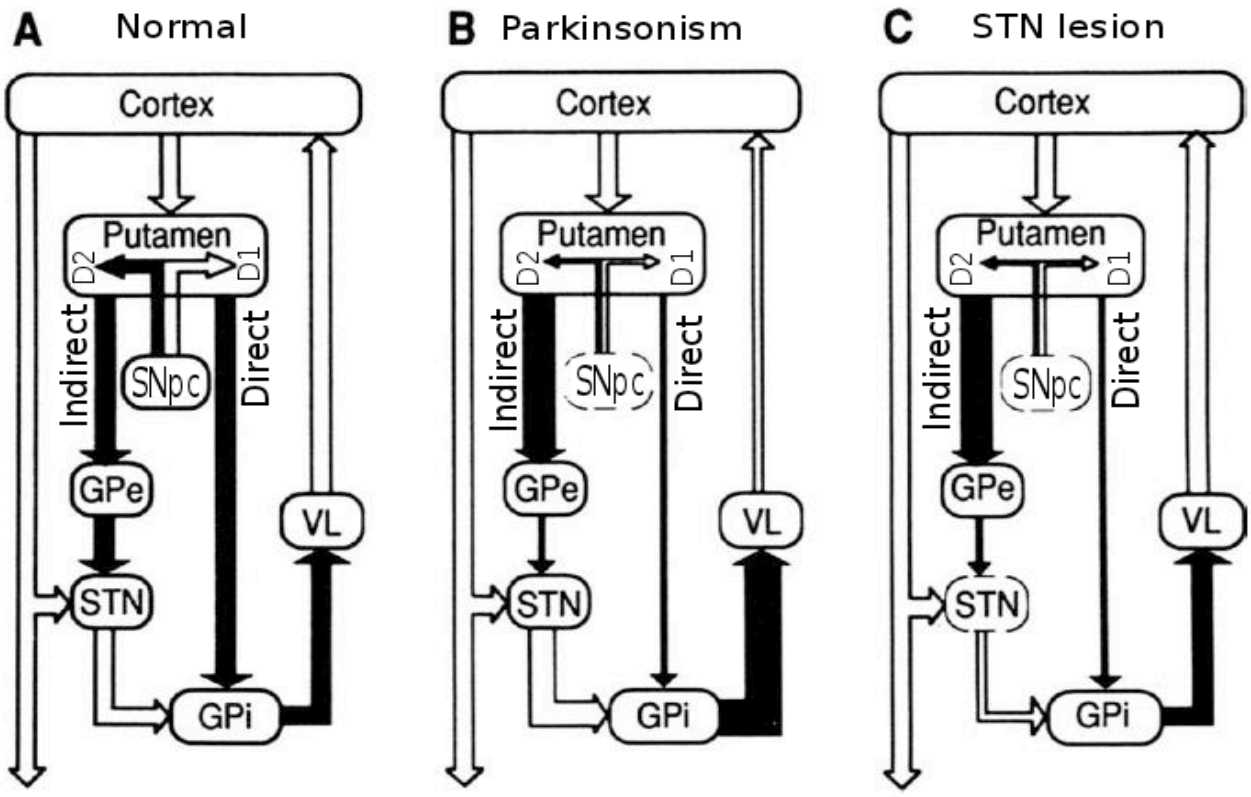


**Figure. 1.2.** The 'rate model' of basal ganglia-thalamocortical motor ciruitry, containing excitatory (open arrows) and inhibitory (filled arrows) connections (A). Dotted lines represent lesioned nuclei and width of arrows represent firing rate. In the parkinsonian state, there is damage to the SNpc and thus decreased dopaminergic input to the putamen. This causes decreased direct pathway activity, and increased indirect pathway activity, resulting in an overly inhibited cortex (B). Inactivation of the STN reduces the inhibition from GPi to ventrolateral thalamus (VL) towards more normal levels, alleviating parkinsonian motor signs(C). (adapted from Bergman et al., 1990)

*1.2.1.2 Relevance of rate model to PD*

With the arrival of the primate MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model, electrophysiological and lesional studies could be carried out in the parkinsonian state. MPTP causes destruction of dopaminergic neurones in the SNpc, resulting in a loss of input to the dopamine receptors in the striatum, thereby increasing inhibitory activity from the putamen to the GPe, and decreasing activity from the putamen to the GPi. As a result, spontaneous firing rates increase in GPi and decrease in GPe, consistent with the rate model of parkinsonism (see below; Miller and DeLong, 1988; Filion and Tremblay, 1991; Bergman et al., 1994; Boraud et al., 1998; Wichmann and DeLong, 2003). In addition bursting and mean variability of firing rate increases with MPTP (Filion and Tremblay, 1991; Filion et al., 1991). The existence of bursting in the MPTP model points to functional changes in activity other than simple alteration in firing rates.

Such drug-induced modifications in BG physiology motivated an interventional approach to studying the function of BG nuclei. In line with this, injection of muscimol (inhibitory GABA agonist) in the STN of MPTP monkeys improved symptoms but also resulted in contralateral dyskinesia (Wichmann et al., 1994). Moreover, STN lesions were found to partially relieve akinesia, rigidity, and tremor, thus implicating this nucleus in both negative and positive parkinsonian symptoms (Burns et al., 1983; Aziz et al., 1991). This was followed up by GABA agonist injections in the STN of PD patients (Levy et al., 2001), which also relieved symptoms. Lastly, high

frequency electrical stimulation (>100 Hz) in normal monkeys induced contralateral dyskenias resembling hemiballismus in humans. This suggested that stimulation reversibly incapacitates the STN and disinhibits the thalamo-cortical pathways, resulting in emergence of involuntary movements (Beurrier et al., 1997). Accordingly, electrical stimulation of the STN showed reversible improvements in the parkinsonian state in the primate (Benazzouz et al., 1993) and human (Limousin et al., 1995).

The model provides an attractive perspective from which to view the pathophysiology of PD. PD is predominantly thought to be caused by degeneration of dopaminergic neurones in the SNpc. This decreases net dopamine input into the striatum. Under conditions of low dopamine, both D1 and D2 receptors would be deprived of stimulation. Thus, there would be a decrease in excitation of the direct pathway, and a decrease in the disinhibition of the indirect pathway. Together, this would increase inhibition of the thalamus and thus decrease activation of the motor cortex. This has formed a basis by which to explain the bradykinesia and akinesia in PD (Galvan and Wichmann, 2008). As well, the presumed overactivity of output nuclei following depletion of dopamine provided the rationale for lesioning the GPi as a treatment for PD (Baron et al., 1996; Lang et al., 1999, 1999). The STN was then explored due its position upstream from the GPi, eventually resulting in DBS of the STN as a therapeutic intervention in PD (Krack et al., 2000).

*1.3.1.3 Criticism of rate model*

The Albin-Delong model has clearly been instrumental in defining research questions to further explore the function of the basal ganglia, and testing predictions in experimental and clinical settings. Nevertheless, however useful as a model, there are some inconsistencies that have emerged which refute some of these predictions and shed doubt on its absolute accuracy. Many experiments have not shown the predicted changes in rate of firing after dopamine depletion (Levy et al., 1997; Boraud et al., 1998; Raz et al., 2000). Modern histochemical techniques have revealed other contrasting evidence, such as co-localization of D1 and D2 receptors on striatal projection neurones (Aizman et al., 2000). Similarly, additional dopamine receptor subtypes have been revealed (Sealfon and Olanow, 2000) along with a more widely distributed pattern of connectivity between the basal ganglia nuclei than previously thought (Bolam et al., 2000; Wu et al., 2000). The STN has also been suggested to have a more important role in basal ganglia function. Reciprocal connections between the STN and GPe (rather than merely GPe to STN connections) have been shown to exist. Moreover, emphasis has been put on the STN as an input nucleus to the basal ganglia via direct connections from the cortex rather than just an relay nucleus (Mink, 1996; Nambu, 2005). Surgical lesions within the basal ganglia in humans intended to relieve the motor symptoms of PD have revealed a number of paradoxical findings. These include improvement of tremor and rigidity following thalamic lesions. Similarly, lesions of the GPi alleviate not just the hypokinetic (as predicted by the Albin-Delong model) but also the

hyperkinetic symptoms of Parkinson's disease (Lang et al., 1999; Lozano and Lang, 2001). Lastly, DBS of the STN is known to alleviate both akinesia and tremor, and thus may have functions beyond a passive relay nucleus in the indirect pathway.

Additional evidence contrary to Albin-Delong model predictions arise from the effects of L-Dopa. Although L-dopa is the primary therapy for PD, its normalizing effect on firing rates seems limited. For example, one study found that dopamine therapy in the MPTP monkey did in fact reverse the pathologically decreased firing rate in the GPe, and increased GPi activity; Additionally, it restored the percentage of correlated neuronal pairs to near normal levels (Heimer et al., 2002). However on closer inspection, though dopamine seems to reverse some MPTP induced changes (neuronal rate, pattern, synchronization), it failed to restore the normal GPe/GPi balance; The GPi still demonstrated a significantly higher fraction of oscillatory cells, with a relatively higher power of oscillations than the GPe. This inability to restore the normal neuronal behaviour and balance of activity among the basal ganglia nuclei may underlie the limitations of dopamine therapy and result in drug-induced side effects (Heimer et al., 2006).

Moreover, lesions of the GPe in monkeys result in increased discharge rate in STN and GPi, similar to MPTP treatment, but does not induce bursting and has no behavioral effects (Soares et al., 2004). Thus, reduction of GPe activity in isolation does not result in parkinsonism. Taken together this suggests that altered discharge patterns and whole scale network changes

such as oscillatory synchrony might play an important role in producing the symptoms of PD (Soares et al., 2004). In summary, it is clear that there is more to the picture than the classic direct-indirect firing rate model.

### 1.2.2 Oscillatory synchrony model

Criticism to the rate model of basal ganglia, along with advances in recordings techniques, have altered traditional perspectives of basal ganglia function. Recordings of neuronal populations in the tens of thousands, as opposed to single units, have given additional insight into large-scale activity in the basal ganglia and motor system. In particular, oscillatory synchronization is increasingly being studied as a mechanism for physiological and pathophysiological activity in the motor system (Brown, 2003; Brown and Williams, 2005; Crone et al., 1998; Jenkinson and Brown, 2011). Neuronal populations are known to communicate and engage in higher-order processing through synchronous activity at particular frequencies (Singer, 1993; Fries, 2009). The earliest studies in cat showed that neurones in partially segregated columns in the visual cortex could synchronize their oscillatory responses, as a possible way to connect features in different parts of the visual field (Gray et al., 1989). These synchronous patterns are representative of repetitive and time-locked fluctuations in the firing rates of large numbers of underlying neurones, and can be recorded with the use of relatively large sensors, non-invasively in the cortex with magnetoencephalography (MEG) or electroencephalography (EEG), and invasively using cortical grids and depth electrodes. In the latter case, local

field potentials (LFPs) can be recorded from implanted electrodes, in particular from the basal ganglia and related nuclei of animals and patients with PD.

*1.2.2.1 Oscillations in the rat motor system*

In the normal state, the rat subthalamic nucleus displays low-frequency oscillatory activity, which is tightly correlated with 1 Hz slow wave activity in the cortex. Dopamine depletion with 6-OHDA in the rat increases the intensity of STN discharge and globus pallidus neurones also develop slow wave activity. Ipsilateral cortical ablation largely abolishes slow wave activity in the STN and globus pallidus, but some parts of the network still oscillate, showing that both cortical and basal ganglia processes are at play (Magill et al., 2001).

Sharott et al. (2005) showed that dopamine depletion in the rat can also preferentially causes synchronization of oscillations between STN and frontal cortex in the beta frequency band (15-30 Hz), which closely parallels the phenomenon in humans (see below). Administration of dopamine and spontaneous movement lead to a suppression of these oscillations and a small upward shift of the peak frequency of coherent beta activity (Sharott et al., 2005).

Chronic disruption of dopamine transmission was necessary for the emergence of pathological beta oscillations in rats. Beta oscillations are not exaggerated until >4 days after lesions, which is surprising as dopamine levels drop to under 20% within 1 hour of a mid-brain 6-OHDA injection. This

suggests that long-term plastic processes in the circuit rather than an acute response to dopamine loss is responsible, at least in part, for the genesis of increased beta oscillations (Mallet et al., 2008).

*1.2.2.2 Oscillations in the primate motor system*

In the primate, early studies showed oscillatory activity between 15 and 50 Hz in primary motor cortex and premotor areas, with oscillations observed infrequently during movement (Sanes and Donoghue, 1993). Likewise, LFP activity at 20-40Hz occurred most often during premovement periods, with a decrease in oscillatory power coinciding with motor action. These oscillations then might represent a global processes active in conjunction with motor planning, but not encoding the details of motor action (Donoghue et al., 1998).

Prominent 10-25 Hz (beta) oscillations characterize LFP activity across large areas of the striatum of normal awake monkeys (Donoghue et al., 1998). In the normal state, changes in beta frequencies may represent an internally-triggered process to prepare the upcoming movement. However, analysis of primary motor cortex and SMA EEG in the MPTP primate shows the emergence of heightened sub-beta and beta band oscillations. Moreover, there is decreased coherence and phase-locking of STN spiking to EEG in frequencies outside the beta band, such as the gamma frequency (Gatev and Wichmann, 2009). Pathological beta oscillation could therefore serve to increase the threshold for activating the basal ganglia system, thus making it difficult for motor signals to flow through, and resulting in akinesia (MacKay

and Mendonça, 1995).

Although oscillations are present in the normal state, the increased synchronized oscillations due to MPTP treatment or PD may restrict the flexibility of single neurone firing. Normally, neurones in the pallidum and STN respond to active arm movements and passive joint rotation, and neurones with similar functional response properties are clustered locally together (DeLong et al., 1985). Cells in the pallidum normally respond to movement about a single contralateral joint in one direction. In the MPTP primate, there is an increased number of neurones responding to movement in the GPi, and a loss of specificity among these neurones following MPTP treatment (Leblois et al., 2006). These data suggest that normal dopaminergic tone supports segregation of the functional subcircuits of the BG, and that BG dysfunction in PD results in the breakdown of independent processing within these subcircuits (Bergman et al., 1998). This implies that the development of parkinsonian symptoms is coincident with the loss of the ability of pallidal neurones to operate completely independently, so that common inputs become more dominant between the subcircuits (Nini et al., 1995). Dopamine therapy may improve symptoms by exerting a desynchronizing effect and reducing the correlation between striatal and pallidal neurones, thereby improving independent information transmission (Heimer et al., 2002).

Tremor-related pallidal oscillations at around 4-6 Hz can also be recorded after MPTP administration to some monkeys of the vervet genus (Raz et al.,

2000). The number of oscillatory neurones was increased in the monkey with more pronounced symptomatology, suggesting that oscillatory activity in the basal ganglia increases dramatically during parkinsonism and is related to the severity of symptoms (Raz et al., 2000). However, in one study, correlated activity in the GPi only increased late in a series of MPTP injections. It was only after the animals became severely bradykinetic, that synchronous oscillations were evident. This questions the causal relationship between synchronous oscillations in the pallidum and parkinsonian motor symptoms (Leblois et al., 2007).

*1.2.2.3 Oscillations in the human motor system and Parkinson's disease*

Jasper and Andrews first reported blocking of the precentral beta rhythm in human electrocorticograms during tactile stimulation in 1938. In 1949 Jasper and Andrews showed the same phenomenon during voluntary hand movement, demonstrating blocking of 25 Hz beta rhythm 1 sec before and after sustained movement, and in the preparation phase before a movement. Gastaut replicated these findings in 1952, and Pfurtscheller went on to demonstrate beta desynchronization in EEG during voluntary hand movement, occuring 2 seconds before movement onset. This beta desynchronization also occurred after median nerve stimulation (Pfurtscheller, 1981). Furthermore, 10 Hz event-related desynchronization 2 seconds prior to movement onset was found to coincide with a 40 Hz oscillation around movement onset (Pfurtscheller and Neuper, 1992).

Thus, this idea of the synchronization of brain waves has been in the literature for some time, especially observations of 8-30 Hz oscillations in mouse, monkey, and human sensorimotor cortices and subcortical areas (Jasper and Penfield 1949; Murthy and Fetz, 1992; Donoghue et al., 1998). The role of these synchronous oscillations is unclear, but one possible function is to promote synchronous neural firing between spatially separated but functionally related neuronal populations (Schwarz and Thier, 1999). The arrival of many synchronized action potentials at a common postsynaptic site may be more effective in exciting the receiving neurone than uncorrelated firing (Gray et al., 1989).

Recently, recordings have been obtained and analyzed from basal ganglia nuclei in patients who have undergone functional neurosurgery. Here, oscillatory activity is present across different frequency bands and nuclei. Levy et al. (2000) reported several rhythms recorded from the STN of PD patients with limb tremor; these included tremor cells with rhythmic activity at tremor frequency, cells with >10 Hz beta oscillations, and cells with both tremor and beta oscillations (Levy et al., 2000). This mirrored previous findings in the primate, which demonstrated GPi oscillations that were synchronized to tremor at 3-5 Hz in MPTP-treated vervet monkeys (Bergman et al., 1998b). However, not all tremor cells in the STN were coherent with each other, suggesting the possibility of several independent tremor-generating circuits in the basal ganglia.

In a study of STN LFPs and simultaneous scalp EEG, oscillations were observed in three major bands: 2-10 Hz, possibly related to the rest tremor, 10-30 Hz, with cortex leading basal ganglia, and 70-85 Hz, with STN leading cortex. The latter high-frequency band increased in power with the administration of L-dopa. Thus, the basal ganglia may receive <30 Hz input from the cortex, and with increased dopaminergic tone, in turn drive the cortex at higher frequencies (Williams et al., 2005).

It was further shown that beta rhythms can be attenuated with L-dopa therapy in PD, and that this effect correlates with improvement in bradykinesia (Brown and Marsden, 1999; Kühn et al., 2006b; Ray et al., 2008). Moreover, the onset of oscillation reduction in the 8-30 Hz band after a go cue and subsequent motor reaction time were correlated (Williams et al., 2005), supporting the idea that suppression of beta synchrony in the STN is related to processing required for motor preparation. The main function of this band then might be to promote an 'idling' population inactivity that would have to be overcome for movement to occur (Brown et al., 2004). This desynchronization is also tightly correlated with a relative increase in firing rates for cells associated with movement (Amirnovin et al., 2004). Beta desynchronization even occurs in response to motor imagery (Kühn et al., 2006a) and action observation (Marceglia et al., 2009), demonstrating its importance in feedforward organization of movement independent of sensory feedback.

Furthermore, levodopa therapy seems to increase the duration and magnitude of beta event-related desynchronisation immediately before and during movement (Doyle et al., 2005). Treatment with levodopa or movement also reduces the <30 Hz oscillations in the STN and replaces it with a new peak at approximately 70 Hz (Brown et al., 2001; Cassidy et al., 2002; Alegre et al., 2005). (See Figure 1.2). The attenuation of the beta might be a mechanism to allow more focal neuronal assembles to activate and drive task-specific processing (Courtemanche et al., 2003). Thus, dopamine and therapeutic stimulation of the STN may inhibit abnormal synchronization of basal ganglia nuclei at beta frequencies which would otherwise propagate throughout the circuit and result in deleterious BG output (Brown et al., 2004). Similarly, the increase and lateralization of gamma power in the STN after dopaminergic therapy may further contribute to a 'pro-kinetic' state (Androulidakis et al., 2007).

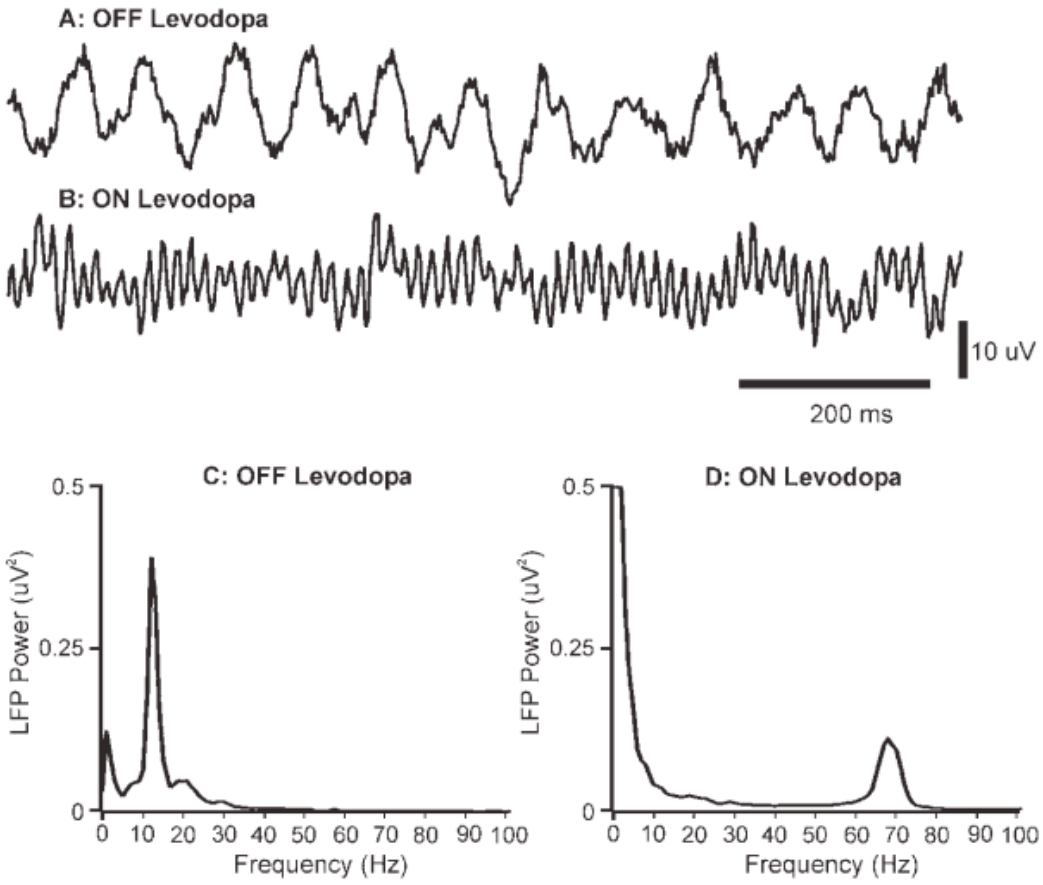


**Figure 1.3**. Local field potentials recorded from the subthalamic area of a patient with PD (A) Field potential signals recorded after overnight withdrawal of medication. Showing prominent low-frequency oscillations. (B) Field potential signals recorded after subsequent levodopa challenge, showing higher frequency oscillations. (C) Power spectrum of field potentials recorded after overnight withdrawal of medication, with a peak at around 13 Hz. (D) Power spectrum of field potential signals recorded after subsequent levodopa challenge, with emergence of a 70 Hz peak (Brown and Williams, 2005).

The emerging picture is that of exaggerated beta oscillations in the basal ganglia being strongly associated with motor symptomatology in PD (Weinberger et al., 2009). However, even in dystonic patients that are treated with tetrabenazine, which depletes dopamine in the brain, low beta power is increased (Kühn et al., 2008). Moreover, in a comparison of PD and essential tremor patients, oscillations within the alpha and beta bands were found only in PD patients, and there was a smaller proportion of gamma band oscillations in PD compared to ET (Steigerwald et al., 2008). The data reviewed here advances the general thesis that synchronization in the beta and gamma bands restricts and promotes movement processing, respectively.

## 1.3 GENERAL FUNCTIONS OF THE BASAL GANGLIA

The basal ganglia have been implicated in a wide variety of motor behaviors. The subsequent three sections provide an introduction to our present understanding of the basal ganglia's role in perhaps the three most widely suggested functions, namely:

- Movement initiation and generation,
- Motor timing and sequencing, and
- Motor learning

### 1.3.1 Movement initiation and generation

#### *1.3.1.1 Movement initiation and beta oscillations*

The basal ganglia have traditionally been heavily implicated with movement initiation, that is, processes that occur in the preparatory phase before movement onset. Evidence from single unit activity has been the main thrust behind this idea. Firing rate increases of pallidal, subthalamic, and motor cortical neurones in the primate precede EMG activity during a movement (Georgopoulos et al., 1983). Neurones in the GPi, STN, and SNpr can change their firing rate 100 ms before movement onset. Evidence supporting movement initiation is also born out on a population level. Beta oscillatory activity desynchronizes prior to and during movement, as seen in the cortex (Zhang et al., 2008; Muthukumaraswamy, 2010) and in the basal ganglia (Kühn et al., 2004; Doyle et al., 2005). This desynchronization can occur even up to 1-2 seconds prior to movement onset (Kühn et al., 2004; Klostermann et al., 2007).

#### *1.3.1.2 Movement generation and gamma oscillations*

Activity in the basal ganglia also reveals processes that occur during or even after movement. Single unit activity in the basal ganglia can scale with aspects such as direction, movement duration, amplitude, and speed (Georgopoulos et al., 1983; Mitchell et al., 1987; Turner and Anderson, 1997; Turner et al., 2003). In addition, when neurones in the motor regions of the GPi were inhibited, the velocity of arm movements was reduced in monkeys (Mink and Thach, 1991; Desmurget and Turner, 2008). Imaging

studies have also shown that activation in the basal ganglia is related to the velocity and amplitude of generated movement (Thobois et al., 2007; Grafton and Tunik, 2011). Taken together, this emphasizes a role for the basal ganglia not only in the pre-processing and initiation of movement, but also in the parameterization and driving of motor kinematics after movement onset.

Is there a correlate of this movement scaling within oscillatory synchronization? Initially, one theory related the basal ganglia to focused attention and grouping together of distributed neuronal responses – the mechanisms for such a process was suggested as gamma band synchronization (Brown and Marsden, 1998). Indeed, increases in the amplitude of higher frequency gamma band activity (60-90 Hz) have been associated with the onset and time course of movement (Muthukumaraswamy, 2010) in the motor cortex (Crone et al., 1998; Ball et al., 2008) and subcortical nuclei (Androulidakis et al., 2007; Kempf et al., 2009; Brücke et al., 2012).

Nevertheless, the functional relevance of gamma oscillations remains unclear. The change in gamma oscillations in relation to motor processing opens the possibility of such high-frequency activity having a direct role in the coding of movement parameters. However, much of the evidence is in the sensory, rather than motor system. For example, gamma activity in the visual cortex predicts the speed of change detection to a sinewave grating stimulus (Womelsdorf et al., 2006; Hoogenboom et al., 2010) and frontal

gamma also shows correspondence to reaction time (Haig et al., 1999; Rodriguez et al., 1999; Gonzalez Andino et al., 2005). Gamma activity may subserve different functions depending on its spatial location, and it has been long thought that synchronization in the gamma band may bind together spatially distributed cortical areas (Fries, 2009). Such binding and heightened processing may well be the case for motor execution as well, however data relating kinematic parameters to gamma activity of the motor system is lacking. One recent study demonstrated a scaling of gamma activity in the globus pallidus of dystonic patients with movement amplitude and velocity (Brücke et al., 2012).

*1.3.1.3 Relationship of oscillations to single unit activity*

It is unlikely that the details of motor processing can be controlled through increases in oscillatory synchrony alone. Thus, given that initiation and scaling of movement correspond to both single unit and oscillatory activity, how might these two levels of processing relate? Alterations in beta and gamma activity may serve to shape incoming stimuli and coordinate the firing of single units to control the efficiency of neural coding. Indeed, it is hypothesized that oscillations in the beta band reduce the amount of information coded by neurones as adjacent neurones within the population lose independent firing and become entrained into the low rhythm (Hammond et al., 2007). Conversely, during periods of gamma oscillatory activity in the subthalamic nucleus, there is a higher spiking frequency and information coding capacity of single neurones (Pogosyan et al., 2006).

Under this schema, beta synchrony, which limits information coding (Hammond et al., 2007), would desynchronize early to allow the flexibility necessary for processing to occur. Subsequently, gamma synchrony would enhance the binding of disparate areas in the motor system and promote a higher rate of firing, which could then in turn code for larger levels of force or velocity.

### 1.3.2 Sequential movement and timing

#### *1.3.2.1 Neural substrates*

The two structures most commonly associated with theories of motor timing are the basal ganglia and cerebellum. It has been proposed that short, millisecond-range timings in the motor system are predominantly regulated by the cerebellum, whereas longer, supra-second interval timings are governed by the basal ganglia (Ivry, 1996). However, some studies contradict this, implicating cerebellar involvement at prolonged intervals (Gooch et al., 2009), and the basal ganglia in millisecond timing (Shih et al., 2009).

The results of an fMRI study by Jahanshahi et al. also did not entirely support this dichotomy between BG and cerebellar timing, as both structures were activated in the timing of both intervals (Jahanshahi et al., 2006). They found the left caudate to be active during milliseconds-range reproduction, and the right putamen during seconds-range reproduction. They postulated that the cerebellum is involved with nonspecific components of timing related to task demands. Lewis and Miall (2003) proposed a sub-second "automatic"

timing system defined by movement and produced by a central pattern generator and a seconds-range "cognitively controlled" timing system, depending on prefrontal and parietal regions.

*1.3.2.2 Timer Mechanism*

The underlying mechanisms for timing control remain disputed (Buhusi and Meck, 2005). The leading model for finger tapping (Wing and Kristofferson, 1973) proposes a central timekeeper that oscillates at a certain frequency. In Wing and Kristofferson's model (1973), the inter-tap interval (ITI) variation can be split into central timekeeper and peripheral motor implementation components. Only the central timekeeper variability depends on the ITI, with the variance of interval perception and production increasing linearly as ITI increases (Doumas and Wing, 2007) within a range of 250-2000 ms. Generally, the central timekeeper is the main source of variability. Motor variance makes only a relatively small contribution, except at short ITI durations, and tends to be consistent for the same person and similar across individuals (Wing, 2002).

*1.3.2.3 Timing and repetitive movement in Parkinson's disease*

There is not much consistency amongst studies on rhythmic motor output in PD patients. Many studies have found that PD patients show abnormal temporal processing in repetitive rhythmic movements because of a higher performance variability compared to controls (Pastor et al., 1992; O'Boyle et al., 1996). The variability is represented in terms of higher central and motor variance, both of which are reduced by dopaminergic therapy (Spencer

and Ivry 2005). Similarly, Koch et al. (2004) showed that both subthalamic nucleus stimulation and dopamine significantly improved time interval reproduction. Some studies, however, have shown normal performance by these patients, even when off medication (Spencer and Ivry, 2005). Because of the high natural variance associated with timing in repetitive movements, it might be difficult to assess timing function in patients with motor deficits such as PD (Shea-Brown et al., 2006). However, even in non-motor tasks, PD patients show reduced discrimination of beat-based rhythms (Grahn and Brett, 2009), and estimation of time intervals (Wild-Wall et al., 2008).

*1.3.2.4 External cues*

In PD, patients often have difficulty initiating and perpetuating movement, increasing their reliance on external cues. As such, it has also been suggested (Currà et al., 1997) that PD patients show greater abnormalities during internally generated movements than in movements made in response to external, environmental cues. In accordance with this, PD patients have demonstrated improvements in gait (Vrancken et al., 2005), including improved cadence with auditory cues and stride length with visual cues (Suteerawattananon et al., 2004). They also showed decreased freezing (Enzensberger and Fischer, 1996) and improvements in reaching tasks (Kritikos et al., 1995) when cued. In an experiment where patients used auditory stimulation in a 3-week gait training regimen, their walking velocity, stride length, and cadence all improved compared to controls (Thaut et al., 1996). When PD patients are presented with a series of buttons to

press, auditory (Georgiou et al., 1993) and visual (Georgiou et al., 1994) cues were shown to improve movement time.

Majsak et al. (1998) had PD patients reach for a stationary and a moving ball, and showed that they were able to generate velocities that exceeded their self-regulated maximal speed in reaching for the moving ball without compromising movement accuracy. From this it was suggested that external temporal cues (moving ball) allow patients to organize the timing and speed of their movement through the activation of cortical and subcortical motor circuits, such as the cerebellum, to compensate for their loss of internal cueing mechanism from the basal ganglia. Glickstein and Stein (1991) had previously suggested this model, arguing that pathways that relay visual stimuli can "bypass damaged basal ganglia and allow the intact cerebellar circuit to be used for visuo-motor control." This could be used to explain why horizontal lines on the floor, or frightening experiences, can produce 'paradoxical' movement in PD patients (see Glickstein and Stein, 1991).

External cues however, cannot always fully rescue impairment. In a finger tapping tasks, Konczak et al. (1997) demonstrated that PD patients could initially match the frequency of tapping to a repetitive stimulus, but tended to collapse while trying to maintain the synchronization for much longer periods. Overall however, they found no differences in temporal stability or kinematic performance with external cues.

Altogether, evidence suggests Parkinson's disease patients have deficits in producing rhythmic movements, sometimes referred to as 'dysrhythmia' (Yahalom et al., 2004; Espay et al., 2011), in some case cases corrected by external cues, dopamine, or DBS.

### 1.3.3 Motor Learning

#### *1.3.3.1 Neural substrates*

Motor learning can be defined as a set of processes associated with practice or experience, leading to relatively permanent changes in the capability for movement (Nieuwboer et al., 2009). According to a classical explanation by Fitts and Posner (1967), learning comprises three main stages (see Figure 1.3). The first is the cognitive stage, which involves receiving instructions and feedback from the examiner and learning how to accomplish the task, a process which is highly variable and error-prone. Secondly, the associate stage occurs when the subject begins associating specific environmental cues with the movements required to achieve the goal (tone, visual stimulus, feedback), and in this time the subject refines their performance and reduces their errors. In the third autonomous stage, the subject performs the task automatically with a high degree of skill and consistency.

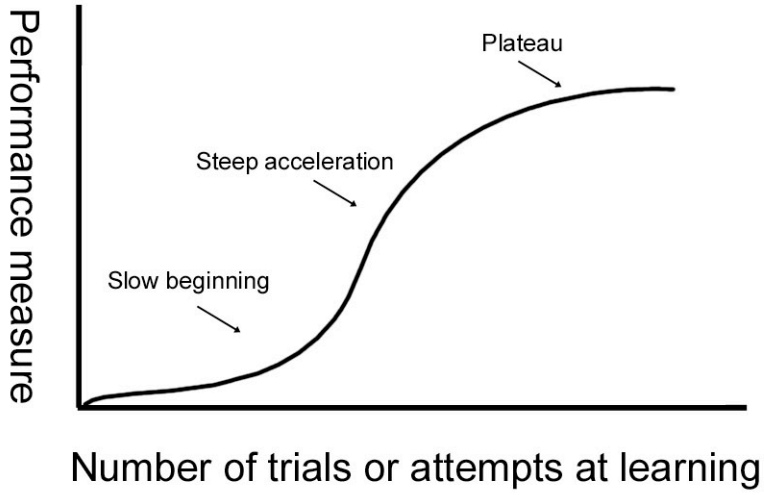


**Figure 1.4.** Fitts and Posner model of motor learning. Comprises three stages: Cognitive (slow), associative (steep), and autonomous (plateau)

Neuropsychological studies have revealed some brain areas that are involved in this type of motor learning, especially sequence learning. Various cortical and subcortical regions have been associated with acquiring motor skills and procedural memories, including the striatum (Doyon et al., 2009). In accordance, studies have shown patients with subcortical diseases involving basal ganglia degeneration, such as PD, progressive supranuclear palsy (PSP) or Huntington's disease have a deficit in motor learning (Butters et al., 1985; Heindel et al., 1988; Saint-Cyr et al., 1988; Grafman et al., 1990; Bondi and Kaszniak, 1991), although a few studies have not found any deficit (Agostino et al., 1996).

The cerebellum has long been known to be involved in motor learning (Marr, 1969; Gilbert and Thach, 1977). Early on, Marr (1969) and Albus (1971) proposed the cerebellum was important in the learning of new movements. In Gilbert and Thach's 1977 study, recordings were made from purkinje cells of the cerebellar cortex while a monkey moved a handle upon which a torque motor applied force. They found increase in complex spike frequency and decrease in simple spike firing as the monkey learned, showing that motor learning might take place in the cerebellum through changes in strength of purkinje cell transmission caused by climbing fibre input. More early evidence that the cerebellum is involved in motor learning comes from vestibulo-ocular studies (VOR), demonstrating that the gain of the VOR can no longer be modified following cerebellar flocculus lesions (Ito et al., 1974). Motor learning produces synaptogenesis in the cerebellar cortex of rats (Black et al., 1990). More recent evidence from patients with cerebellar disease or damage adds weight to the assertion that the cerebellum has a significant role in motor learning (Sanes et al., 1990; Rabe et al., 2009). Additionally, disruption of the cerebellum of healthy individuals with transcranial magnetic stimulation causes a deficit in motor learning in the form of saccadic adaptation (Jenkinson and Miall, 2010). Some studies show long-term representation of motor skills stored in cerebellum (Sanes et al., 1990; Rabe et al., 2009) while others show distributed network of structures outside cerebellum in retention and expression of learned behaviours (Houk and Wise, 1995; Bloedel et al., 1997).

Several theories are available to explain cerebellar involvement in motor control, including the combining of individual movements and motor context into 'movement synergies' (Thach et al., 1992), motor and perceptual timing (Ivry, 1996), sensorimotor integration (Gao et al., 1996), and error detection (Fiez et al., 1992). These abilities might be mediated by interaction with sensory areas, perhaps most importantly the visual system. The cerebellum does indeed have strong connections to extrastriate visual regions (Mower et al., 1980). In addition, motor cortex, premotor, and SMA project via the pons to the contralateral cerebellum in primates (Brodal, 1978; Glickstein et al., 1980, 1985). Patients with cerebellar pathology also exhibit impairment in the skilled performance of movements suggesting that the cerebellum and associated input pathways have a role in motor skills learning (Sanes et al., 1990). All these classic studies have led the cerebellum to be described as the "teaching machine" of motor cortex (Marr, 1969; Ito et al., 1974; Gilbert and Thach, 1977).

However there are further changes as learning progresses. Seitz et al. showed with PET that early learning caused significant activation of the ipsilateral dentate nucleus (cerebellum) with decreases in the striatum, however as the task is learned cerebellar activity is decreased while striatum as well as premotor cortex activity is increased. This suggests that learning new movements involves the cerebellum while overlearned movements activate the prefrontal cortex and basal ganglia and no longer require as much cerebellar activation (Seitz et al., 1990, 1994). Friston et al. (1992) also demonstrated activation in the premotor cortex, left putamen, left

thalamus, and cerebellar nuclei, with a decline in activity in the cerebellar cortex and nuclei as a finger to thumb opposition task was mastered (Friston et al., 1992).

Accumulated evidence suggests the basal ganglia may be critical for the internalization and expression of innate motor routines (Graybiel, 1995; Doyon et al., 1998; Karni et al., 1998). In one experiment, subjects were tested in early learning (day 1), late learning (day 5), and delayed recall (4 weeks after with no additional practice). Predictably, the early learning activated the cerebellar cortex, after 5 days the cerebellar activity decreased, and there was greater activity in the basal ganglia and frontal lobe. At delayed recall, there was significant activation in M1, PMC, and parietal lobe, with no significant activity in cerebellum or basal ganglia. This supports the idea that early motor sequence learning requires cerebellum, with basal ganglia involved more with later automatization phase, and delayed recall mediated by a cortical network (Penhune and Doyon, 2002; Ungerleider et al., 2002).

Clearly the cerebellum and basal ganglia both have an important role in motor learning, likely facilitated by the multiple, parallel loop circuits with the cortex via the thalamus (Alexander et al., 1990). The interaction between these multiple networks - cortico-basal, cortico-cerebellar, and cortico-cortico - is perhaps what is important in facilitating and optimizing motor skill learning (Hikosaka et al., 1999; Doya, 2000).

*1.3.3.2 Consolidation of learned skills*

By what mechanisms do learned motor skills, everything from buttoning a shirt to riding a bike, pass the test of time? Memory moves through a series of manifestations, from a short-lived fragile phase to a more long-lasting stable form (Bailey et al., 1994; DeZazzo and Tully, 1995; Shadmehr and Brashers-Krug, 1997). Off-line improvement of the motor memory without intervening practice is referred to as consolidation (Krakauer et al., 2005). Under the assumption that consolidation could be demonstrated by the resistance of memory to interference, Brashers-Krug et al. showed that in learning a forcefield task there is a change in the stage of resistance of a motor memory and thus consolidation even within a few hours after. This could be the result of a switch between a labile form of neuronal firing pattern to a stronger form that is made semi-permanent through synaptic plasticity. Learning another motor skill in that fragile window could disrupt consolidation and formation of a long-term motor memory, but if undisturbed, a motor memory could be strengthened after several hours and become resistant to disruption (Brashers-Krug et al., 1996; Shadmehr and Brashers-Krug, 1997).

*1.3.3.3 Motor adaptation*

A well-established way to probe motor learning is to use a motor adaptation task. Adaptation is defined as the reduction in systematic errors introduced by altered environmental conditions in order to return to a former level of performance (Krakauer, 2009). Adaptation requires a remapping between

well-learned movements and a new spatial goal, unlike motor sequence learning which requires acquisition of a new pattern of muscle activations. For example, in visuomotor rotation, when exposed to a continuous discrepancy between movements of the subject's hand and of a computer cursor, subjects have to adapt their movements in order to reach the target accurately. This produces a 'systematic directional bias' around the hand and thus can be used to understand the adaptive processes of planning and reaching towards a target. As the subject adapts, error reduction occurs exponentially, adaptation shows limited generalization to other directions, and has prolonged aftereffects (Krakauer, 2009). In visuomotor adaptation, the occurrence of consolidation (off-line improvement) is controversial. Rather, improved performance on a second session is conceptualized in terms of 'savings', which may be due to the persistence of the first adapted state over time (Yamamoto et al., 2006), or a faster rate of re-learning (Krakauer et al., 2000).

*1.3.3.4 Motor learning in Parkinson's disease*

Given the role of the basal ganglia in motor learning, it would be natural to assume that basal ganglia pathology, particularly in PD, would effect the ability to perform these tasks. And indeed this is sometimes the case. Striatal dopamine deficiency of Parkinson's disease leads to impaired procedural learning (Harrington et al., 1990).

A similar result is seen in a study by Contreras-Vidal et al., (2003) showing PD patients' lower performance in learning a 90 degree visuomotor

adaptation, as they continued to produce spiral trajectories to the target rather than straight lines. Moreover, they had a decreased after effect when switching back to a non-rotated task (2003).

Similarly, Teulings et al. (2002) showed an inability of PD patients to learn a writing adaptation task where perception of the size of handwriting was changed, and also demonstrated a reduced aftereffect. This interesting lack of an aftereffect is also described in PD and Huntington's patients after a prism adaptation task (Fernandez-Ruiz et al., 2003). Paquet et al. (2008) found that error reduction in a visuomotor task was worse in patients not treated with L-Dopa, whereas no difference was observed between PD patients and controls. In contrast, other studies have shown no adaptation deficit during a visuomotor rotation task (Bédard and Sanes, 2009; Marinelli et al., 2009).

Can PD patients retain a learned task over time? There are very few studies that address this. One experiment by Marinelli et al. (2009) point to some retention deficits in PD patients in a task requiring adaptation to a 30 degree rotated visual display while moving a cursor out and back to one of eight radial targets. They found that PD patients showed only significantly less improvement of adaptation rate at retesting whereas there was no significant difference in initial learning of the task. There was also no difference between the on and off drug state, although all patients were in the early stages of PD. Sanes et al. similarly showed a decreased rate of adaptation to a visuomotor task on re-testing for PD patients, but not initial learning

(Bédard and Sanes, 2009). Mochuzuki-Kawai (Mochizuki-Kawai et al., 2004) using a bilateral coordinated training task showing PD patients with reduced retention at 3-18 months as compared to Alzheimer's patients. Such deficits in retention of motor skill could result in the lack of effective rehabilitation for Parkinson's disease patients. Indeed, the evidence for a benefit of rehabilitation in PD is discouraging (Gage and Storey, 2004).

## 1.4 RESEARCH QUESTIONS AND EXPERIMENTAL SUMMARIES

Two main aspects will be investigated in the following thesis: 1) the neuronal mechanisms of basal ganglia-mediated behaviors (described above), and 2) ways in which the motor system can be manipulated to improve motor performance. These two elements are not mutually exclusive. On the one hand, studying underlying neuronal mechanisms can give strong indications towards possible therapeutic options and ways to exploit these mechanisms to improve motor behavior. In this thesis, such mechanisms were explored by recording neuronal activity from the subthalamic nucleus of Parkinson's patients. On the other hand, the effects of treatments and therapeutic manipulations on motor performance can offer insight into the circuitry, physiology, and pathophysiology of the motor system and basal ganglia. This thesis makes use of three stimulation techniques to probe and improve motor function: Deep brain stimulation (DBS), transcranial direct current stimulation (TDCS), and transcranial alternating current stimulation (TACS).

In the first three experimental chapters, the roles of the subthalamic nucleus and oscillatory activity within the STN in the control of ballistic movement were explored. In chapter 2, stimulation of the subthalamic nucleus in PD was found to improve the velocity, but not reaction time, of ballistic movements in PD. In chapter 3, recordings from the STN demonstrated that fast ballistic movements are preceded by early suppression of beta oscillations and accompanied by dramatic increases in gamma oscillations, as compared to slower movement. In chapter 4, the posited roles of beta and gamma oscillations are tested for a causal influence on motor behavior by stimulating the motor cortex of healthy individuals at beta or gamma frequency; these two oscillations produced opposing effects in the motor system and enhanced motor performance. These results support 'anti-kinetic' and 'pro-kinetic' roles of beta and gamma oscillations, respectively.

In the subsequent two chapters, the role of the basal ganglia in repetitive movement and timing were studied. Chapter 5 demonstrates that stimulation of the subthalamic nucleus can improve repetitive tapping behavior in Parkinson's disease by reducing the inter-tap variability. In chapter 6, the neuronal basis of timed tapping was explored, revealing that beta oscillations in the subthalamic nucleus are suppressed in correspondence with the rate of tapping. These results implicate the STN in rhythmic movement, and suggest that continuous suppression of beta activity could represent a mechanism for the facilitation of repetitive movement. Such a mechanism could also explain why cued repetitive movements are often easier to perform than single, discrete movements in

PD. Lastly, motor adaptation in PD was examined. In chapter 7 PD patients show a striking deficit in the retention of a learned visuomotor adaptation and a reduced effect of interference. In the final experimental chapter, chapter 8, we demonstrated that TDCS improved the learning and retention of the same visuomotor task in PD and healthy controls. These findings offer insight into the role of the basal ganglia in motor adaptation, and possible therapeutic options in improving adaptation and rehabilitation in PD.

# 2. DEEP BRAIN STIMULATION OF THE SUBTHALAMIC NUCLEUS IMPROVES VELOCITY OF BALLISTIC MOVEMENTS IN PARKINSON'S DISEASE


## -Abstract-

High-frequency stimulation of the subthalamic nucleus can dramatically improve motor function in patients with Parkinson's disease. However, the underlying mechanisms mediating these improvements are not well understood. In particular, whether motor function is differentially improved in distal or proximal movements is not fully determined. Also, whether reaction time is improved along with other motor parameters is still a matter of debate. Here, we test patients OFF and ON subthalamic nucleus stimulation by capturing simple ballistic movements across four joints using kinematic motion analysis. We show that velocity, but not reaction time, is significantly improved with stimulation. There was no strong differential effect between joints. These results add evidence that deep brain stimulation of the subthalamic nucleus can enhance motor performance in Parkinson's disease, and demonstrate that the subthalamic nucleus may be important in driving parameters of motor control after the response has been initiated.

## 2.1 INTRODUCTION

The subthalamic nucleus is the most common deep brain stimulation target (STN-DBS) for the treatment of Parkinson's disease (PD) (Brock et al., 1998; Krause et al., 2001). High frequency stimulation (>100 Hz) often dramatically ameliorates aspects of the motor symptoms of PD, resulting in 30-60% improvements in rigidity and akinesia (Kumar et al., 1998). Despite these large global improvements in motor performance, existing clinical tests such as the Unified Parkinson's Disease Rating Scale (UPDRS) do not capture the more selective and specific changes that make up these gross benefits. For example, whether axial or distal muscle groups demonstrate differential improvement following STN-DBS has not been adequately explored, unsurprisingly since the UPDRS motor sub-score does not differentiate strictly between proximal and distal muscle groups. Also, everyday activities involve combinations of proximal and distal muscle activations, making it difficult to discern where most patients derive the greatest benefit of stimulation. STN-DBS is known to improve distal motor function when tested with tasks such as tapping (Taylor Tavares et al., 2005) or pinch grip (Vrancken et al., 2005), and axial improvements have been demonstrated in gait and balance following STN-DBS (Ferrarin et al., 2005; Crenna et al., 2006). Yet whether there is a differential response to STN-DBS between the muscle groups involved remains to be determined.

Some studies have addressed the selective impact of STN-stimulation with conflicting results. Timmermann et. al. demonstrated a differential effect of

STN-DBS and L-Dopa, showing greater improvement in the frequency and amplitude of repetitive distal finger movements with L-DOPA, but greater improvement in proximal diadochokinesia with stimulation (Timmermann et al., 2008). These findings are supported by data from a grip lift task (Wenzelburger et al., 2003) demonstrating benefit during the early grip phase under L-Dopa but greater improvement in the late, proximal phase for STN-DBS whilst off medication. Furthermore, Potter-Nerger and colleagues (Potter-Nerger et al., 2009) showed significant improvement in distal (finger) and proximal (elbow and shoulder) repetitive tapping under STN-DBS, but with a greater impact on proximal compared to distal tapping. Contrasting evidence is presented by Dafotakis et al (Dafotakis et al., 2008) who demonstrate that STN-DBS improved equally the kinematics of simple finger tapping and horizontal pointing movements. However, when the subjects executed a more complex reach-to-grasp task, the beneficial effects of STN-DBS were more pronounced for the distal grasp component.

It is also unclear which aspects of movement undergo the most pronounced modulation during STN-DBS. It is known that parameters following movement initiation such as force or speed can be increased, but the effect on movement initiation itself, or reaction time, remains unresolved. Several studies have shown an improvement in simple reaction time (Kumru et al., 2004; Temel et al., 2006) and choice reaction time (Kumru et al., 2004; van den Wildenberg et al., 2006; Ray et al., 2009), though two of the choice-reaction time studies also examined simple reaction time and demonstrated no significant difference (Kumru et al., 2004; van den Wildenberg et al.,

2006). Further, several more studies have failed to show any difference on reaction time due to stimulation during a stop-signal reaction time task (Ray et al., 2009; Mirabella et al., 2011; Swann et al., 2011), simple (distal) reaction time (Nakamura et al., 2007), postural reaction time (Shivitz et al., 2006), or force reaction time (Vrancken et al., 2005). However these studies did show improvements in several other parameters of performance (ie. movement time, velocity, force rate) with stimulation.

These data are difficult to reconcile, and thus the exact nature of STN-DBS remains ambiguous. Varying task types, complexity and implementations between studies make global inferences difficult. Thus, we adopted a simplified approach to determine which limbs and parameters are most improved by STN-DBS by analyzing simple ballistic movements. We sought to identify the greatest point of improvement by systematically assessing arm kinematics between 4 different types of arm movements: Shoulder extension, elbow extension, wrist extension, and finger extension.

## 2.2 METHODS

### *2.2.1 Patients and stimulation*

We studied 9 patients with Parkinson's disease treated with bilateral high frequency STN stimulation (1 female, mean age: 61$\pm$ 7.6 years, disease duration 14.1 $\pm$ 8.0 years, post-op duration 3.56 $\pm$ 2.34 years). All patients fulfilled the UK Brain Bank criteria for idiopathic PD. Informed written

consent was obtained from each subject prior to participation and the study was approved by the Oxfordshire Research Ethics Committee. Subjects were tested in two conditions: bilateral STN stimulation was either switched ON or OFF, during maintenance of normal anti-Parkinsonian medication. Stimulation order was randomized, with approximately 25 minutes break after any change in stimulation. 5 patients began with STN stimulation OFF, and 4 patients began with it ON. For a summary of clinical data see Table 2.1.

**Table 2.1 Clinical details**

| Patient | Age (years) | Disease duration (years) | Medication | Post-op duration (years) |
|---|---|---|---|---|
| 1 | 64 | 17 | Sinemet<br>Mirapexin | 3 |
| 2 | 51 | 21 | Sinemet<br>Ropinirole | 9 |
| 3 | 62 | 9 | Madopar<br>Tolcapone | 4 |
| 4 | 61 | 7 | Sinemet<br>Ropinirole | 3 |
| 5 | 49 | 10 | Sinemet<br>Entacapone<br>Mirapexin | 1.5 |
| 6 | 57 | 11 | Zelapar<br>Ropinirole<br>Madopar | 2 |
| 7 | 72 | 32 | Amantadine<br>Sinemet<br>Ropinirole | 5 |
| 8 | 68 | 10 | Sinemet<br>Ropinirole | 3 |
| 9 | 66 | 10 | Pramipexole<br>Rotigotine | 1.5 |

*2.2.2 Task*

Patients were cued by a beep presented at a randomized interval of 4 - 5 seconds, to make the required movement (see below) as quickly as possible. All movements were performed with the patient's most affected side (6 right side, 3 left side). A reflective marker was placed on the limb for kinematic capture by a two-camera 3D motion capture system (ProReflex, Qualisys AB, Sweden). Positions of the markers were labeled so as to keep the same position between stimulation sessions. Subjects were cued to make 30 movements, in 2 blocks of 15. Breaks of 1 minute were given between session of the same joint, and 2 minutes between different joints. Extra time was given if the patient was fatigued.

The following instructions were given for each movement:

1. Shoulder movements: The arm was held straight out with elbow locked and fingers pointing towards a marker at eye level. Patients were instructed to move the entire arm downwards using only the shoulder joint into a cushion on the patient's lap, which acted as the movement endpoint. Patients were then to slowly bring their arm to the previously raised position and prepare for the next movement. The marker was placed on the wrist to capture the arm movement.

2. Elbow movements: The elbow was bent upwards with fist closed so that the arm was in a fully flexed position. An extension movement was made at the elbow joint from this fully flexed position downwards into a cushion. Patients were then to slowly resume the flexed

position and prepare for the next movement. The marker was placed on the knuckle closest to the cameras.

3. Wrist movements: The arm was supported by a cushion and the wrist relaxed over the edge, with the hand open and the palm facing down. Movements were made from this relaxed position to a fully extended wrist position. Patients were then to relax and prepare for the next movement. The marker was placed on the outside knuckle facing the cameras.

4. Finger movements: The hand was relaxed on the table and the fingers parallel to the table. Thumb and finger were lightly touching, and movements were made with the index finger to a fully extended finger position. Patients were then to again touch their thumb with their index finger and prepare for the next movement. The marker was placed on the tip of the index finger.

*2.2.3 Data Recording and Analysis*

Camera data were sampled at 60 Hz, synchronized with Spike2 software (Cambridge Electronic Design, Cambridge, UK) so that timing of the auditory cues could be compared with the recording. Data was then exported and analyzed in Matlab (Mathworks). The data was first converted using the MoCap toolbox then analyzed with in-house scripts. Movement traces were differentiated to obtain velocity. A principal components analysis (PCA) reduced the three axes of motion into one velocity trace along the plane of greatest variance. The following parameters were extracted from these

traces: (i) Reaction time, (ii) initial velocity, and (iii) peak velocity. Reaction time was obtained by taking the time between the auditory cue and the time of threshold crossing at 5% of each trial's maximal velocity value. Initial velocity was taken as the velocity averaged from the reaction time point to the peak velocity. Trial parameters were averaged within subject for each limb to obtain a mean value for each measure.

A 2x3 repeated measures ANOVA was used for each parameter with factors stimulation (stimulation off or on) and joint (shoulder, elbow, wrist, or finger) to test for global effects of stimulation. Post-hoc t-tests were performed between off and on states of the individual joints when an interaction was found. Due to the small number of planned comparisons, we maintained our significant p threshold at $<0.05$.

## 2.3 RESULTS

### *2.3.1 Effect on velocity*

We will first consider the initial velocity taken as the mean from the reaction time to peak velocity. An example average velocity trace aligned to response onset (5% of peak velocity) from patient 1 is displayed in Figure 2.1. Mean changes for initial velocity are shown in Figure 2.3B. A repeated measures ANOVA with factors stimulation (off or on) and joint (shoulder, elbow, wrist, and finger) was significant for stimulation ($F_{1,8} = 2.641$, $p = 0.029$), joint

($F_{3,24}$ = 23.363, p <0.0001), but there was no stimulation x joint interaction ($F_{3,24}$ = 1.417, p = 0.271).

Individual changes for peak velocity are shown in Figure 2.2. There was a significant effect of stimulation ($F_{1,8}$ = 10.329, p = 0.012), joint ($F_{3,24}$ = 22.147, p < 0.0001), and a significant interaction ($F_{3,24}$ = 4.2, p=0.032). Post-hoc t-tests showed a non-significant change in shoulder (1.89 $\pm$ 0.27 m/s OFF versus 2.10 $\pm$ 0.26 m/s ON, t8 = -1.65, p = 0.138), but a significant change in elbow (1.42 $\pm$ 0.28 m/s versus 1.92 $\pm$ 0.26 m/s, t8 = -3.171, p = 0.013), wrist (0.347 $\pm$ 0.052 versus 0.59 $\pm$ 0.063 m/s, t8 = -5.375, p = 0.001), and finger (0.496 $\pm$ 0.072 versus 0.635 $\pm$ 0.078 m/s, t8 = -2.59, p = 0.032) velocities.

*2.3.2 Effect on reaction time*

Lastly, we assessed if there were similar changes in reaction time, as defined by our response threshold. Here, there was no significant effect of stimulation ($F_{1,8}$ = 2.631, p = 0.143), joint ($F_{3,24}$ = 2.578, p = 0.122), or interaction ($F_{3,24}$ = 1.273, p=0.306, Figure 2.3A).

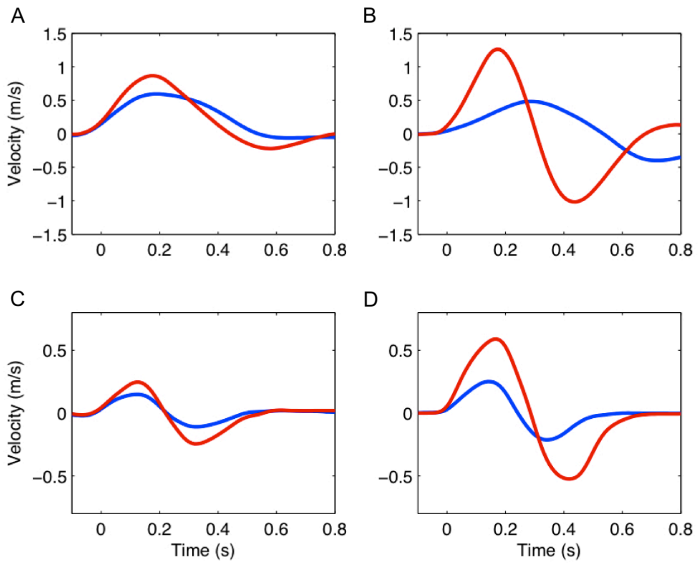


**Figure 2.1.** Example of effects of subthalamic nucleus stimulation on velocity. Above traces are from patient 1, showing velocity in OFF (blue) and ON (red) states for shoulder (A), elbow (B), wrist (C), and finger (D). Traces are averages of all individual trials, aligned to response onset (at time 0).

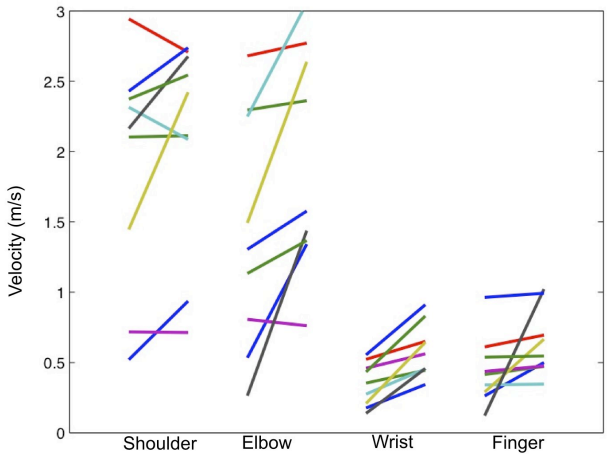


**Figure 2.2.** Individual changes in peak velocity. All 9 subjects are displayed in different colours changing from OFF to ON stimulation (left to right).

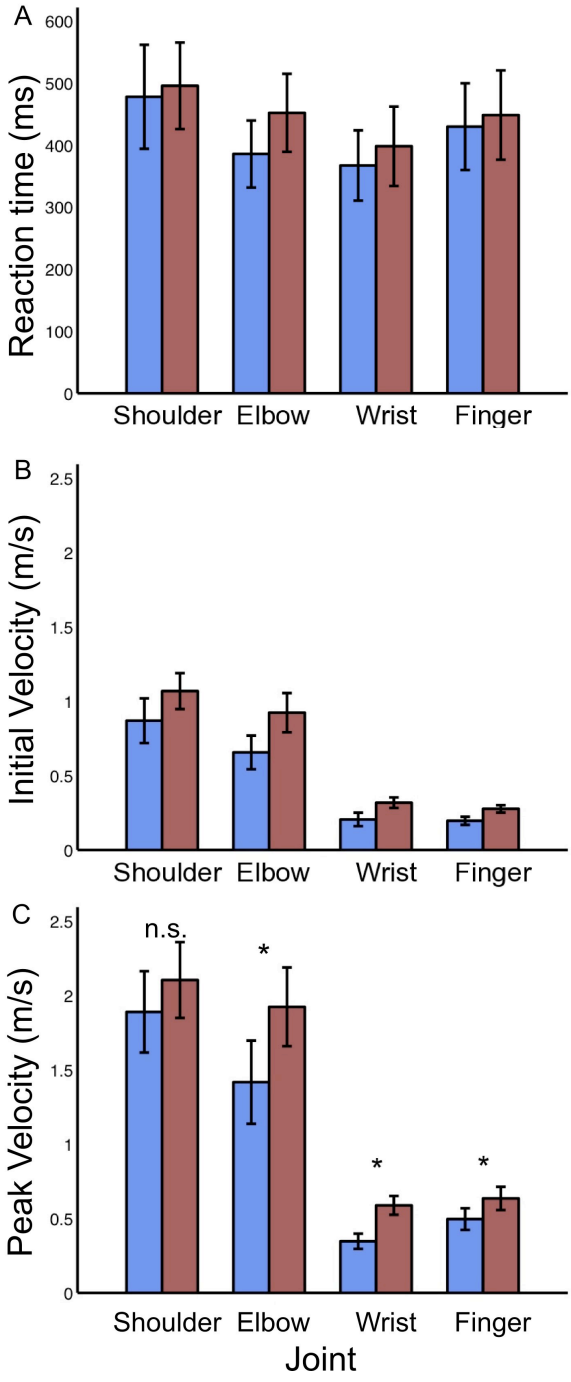


**Figure 2.3.** Effect of stimulation on kinematic parameters. Mean values with error bars denoting standard error of the mean are displayed for reaction time (A), initial velocity (B), and peak velocity (C), comparing OFF (blue) and ON (red) stimulation.

## 2.4 DISCUSSION

In this study, subthalamic nucleus stimulation significantly improved initial and peak ballistic movement velocity. In contrast, stimulation had no effect on reaction times.

There was a significant effect of STN stimulation at improving both initial and peak velocity. However, there was no clear differential benefit of stimulation on movement around a particular joint. Nevertheless we did see an interaction for peak velocity, revealing an increase for peak elbow, wrist, and finger velocity, but not shoulder, which may point to a broadly preferential increase in velocity for more distal arm movements. This results are seemingly at odds with some published works. For example, Timmermann et al. showed greater effect for proximal dysdiadochokinesia (forearm rotation) versus distal finger movements (Timmermann et al., 2008). However, dysdiadochokinesia is a repetitive, complex and sequenced movement, unlike the simple ballistic movement examined here. Moreover, the most proximal movement in that study involved manipulation of the elbow joint, rather than the shoulder. Similarly, other tapping tasks (Potter-Nerger et al., 2009) have a repetitive, rhythmic component that might impact on performance. In contrast, Dafotakis et al. (Dafotakis et al., 2008) showed distal (finger tapping) and proximal (horizontal pointing) movements being similarly improved by STN-DBS when performed separately. This latter finding in part agrees with ours, possibly as the study employed a horizontal pointing task

which included a substantial contribution from elbow joint movements, while in our study elbow improvement was no different to finger movements.

In our simplified approach, we attempted to standardize the type of motor output between joints by making all movements ballistic extensions and instructing subjects to perform at maximum speed. We found a general enhancement of velocity in all joints, although shoulder movements did not significantly increase in peak velocity. However, this must be taken with caution given our relatively low sample size and testing of only the affected hand. In addition, differing muscle dynamics during shoulder movements or ceiling effects may have contributed to the lack of benefit or even decrease in performance due to DBS. Indeed, two high performers showed worsening on shoulder peak velocity with DBS. In contrast to this increase in velocity, reaction time remained unchanged with stimulation, and even worsened on average. The lack of effect on reaction time is in accordance with previous evidence demonstrating the limited effect of subthalamic stimulation on movement initiation (Vrancken et al., 2005; Brown et al., 1999).

Given the wide-ranging connections of the STN, and the large representation of the whole arm within the STN (Nambu, 2011), it is perhaps not surprising it might mediate velocity of both distal and proximal arm movements. However the ineffectual nature of stimulation with regards to reaction time raises the question of why motor processing would be enhanced only after initiation. The basal ganglia, in particular the STN, have been implicated in response selection (van den Wildenberg et al., 2006; Hershey et al., 2010),

as suggested by the fact that choice reaction times, and not simple reaction times, are improved by stimulation (Kumru et al., 2004). In contrast, stimulation of the pedunculopontine nucleus improves simple reaction time during ballistic movements but not choice reaction times (Thevathasan et al., 2010). In our study only simple reaction times were measured. It may be the case that brainstem/pedunculopontine structures are more directly involved with motor pre-programming and initiation, while the basal ganglia/STN drive subsequent movement parameters.

We have demonstrated that subthalamic nucleus stimulation improves velocity in simple ballistic tasks across all joints, with a possible preference towards more distal movements. Moreover, reaction time remains unaffected, pointing to a role for the subthalamic nucleus in selectively driving movement velocity, rather than motor initiation.

# 3. OSCILLATORY ACTIVITY IN THE SUBTHALAMIC NUCLEUS DURING ARM REACHING IN PARKINSON'S DISEASE


## -Abstract-

Oscillatory activity in the brain within the beta (15-30 Hz) and gamma (70-90 Hz) ranges has been implicated in the generation of voluntary movement. However, their roles remain unclear. Chapter 2 implicated the subthalamic nucleus in the production of ballistic movements. Here, we search for neural correlates of such ballistic movement by recording local field potential activity from the region of the subthalamic nucleus during movement of the contralateral limb in 11 patients with Parkinson's disease. Patients were on their normal dopaminergic medication and were cued to perform arm-reaching movements after a delay period at three different cued speeds: 'slow', 'normal', and 'fast'. Beta activity desynchronized earlier in response to the cue indicating an upcoming fast reach than to the cues for slow or normal speed movement. There was no difference in the degree of beta desynchronization between reaching speeds and beta desynchronisation was established prior to movement onset in all cases. In contrast, synchronization in the gamma range developed during the reaching movement, and was especially pronounced during fast reaching. Thus the timing of suppression in the beta band depended on task demands, whereas the degree of increase in gamma oscillations depended on movement speed.

These findings point to functionally segregated roles for different oscillatory frequencies in motor preparation and performance.

## 3.1 INTRODUCTION

Changes in oscillatory brain activity is known to occur during the processing and execution of voluntary movement. Beta oscillatory activity (15 – 30 Hz) desynchronizes prior to and is sustained during movement in the cortex (Zhang et al., 2008; Muthukumaraswamy, 2010) and basal ganglia (Kühn et al., 2004; Doyle et al., 2005). Evidence suggests that beta oscillations improve maintenance of the current motor state while impairing the generation of new movements (Gilbertson et al., 2005; Androulidakis et al., 2007a; Joundi et al., 2012). Beta desynchronization is thought to play a 'gating' role to facilitate processing and initiation of movement, and accordingly is often observed up to 1 or 2 seconds prior to movement onset in self-paced movements (Kühn et al., 2004; Klostermann et al., 2007). In contrast, synchronization of neuronal activity at gamma band frequencies (70-90 Hz) has been observed during movement at cortical (Crone et al., 1998; Ball et al., 2008) and subcortical (Androulidakis et al., 2007b; Kempf et al., 2009; Brücke et al., 2012) sites. The prominence of movement-related increases in gamma activity in the contralateral cortex (Gonzalez Andino et al., 2005; Muthukumaraswamy, 2010) and the tight temporal relationship between gamma increase and movement advances the idea that it plays a 'pro-kinetic' role in the motor system (Lalo et al., 2008).

Nevertheless, data relating oscillatory activity in the basal ganglia to motor performance are sparse. One recent study has demonstrated a scaling of gamma synchronization with movement amplitude and velocity in the globus pallidus of dystonic patients, whereas beta desynchronization did not differ between movements (Brücke et al., 2012). However, responses to the cue and motor-related processing were not disambiguated. Here, we determine whether the same changes in oscillatory activity during movement are found in the region of the subthalamic nucleus (STNr) in patients with Parkinson's disease, using a paradigm that separates cue responses from movement. Recordings from the STNr have previously revealed desynchronization in beta and synchronization in gamma activity concurrent with movement (Androulidakis et al., 2007b). Furthermore, dopamine replacement therapy reduces beta synchrony and increases 70 Hz oscillations (Lalo et al., 2008), furthering the possibility of gamma activity being physiological, dopamine dependent, and 'pro-kinetic' (Brown, 2003). Therefore, we tested people with Parkinson's disease on their normal therapeutic dopaminergic medication to maximize the possibility of capturing spectral changes in their most normalised state. We recorded activity during a naturalistic reaching task where patients were asked to perform arm movements of the same distance but at three different speeds. We sought to identify any differential modulation of beta and gamma activity in response to cues during motor preparation and subsequent movement.

## 3.2 METHODS

### *3.2.1 Patients and surgery*

Eleven right-handed patients with idiopathic PD (1 female, mean age 63.5 $\pm$ 9.4 years (SD), disease duration 8.1 $\pm$ 5.6 years) who had deep brain stimulation (DBS) electrodes implanted targeting the STN for the treatment of PD participated in the study. All patients gave their informed written consent to participate in the study, which was approved by an Oxford Research Ethics Committee according to the Declaration of Helsinski. Five patients were implanted unilaterally, and the remaining bilaterally. Clinical details are summarized in Table 3.1. The macroelectrodes used in all cases were Medtronic model 3389 (Medtronic Neurological Division, Minneapolis, USA) with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a contact-to-contact separation of 0.5 mm. Intended coordinates for the STN were 12 mm lateral from the midline, 3 mm behind the midcommissural point, and 4 mm below the AC-PC. Individual adjustments were made according to pre-operative stereotactic T2-weighted magnetic resonance imaging. During the surgical procedure intra-operative macroelectrode stimulation and clinical evaluation were carried out to identify best placement for the electrode. Post-operative CT images fused to pre-operative MRI was performed to confirm accurate targeting.

**Table 3.1. Clinical Details**

| Patient Number | Age, Sex | Disease duration (years) | Predominant symptoms | Levodopa equivalent daily dose at surgery (mg) | Pre-op UPDRS off-meds | Pre-op UPDRS on-meds |
|---|---|---|---|---|---|---|
| 1 | 58, M | 2 | Tremor | 200 | 19 | 6 |
| 2 | 65, F | 17 | Dyskinesias, Freezing | 963 | 29 | 8 |
| 3 | 80, M | 4 | Tremor | 116 | 29 | 26 |
| 4 | 63, M | 10 | Bradykinesia, Rigidity, Tremor | 1610 | 40 | 22 |
| 5 | 66, M | 16 | Bradykinesia, Rigidity, Dyskinesia, Tremor | 415 | 33 | 7 |
| 6 | 70, M | 4 | Tremor | 520 | 36 | 18 |
| 7 | 65, M | 11 | Gait, Dyskinesias, Tremor | 805 | 33 | 6 |
| 8 | 60, M | 7 | Gait, Tremor | 66 | 25 | 13 |
| 9 | 60, M | 2 | Tremor | 200 | 39 | 33 |
| 10 | 42, M | 6 | Rigidity, Tremor | 500 | 50 | 38 |
| 11 | 70, M | 12 | Gait, Tremor | 1000 | 62 | 29 |

### *3.2.2 Recordings*

Recordings were obtained 4-6 days after surgery to implant the electrodes and prior to internalization of the DBS leads and pacemaker. Local field potentials (LFPs) were recorded from the DBS electrodes at 2.5 kHz and amplified (CED 1902 amplifiers, Cambridge Electronic Design, Cambridge, UK), digitized at a sampling rate of 1 kHz (CED 1401, CED Cambridge, UK), and recorded to disk (CED Spike2, CED, Cambridge, UK). Data were analysed off-line using in-house scripts written in Matlab (Mathworks, Natick, MA, USA). STNr LFPs were recorded as bipolar channels, in order to cancel out common signals due to volume conduction and ensure the LFPs recorded were as focal as possible to the electrode. Three bipolar channels in the STNr contralateral to the task limb were acquired from each patient for analysis.

### *3.2.3 Task*

The patients were seated on a comfortable chair in front of a keyboard and LCD monitor, positioned 50 cm apart. Stimuli were presented on the monitor using Presentation software (Neurobehavioural Systems Inc., CA, USA). All patients performed the task with their right arm, except for one patient who used their left arm due to a right-sided unilateral electrode. The full paradigm is displayed in Figure 3.1. The patients were first instructed to lightly depress the spacebar on a keyboard, to start the task. There followed a 1 second period in which the screen was blank, of which the latter 500 ms (or PRE-CUE period) was used as a baseline period for the LFP

recordings for subsequent power changes. The PRE-CUE period was followed by a cue consisting of the speed instruction; the word "FAST", "NORMAL", or "SLOW" presented on the screen for 500 ms. The speed cue then disappeared, followed by a random delay between 500 and 1500 ms. The patients had to maintain their hold on the spacebar during this delay period, which will be referred to as DELAY. The gap was intended to identify activity that may be involved in the preparation of movement at different speeds. A randomized period was selected so that subjects would not anticipate the subsequent imperative cue. After the gap, a movement cue of a green square 5x5 cm was presented at the middle of the monitor screen. On this cue the subject released the spacebar and reached towards the movement cue at the instructed speed. The brief period between presentation of the movement cue and release of the spacebar will be referred to as REACT. No explicit instruction was given regarding the reaction time itself, only to adjust speed of the subsequent reach. If "NORMAL" was presented, the subjects were to reach at a comfortable speed towards the cue. During "SLOW" trials the subjects were instructed to make a slower than normal ('slow-motion') movement towards the cue, while for "FAST" trials subjects were instructed to reach as quick as possible to the screen. Subjects were instructed to press the target on the screen with their index finger, whereupon they received an auditory beep, providing feedback. The period between spacebar release and touching the target will be referred to as REACH. Subjects then returned their finger to the spacebar to start the next trial. Each block consisted of 45 trials in total, with a pseudo-randomized distribution of 15 of

each fast, normal, and slow trials. Between each block patients were reminded to keep their slow movements 'slower than normal' and their fast movements 'as fast as possible'. The number of blocks varied from 2-4 for each patient, with the exception of 1 patient who completed a single block due to fatigue.

*3.2.4 Analysis*

Due to the relationship between contralateral gamma and movement we analysed data only from the STNr contralateral side to movement. Data were imported into Matlab, band-pass filtered between 2 and 100 Hz, and notch filtered to remove mains noise. Data were epoched to speed cue onset (-200 to 500 msecs) and movement onset (-1000 to 2000 msecs). Spectrograms were generated using a Hermite functions approach (Bayram & Baranuik 2000). Hermite functions represent an extension of Thomson's multitaper method (Thomson 1982) to the time-frequency plane, providing improved bias and variance properties that are beneficial when examining non-stationary data. With an emphasis towards time-evolving spectra, spectrograms were generated using a time-frequency localisation parameter A/2 = 5 (see Brittain et al., 2007) providing a full-width half-maximum resolution of 167 ms x 2.7 Hz. The electrode contact with the highest movement-related gamma synchronization was determined and chosen for subsequent analysis. Spectrograms were evaluated through point-wise paired t-tests over log-spectral values at p = 0.05. A baseline period 500 ms prior to speed cue presentation was taken (PRE-CUE period). Time-evolving

band-limited power profiles were extracted from their corresponding spectrograms, baseline subtracted and normalized over the baseline period to provide percentage change measures.

Finally, to quantify the relative changes in power within beta (15-30 Hz) and gamma (70 – 90 Hz), percentage change differences were averaged for the three different task periods (DELAY, REACT, REACH) for each data set. In addition, each task period was normalized to the oscillatory power in the preceding period (REACT to DELAY, and REACH to REACT) to determine any sequential change in power for each time period.

All statistical analyses were conducted using SPSS v12 (SPSS Inc., Chicago, IL, USA), except significance spectrograms, which were generated using one-sample t-tests in MATLAB. Percentage change values of beta and gamma were normally distributed as confirmed by the one-sample Kolmogorov-Smirnov test. Mauchley's test confirmed the sphericity of the data. One-way repeated analysis of variance (ANOVA) tests were conducted for speed of movement as well as power in both the beta and gamma bands in each task period (DELAY, REACT, REACH). Post-hoc paired t-tests, with Bonferonni correction, were used to compare between conditions (significant p value < 0.05). Significant differences from baseline for each condition were also calculated using one-sample t-tests (significant $p < 0.05$). Reach times were also correlated with increases in beta and gamma activity using Pearson's product moment correlation.

## 3.3 RESULTS

### *3.3.1 Selected contacts*

The contact pairs demonstrating the highest movement-related gamma modulation were selected for analysis. All patients demonstrated a clear maximum in one of the 3 contact pairs on the side contralateral to movement. The largest increase in gamma power was 67.4 ± 17.6% (SEM) higher than the mean of the remaining contact pairs from the same electrode. We used the contact with the highest gamma activity to generate the spectrograms and band-limited measures of gamma change for all conditions. However, for band-limited changes in the beta range (15-30 Hz), we similarly selected the contact with the highest movement-related modulation in beta activity. There was 57.9 $\pm$ 6.7% more beta desynchronization in the selected contact than the mean of the remaining contact pairs. 8 out of 11 patients had the same contact selected for gamma and beta activity. Furthermore, recordings in 10 out of 11 patients exhibited polarity reversal across two of the contact pairs, suggesting local generation of potentials. All contacts selected for analysis from these 10 patients were among those with polarity reversal.

### *3.3.2 Movement time*

Patients successfully varied the speed of their reaching movements according to the cued instructions, demonstrating significantly different movement times ($F_{2,20}$ = 51.3, $p<0.0001$; Figure 3.1B). 'Slow' movements (1612 $\pm$ 211 ms) had significantly longer movement times than 'normal' speed (1126 $\pm$

109 ms; $t_{10}$ = 4.27, p <0.0001) and 'fast' (647 ± 57 ms; $t_{10}$ = 5.73, p <0.0001). Importantly, 'fast' movements were significantly shorter than normal ($t_{10}$ = 7.34, p <0.0001).

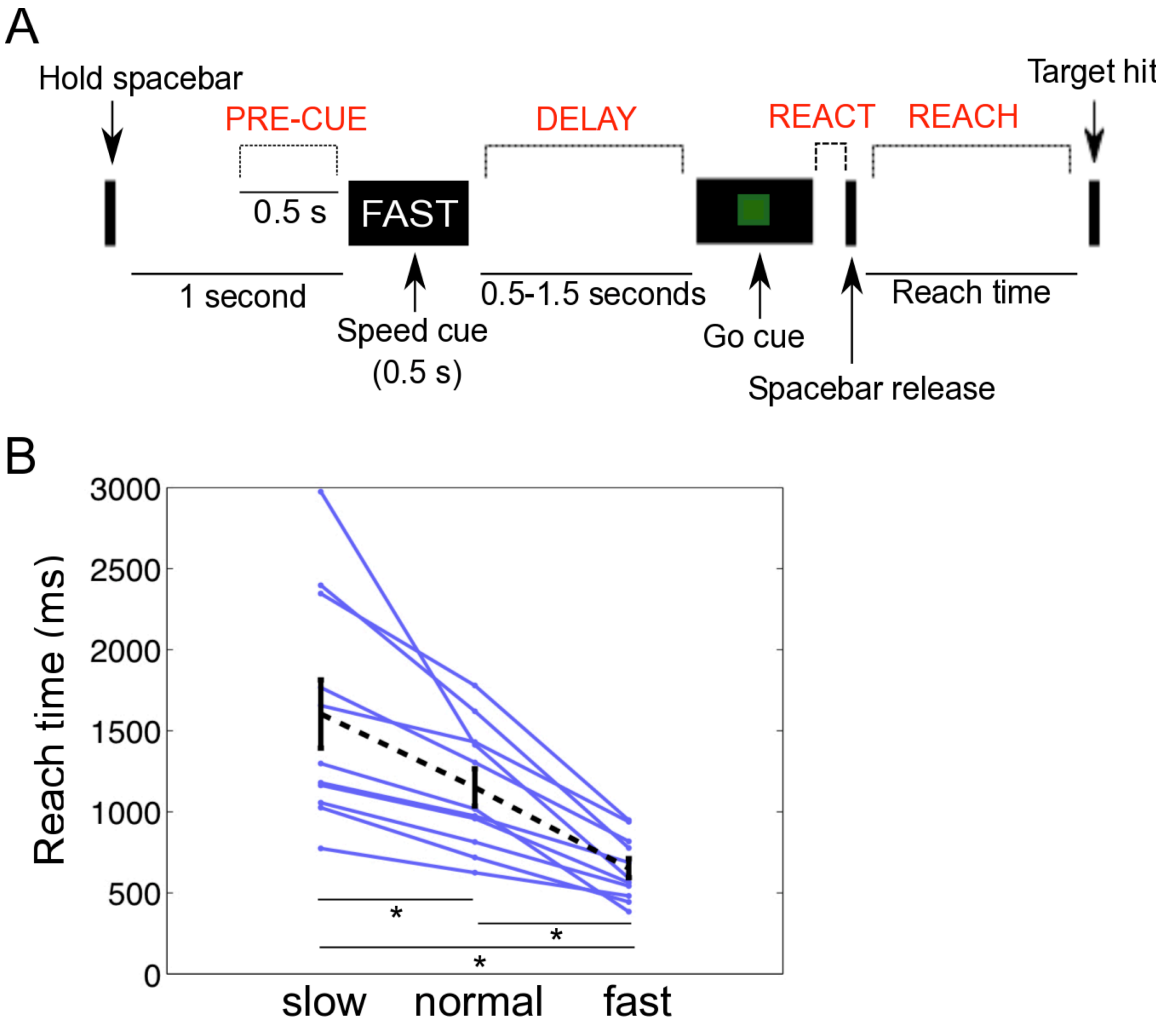


**Figure 3.1.** Schematic of paradigm (A) and movement times (B) for the three different cued speeds. Subjects respond according to cues and have sequentially shorter movement times from slow to normal to fast. *p<0.05.

*3.3.3 Oscillatory activity during preparation*

Figure 3.2A displays the spectrogram of selected channels in the DELAY period aligned to speed cue onset for slow, medium and fast trials. Significance spectrograms (Figure 3.2B) show areas of oscillatory change at $p < 0.05$ across patients. Apparent is a significant desynchronization in the lower beta range of around 13-20 Hz, beginning at cue onset only in the fast condition. In contrast, slow and medium trials have no major oscillatory changes in response to the cue.

Band limited activity for beta (15-30 Hz) and gamma (70-90 Hz) is plotted in Figure 3.2C. Here again, a significant beta desynchronization occurs after the fast cue, with non-significant decreases in beta activity after normal and slow cues. Activity in the low (13-20 Hz) and high (21-30 Hz) beta ranges are plotted in Figure 3.2D, showing a more dramatic decrease in low beta after fast cue onset. In contrast, there is no obvious change in band-limited gamma activity in response to the cue.

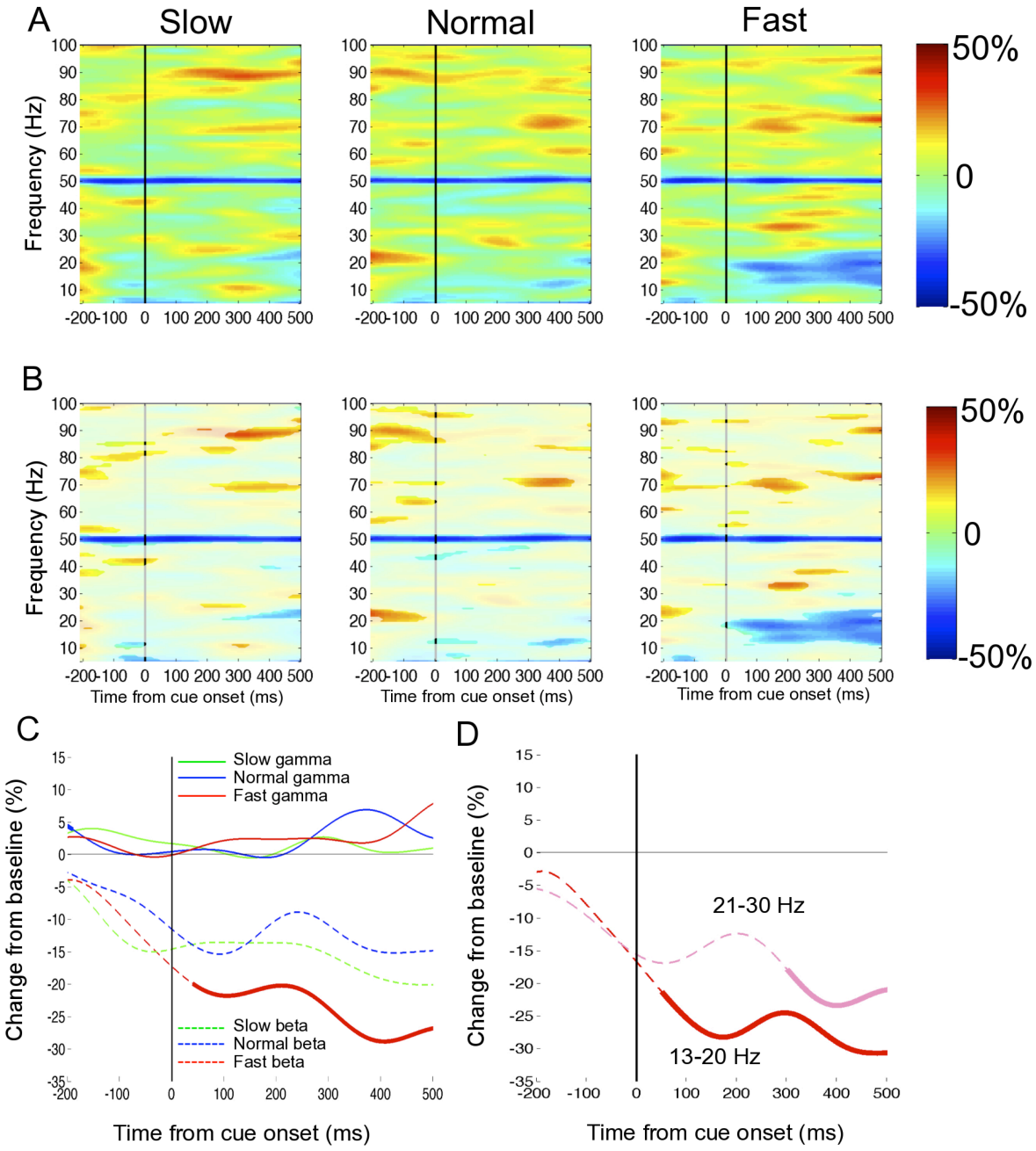


**Figure 3.2** Oscillatory changes after speed cue (DELAY period). A) Spectrograms aligned to speed cue onset showing frequencies from 5-100 for all three cue types, normalized to the PRE-CUE baseline region, displayed from 200 ms prior to cue onset to 500 ms after (common to all trials). Color bars show degree of percentage change. In B) spectrograms are masked

where $p > 0.05$; A significant suppression of 15-30 Hz activity is seen after cue onset only in the fast condition. The specific change in beta activity is confirmed in (C), when averaging over beta range (15-30 Hz, dashed lines) and gamma range (70-90 Hz, solid lines) for fast (red), normal (blue), and slow (green). Lines are emboldened in areas of significant departure from baseline ($p < 0.05$). The only significant change is a decrease in beta activity after presentation of the fast cue, specifically in the low-beta band (D).

### *3.3.4 Oscillatory activity during reaching*

Figure 3.3 displays the spectrograms of the LFP activity during the REACH period. Decreases in beta activity were evident before reach onset (especially for the fast condition), and beta activity was further suppressed after reaching began. This decrease was significant and continuous throughout the reach period for all three conditions.

Increases in gamma activity were observed around the time of reach onset in all three conditions, however there was substantially larger increase in gamma activity immediately after reach onset in the fast condition. Areas of significance for gamma activity were apparent only in the fast condition between approximately 70-90Hz. There were also large increases in 40-60 Hz activity but this was not significant as power increases in this range occurred in only 2 subjects.

Beta activity averaged over 15-30 Hz demonstrated a significant decrease prior to and during reaching (Figure 3.3C), resolving to non-significant levels approximately 500 ms after reach end. There were no differences in absolute power changes between speeds, apart from a quicker resynchronization in the fast condition due to the reduced movement time. There was an increase in band limited gamma activity immediately prior to and during the reach. Slow and normal speeds had a modest increase in gamma activity, peaking at about 25%, with very brief periods of significance from baseline. Fast reaching resulted in a substantially higher increase in gamma, achieving a peak increase of approximately 60%, and remaining significantly above baseline throughout the reach period.

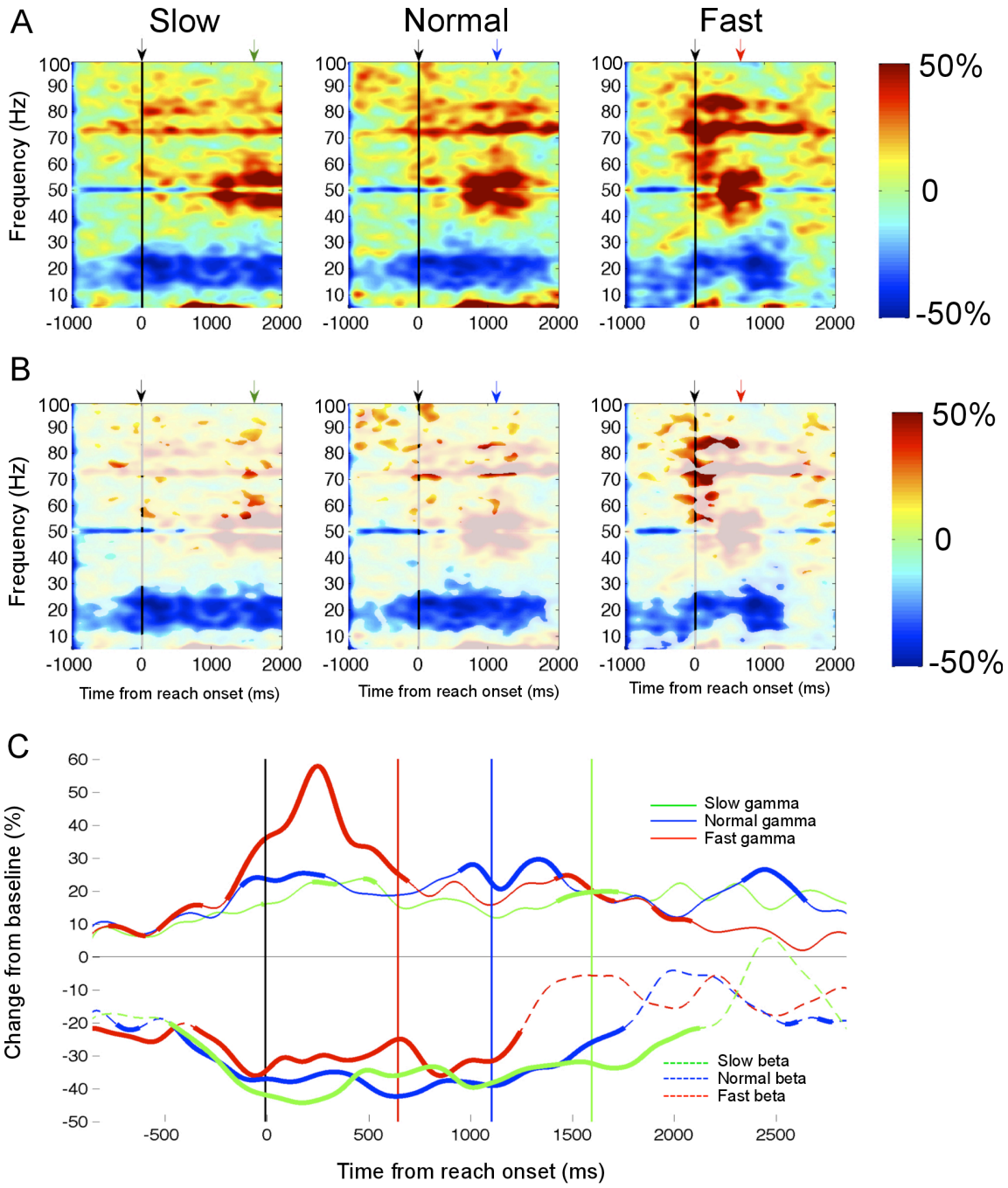


**Figure 3.3** Oscillatory changes during reaching. A) Spectrograms aligned to reach onset showing frequencies from 5-100 for all three reaching speeds, normalized to the PRE-CUE baseline region. Color bars show degree of percentage change. Overlying arrows show time of reach onset (black), and mean time of reach end for slow (green), normal (blue), and fast (red). In

B) spectrograms are masked where $p > 0.05$; A similar significant suppression of 15-30 Hz activity is seen before and during reach in all conditions. However gamma activity, centred at around 75 Hz, is highest and achieves significance only in the fast reach. Areas of significance span from 70-90 Hz. Changes in the beta and gamma bands are confirmed in (C), when averaging over beta (15-30 Hz) and gamma (70-90 Hz) ranges. Lines are emboldened in areas of significant departure from baseline ($p < 0.05$). Beta activity desynchronizes to a similar extent for all three reaching conditions. However gamma activity increases substantially more in the fast condition (~60%) compared to normal or slow, with a much longer period of significance.

*3.3.5 Average beta power in the three task periods*

To quantitatively assess changes in oscillatory activity, the average percentage change in beta band power was calculated for the three task periods, from a common baseline period of 500 ms preceding speed cue presentation (PRE-CUE). We additionally baselined REACT to DELAY, and REACH to REACT, in order to visualize the incremental change across task periods (Figure 3.1A).

In DELAY (Figure 3.4A), there was a significant decrease in beta activity for fast ($t_{10} = -2.9$, $p = 0.017$), but not slow ($t_{10} = -2.0$, $p = 0.079$) or normal speeds ($t_{10} = -1.7$, $p = 0.13$). An ANOVA across the three speeds revealed a differential effect ($F_{2,20} = 15.1$, $p = 0.001$), accounted for by significantly

more suppressed beta activity in fast compared to slow ($t_{10}$ = -3.6, p = 0.016) and normal ($t_{10}$ = -6.8, p = 0.0001) trials.

In REACT as compared to DELAY (Figure 3.4B), beta activity decreased significantly for slow ($t_{10}$ = -3.7, p = 0.0041), normal ($t_{10}$ = -4.3, p = 0.0016), but not fast ($t_{10}$ = -1.2, p = 0.26) trials. There was a significant difference across conditions ($F_{2,20}$ = 12.6, p = 0.0002), accounted for by a larger change in slow compared to fast trials ($t_{10}$ = -4.2, p = 0.005) and normal compared to fast ($t_{10}$ = -4.3, p = 0.005). When compared to the pre-cue period (Figure 3.4D), REACT showed significant beta desynchronizations for slow ($t_{10}$ = -4.0, p < 0.0024), normal ($t_{10}$ = -3.5, p = 0.0061), and fast ($t_{10}$ = -3.5, p = 0.0058) trials. However there was no difference between conditions ($F_{2,20}$ = 2.1, p = 0.066). Thus beta desynchronisation in slow and medium speed trials caught up with the earlier desynchronisation in the fast trials.

Beta activity did not change significantly between REACT and REACH (p > 0.05) and there was no difference between conditions ($F_{2,20}$ = 0.018, p = 0.93, Figure 3.4C). When comparing REACH to the PRE-CUE period (Figure 3.4E), beta activity was significantly suppressed during slow ($t_{10}$ = -5.9, p = 0.0001), normal ($t_{10}$ = -4.4, p = 0.0013), and fast trials ($t_{10}$ = -3.7, p = 0.0038). However, there was no differential effect between the three speeds ($F_{2,20}$ =0.29, p = 0.75).

In summary, the 'fast' cue elicited early beta desynchronization in DELAY and maintained this decrease throughout reach preparation and execution. In

contrast, beta desynchronized later (during REACT) in the slow and normal conditions. In all conditions, there was no change between REACT and REACH, suggesting that most of the drop in beta occurred prior to movement.

*3.3.6 Average gamma power in the three task periods*

In DELAY (Figure 3.4F), gamma activity showed no significant change from the DELAY period in slow or normal trials ($p > 0.05$), but a significant increase for fast trials ($t_{10} = 2.9$, $p = 0.016$). However, there was no significant difference between conditions ($F_{2,20} = 1.7$, $p = 0.211$).

There were no significant changes from DELAY to REACT ($p > 0.5$, Figure 3.4G), and no difference between conditions ($F_{2,20} = 0.88$, $p = 0.43$). Similarly there were no significant increases as compared to the PRE-CUE period (Figure 3.4I) across speeds ($p > 0.05$), and no significant difference between conditions ($F_{2,20} = 2.3$, $p = 0.13$).

Comparing REACT and REACH, a significant increase in gamma activity emerged (Figure 3.4H; slow: $t_{10} = 3.3$, $p = 0.0077$, normal: $t_{10} = 3.2$, $p = 0.0085$, fast: $t_{10} = 4.7$, $p = 0.0008$). Furthermore, there was a significant difference between conditions ($F_{2,20} = 8.56$, $p = 0.002$). The difference was due to significantly higher gamma in the fast compared to slow ($t_{10} = -3.1$, $p = 0.033$) and normal ($t_{10} = -2.8$, $p = 0.033$) trials, but not between slow and normal trials ($t_{10} = -1.2$, $p = 0.76$). Overall power compared to the PRE-CUE period (Figure 3.4J) showed significant gamma increases across all three conditions (slow: $t_{10} = 2.9$, $p = 0.014$, normal: $t_{10} = 2.9$, $p = 0.015$, fast: $t_{10}$

= -3.3, p = 0.0075). Furthermore, there was a significant difference between conditions ($F_{2,20}$ = 7.7, p = 0.015), due to significantly higher gamma in the fast reach (58.4 $\pm$ 0.15%) compared to slow (17.9 $\pm$ 0.06%, $t_{10}$ = 2.8, p = 0.04) and normal (25.2 $\pm$ 0.09%, $t_{10}$ = 3.1, p = 0.037) trials, but not between slow and normal speeds ($t_{10}$ = -1.3, p = 0.42).

In summary, gamma power changed minimally during preparation but increased dramatically upon the onset of reaching. The increase in gamma power was most pronounced for the fast reach trials.

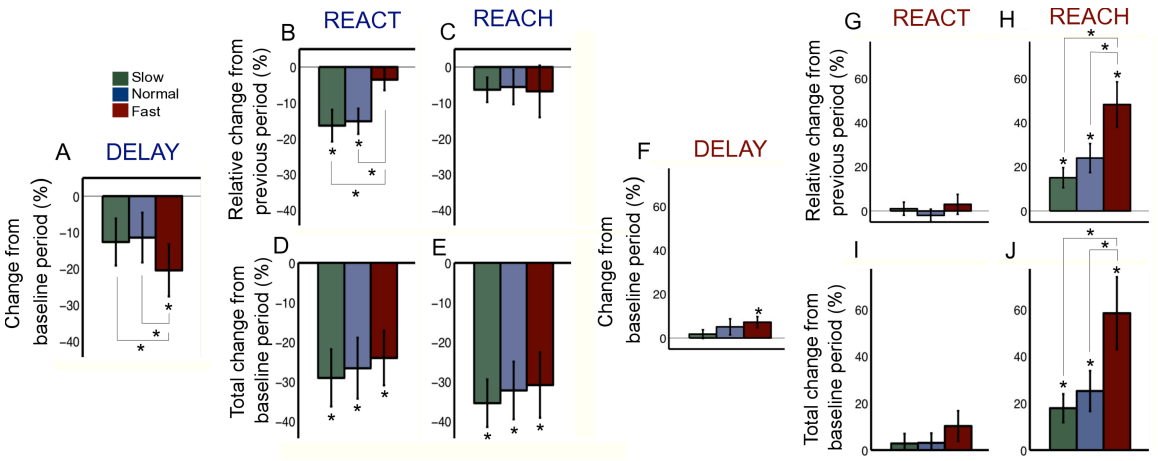


**Figure 3.4.** Mean power of beta (A-E) and gamma activity (F-J) during the various epochs of the task. The fast cue (red bar) elicits earlier desynchronization for beta, most of which occurs in DELAY (A) immediately after the speed cue. Slow (green bar) and normal (blue bar) conditions are slower to desynchronize, with most occurring between DELAY and REACT (B). There is minimal change between REACT and REACH (C). Normalizing all data to the common PRE-CUE period, there is accumulation of

desynchronized activity between DELAY (A), REACT (D), and REACH (E), however the only differential effect is during DELAY with more desynchronization in response to the fast cue. On the other hand, gamma activity is minimal and shows no difference between conditions during DELAY (F) and REACT (E, I), but shows a strong increase during reaching, specifically during the fast reaches (H, J). *p<0.05

*3.3.7 Correlations between speed of reach response and gamma activity*

To determine if gamma activity was related to speed of movement on a trial-by-trial basis we correlated the mean gamma increase (as percentage change) from REACT to REACH with the mean speed of movement (taken as the log of the reach time) for each subject. The average of the R value in all patients was -0.29 $\pm$ 0.07, and this was significant when tested against zero ($t_{10}$ = -4.0, p = 0.0027, Figure 3.5A). Thus, shorter reaching times (higher speeds) were associated with larger gamma increases. For beta activity, the mean R value was 0.16 $\pm$ 0.39 which was not significantly different from zero ($t_{10}$ = 1.4, p = 0.20, Figure 3.5A). Gamma and beta R values were also significantly different from each other (t = 2.5, p = 0.03). Examples of two individual gamma correlations are shown in Figure 3.5B. There was no significant correlation between average gamma increase and reach time across subjects (R = -0.27, p = 0.13).

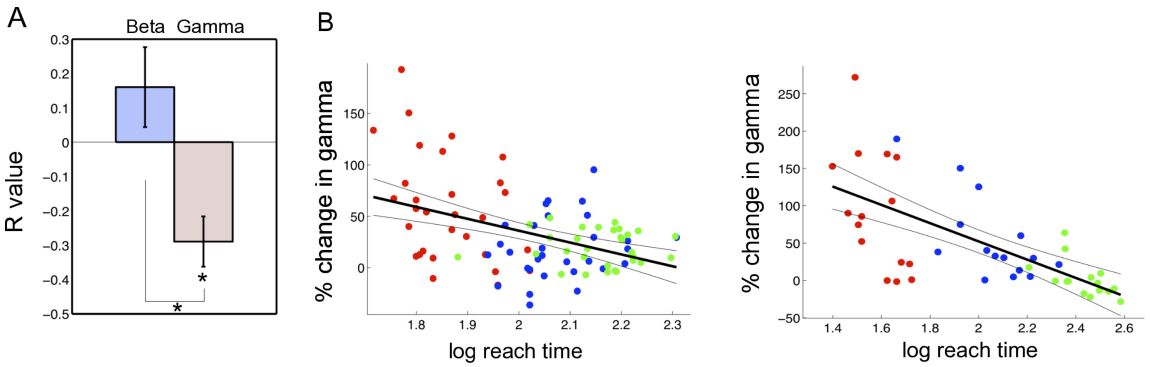


**Figure 5.** Correlations between speed and oscillatory activity. (A) There is a significant negative mean R value for gamma activity when averaging across all individual correlations between reach time and gamma power. There was no significant mean R value for beta activity. (B) shows two examples of correlations in patient 2 and patient 11, respectively ($r = -0.43$, $p < 0.0001$ and $r = -0.67$, $p < 0.0001$), with slow (green), normal (blue), and fast (red) reaches. *$p < 0.05$.

## 3.4 Discussion

We sought to determine if beta and gamma activity in the region of the subthalamic nucleus were related to task demands during arm reaching. We found a dramatic increase in the amplitude of gamma oscillatory activity with fast reaching movements. In contrast, activity in the beta range desynchronized prior to and during movement. Although the eventual level of

beta desynchronization did not differ between slow, medium and fast speed movements, the desynchronisation in fast movements had an earlier onset. Thus, for a movement that can be programmed before execution - as in the task here - the depth of beta desynchronisation is relatively fixed (see also Brucke et al, 2012), consistent with the hypothesis that beta activity serves to 'gate' motor output. This gate can be opened earlier if the anticipated task is demanding. The latter is in accord with the notion that beta suppression is important in securing resources for the planned action (Jenkinson and Brown, 2011).

The above may be an over-simplified account of the behavior of beta activity as it does not consider variation within the frequency band. Subdivision of the beta band revealed that the earlier onset of beta desynchronisation in fast movements occurred in the lower beta frequencies (13-20 Hz). Kempf et al. (Kempf et al., 2007) likewise found that the earliest motor related reactivity was seen over 6-18 Hz, although this study failed to distinguish alpha from lower frequency range beta activity. Still, the latter authors found that the early desynchronisation occurred when more demanding movements had to be performed. That the timing of beta desynchronisation has functional consequences is supported by the correlation between the onset of beta desynchronisation and reaction time under conditions of time pressure (Kühn et al., 2004; Doyle et al., 2005). Thus beta suppression, particularly that in the lower range of the frequency band, may occur earlier when more demanding movements have to be executed or when cued movements are made under time pressure.

Gamma activity has been observed in a variety of neural systems and in different frequency bands depending on function and brain area. The most consistent gamma activity in our records was between 70-90 Hz. Such activity has been previously reported in the basal ganglia (Alegre et al., 2005; Androulidakis et al., 2007b; Kempf et al., 2009; Brücke et al., 2012) and primary motor area of the cortex (Crone et al., 1998; Gonzalez Andino et al., 2005; Ball et al., 2008; Muthukumaraswamy, 2010). The increase in 70-90Hz gamma with increased speed seen here compliments a recent study demonstrating a similar relationship between gamma and movement velocity seen in LFPs from the globus pallidus of dystonic patients (Brücke et al., 2012). In the latter study gamma activity scaled with both amplitude and velocity, but not direction, yet it was not fully possible to disentangle the former two. Here we kept amplitude constant and observed an increase in gamma with speed alone. Alternatively, the gamma modulation could be related to the presumed increase in force with higher speeds. There is prior evidence that cortical gamma activity may be important in the coding of force, as gamma increases in the cortex are more prominent with large rather than small force production (Muthukumaraswamy, 2010), and electrical stimulation of the motor cortex at 70 Hz can produce increases in force rate production in healthy humans (Joundi et al., 2012).

However, any relationship between gamma activity and force could also be secondary to the coding of motor effort by oscillatory activity in the 70-90 Hz band. Recent evidence implicates the basal ganglia in the scaling of effort in response to the energetic demands of a particular movement (Mazzoni et al.,

2007). Gamma activity has also been considered to play a role in attention and arousal (Bauer et al., 2006) and it could be argued that the higher gamma activity with faster movements related to the higher degree of attention required. However, slow reaching trials also necessitated attention in order to inhibit oneself from moving at normal speeds. In addition, the major component of gamma synchronization occurred after movement onset, whereas attention might be expected to have been highest immediately following the imperative cue.

Recording from the STN of patients with Parkinson's disease creates inherent challenges, as any attempts to study physiology are potentially affected by the known pathology in the basal ganglia. Additionally, bradykinesia will have prevented many patients from generating very fast speeds thereby limiting the range of velocities that could be studied. However, we opted to study patients on their normal dopaminergic medication so as to increase motor performance during the task, reduce fatigue, and, as far as possible, restore physiological functioning to the STN. Dopaminergic therapy is known to suppress the heightened pathological beta activity and increase gamma activity in PD (Brown, 2003), allowing us to more effectively study gamma oscillations compared to studies off medication. Even so, our results may still have been influenced by the presence of motor dysfunction and pathological alteration in the basal ganglia. Nevertheless, the general similarities of the findings from healthy, dystonic and Parkinson's disease subjects suggests a common physiological role for gamma synchronization in the control of movement.

In summary, we have shown that beta and gamma activity in the region of the subthalamic nucleus are modulated prior to and during naturalistic reaching movements. In line with previous reports, the direction and the timing of the changes differs between the frequency bands. The differences lead us to suggest that beta band desynchronisation gates motor processing and thus necessarily develops before movement. In contrast, gamma band changes are only fully developed once movement has started. We suggest that gamma band increases are more closely related to motor processing, and in particular help scale movement through the coding of velocity, force or possibly motor effort.

# 4. DRIVING OSCILLATORY ACTIVITY IN THE HUMAN CORTEX ENHANCES MOTOR PERFORMANCE


***-Abstract-***

The role of oscillatory activity in the brain remains one of the most important and unresolved questions in neuroscience. Chapter 3 demonstrated that beta and gamma oscillations in the subthalamic nucleus were related to the preparation and performance of arm reaching movements. However, this evidence is merely correlative, and thus we sought to demonstrate a causal relationship between oscillatory activity and motor output. Here, we show that the driving of oscillations in cortical motor areas with transcranial alternating current stimulation can alter performance in healthy subjects in opposite ways depending on frequency. The scale of the effects depends on the subject's prevailing intention, and is both quantitatively important and enhances performance over and above that achieved through maximum voluntary effort. Our findings are important as they prove that cortical oscillations are of causal importance in motor behavior, with effects dependant on the frequency of stimulation. Moreover, we can improve motor performance through non-invasive stimulation, opening up new treatment approaches in diseases dominated by insufficient or excessive movement, such as Parkinson's disease and Tic disorders.

## 4.1 INTRODUCTION

Voluntary movement is accompanied by changes in the degree to which neurones in the brain synchronise their activity within discrete frequency ranges. Two patterns of movement-related oscillatory activity stand out in human cortical motor areas. Activity in the beta frequency (15-30 Hz) band is prominent during tonic contractions, but is attenuated prior to and during voluntary movement (Engel and Fries, 2010). Without such attenuation movement may be slowed, leading to the suggestion that beta activity promotes postural and tonic contraction, possibly at a cost to the generation of new movements (Gilbertson et al., 2005; Pogosyan et al., 2009). In contrast, activity in the gamma (60-90 Hz) band increases during movement (Muthukumaraswamy, 2010). The direction of change suggests that gamma activity might facilitate motor processing. In correspondence with this, increased frontal gamma activity is related with reduced reaction times (Gonzalez Andino et al., 2005). Yet the possibility remains that these functional correlations reflect an epiphenomenal rather than causal relationship. Here we provide strong evidence that oscillatory activities at the cortical level are mechanistically involved in determining motor behavior and can even improve performance. By driving cortical oscillations using non-invasive electrical stimulation we show opposing effects at beta and gamma frequencies and interactions with motor task that reveal the potential quantitative importance of oscillations in motor behavior.

## 4.2 METHODS

### *4.2.1 Task and stimulation*

The Oxfordshire REC B committee approved the study and all subjects gave informed written consent. Nineteen healthy subjects were recruited. To demonstrate that oscillatory cortical activities can modify motor behavior we used transcranial alternating current stimulation (TACS) to entrain oscillatory activity in the cortex with low amplitude currents at specified frequencies in a completely non-invasive manner (Pogosyan et al., 2009). Such stimulation has been demonstrated to increase oscillatory activity in the brain at the frequency of stimulation (Zaehle et al., 2010). Thus we were able to investigate how such stimulation modulated motor performance in a go/no-go paradigm, which contrasts two very different intentions, action and motor inhibition. Eighteen healthy subjects who were unable to detect periods of active stimulation were asked to hold a grip force sensor (MIE Medical Research ltd, United Kingdom) with their right hand while seated and attending to a go/no-go task presented on a computer screen in front of them (Figure 4.1). The paradigm consisted of the presentation of a fixation cross which lasted 3 seconds, followed by a pre-cue (Figure 4.1). The pre-cue was displayed for between 250-750 ms and was followed immediately by either a go or a no-go signal lasting 250 ms, randomly selected with a 2:1 ratio. This ratio was chosen so as to increase the possibility of errors on no-go trials due to a heightened expectation of go cues. Sessions consisted of 4 blocks, each with 42 trials. Subjects were reminded before each block to

remain vigilant and respond as quickly as possible to go cues. Stimulation was randomly applied in 50% of trials and ramped up over 0.5s simultaneously with the presentation of the fixation cross. Stimulation was on for 3 seconds before the subjects responded, and lasted a total of 5 seconds before ramping down over 0.5 s. Stimulation was delivered using a bipolar current stimulator (DC-Stimulator Plus, NeuroConn, Ilmenau, Germany) via sponge electrodes soaked in saline. We placed the target electrode (area 5 x 7 cm) on the scalp overlying the hand area of the left motor cortex, as identified by single monophasic pulses of Transcranial Magnetic Stimulation (MagStim 200, Whitland, Wales, UK), and the reference electrode (5 x 10 cm) on the ipsilateral shoulder. Subjects came for two separate sessions in which either 20 Hz or 70 Hz stimulation was delivered. Sessions were separated by approximately 7 days and the order of 20 Hz and 70 Hz stimulation was counterbalanced.

*4.2.2 Blinding*

During the first session, the subject's phosphene or scalp sensation threshold (whichever was lowest) to 20 Hz stimulation was determined, and an amplitude 50 μA below this was selected for subsequent testing stimulation. Impedance during all stimulation sessions was always kept below 15 mΩ. Sub-threshold stimulation was confirmed by a forced-choice task comprising of 20 rounds of stimulation. One subject was always aware when stimulation was being applied and was therefore excluded from the study. A further two subjects experienced scalp sensations or phosphenes when stimulated at the

selected intensity in the second session and so the intensity in the second session was lowered by a further 100μA. There was no significant difference between the mean stimulus amplitude of the two sessions (903 ± 111 μA for beta and 915 ± 98 μA for gamma stimulation, $t_{[13]}$=-0.128, p=0.901, paired t-test).

*4.2.4 Analysis*

For go trials, we determined response onset by thresholding force responses at 2% of maximum force output on a trial-by-trial basis. We aligned trials according to this response onset within subjects, and the thresholding latency was used to determine reaction time, with the exception that any responses made within 100 ms of target presentation were rejected. Any go-trials in which no response was made were also rejected. We then differentiated the force response to obtain rate of force, with trials where peak rate was outside 2 SD of the mean rejected. Collectively, these rejection criteria resulted in the exclusion of less than 10% of trials in any condition (Table 4.1). Moreover, there was no significant difference in the number of trials eliminated across conditions (Table 4.1). To determine the initial rate of force development, individual force rate averages were realigned across subjects according to 5% of peak force rate, and the average taken from that point to the peak force rate. To determine peak force and the peak rate of force development, force and differential force traces were aligned to peak values (See Figure 4.2 for example of individual

averages during no-stimulation). Grand averages were then constructed about both initial rate and peak rate.

## 4.3 RESULTS

### *4.3.1 Forced-choice*

To assess the subject's perception of the stimulation, we employed a force-choice test prior to the experiment in which the subjects would attend to the task cues but instead of making a motor response they would indicate whether or not they thought the stimulation was active each time a response cue was presented (either red or green). The stimulation setting (ON or OFF) and their response (ON or OFF) was recorded for 20 trials. We then coded correct responses as 1 and incorrect responses as 0 and performed a binomial test on each dataset. The p value was always insignificant and ranged from 0.2 to 1, with the exception of one case which was 0.077. This confirmed that subjects were not aware of any active stimulation during the task.

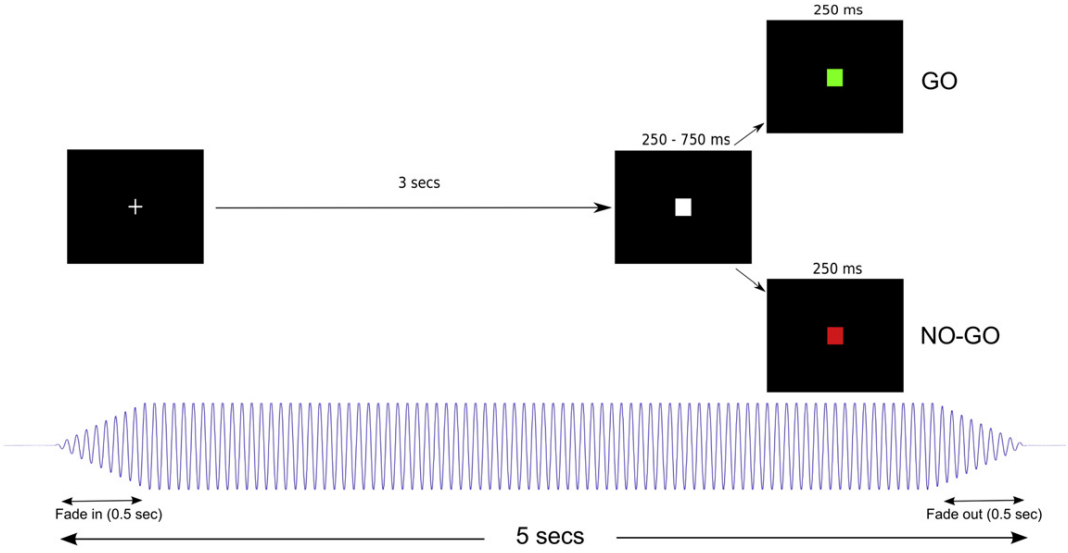


**Figure 4.1**

Schematic of paradigm used for go/no-go task. A fixation cross is presented which triggers the onset of sinusoidal stimulation shown below. After 3 seconds a square white pre-cue is presented followed quickly (250-750 ms, randomized) by either a square green go cue or red no-go cue, which lasted 250 ms. Subjects were instructed to squeeze as quickly and as hard as they could in response to the go cue, and withhold their response on no-go cues. Stimulation had a 0.5s ramp up and down, and lasted for a total of 5 seconds, which meant that it continued throughout the behavioral response and faded away shortly thereafter. There was then a 6 s delay between the response cue and subsequent fixation cross for the next trial, during which the subject was at rest.

*4.3.2 Effect of stimulation on go trials*

There was no change in reaction time or peak force during either 20 or 70 Hz stimulation (Table 4.1). However, stimulation at 20 Hz reduced the initial rate of force development by 1.89 ± 0.74 % compared to no-stimulation ($t_{17}$ = -2.541 , p =0.0211, one-sample t-test; drop from 1036 ± 101 N/s (SEM unless stated otherwise) to 1024 ± 103 N/s, $t_{[17]}$ =1.781, p =0.1057; Figures 4.3A, 4.3E, & 4.3G), and led to a reduction in peak force rate of 2.56 ± 0.87 % ($t_{17}$ = -2.934 , p =0.0092; drop from 1919 ± 176 N/s to 1883 ± 179 N/s, $t_{17}$ = 3.414, p = 0.0033; Figures 4.3B, 4.3F, & 4.3G).

Gamma stimulation had the opposite effect. The initial rate of force development increased by 5.37 ± 1.3 % ($t_{17}$ = 3.92, p =0.0011; rise from 996 ± 105 N/s to 1043 ± 109 N/s, $t_{[17]}$ =-4.95, p = 0.0001; Figures 4.3C, 4.3E, 4.3G). Peak force rate increased by 2.08 ± 0.82 % relative to no-stimulation ($t_{17}$ = 2.537, p =0.0212; rise from 1806 ± 171 N/s to 1837 ± 170 N/s, $t_{17}$ =-2.32, p = 0.0344; Figures 4.3D, 4.3F, & 4.3G).

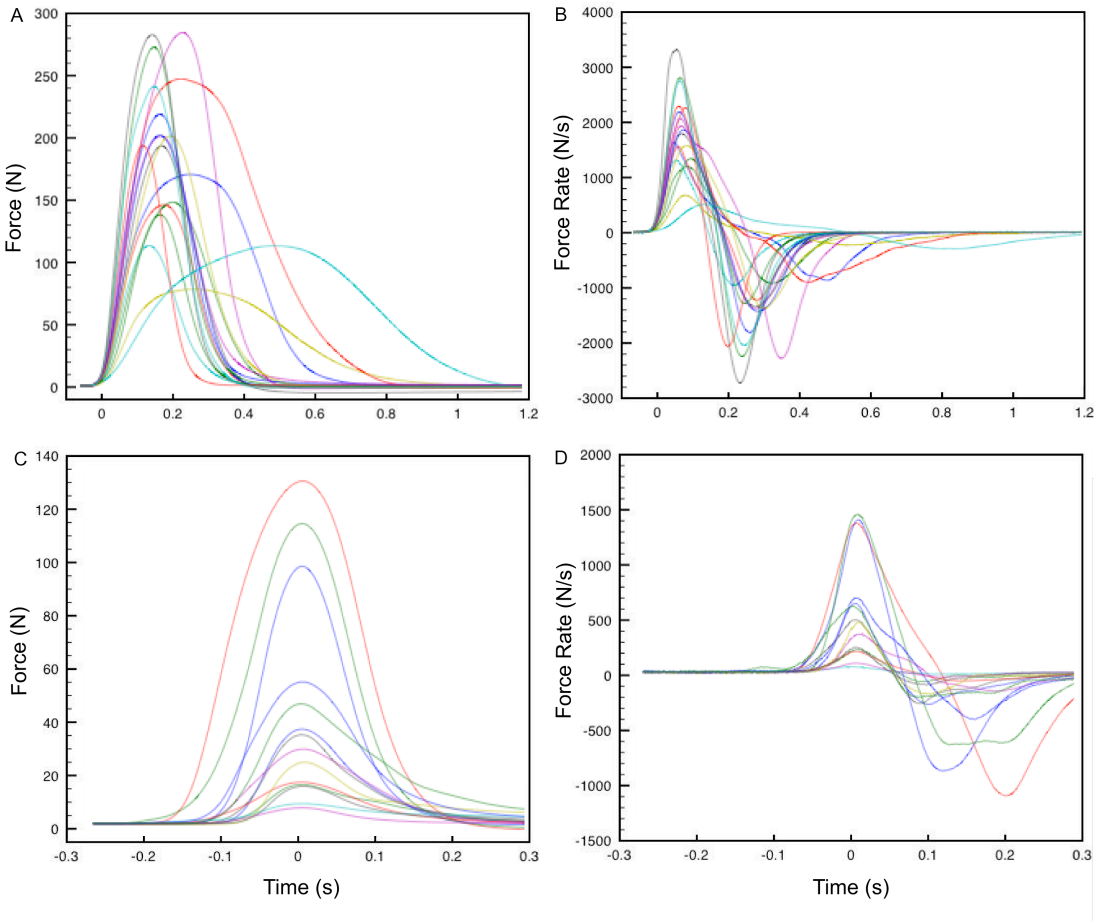


**Figure 4.2**. Individual subject averages during no-stimulation. Average traces per subject during no-stimulation trials in the 20 Hz session, shown for (A) go force aligned to onset, (B) go force rate aligned to onset, (C) no-go force aligned to peak, and (D) no-go force rate aligned to peak. Subjects are color matched across panels.

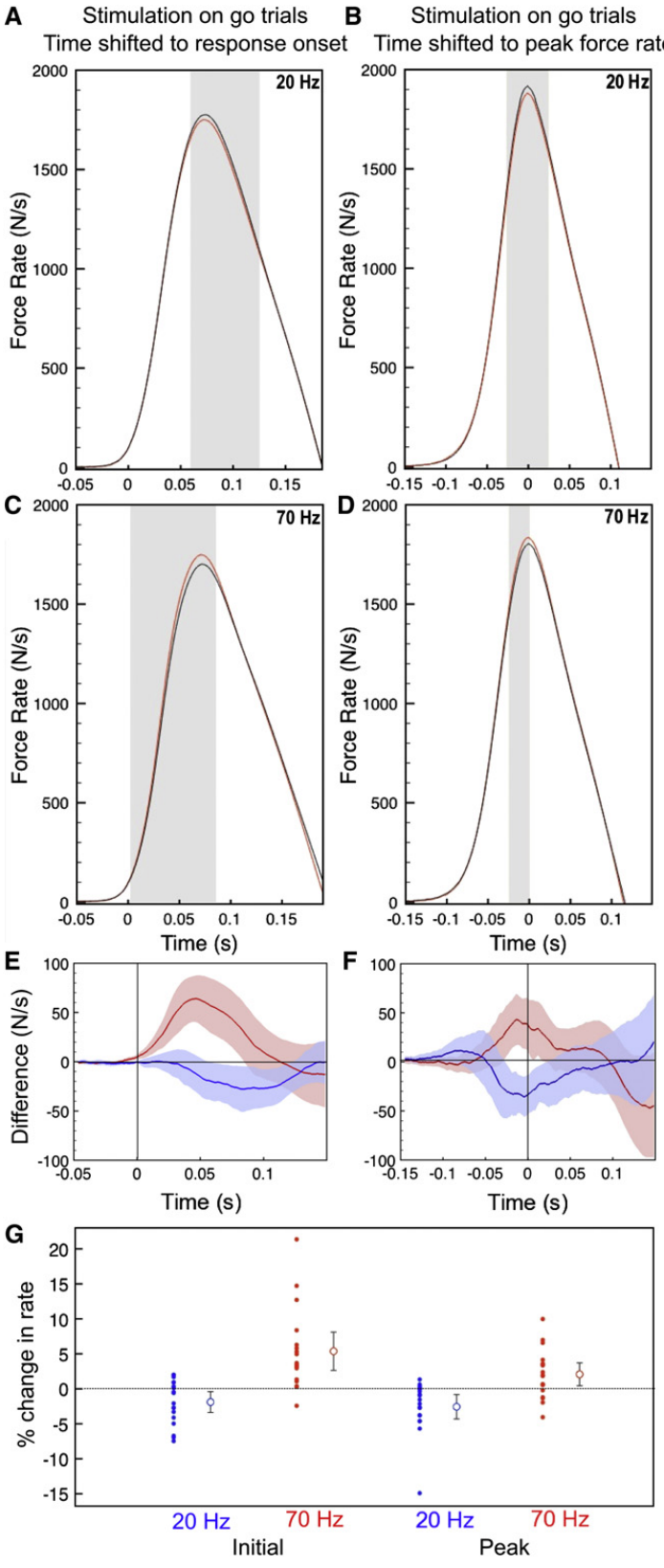
A
Stimulation on go trials
Time shifted to response onset
B
Stimulation on go trials
Time shifted to peak force rate
20 Hz
70 Hz
Force Rate (N/s)
Time (s)
C
D
E
F
Difference (N/s)
G
% change in rate
20 Hz
70 Hz
Initial
Peak

**Figure 4.3**

Effect of stimulation on go trials. In (A) and (B), stimulation is applied at 20 Hz, and in (C) and (D) at 70 Hz. Black traces show no-stimulation trials and red traces stimulation trials. Traces are grand averages of all subjects' force rates aligned to the point of first development of 5% peak force rate (A & C) or peak rate of force generation (B & D). Vertical gray bars demonstrate areas of significant difference between stimulation and no-stimulation (serial two-tailed paired t tests, $p<0.05$). (E & F) are the mean differences with confidence intervals of $\pm$ 2 SEM between stimulation and no-stimulation conditions for 20 Hz (blue) and 70 Hz (red), aligned as above. Vertical lines at time 0 represent the point of first development of 5% peak force rate (E) and point of peak force rate (F). In (G), percent changes for each subject are shown for both initial rate and peak rate, for 20 Hz (blue) and 70 Hz (red) stimulation. Adjacent to individual changes are mean changes with ± 2 SEM. See also Figure 4.2 for example of individual traces.

*4.3.3 Effect of stimulation on no-go trials*

Our paradigm elicited contrasting intentions; action on go trials or motor inhibition on no-go trials. During no-go trials, false responses provided a behavioral measure of performance in which motor inhibition was only partially successful. Such errors of commission were absent in 4 out of the 18 subjects, and in the remaining subjects occurred in an average of 45% of trials (Table 4.2). In these subjects peak force in error trials was far smaller

than in go trials, confirming that motor inhibition was present, but not entirely successful during these trials (40.0 ± 9.9 N versus 212.0 ± 11.7 N, $p<0.001$, paired t-test).

Beta stimulation led to a dramatic 34.5± 10.7 % drop in the peak rate of force development in error trials relative to no-stimulation ($t_{13}$ = -3.215, p =0.0068; from 607 ± 135 N/s to 413 ± 127 N/s, $t_{13}$ =4.31, p = 0.00084; Figure 4.4C). A comparable 35.7± 10.2% decrease in peak force was seen ($t_{13}$ = -3.49, p =0.004; from 462 ± 109 N to 316 ± 104 N, $t_{13}$ =-4.45, p=0.00053; Figures 4.4A & 4.4C). The effects of gamma stimulation were more variable and showed no significant difference in either peak force (32.2 ± 31.2 %, $t_{13}$ = 1.033, p =0.3204), or peak rate of force generation (14.8 ± 37.2 %, $t_{13}$ = 0.3891, p =0.6971; Figure 4.5). This variability was mainly due to three results from two subjects who had percent increases more than 4 times the standard error from the mean during gamma stimulation. However, the effect of gamma stimulation remained insignificant even when these results were eliminated (Figure 4.4C; Table 4.3).

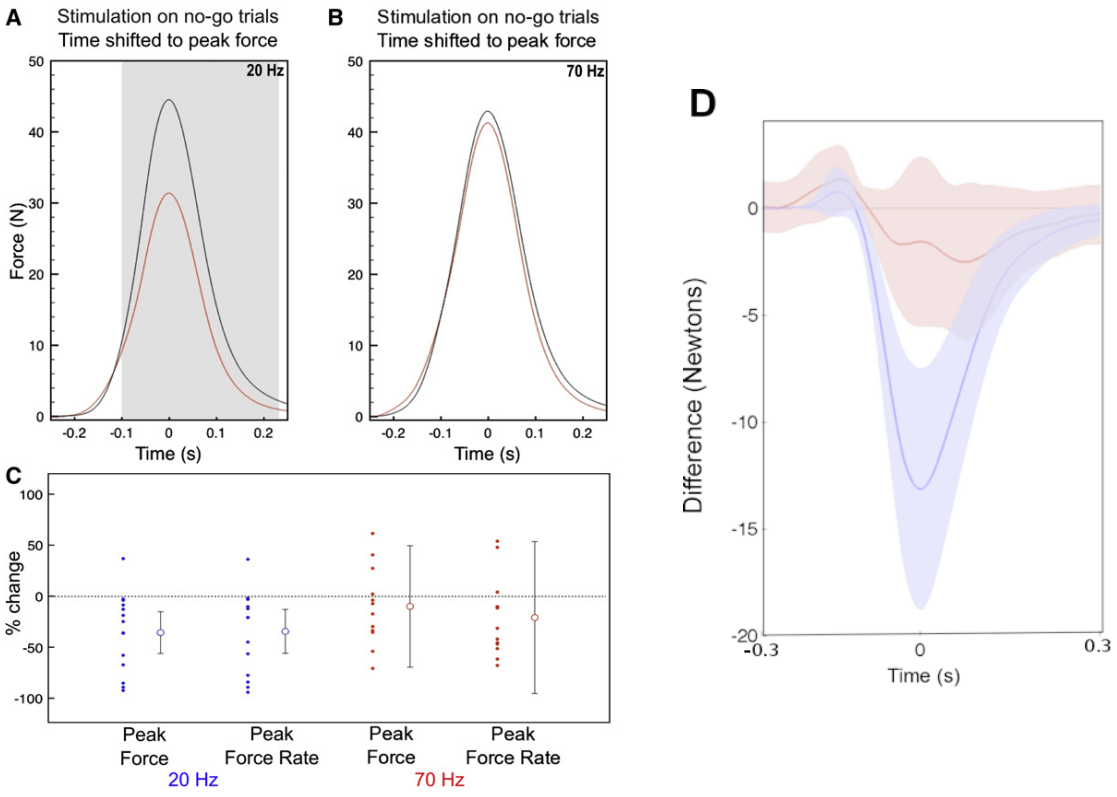


**Figure 4.4**

Effect of stimulation on no-go trials. Grand averages for no-go trials aligned to peak force are displayed for 20 Hz (A) and 70 Hz (B), with the gray bar showing an extended period of significant suppression for 20 Hz but not 70 Hz. Individual percent changes are shown in (C) for 20 Hz (blue) and 70 Hz (red) for peak force and peak rate of force generation along with means ± 2 SEM (displayed with 2 outliers not shown from gamma peak force, and 1 from gamma peak velocity. Outliers are shown in Figure 4.5). See also Figure 4.2 for example of individual traces. D) is the mean difference with confidence intervals of 2 $\pm$ SEM between stimulation and no-stimulation conditions for 20 Hz (blue) and 70 Hz (red) on no-go trials.

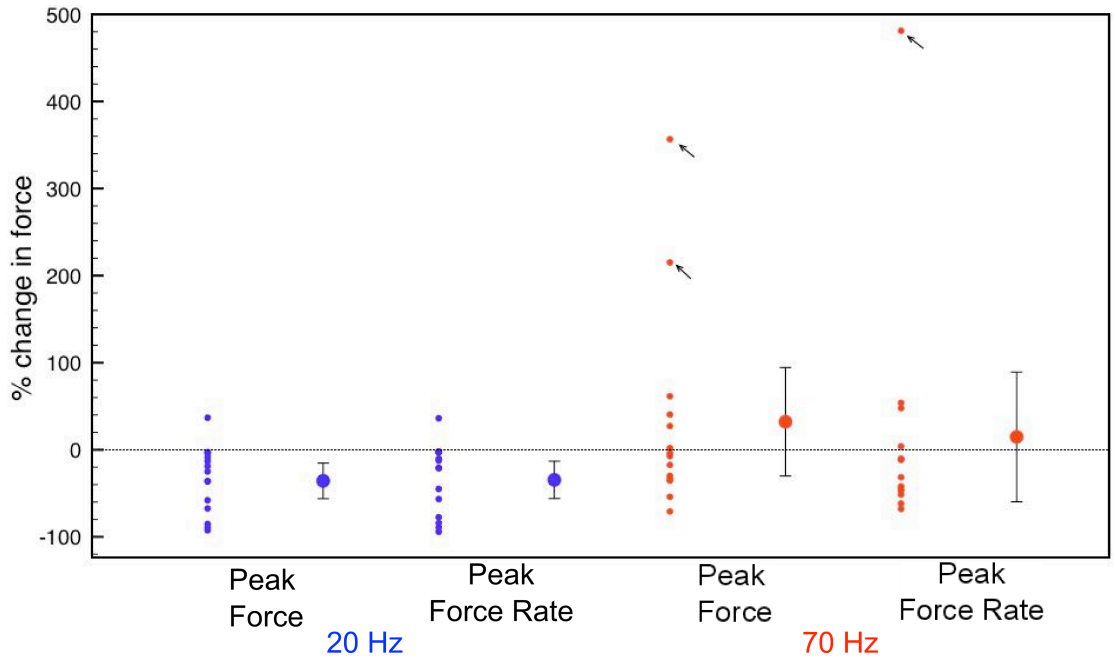


**Figure 4.5**. No-go % change with outliers included. Individual % changes are shown for 20 Hz (blue) and 70 Hz (red) for peak force and peak rate along with means ± 2 SEM. Outliers are identified with arrows.

*4.3.4 Correlation between go and no-go effects*

The impairment of force generation in both go and erroneous no-go trials with 20 Hz stimulation raised the question: are these effects related? In line with this, there was a significant correlation between percent change of peak rate of force generation in go trials and no-go trials during 20 Hz stimulation, ($r=0.728$, $p=0.0032$, Figure 4.6) with no such correlation for 70 Hz ($r=0.270$, $p=0.35$), suggesting a relationship between the mechanisms of force rate inhibition.

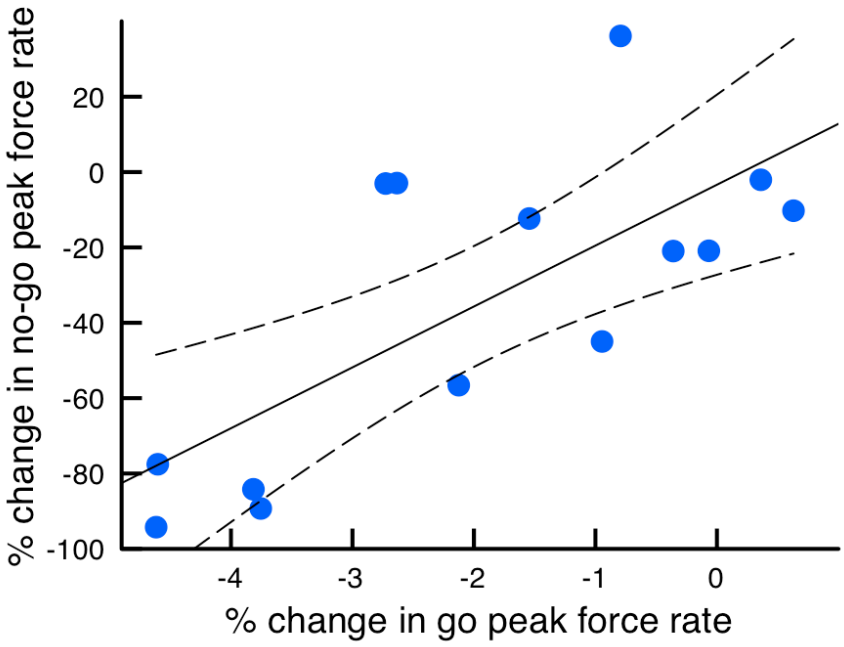


**Figure 4.6**

Correlation and 95% confidence intervals between go and no-go trials with 20 Hz stimulation. Percent change in peak force rate is significantly correlated between go and no-go trials, suggesting a common inhibitory effect of 20 Hz stimulation ($r=0.728$, $p=0.0032$; $n = 14$ as errors of commission were absent in no-go trials in 4 of the 18 subjects).

**Table 4.1.** Non-significant differences for go trials. There was no difference between stimulation and no-stimulation for either reaction time or peak force.

| Condition | No Stimulation (mean ± SEM) | Stimulation | Significance (paired t-test) |
|---|---|---|---|
| **Go reaction time** | | | |
| 20 Hz | 271 ± 7.1 ms | 268 ± 8.3 ms | P=0.373 |
| 70 Hz | 266 ± 11 ms | 262 ± 8.4 ms | P=0.416 |
| **Go Peak force** | | | |
| 20 Hz | 200 ± 15 N | 199 ± 15 N | P = 0.198 |
| 70 Hz | 206 ± 17 N | 207 ± 17 N | P = 0.546 |
| **Percentage go trials rejected** | | | |
| 20 Hz | 6.5 ± 1.5 | 7.4 ± 1.7 | P=0.511 |
| 70 Hz | 5.8 ± 0.9 | 6.1 ± 1.0 | P=0.705 |
| **Force between fixation cross and pre-cue** | | | |
| 20 Hz | 9.3 ± 6.4 N | 9.4 ± 6.4 N | P=0.319 |
| 70 Hz | 10.0 ± 6.2 N | 10.1 ± 6.2 N | P=0.655 |
| **Force between pre-cue and response** | | | |
| 20 Hz | 9.3 ± 6.4 N | 9.4 ± 6.4 N | P=0.311 |
| 70 Hz | 10.0 ± 6.2 N | 10.1 ± 6.2 N | P=0.580 |

**Table 4.2.** Percentage of errors of commission and total number of nogo trials per stimulation frequency

| Condition | No Stimulation | Stimulation | Significance (paired t-test) |
|---|---|---|---|
| **Percentage relative to total number of trials** | | | |
| 20 Hz | 44.5% $\pm$ 6.1 | 41.6% $\pm$ 7.0 | P=0.336 |
| 70 Hz | 45.3% $\pm$ 5.3 | 45.0% $\pm$ 5.5 | P=0.947 |
| **Absolute number of trials** | | | |
| 20 Hz | 13.3 $\pm$ 1.7 | 12.8 $\pm$ 1.7 | P=0.758 |
| 70 Hz | 13.0 $\pm$ 1.4 | 12.6 $\pm$ 1.5 | P=0.664 |

**Table 4.3, related to Figure 4.3C.** 70 Hz no-go trials, outliers removed. Gamma stimulation remains insignificant.

| **Parameter** | **% change** | **Significance** |
|---|---|---|
| Peak Force | -10.1 + 11.2 | P=0.3863 |
| Peak Rate | -21.0 + 11.1 | P=0.0728 |

**Table 4.4.** Significant differences between 20 Hz and 70 Hz stimulation. Go and no-go trials were different for all parameters.

| | Significance (paired t-test) |
|---|---|
| **GO** | |
| Initial velocity | P<0.001 |
| Peak velocity | P<0.001 |
| Time to peak | P=0.0037 |
| **NO-GO** | |
| Peak force | P = 0.0193 |
| Peak velocity | P = 0.0212 |

**Table 4.5.** Non-significant correlations. There was no correlation between percent changes during 20 Hz and 70 Hz stimulation, or between intensity of stimulation and performance.

| Parameter 1 | Parameter 2 | r value | Significance |
|---|---|---|---|
| **% change between 20 Hz and 70Hz stimulation** | | | |
| Go trial initial rate with 20 Hz | Go trial initial rate with 70 Hz | -0.0356 | P = 0.889 |
| Go trial peak rate with 20 Hz | Go trial peak rate with 70 Hz | 0.2359 | P=0.346 |
| **Intensity of stimulation and % change in performance** | | | |
| Stimulation Intensity | Go initial rate with 20 Hz | 0.0851 | P=0.763 |
| Stimulation Intensity | Go peak rate with 20 Hz | 0.0929 | P=0.742 |
| Stimulation Intensity | Go initial rate with 70 Hz | -0.2125 | P=0.447 |

| | | | |
|---|---|---|---|
| Stimulation Intensity | Go peak rate with 70 Hz | -0.1075 | P=0.703 |
| Stimulation Intensity | Go peak force with 20 Hz | -0.2917 | P=0.291 |
| Stimulation Intensity | Go peak force with 70 Hz | 0.2987 | P=0.280 |
| Stimulation Intensity | Nogo peak force with 20 Hz | 0.1073 | P=0.7271 |
| Stimulation Intensity | Nogo peak rate with 20 Hz | 0.0846 | P=0.7836 |
| Stimulation Intensity | No-go peak force with 70 Hz | -0.2589 | P=0.442 |
| Stimulation Intensity | No-go peak rate with 70 Hz | -0.2405 | P=0.476 |

## 4.4 DISCUSSION

There is considerable evidence that oscillatory activity in the brain is modulated in a task specific manner (Varela et al., 2001; Omlor et al., 2007; Chakarov et al., 2009; Fries, 2009). However, whether synchronized oscillations arise as an epiphenomenal product of brain physiology, or are causal to our behavior, remains an open question. The frequency dependent bi-directional influence of cortical entrainment on motor control shown here, and its quantitative dependence on the motor task triggered by the imperative cue, lend strong support to the possibility that, at least in the motor domain, synchronized oscillations are fundamental to brain function.

It has previously been demonstrated that TACS at similar intensities does drive motor cortical oscillations as evidenced by changes in cortico-muscular

coherence (Pogosyan et al., 2009), but could it be that changes in cortical excitability also occur and actually underscore the behavioral effects? This seems unlikely as the tonic grip force before the warning cue remained unchanged during stimulation. In addition, TACS at 80 Hz has no impact on cortical excitability after as long as 10 minutes of stimulation at 1000μA (Moliadze et al., 2010). TACS at 20 Hz can, following 90s of stimulation, selectively increase motor cortical excitability at rest (Feurra et al., 2011), which is difficult to reconcile with the reduction in the rate of force generation shown here. Perhaps, the effects on behavior are independent and the excitability changes require longer periods of stimulation. Alternatively, and as suggested by the authors of the excitability study, entrainment-induced excitability of a population of neurones at beta frequency may come at the expense of selective motoneuronal recruitment, thereby impairing performance (Feurra et al., 2011). Could stimulation have brought non-specific attentional processes to bear? We were careful to keep stimulation below perceptual threshold and, in line with this, reaction time was unaffected by stimulation. Moreover, any shift in attention due to subliminal scalp sensation or phosphenes could not readily explain the opposite effects of stimulation at different frequencies.

We elected to entrain motor cortical function at two specific frequencies so as to test the hypothesized contrasting roles of oscillatory activities in the 'antikinetic' beta and 'prokinetic' gamma bands**.** We chose these particular frequencies because oscillatory activity in the motor cortex during movement is commonly centered around 20 Hz (Brown, 2003) and 70 Hz

(Muthukumaraswamy, 2010). Beta activity in the motor system has been considered 'antikinetic' in so far as it associated with slower voluntary movements both in health (Gilbertson et al., 2005) and disease (Hammond et al., 2007). Conversely, gamma activity has been suggested to be 'prokinetic' given that it is increased in the basal ganglia-cortical motor loop during voluntary movement (Brown, 2003). Our experimental manipulations support this dissociation, albeit a convenient but gross simplification of the behavioral relevance of oscillations in the cortico-basal ganglia system. In particular, it must be stressed that both the beta and, especially, the gamma band are very wide and have the potential to encompass oscillatory activities with different functional roles, according to their precise spatio-spectral characteristics (Fründ et al., 2007).

One of the remarkable observations made here is the interaction between cortical entrainment at 20 Hz and the motor task triggered by the imperative cue. Stimulation at 20 Hz afforded a significant but modest slowing of force production in the go task, akin to the results of Pogosyan et al (Pogosyan et al., 2009). However, stimulation in no-go trials, where the triggered motor task involved inhibition, led to a major reduction in force generation during errors of commission in a performance-enhancing direction. Nevertheless, the behavioral effects during go and no-go trials with 20 Hz stimulation were related as indicated by their correlation across subjects. Several studies have now suggested that sensorimotor cortical areas may have a natural resonance frequency of about 20 Hz (Tobimatsu et al., 1999; Eusebio et al., 2009;Feurra et al., 2011a). The implication is that stimulation interacts with

this rhythm to drive oscillations (Rosanova et al., 2009;Eusebio et al., 2009; Feurra et al., 2011a), but that the degree to which resonance phenomena are damped in the cortex is dynamically determined by task demands. In our paradigm the latter are set by the imperative cue to either action or motor inhibition. Voluntary action was associated with a modest effect of 20 Hz stimulation and, as previously noted, is well established to be preceded and accompanied by an attenuation of spontaneous beta oscillations in line with increased damping of cortical resonance in the beta band. In contrast, motor inhibition was associated with a pronounced effect of 20 Hz stimulation and is known to be preceded and accompanied by an increase in spontaneous beta oscillations in no-go trials at cortical (Swann et al., 2009) and subcortical (Kühn et al., 2004) levels.

The performance enhancement was also seen in go trials, but only during stimulation with 70 Hz TACS. Such stimulation, in contrast to 20 Hz TACS, improved the rate of force generation, particularly early in the grip, effectively raising the subjects' mean maximal voluntary output. Although TACS in the gamma band has been shown to influence sensory function (Laczó et al., 2011; Feurra et al., 2011b), we show for the first time that motor behavior can be improved by imposing synchronised oscillatory activity upon motor cortical regions. The improvement in the rate of force generation was significant but relatively modest in size, perhaps because of a ceiling effect whereby performance could not be improved much more. Nevertheless, in conjunction with the results of 20 Hz stimulation, the findings provide proof of principle for the anti/pro-kinetic model of beta and

gamma oscillations. In addition, the results with 70 Hz stimulation provide further evidence for a dynamic change in cortical susceptibility to oscillatory driving according to motor task. Improvements in force generation were only seen during go trials, *i.e.* when action was intended and spontaneous gamma activity is known to increase (Muthukumaraswamy, 2010). In contrast, 70 Hz TACS was ineffective during errors of commission following no-go cues, presumably a consequence of the reconfiguration of cortical resonance properties during motor inhibition. The basal ganglia are one system likely to regulate cortical damping and resonance (Eusebio et al., 2009) .

Our observations are important in providing interventional evidence that oscillatory activity of the brain is causally linked to aspects of motor behavior, but also in suggesting more targeted approaches to interventional treatments in diseases dominated by insufficient or excessive movement. In particular, the prominent effect of 20 Hz TACS in promoting the inhibition of unintended movements in no-go trials raises the possibility that similar stimulation of the cortex may be effective in suppressing unwanted or excessive output of the motor system, such as tics or dyskinesias.

# 5. HIGH-FREQUENCY STIMULATION OF THE SUBTHALAMIC NUCLEUS SELECTIVELY DECREASES CENTRAL VARIANCE OF RHYTHMIC FINGER TAPPING IN PARKINSON'S DISEASE


## -Abstract-

Timing is central to all motor behavior, especially repetitive or rhythmic movements. Such complex programs are underpinned by a network of motor structures, including the cerebellum, motor cortex, and basal ganglia. Patients with Parkinson's disease (PD) are impaired in some aspects of timing function, presumably as a result of the disruption to basal ganglia function. However, direct evidence that this deficit is specifically due to basal ganglia dysfunction is limited. In chapters 2 and 3 we demonstrated that the subthalamic nucleus (STN) was involved in the control of simple ballistic movements. However this does not capture the more complex and sequential movement more relevant to daily life, particularly timing. Here, we sought to further understand the role of the basal ganglia in motor timing by studying PD patients with implanted subthalamic nucleus (STN) electrodes. Patients performed a synchronization-continuation tapping task at 0.5 Hz and 2 Hz both off and on therapeutic high frequency stimulation of the STN. Our results show that the mean tap interval was not affected by STN stimulation. However, in the un-stimulated state variability of tapping was abnormally high relative to controls, and this deficit was significantly improved, even normalized, with stimulation. Moreover, when partitioning

the variance into central and peripheral motor components according to the Wing and Kristofferson model (1973), a selective reduction of central, but not motor, variance was revealed. The effect of stimulation on central variance was dependent on off-stimulation performance. These results demonstrate that STN stimulation can improve rhythmic movement performance in PD through an effect on central timing. Our experimental approach strongly implicates the STN, and more generally the basal ganglia, in the control of timing stability.

## 5.1 INTRODUCTION

Timing is a subtle yet fundamental aspect of our daily actions and behaviors. Although biological timing mechanisms can operate over long periods, for example in circadian rhythms (Buhusi & Meck, 2005), motor control depends specifically on millisecond-to-second timing (Mauk & Buonomano, 2004). Intact timing at these intervals is necessary for controlling complex movements, such as walking (Hausdorff et al., 1998), reaching (Gribova et al, 2002), or speech (Schirmer, 2004).

A leading theoretical model of repetitive movement timing (Wing & Kristofferson, 1973) proposes a central timekeeper that oscillates at a specified interval and triggers motor commands at the end of each interval. In the Wing and Kristofferson model (1973), the inter-response interval (IRI)

variability can be split into central variance (timekeeping within the brain) and motor variance (peripheral implementation). Only the central timekeeper variance depends on the IRI, demonstrating a linear relationship, whereas the motor variance theoretically remains constant (Doumas & Wing, 2007). The model implies that central and motor variance are processed independently of one another, and are therefore underpinned by separate biological substrates.

One of the biggest indicators of the basal ganglia's involvement in motor timing in humans comes from studies that demonstrate impairments of timing processes in patients with Parkinson's disease (PD) (Harrington, Haaland, & Hermanowicz, 1998; Malapani et al., 1998; Pastor et al., 1992). Unfortunately there is little consistency in PD timing studies. Many have found that PD patients show abnormal temporal processing in repetitive rhythmic movements compared to controls (Artieda et al., 1992; Harrington et al., 1998; O'Boyle, Freeman, & Cody, 1996; del Olmo et al., 2006). Other studies, however, have shown normal performance by patient cohorts, even when withdrawn from their medication (Spencer & Ivry, 2005). The motor deficits in PD create challenges for specifically assessing motor timing, which inherently involve movement (Shea-Brown et al., 2006). However, even in non-motor tasks PD patients show timing deficits, such as reduced discrimination of beat-based rhythms (Grahn & Brett, 2009), and impaired estimation of time intervals (Wild-Wall et al., 2008). This has led to the suggestion that the central timer, or 'internal clock', proposed by Wing and Kristofferson is regulated by the basal ganglia (Meck, Penney, & Pouthas,

2008; Pastor et al., 1992).

Despite the many studies on repetitive movement timing in PD, the specific role of the basal ganglia remains unclear. To this end, we studied PD patients implanted with deep brain stimulation electrodes in the subthalamic nucleus (STN). We employed the most common test of motor timing: the synchronization-continuation repetitive tapping task (Wing & Kristofferson, 1973), which has been used extensively to test motor timing in PD (Jahanshahi et al., 2006; O'Boyle, Freeman, & Cody, 1996). We tested performance in the tapping task, as measured by IRI and variability at two different frequencies of movement, off and on therapeutic high frequency stimulation of the STN. Furthermore, we partitioned the unpaced tapping variance according to the Wing-Kristofferson model (1973) in order to assess whether stimulation was predominantly acting on central or peripheral motor timing. Our primary hypotheses were that (i) stimulation of the STN would improve motor timing in PD, and (ii) these improvements would be predominantly due to an impact on the central timing component.

## 5.2 METHODS

### *5.2.1 Patients and stimulation*

We studied 11 non-tremorous patients PD treated by chronic bilateral high frequency STN stimulation (1 female, mean age: 60.6 $\pm$ 7.0 (standard deviation) years, disease duration 13.6$\pm$ 7.2 years, post-op duration 3.5 $\pm$ 2.2 years). All patients fulfilled the UK Brain Bank criteria for idiopathic PD. Informed written consent was obtained from each subject prior to

participation and the study was approved by the local Ethics Committee. Stimulation in the 'on' condition was at therapeutic settings, with stimulation amplitude at $\geq$ 2V and frequency $\geq$ 130 Hz in in all patients. Subjects were tested in two conditions: during bilateral STN stimulation (PD-on-stim) or with no stimulation (PD-off-stim). The patient's normal anti-Parkinsonian medication was maintained throughout the study to minimize motor impairment. The order of the two conditions were counter-balanced, with approximately 25 minutes break after the change in stimulation. For a summary of clinical data see Table 5.1. We also recruited 11 age-matched healthy controls (5 females, mean age 60.1 $\pm$ 8.7 years).

**Table 5.1. Clinical Details**

| Patient | Age (years) | Disease duration (years) | Medication | Post-op duration (years) |
|---|---|---|---|---|
| 1 | 64 | 17 | Sinemet<br>Mirapexin | 3 |
| 2 | 51 | 21 | Sinemet<br>Ropinirole | 9 |
| 3 | 62 | 9 | Madopar<br>Tolcapone | 4 |
| 4 | 61 | 7 | Sinemet<br>Ropinirole | 3 |
| 5 | 49 | 10 | Sinemet<br>Entacapone<br>Mirapexin | 1.5 |
| 6 | 57 | 11 | Zelapar<br>Ropinirole<br>Madopar | 2 |
| 7 | 72 | 32 | Amantadine<br>Sinemet<br>Ropinirole | 5 |
| 8 | 68 | 10 | Sinemet<br>Ropinirole | 3 |
| 9 | 66 | 10 | Pramipexole<br>Rotigotine | 1.5 |
| 10 | 61 | 12 | Mirapexin<br>Sinemet | 5 |
| 11 | 56 | 11 | Madopar<br>Mirapexin<br>Selegiline | 1.5 |

*5.2.2 Task*

Patients and healthy controls were seated comfortably in a chair with their right arm supported by a cushion and their hand resting on a table. The tapping apparatus consisted of a 5 x 5 cm square force-sensitive resistor (FSR; Steadlands, Surrey, UK) and pre-amplifier (in house) connected to a data acquisition box (NIDAQ 6008), which relayed data to a laptop computer. Data was collected using the Mattap toolbox (Elliott, Welchman, & Wing, 2009). Mattap was used to output repetitive sound pulses, each of 30 Hz tone and 200 msec length, at two timing frequencies: 0.5 Hz and 2 Hz. These two frequencies were chosen to test performance at both sub- and supra-second timing intervals.

The FSR was centred under the participant's index finger. The large size of the force plate ensured that individual taps occurred within the sensitive range of the pad. The patients were instructed to relax all of their fingers except their index finger, which they were to flex and extend at the metacarpophalangeal (MCP) joint. A short plastic bar (2.5 cm) stood directly in front of the FSR to indicate the height to which the finger should be raised, so as to keep consistency in tap amplitude across conditions and subjects. The consistent, relatively small amplitude deviation also minimized the contribution of changing motor performance between on and off stimulation conditions. Nevertheless, since DBS can produce marked improvements in motor performance, we objectively quantified the tapping movements with a goniometer (Biometrics Ltd, Newport, United Kingdom)

over the MCP joint on the index finger to ensure that the amplitude of movement was similar across conditions.

One trial block consisted of 23 consecutive auditory beeps, followed by a period of silence. During the auditory cueing, patients were instructed to tap in time to the beat over the full 23 taps and then continue tapping (self-generated), maintaining the same frequency for a further 23 taps. Following each run the subject was permitted to relax for at least 1 minute before the start of the next trial. Each frequency (0.5 Hz and 2 Hz) was tested in a counter-balanced order across patients. Four trials were completed per frequency, repeated with DBS off and on in the patient group.

### *5.2.3 Analysis*

#### *5.2.3.1 Main parameters*

Data were exported from Mattap and analyzed with in-house routines using Matlab (Mathworks, Natik, MA, USA). We discarded the first 3 taps in both the synchronization and continuation phases to avoid transition periods and permit patients to either synchronise to the cue or settle into the continuation rhythm. When movements occur in synchrony with a beat, it has been shown that a stable phase relation between stimuli and response generally occurs within 3-5 taps (Repp, 2005).

The remaining 20 taps for both synchronization and continuation blocks were then analysed for each run across frequencies. Two main outcome measures were extracted from the data: (i) mean inter-response interval (IRI),

obtained by taking the difference between successive taps in both the synchronization and continuation phases, and (ii) coefficient of variation of the IRI. The mean IRI was determined for each run and averaged across runs to obtain a single value per subject for each frequency of tapping and phase (synchronization versus continuation). The standard deviation of the IRIs for each run was also determined, and an average value for each frequency and phase obtained. This value was then divided by the mean IRI to obtain the coefficient of variation, which was subsequently used as our primary measure of tapping variability.

To ensure that tap amplitude was similar between both tapping rates, we determined the amplitude of the taps by taking the root-mean-square amplitude of the goniometer traces from each run.

*5.2.3.2 Wing-Kristofferson Model for unpaced tapping*

After analysis of IRI and variability, we further explored the changes in variance across conditions, employing the Wing-Kristofferson timing model (Wing & Kristofferson, 1973). This allowed us to partition the total observed tapping variance into a hypothesized central 'clock' variance and motor variance. The model is primarily intended for unpaced tapping; we therefore applied it only to the continuation phase. For each run of 20 taps, the lag(1) IRI autocorrelation was determined and multiplied by the total IRI variance to provide the lag(1) autocovariance. The autocovariance is related to motor variance (Wing, 2002) via:

*(1) autocovariance(lag1) = -(Motor variance)*

We then took the motor variance and the total variance and algebraically determined the central variance:

*(2) Total variance = Central variance + 2(Motor variance)*

Motor variance is multiplied by 2 in the above equation due to the fact that each IRI is composed of two finger taps (one to start the interval and one to end it) with a single central timing interval between them. Central and motor variance were then averaged across all 4 runs for each frequency, and transformed to standard deviation by taking the square root (Harrington et al., 1998; O'Boyle, Freeman, & Cody, 1996).

*5.2.3.3 Statistics*

We used within-subject 2x2 repeated measures analyses of variance (ANOVA) to look for main effects in the variables of interest with stimulation (on and off) and frequency (0.5 Hz, 2 Hz) as factors. Controls were compared to PD patients in off and on states separately using between-subject 2x2 repeated measures ANOVAs. Because some variables violated the assumption of sphericity, we used the Greenhouse-Geisser correction where necessary. Post-hoc t-tests were subsequently performed between on and off states where the interaction was significant, with p-value thresholds corrected for number of comparisons (2), and therefore set at $\leq$ 0.025.

## 5.3 RESULTS

*5.3.1 Effect of stimulation on IRI and variability*

We began by comparing PD patients between off and on stimulation states in the synchronization phase. For IRI, there was no significant main effect of stimulation ($F_{1,}10=0.23$, $p=0.64$, Figure 5.1A), an expected significant effect of frequency due to the large difference in tap intervals between conditions ($F_{1,10}=173429$, $p<0.0001$), but no stimulation x frequency interaction ($F_{1,10}=0.22$, $p=0.65$). In other words, patients were able to produce the same intervals on average regardless of stimulation condition.

Although stimulation of the STN had no effect on the IRI of the patients' tapping, it produced a significant decrease in variability, as measured by the coefficient of variation ($F_{1,10}=11.59$, $p=0.007$, Figure 5.1B), with no significant effect of frequency ($F_{1,10}=4.37$, $p=0.063$), and no stimulation x frequency interaction ($F_{1,10}=2.75$, $p=0.13$).

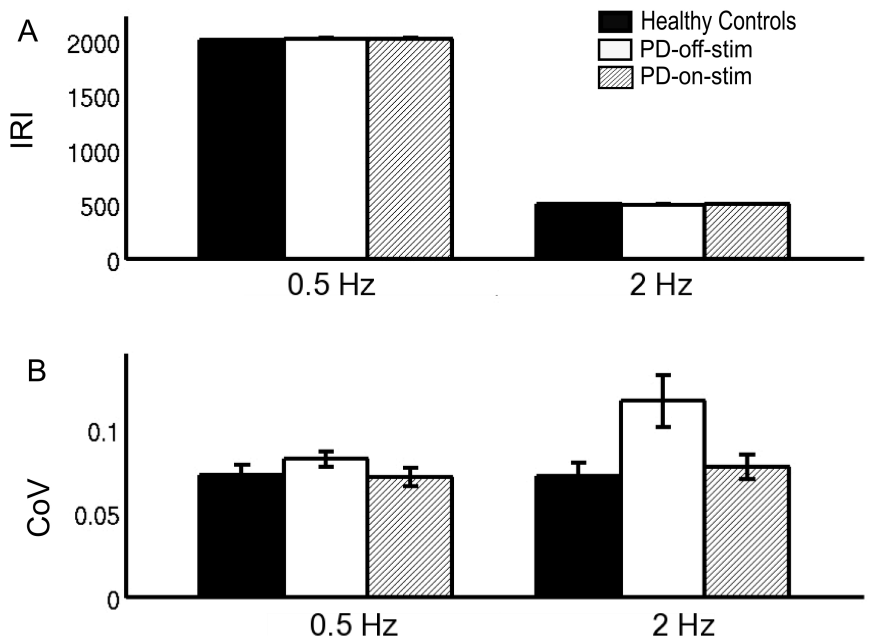


**Figure 5.1.** Mean inter-response intervals (IRI) and coefficient of variation (CoV) in the synchronization phase across both frequencies. Bars display controls (black), PD-off (white), and PD-on (hatched). There is a significant reduction in variability, but not IRI, with stimulation.

We then assessed changes in timing in the continuation phase. Here again, there was no difference in the mean IRI between the on and off stimulation conditions (stimulation, $F_{1,10}$=1.61, p=0.23; frequency, $F_{1,10}$=493.12, p<0.0001; interaction, $F_{1,10}$=0.48, p=0.50, Figure 5.2A). There was again a significant decrease in variability in the stimulation on condition ($F_{1,10}$=7.66, p=0.02, Figure 5.2B), regardless of frequency ($F_{1,10}$ = 1.18, p = 0.31), and no interaction ($F_{1,10}$ = 0.04, p = 0.85). Thus, stimulation induced a significant reduction in variability for both synchronization and continuation

phases; however this could not be attributed to a particular frequency of movement.

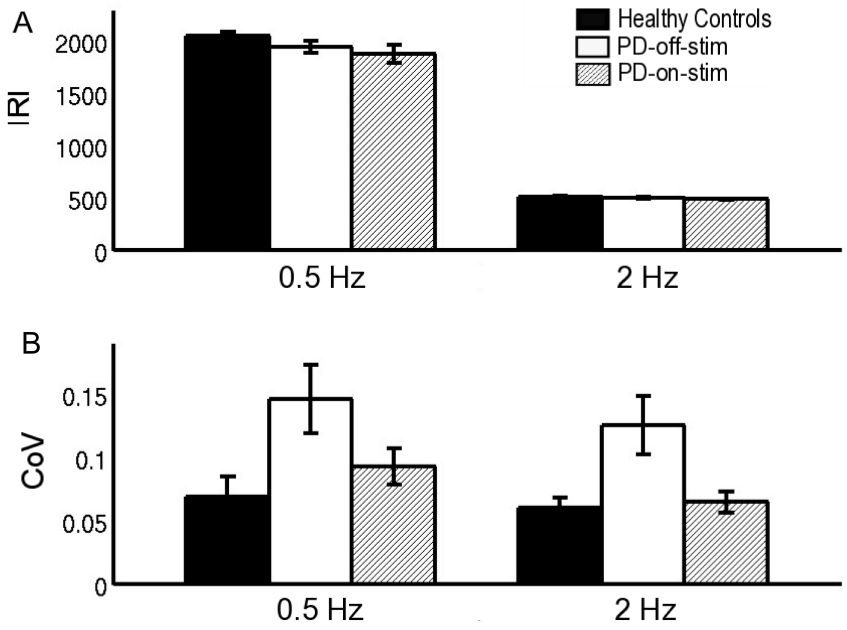


**Figure 5.2.** Mean inter-response intervals (IRI) and coefficient of variation (CoV) in the continuation phase across both frequencies. Bars display controls (black), PD-off (white), and PD-on (hatched). There is a significant reduction in variability, but not IRI, with stimulation.

*5.3.2 Tap amplitude*

To confirm that the differences in variability between off and on stimulation were not simply due to changes in tapping kinematics, we performed an ANOVA over the tap amplitude with factors stimulation and frequency. There was no significant difference in the synchronization phase (stimulation,

$F_{1,10}$=1.93, p=0.21; frequency, $F_{1,10}$=2.44, p=0.17; interaction, $F_{1,10}$=1.45, p=0.28) or continuation phase (stimulation, $F_{1,10}$=4.09, p=0.074; frequency, $F_{1,10}$=0.139, p=0.72; interaction, $F_{1,10}$=0.014, p=0.91). Thus, tap amplitude was similar regardless of stimulation.

*5.3.3 Comparison of IRI between PD and controls*

There was no significant difference between age of controls and that of PD patients (p=0.87, independent t-test). Since there was no "on stimulation" condition in the control group, we statistically analyzed differences by conducting separate repeated measures ANOVAs between control subjects and either PD state. Examining the mean IRI in the synchronization phase between controls and PD-off-stim showed no main effect of group ($F_{1,10}$=0.704, p=0.411, Figure 5.1A), a main effect of frequency ($F_{1,10}$=199207, p<0.0001), and a significant group x frequency interaction ($F_{1,10}$=7.67, p=0.011). Post-hoc t-tests showed non-significant changes for either frequency, but a trend towards longer IRIs in the PD-off-stim group at 0.5 Hz ($t_{20}$=-1.96, p=0.065) but not the 2 Hz condition ($t_{20}$=1.17, p=0.256). There was again no main effect of group when comparing with PD-on-stim ($F_{1,10}$=3.90, p=0.062, Figure 5.1A), a significant effect of frequency ($F_{1,10}$=242359, p<0.0001) and a significant interaction ($F_{1,10}$=6.04, p=0.023). Post-hoc t-tests again showed significantly longer IRIs at 0.5 Hz for PD-on-stim ($t_{20}$=-2.44, p=0.024), but no difference at 2 Hz ($t_{20}$ = 0.55, p=0.59).

In the continuation phase, comparisons of mean IRI between controls and PD-off showed no main effect of group ($F_{1,10}$=2.71, p=0.12, Figure 5.2A), an effect of frequency ($F_{1,10}$= 2088, p<0.0001), and no interaction ($F_{1,10}$=2.33, p=0.14). This was the same for PD-on-stim (group, $F_{1,10}$= 4.12, p=0.56; frequency, $F_{1,10}$=944, p<0.0001; interaction $F_{1,10}$=2.50, p=0.13, Figure 5.2A). Therefore, during synchronization patients seemed to have longer IRIs in the 0.5 Hz condition as compared with controls, but not during continuation. Importantly, as noted previously, IRIs were not affected by stimulation.

*5.3.4 Comparison of variability between PD and controls*

Variability of synchronization tapping was significantly different between controls and the PD-off-stim condition ($F_{1,10}$=8.99, p=0.007, Figure 5.1B), with no effect of frequency ($F_{1,10}$=3.07, p=0.095) and no interaction ($F_{1,10}$=3.44, p=0.078). In contrast, a comparison with PD-on-stim showed no effect of group ($F_{1,10}$=0.11, p=0.74, Figure 5.1B), frequency ($F_{1,10}$=0.14, p=0.71), or interaction ($F_{1,10}$=0.27, p=0.61). For the continuation phase, there was a significant main effect of group between controls and PD-off-stim in variability ($F_{1,40}$=13.41, p=0.002, Figure 5.2B), with no significant effect of frequency ($F_{1,10}$=0.54, p=0.47) or interaction ($F_{1,10}$=0.86, p=0.77). This main effect was again rendered non-significant comparing controls and PD-on-stim (group, $F_{1,10}$=1.44, p=0.25; frequency, $F_{1,10}$=2.18, p=0.16; interaction, $F_{1,10}$=0.58, p=0.46, Figure 5.2B). Altogether, this highlighted a significantly higher variability in PD as compared with controls, that was

normalized with stimulation for both synchronization and continuation phases.

*5.3.5 Effect of stimulation on central and motor variance*

Central variance showed a main effect of stimulation ($F_{1,10}$=5.53, p=0.041, Figure 5.3B), an effect of frequency ($F_{1,10}$=38.40, p<0.0001) and no interaction ($F_{1,10}$=2.82, p=0.124), while motor variance showed no main effect of stimulation ($F_{1,10}$=0.001, p=0.972, Figure 5.3A), an effect of frequency ($F_{1,10}$=13.02, p=0.004) and no interaction ($F_{1,10}$=0.135, p=0.72). Therefore, stimulation significantly improved central variance with no significant change in motor variance.

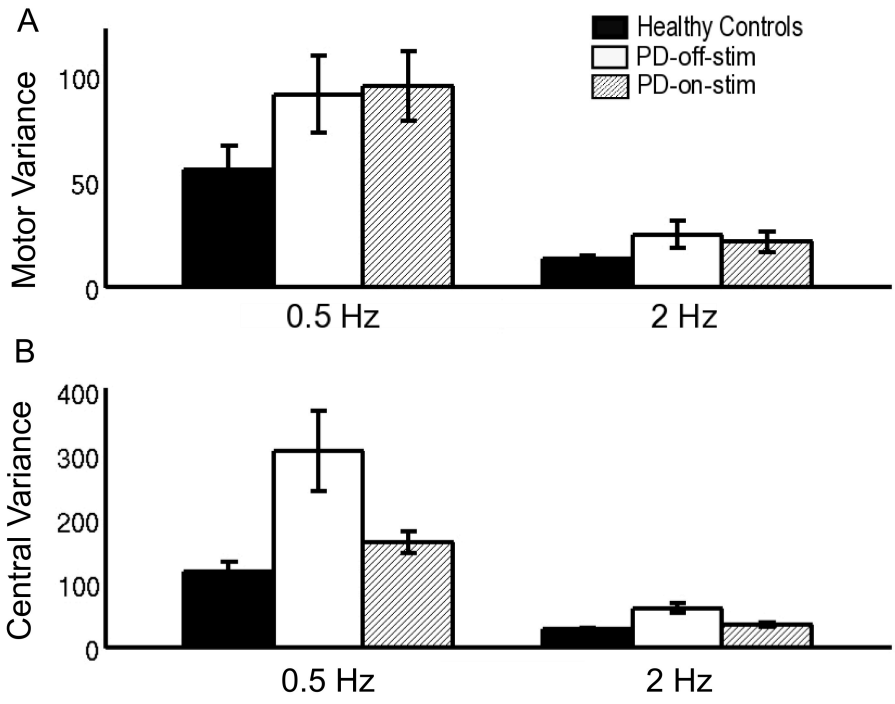


**Figure 5.3**. Mean central and motor variance (standard deviation) across both frequencies. Bars display controls (black), PD-off (white), and PD-on

(hatched). There is a significant reduction in central, but not motor, variability with stimulation.

We confirmed this differential effect on central variance by collapsing the 0.5 and 2 Hz group data and conducting a 2x2 ANOVA with factors stimulation (off or on) and type of variance (central or motor). The analysis revealed a significant effect of type of variance ($F_{1,21}$=21.2, p<0.0001), no effect of stimulation ($F_{1,21}$=3.83, p=0.064), and a significant interaction ($F_{1,21}$=6.46, p=0.019). The interaction was due to a large decrease in central, but not motor, variance (Figure 5.4).

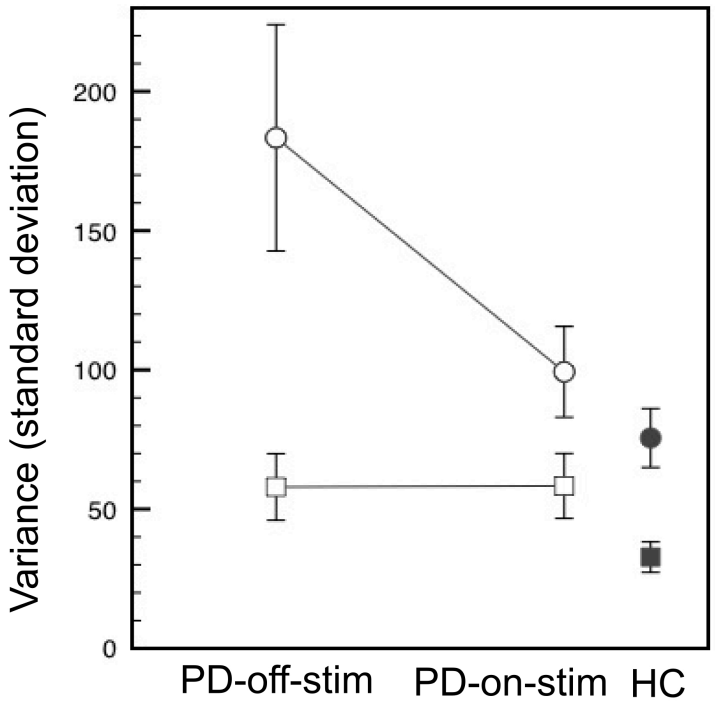


**Figure 5.4.** Mean central and motor variance (standard deviation) collapsed across both frequencies displayed for PD patients (open symbols), and

healthy controls (filled symbols). Central variance (circles) shows a dramatic reduction with stimulation, whereas motor variance (squares) does not change.

*5.3.6 Comparison of central and motor variance between PD and controls*

We then compared the control data for the partitioned variance to both PD-off-stim and PD-on-stim states. Considering central variance between controls and PD-off-stim, there was a significant main effect of group ($F_{1,10}$=11.82, p=0.003, Figure 5.3B), frequency ($F_{1,10}$=26.97, p<0.0001), and a significant interaction ($F_{1,10}$=5.78, p=0.026). Post-hoc tests revealed a significant difference between controls and PD-off-stim at both frequencies (0.5 Hz, $t_{20}$=-2.94, p=0.008; 2 Hz, $t_{20}$ = -4.05, p = 0.001). Comparing controls to PD-on-stim showed a smaller, but still significant difference (group, $F_{1,10}$=5.46, p=0.03; frequency, $F_{1,10}$=98.78, p <0.0001; interaction, $F_{1,10}$= 3.31, p=0.092, Figure 5.3B).

Comparing motor variance between controls and PD-off-stim showed a significant effect of group ($F_{1,10}$=4.56, p=0.045, Figure 5.3A), frequency ($F_{1,40}$ = 21.82, p<0.0001), but no significant interaction ($F_{1,40}$=1.08, p=0.31). The difference persisted with PD-on-stim (group, $F_{1,40}$=7.75, p=0.011; frequency, $F_{1,40}$=36.60, p <0.0001; interaction, $F_{1,10}$=4.14, p=0.056, Figure 5.3A). Taken together, stimulation significantly decreased only central variance in PD, however both central and motor variance remain higher than controls with or without stimulation (see figure 5.4).

*5.3.7 Correlation between baseline performance and impact of stimulation*

Lastly, we sought to determine if the effect of stimulation on central variance was dependent on baseline (off-stimulation) performance. In the 0.5 Hz condition, we found a significant correlation between baseline central variance and the percentage change between off and on stimulation ($r=-0.86$, $p=0.0007$, Figure 5.5A), but no such correlation between baseline motor variance and percentage change ($r=-0.48$, $p=0.12$). Similarly for 2 Hz, there was a significant correlation between baseline central variance and percentage change ($r=-0.83$, $p=0.0015$, Figure 5.5B), but not so for baseline motor variance ($r=-0.59$, $p=0.054$). Thus, the effect of stimulation was dependent on baseline performance; the larger the baseline central variance, the more percentage improvement resulted from STN stimulation.

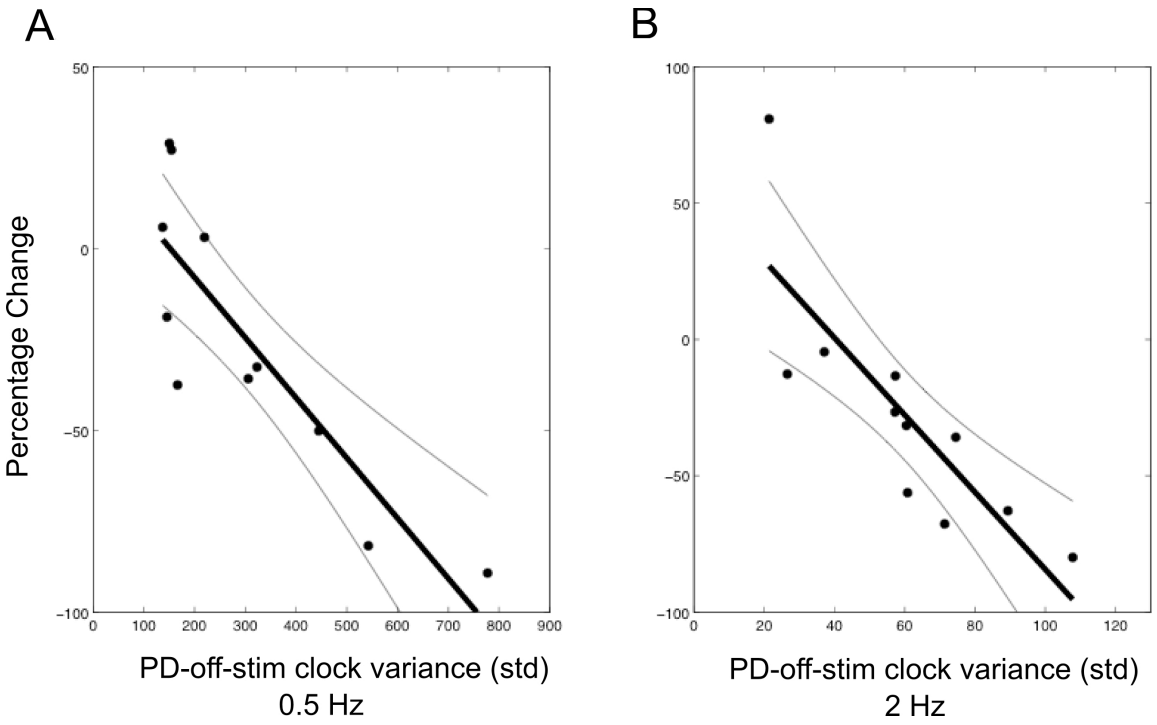


**Figure 5.5.** Correlation between baseline variance and effect of stimulation (percentage change from off to on stimulation) for both frequencies. For both 0.5 Hz and 2 Hz, a higher off-stim variance results in a larger drop in variance (percentage change) between off-stim and on-stim. Line of best fit and 95% confidence intervals are displayed.

## 5.4 DISCUSSION

Our study demonstrates for the first time that deep brain stimulation of the subthalamic nucleus reduces variability of repetitive tapping movements through a selective effect on central variance. There is no concomitant change in the mean IRI, or variance of motor implementation. These results

give strong support for a major role of the basal ganglia in the production of rhythmically accurate repetitive movements.

The basal ganglia have been widely implicated in the control of timed movements. Indeed, imaging studies have shown that the SMA and basal ganglia are involved with internally and externally paced motor timing (Cunnington et al., 1996; Deiber et al., 1999; Lewis et al., 2004; Rao et al., 1997). It is likely that a network of brain areas, including the basal ganglia, cerebellum, and frontal lobe, are involved in coordinating the production of rhythmic, timed movements (Jahanshahi et al., 2006). Nevertheless, the basal ganglia seem to play a central role and are consistently implicated in a wide range of lesional, electrophysiological, and imaging studies (Buhusi & Meck, 2005).

Hitherto, a major experimental model that has been used to test the role of the basal ganglia in movement timing is the effect of dopaminergic therapy in patients with PD on timing behaviour (Pastor et al., 1992; O'Boyle et al., 1996). However, dopaminergic therapy is not selective to the basal ganglia and is known to influence many motor areas (Buhmann et al., 2003), thus making it difficult to generate causal claims about these observed changes. Stimulation of the STN also induces a widespread pattern of activation in the brain (Limousin et al., 1997), however it increases activity in basal ganglia i.e globus pallidus, and associated nuclei such as the ventrolateral thalamus more effectively than dopamine (Bradberry et al., 2011). Here, by stimulating the STN we provide evidence that manipulation of the basal

ganglia has a direct, relatively immediate and reversible influence on rhythmic movement performance.

We examined two major components of timed movements: the IRI and variability. We first demonstrate that stimulation of the STN does not influence IRI of tapping, in line with a previous stimulation study (Wojtecki et al., 2011). Unlike IRI, we show an overall decrease in variability in PD patients during stimulation, which normalized the deficit relative to controls. Additionally, the decrease in variance was specific to central variance, which demonstrated a dramatic and significant decrease with stimulation. Conversely, motor variance was unaffected by stimulation. The finding that STN DBS has a selective influence on central variance is contrary to the effects of dopaminergic medication. Pastor et al. (1992) found that PD patients were impaired in both central and motor variance relative to controls during repetitive wrist movements, and dopaminergic therapy reduced both types of component variance (Pastor et al., 1992). Another study showed a similar decrease in both types of variance after medication (O'Boyle, Freeman, & Cody, 1996), although here motor variance was reduced to control levels whereas central variance remained higher. We elected to study patients on their therapeutic medication so as to avoid the general motor impairment that would result from being off both stimulation and medication, as our focus was on motor timing. We thus opted for patients to be as close as possible to a normal state in order to assess the specific effects of stimulation. Given that in our study motor variance would already be reduced by dopaminergic therapy it is possible that the lack of an effect of

STN stimulation on motor variance was due to the medicated state of our patients. However, motor variance in PD patients was still significantly higher than controls even with stimulation. Therefore improvements in motor variance were still theoretically possible, but did not occur. This is particularly striking when comparing with the dramatic drop in central variance. Moreover, there was a significant correlation between baseline central variance and percentage change from off to on stimulation; this was not the case for motor variance, emphasizing the selectivity of the effect.

In our study we had a proportion of patients (30-40%, depending on the condition) that violated an assumption of the Wing-Kristofferson model, namely that the autocovariance value lies between 0 and -0.5. However, violations of this nature regularly occur, as seen in a number of studies (Pastor et al., 1992; Turvey, Schmidt, & Rosenblum, 1989). Adjustments have sometimes been made to the data so as to allow for more appropriate autocovariance values, such as eliminating IRIs which are outside of a certain range, however this might distort the data and remove important disease-related phenomena (Harrington et al., 1998; O'Boyle, Freeman, & Cody, 1996). Nevertheless, calculation of variance despite these violations does not change values to a significant degree (O'Boyle, Freeman, & Cody, 1996). The model therefore appears robust to such violation and, to avoid unnecessarily loss of data, we included all patients and used the absolute value of the autocovariance to calculate the central and motor variance. Another important issue is the applicability of the model to various movement frequencies. In the original paper and in most studies it has been

used to assess sub-second tapping variance (Wing & Kristofferson, 1973). However it has been used at longer IRIs, but similar to our study seems to inflate variance values at these IRIs (Pastor et al., 1992), especially motor variance. Despite this, the relationship between central and motor variance in our data was consistent across both frequencies (much higher central than motor variance). And even when considering only the 2 Hz interval, one in which the Wing-Kristofferson model has been applied thoroughly, we see a large drop in central, but not motor, variance.

In conclusion, we demonstrate that stimulation of the basal ganglia has no significant effect on the IRI of repetitive tapping movements, but significantly improves variability. In particular, by selectively reducing central variance we provide interventional evidence for the possible mediation of the theorized central clock (Wing & Kristofferson, 1973) by the basal ganglia. It is possible that this decrease in central variance due to stimulation in PD underlies the gross improvements observed in important daily activities, such as gait (Hausdorrf et al., 1998), that require a high degree of rhythmic performance.

# 6. PERSISTENT SUPPRESSION OF SUBTHALAMIC BETA-BAND ACTIVITY DURING RHYTHMIC FINGER TAPPING IN PARKINSON'S DISEASE


## -Abstract-

The function of synchronous oscillatory activity at beta band (15-30 Hz) frequencies within the basal ganglia is unclear. Here we sought support for the hypothesis that beta activity has a global function within the basal ganglia and is not directly involved in the coding of specific biomechanical parameters of movement; rather its level relates to the likelihood that a new voluntary action will need to be actuated and so helps underpin motor readiness (Jenkinson & Brown, Trends in Neurosciences, 34: 611-8, 2011). This hypothesis leads to two predictions: [1] task-related beta suppression should be independent of specific biomechanical aspects of movement and [2] beta suppression should be sustained as long as movements are made as part of a related sequence. In chapter 5 we demonstrated that repetitive tapping could be improved with stimulation of the STN, and thus might be a relevant structure for the control of sequential movement. Accordingly, we recorded local field potential activity from the subthalamic nucleus of 11 patients with Parkinson's disease during movements of the contralateral hand. Patients were on their normal medication and performed a synchronized tapping task at three different externally cued rates. Beta activity was suppressed during tapping, reaching a minimum that differed

little across the different tapping rates despite an increase in velocity of finger movements. Thus beta power suppression was independent of specific motor parameters. Moreover, although beta oscillations remained suppressed during all tapping rates, periods of resynchronization between taps were markedly attenuated during high rate tapping. Thus a superimposed beta rebound between taps at the lower rates was absent at the high rate. These findings implicate consistent beta suppression in the facilitation of continuous, predictable movement sequences.

## 6.1 INTRODUCTION

Synchronized neuronal oscillations at beta frequencies are prevalent in the human motor system, but the function of this neuronal activity is uncertain. They are particularly prominent in the basal ganglia of patients with Parkinson's disease (PD) (Hammond et al., 2007), but are also recorded at lower levels in patients without PD (Sochurkova & Rektor, 2003), in healthy rodents (Leventhal et al., 2012) and non-human primates (Courtemanche et al., 2003). Initially beta oscillations were thought to be a marker of idling activity (Pfurtscheller et al., 1996). However, this theory was superseded by the view that beta activity in the basal ganglia-cortical loop might help reinforce the motoric status quo, promoting tonic activity at the expense of voluntary movement (Gilbertson et al., 2005). The latter hypothesis was

motivated by the fact that exaggerated levels of beta activity are seen in PD, and increases are seen during stop or change tasks that require motor inhibition (Kühn et al., 2004; Zhang et al., 2008; Ray et al., 2012). More recently it has been suggested that beta levels may provide a measure of the likelihood that a new voluntary action will need to be actuated and hence facilitate the resourcing and preparation of potential actions (Jenkinson & Brown, 2011). In this theory salient external and internal cues serve to suppress beta activity and this helps determine motor readiness. All these theories consider beta suppression to subserve a global function within the motor system rather than the explicit coding of the biomechanical parameters of any given movement. Accordingly the level of task-related beta suppression should be unrelated to such parameters. However, reports differ in the extent to which activity in the beta frequency band behaves in the predicted way (Kempf et al., 2007; Brücke et al., 2012). The hypothesis that beta activity is suppressed according to the likelihood of new motor processing leads to a further specific prediction: that phasic suppression of beta activity prior to a voluntary action will be replaced by a persistent suppression during a sequence of related movements, such as in rhythmic tapping.

Hitherto, the above predictions have been supported by magnetoencephalographic and electroencephalographic studies showing that beta activity in the cerebral cortex of healthy humans during finger tapping maintains a constantly desynchronized state with faster finger movements

(Toma et al., 2002; Erbil & Ungan, 2007; Muthukumaraswamy, 2011). Here, we test these predictions in the basal ganglia by recording local field potential (LFP) activity from the subthalamic nucleus region (STN) in patients with PD. In contrast to an earlier study (Androulidakis et al., 2008), we recorded patients following treatment with the dopamine prodrug levodopa, so as to normalize as far as possible the function of the basal ganglia, and maximize possible inferences about physiological functioning. We studied patients while they made externally paced rhythmic tapping movements with their index finger as this provided a predictable sequence of movements. We asked subjects to perform finger tapping at different rates so that the dependence or otherwise of beta activity on sequential movement and velocity could be determined. Moreover, we could reasonably expect changes in beta activity in the subthalamic nucleus of treated patients in this task as the basal ganglia are implicated in the execution of movement sequences (Georgiou et al., 1993) .

## 6.2 METHODS

### *6.2.1 Patients and surgery*

Eleven patients with idiopathic PD (1 female, mean age 64 $\pm$ 2.9 years, mean disease duration 8.2 $\pm$ 1.6 years) who underwent implantation of deep brain stimulation (DBS) electrodes in the STN participated in the study. All patients gave their informed written consent to participate in the study, which was approved by the Oxford Research Ethics Committee A and carried out according to the Declaration of Helsinski. Four patients were implanted

unilaterally, and the remaining bilaterally. Clinical details are summarized in Table 6.1. The macroelectrode used was model 3389 (Medtronic Neurological Division, Mineapolis, USA) with four platinum-iridium cylindrical contacts (1.27 mm diameter and 1.5 mm length) and a contact-to-contact separation of 0.5 mm. Intended coordinates for the STN were 12 mm lateral from the midline, 3 mm behind the midcommissural point, and 4 mm below the AC-PC. Individual adjustments were made according to pre-operative stereotactic T2-weighted magnetic resonance imaging. As well, during the surgical procedure intra-operative macrostimulation and clinical evaluation of the patient was carried out to identify best placement of the electrode. Post-operative CT was performed to confirm targeting in conjunction with image fusion.

**Table 6.1. Clinical Details**

| Patient Number | Age, Sex | Disease duration (years) | Predominant symptoms | Levodopa equivalent daily dose at surgery (mg) | Pre-op UPDRS off-meds | Pre-op UPDRS on-meds |
|---|---|---|---|---|---|---|
| 1 | 58, M | 2 | Tremor | 200 | 19 | 6 |
| 2 | 65, F | 17 | Dyskinesias, Freezing | 962.5 | 29 | 8 |
| 3 | 80, M | 4 | Tremor | 116 | 29 | 26 |
| 4 | 63, M | 10 | Bradykinesia, Rigidity, Tremor | 1610 | 40 | 22 |
| 5 | 66, M | 16 | Bradykinesia, Rigidity, Dyskinesia, Tremor | 415 | 33 | 7 |
| 6 | 70, M | 4 | Tremor | 520 | 36 | 18 |
| 7 | 70, M | 10 | Bradykinesia, Falls | 1000 | n/a | n/a |
| 8 | 60, M | 7 | Gait, Tremor | 66 | 25 | 13 |
| 9 | 60, M | 2 | Tremor | 200 | 39 | 33 |
| 10 | 42, M | 6 | Rigidity, Tremor | 500 | 50 | 38 |
| 11 | 70, M | 12 | Gait, Tremor | 1000 | 62 | 29 |

### *6.2.2 Recordings*

Recordings were obtained 4-6 days after the initial implantation of the DBS electrodes, prior to internalization of the pacemaker. LFPs were recorded from the DBS electrodes through 1902 amplifiers (Cambridge Electronic Design, Cambridge, UK), and digitised at a sampling rate of 1 kHz with a CED 1401 analog-to-digital converter. Data were recorded using CED Spike2 software and analysed using in-house scripts written in Matlab (Mathworks, Natick, MA, USA). STN LFPs were recorded bipolarly from the four adjacent contacts of each DBS electrode in order to cancel out common signals such as volume conduction and ensure recorded activity was as focal as possible to the electrode.

### *6.2.3 Task*

All patients performed a synchronized tapping task. Patients were seated comfortably in a chair with their right arm supported by a cushion and their hand resting on a table. The left hand was used in one patient due to a right-sided unilateral electrode implantation. The tapping apparatus consisted of a 5 x 5 cm square force-sensitive resistor (FSR; Steadlands, Surrey, UK) and pre-amplifier connected to a data acquisition box (NIDAQ 6008, National Instruments), which relayed data to a laptop computer. Mattap toolbox (Elliott et al., 2009) was used to output repetitive sound pulses, each of 30 Hz tone and 200 msec length, at three different rates: 0.5 Hz (once every 2000 milliseconds), 1 Hz (once every 1000 milliseconds), and 2 Hz (once every 500 milliseconds). These tapping rates will subsequently

be referred to as low rate (0.5 Hz), medium rate (1 Hz), and high rate (2 Hz).

The FSR was centred under the participant's index finger. The large size of the force plate ensured that individual taps occurred within the sensitive range of the pad. The patients were instructed to relax all of their fingers except their index finger, which they were to flex and extend at the metacarpophalangeal joint. A short plastic bar (3 cm) stood directly in front of the FSR and index finger to indicate the height to which the finger should be raised, so as to keep consistency in tap amplitude across conditions and patients. In 9 out of 11 patients, we objectively quantified the tapping movements with a goniometer (Biometrics Ltd, Newport, United Kingdom) over the MCP joint on the index finger in order to relate the continuous movements to LFP activity.

One trial block consisted of 30 consecutive auditory beeps. During auditory cueing, patients were instructed to tap in time to the beat over the full 30 taps. Each run lasted either 1 minute (low rate), 30 seconds (medium rate), or 15 seconds (high rate). Following each run the participant rested for at least 30 seconds before the start of the next trial. Each movement rate was tested in a counter-balanced order across patients, with a single block being defined as one run for each rate. The number of blocks differed from 2-4 depending on the patient's level of fatigue. A control task was performed in 8 of the 11 patients. In this, the sound cue only was played while the patient

was instructed to be attentive to the cue but not respond; this was interleaved with the movement runs.

*6.2.4 Analysis*

Due to the fact that three patients had unilateral electrode implantation, we focused our analysis on the contralateral side to task performance. Data was also recorded from the ipsilateral STN region in the patients with bilateral implants, as addressed in the results section. Raw LFP data were imported into Matlab, band-pass filtered between 2 and 100 Hz, and notch filtered from 45-55 Hz to ensure removal of any mains noise. Epochs were generated around each tap onset for a period of 2 seconds before until 2 seconds after. Spectrograms were generated from 5-35 Hz using a Hermite functions approach (Bayram & Baranuik, 2000). With an emphasis towards time-evolving spectra, spectrograms were generated using a time-frequency localisation parameter A/2 = 5 (see Brittain et al., 2007) providing a full-width half-maximum resolution of 167 ms x 2.7 Hz. The baseline period was taken as a 30 second period of rest before beginning the task for each patient. We determined the ratio of beta power (15-30 Hz) to overall power (2-100 Hz) in the baseline period for each contact in each patient. We determined the ratio of beta power (15-30 Hz) to overall power (2-100 Hz) in the baseline period for each contact in each patient. Previous studies have demonstrated that maximal beta power is a marker for accurate electrode position within the STN (Kühn et al., 2004; Weinberger et al., 2006; Ray et al., 2008). Therefore, the contact pair with the highest mean beta power

was chosen for subsequent analysis. Spectrograms were evaluated through point-wise paired t-tests over log-spectral values at $p < 0.05$. Time-evolving band-limited power profiles were first extracted from their corresponding spectrograms, then baseline subtracted and normalised over the baseline period. This provided a percentage change measure of power fluctuation relative to baseline. Once extracted, the traces were compared across the three movement frequencies. Analysis was first conducted over broadband beta activity (15-30 Hz). However, since we were also interested in relative rebound activity, we determined the frequency with the maximal rebound (FMR) within the 15-30 Hz range for each subject and condition. Similarly, we determined the frequency with the maximal suppression (FMS) for each subject and condition. For FMR and FMS, percentage change measures across the epoch were extracted for that particular frequency and averaged across subjects.

We then quantified two different parameters from the broadband, FMR, and FMS beta traces for each patient: (i) maximal desynchronisation, and (ii) maximal synchronisation or rebound, representing the peak in beta power between movements.

Goniometer traces were epoched around contact with the FSR as with LFPs. Maximum tap amplitude was taken for each patient at each movement rate. The goniometer position trace was then differentiated to obtain velocity.

Lastly, we calculated the relative stationary period when no movement occurred in between consecutive taps for all conditions. We accomplished

this by first determining a threshold of the maximal point of the mean goniometer trace for each subject. We designated a threshold of 10% of the maximum deviation in that cycle and found the points that crossed this threshold in either direction from the maximum. This provided time points at which the finger rose over and fell under the 10% threshold, and the time difference between them served as our stationary period. This method was reliable in isolating the area in which relatively little movement occurred.

All statistical analyses were conducted using SPSS v12 (SPSS Inc., Chicago, IL, USA), except significance levels for spectrograms, which were generated using one-sample t-tests in MATLAB. Percentage change values of beta were normally distributed as confirmed by the one-sample Kolmogorov-Smirnov test. One-way repeated measures analysis of variance (ANOVA) was conducted over the three movement rates to determine differences between the tapping rates. Mauchley's test was used to assess sphericity of the data, and when significant deviations from sphericity occurred the Greenhouse-Geisser correction was applied. Post-hoc paired t-tests between conditions were Bonferonni corrected and thus we maintained our significant p threshold at 0.05. Furthermore, one-sample t-tests were used to assess changes in power from baseline for each tapping condition, with significant $p < 0.05$. Correlation between log of stationary period time and beta rebound was conducted using Pearson's product moment correlation.

## 6.3 RESULTS

### *6.3.1 Selected contacts*

The contact pair demonstrating the highest beta power during the rest period was selected for analysis. In all patients there was a clear maximum at one of the 3 contact pairs on the side contralateral to movement. The mean reduction in beta power between this contact and the mean of the remaining 2 contacts was -51.5 % $\pm$ 15.3 (SEM). Furthermore, recordings in 9 out of 11 patients exhibited polarity reversal across two of the bipolar contact pairs on each side, and all contacts selected for analysis were among those with polarity reversal. Polarity reversals suggest that the potential recorded is being generated local to the contacts.

### *6.3.2 Behavioral data*

Mean goniometer amplitude did not differ between conditions ($F_{2,20}$ = 0.36, p = 0.71, one-way ANOVA). However, mean velocity was different across conditions ($F_{2,20}$ = 4.4, p = 0.03). Post hoc t-tests revealed no significant velocity difference between low and medium rate tapping ($t_{10}$ = -0.86, p = 0.41), or between medium and high ($t_{10}$ = -1.92, p = 0.091). However, the high rate condition had significantly higher velocity than low rate ($t_{10}$ = -2.6, p = 0.032). Therefore, patients maintained the same size of tap throughout the three movement rates, but had expectedly higher velocities during the high rate movement compared to the low rate.

We also calculated the timing of taps (impact with the force transducer) with respect to the onset of the auditory cue. An ANOVA showed that tap asynchrony differed according to tapping rate ($F_{2,20}$ = 15.47, p = 0.003), and this was due to the high rate condition having an earlier tap with respect the cue (-24.8 ms $\pm$ 17.2) as compared with low rate (32.9 ms $\pm$ 15.3, $t_{10}$ = -3.1, p = 0.021), and medium rate (29.9 ms $\pm$ 14.6, $t_{10}$ = -3.67, p = 0.005).

*6.3.3 General pattern of tapping-related change in oscillatory activity*

Figure 6.1A demonstrates the normalized spectrograms constructed from the LFPs for frequencies from 5-35 Hz for all three rates of tapping, epoched from 2 seconds before to 2 seconds after the tap. Two features can be observed. Firstly, there was a suppression of beta power (desynchronisation) before and after the onset of the tap for all conditions. Secondly at the low and, partially, at the medium tapping rate, periods between taps were punctuated with bursts of relative rebound activity (synchronization) in the beta band. However, the latter never become significantly different to baseline (Figure 6.1B).

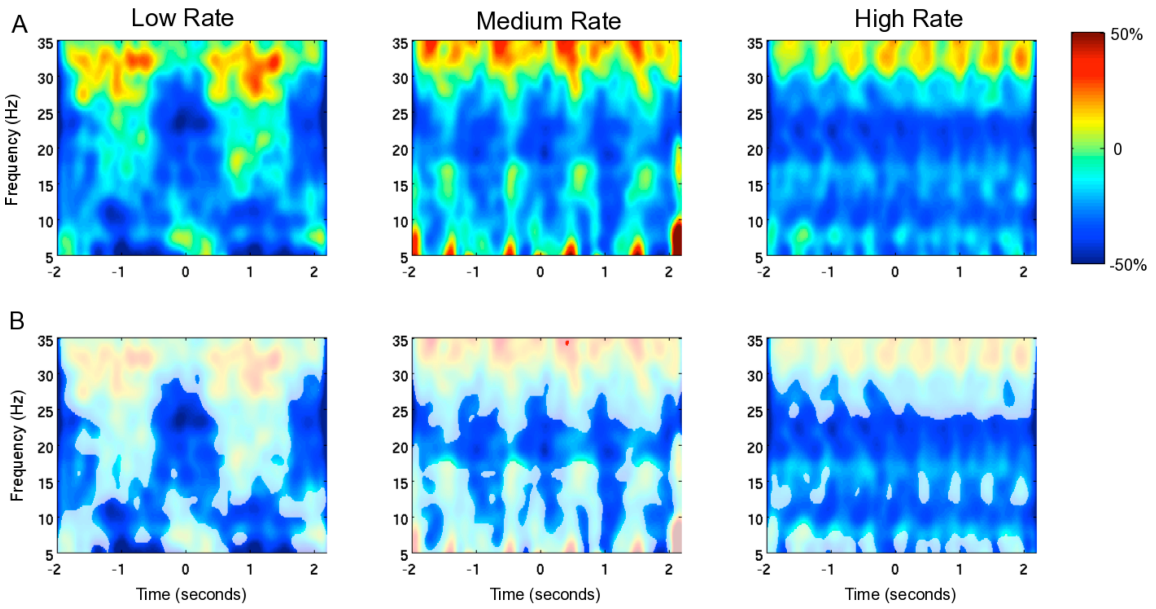


**Figure 6.1**. Oscillatory changes during repetitive finger tapping. Spectrograms showing frequencies from 5-35 Hz are displayed for all three rates of tapping (A) normalized to a resting baseline region. In (B), spectrograms are masked where paired t-tests failed to show a significant difference from baseline at $p<0.05$ level. Zero point indicates time of tap onset (contact with force-sensitive resistor). Stereotypical pattern of desynchronization and rebound are seen in the 15-30 Hz beta range for low and medium rate, although only desynchronization can be seen throughout the epoch with the high rate tapping.

*6.3.4 Time course of spectral changes in the beta range*

Percentage change in power was averaged across the beta range (15-30 Hz) and is displayed in Figure 6.2 for all three rates of tapping. At all three rates, a similar maximal suppression of beta of about 35-40 % occurred. However, whereas in the low and medium rates beta resynchronized post-movement to non-significant levels, beta in the fast tapping rate remained significantly suppressed throughout the task.

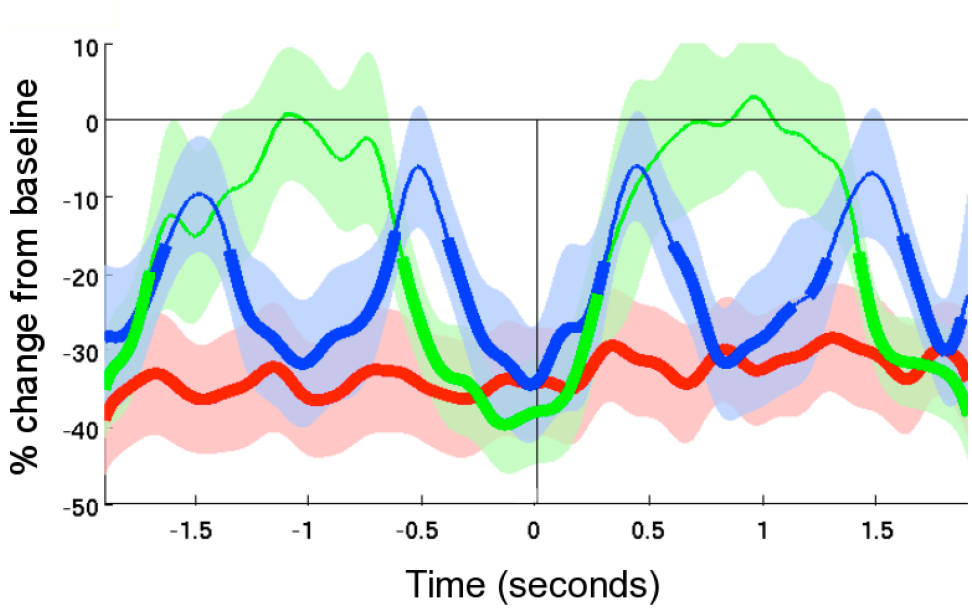


**Figure 6.2.** Broadband (15-30 Hz) beta activity across movement rates. Average beta (15-30 Hz) power $\pm$ standard error (shaded area) is shown over a 4 second period centred on tap occurrence (0 ms) for low rate (green), medium rate (blue) and high rate (red) conditions. Periods of

significance from baseline ($p<0.05$) are shown with an emboldened line. A continuous suppression of beta activity is only evident with the high tapping rate, although all conditions have similar degrees of beta suppression around the time of the tap contact.

We explored the responses in the beta band still further by selecting, to the nearest Hz, the frequency of maximal rebound (FMR) power between taps, and the frequency with the maximal suppression (FMS) for each subject. The average FMR was 17.3 Hz $\pm$ 1.4 for low, 20. 9 Hz $\pm$ 1.6 for medium, and 20.0 Hz $\pm$ 1.3 for high rate tapping. FMS was 24.5 Hz $\pm$ 0.9 for low, 25.9 Hz $\pm$ 0.8 for medium, and 23.7 Hz $\pm$ 1.1 for high rate tapping. Thus the frequency of maximal suppression was higher than that of maximal rebound in all three conditions ($p < 0.05$). The average traces for these selected frequencies are plotted in Figure 6.3 along with the simultaneously recorded mean goniometer trace. FMS showed a clear tap-related suppression of activity, with a rebound after the tap that remained below baseline for all conditions. This relative synchronization was diminished in the fast rate condition. Overall, beta activity was continuously suppressed in the FMS, regardless of condition. In contrast, the FMR showed rebound activity with slow and medium tapping rates, with increases in power above baseline. In low and medium rate tapping, rebound above baseline coincided with periods of no or minimal movement, whereas rebound activity during fast tapping was effectively absent.

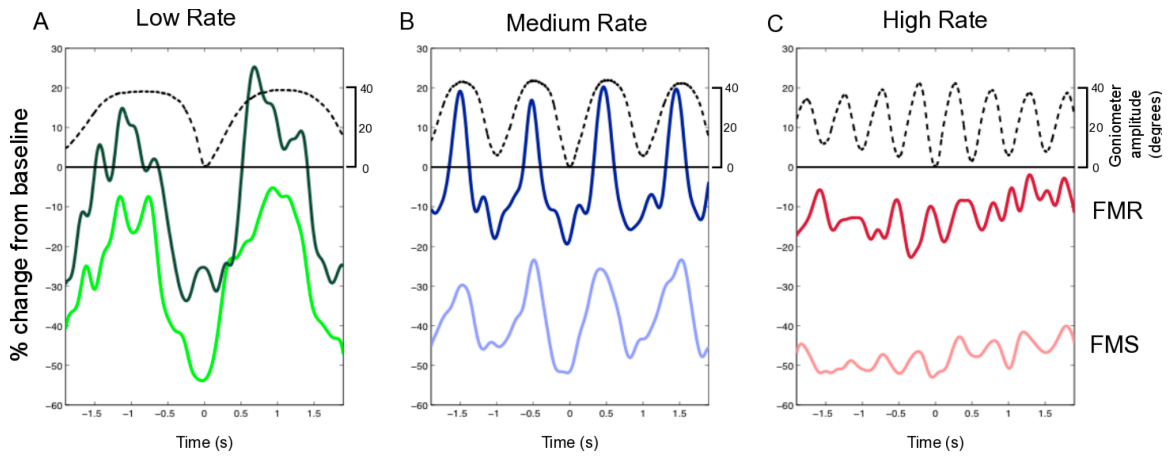


**Figure 6.3.** Time-evolving profile of selected frequencies. Frequency of maximal suppression (FMS) is shown for low tapping rate (A, light green), medium tapping rate (B, light blue), and high tapping rate (C, light red). Power is always below baseline for FMS and shares a similar mimimum of about -50 % for all frequencies. Frequency of maximal rebound (FMR) is shown for low tapping rate (A, dark green), medium tapping rate (B, dark blue), and high tapping rate (C, dark red). Here, a prominent rebound between taps is observed in low and medium conditions, but absent in the high rate condition.

### *6.3.4 Quantitative comparison of beta changes between tasks*

Task related changes in beta power were quantitatively assessed (Figure 6.4). Maximal desynchronisation (Figure 6.4A) was significantly different to baseline for all beta power measures and tapping rates ($p < 0.05$). However, there were no differences in maximal desynchronization between

tapping rates in either broadband beta ($F_{2,20}$ = 1.39, p = 0.27), FMR ($F_{2,20}$ = 0.036, p = 0.965) or FMS ($F_{2,20}$ = 2.96, p = 0.075).

For broad-band beta power, maximal synchronisation (Figure 6.4B) was not significantly different from baseline during low and medium tapping, but was below baseline during tapping at the high rate ($t_{10}$ = -3.19, p = 0.01). There were also differences between tapping rates ($F_{2,20}$ = 8.05, p = 0.01). Post-hoc tests revealed that maximal synchronisation was less during high compared to both low ($t_{10}$ = 3.06, p = 0.036) and medium ($t_{10}$ = 3.15, p = 0.031) tapping rates.

Similarly, FMS only differed from, and was lower than, baseline at the high tapping rate ($t_{10}$ = -4.29, p = 0.002). There were also differences in FMS between tapping rates ($F_{2,20}$ = 15.75, p < 0.0001), accounted for by a significantly reduced maximal synchronization during high compared to low ($t_{10}$ = 4.74, p = 0.002) and a trend between high and medium ($t_{10}$ = 2.60, p = 0.08) tapping rates. Maximal synchronization was also reduced during medium compared to low rate tapping ($t_{10}$ = 3.49, p = 0.017).

Lastly, FMR displayed maximal synchronisation significantly above baseline for low and medium tapping rates (low: $t_{10}$ = 3.61, p = 0.005, medium: $t_{10}$ = 4.02, p = 0.002), but there was no difference from baseline in the high rate. There were also significant differences across conditions ($F_{2,20}$ = 4.90, p = 0.039), between low and high ($t_{10}$ = 2.83, p = 0.049), and medium and high ($t_{10}$ = 3.19, p = 0.024) tapping rates.

In summary, the results showed similar maximal desynchronisation of beta activity across tapping rates, but a consistently reduced maximal synchronisation during tapping at the high rate.

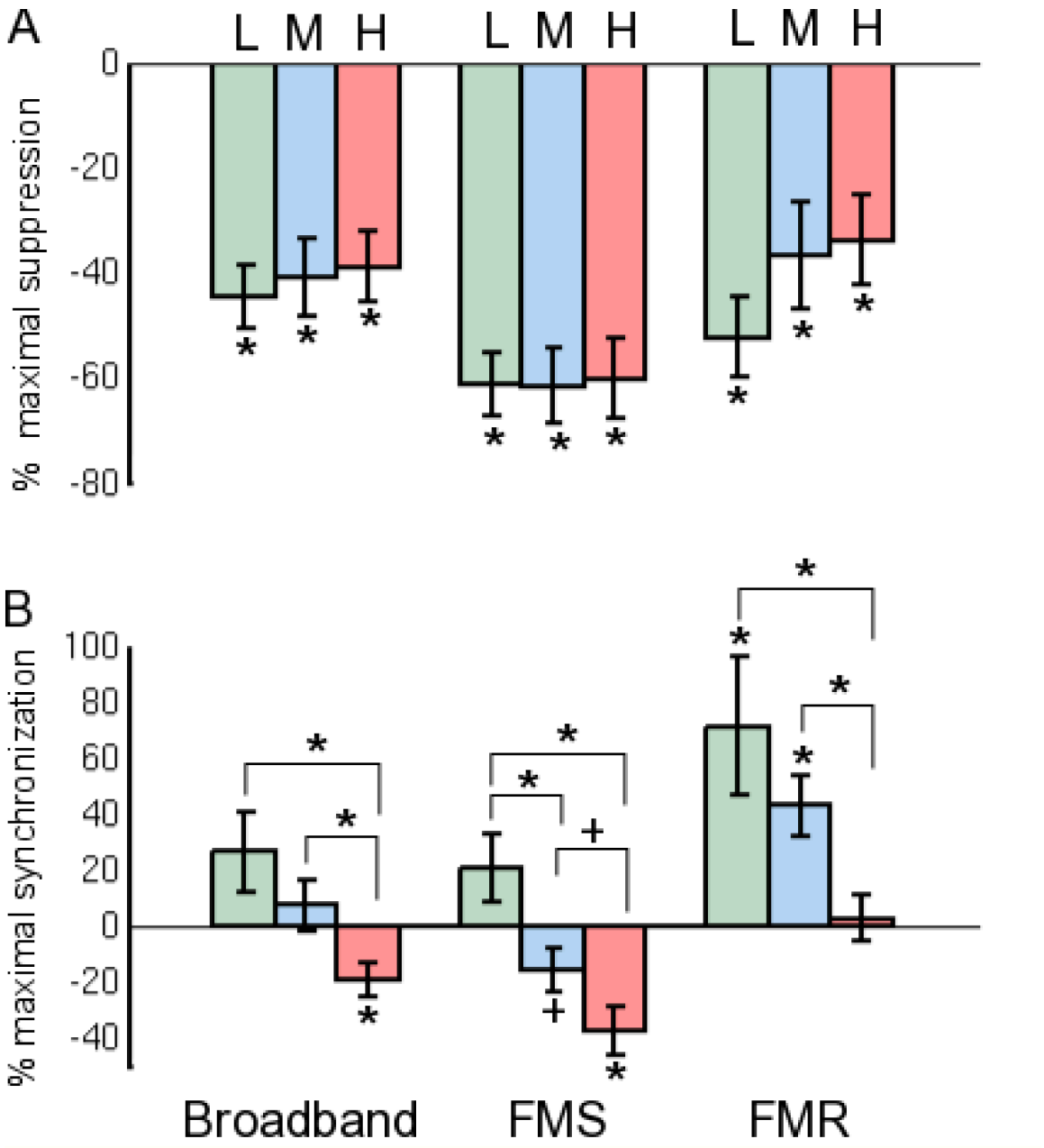

**Figure 6.4.** Quantitative analysis of power changes during tapping for low rate (L, green), medium rate (M, blue), and high rate (H, red). There is similar maximal suppression across tap rates (A), but diminished resynchronization (B) during tapping at the high rate. Significant differences from baseline taken as $p<0.05$, and differences between conditions as $p<0.05$, Bonferroni corrected. + $p = 0.08$.

*6.3.5 Relationship between stationary period and beta rebound*

The timing of the strong FMR rebound in relation to the goniometer (Figure 6.3) suggested that this effect may be related to the relatively stationary period between taps during which minimal movement occurred. Accordingly we calculated the average stationary period for each tapping rate in each subject and plotted the log of these values against the maximal beta rebound (Figure 6.5A). This demonstrated that the lack of rebound during tapping at high rates was associated with a reduced stationary period. In contrast, tapping at medium and low rates had longer stationary periods and involved maximal synchronizations above baseline. Taking all conditions and subjects together (Figure 6.5A), there was a significant correlation between log stationary period duration and rebound size ($R = 0.55$, $p = 0.029$). Figure 6.5B shows an example of a similar relationship within a condition (medium tapping rate) in a single patient.

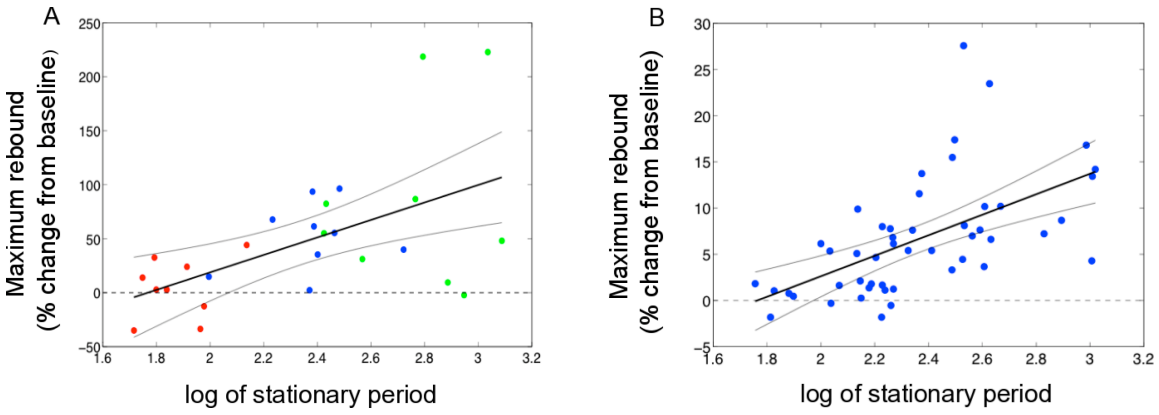


**Figure 6.5.** Relationship between stationary period and rebound**.** (A) displays the relationship between average log stationary period duration between taps (no movement), and maximal rebound size in FMR, for low rate (green), medium rate (blue), and high rate (red) tapping (R = 0.55, p = 0.0029). High rate tapping demonstrates substantially shorter stationary periods in correspondence with suppressed or minimal beta rebound. (B) shows all trials from a single patient during tapping at the medium rate. Log stationary period duration correlates with rebound size (R = 0.57, p <0.0001).

### *6.3.6 Auditory cues*

To ensure that the auditory cues alone were not an important contributor to the changes in beta activity observed here, we recorded activity in the STN in 8 of the 11 patients during trains of auditory cues while participants were at

rest, but attending to the cue. Beta activity showed a similar pattern of modulation as in trials with tapping, but this was greatly attenuated and did not differ between rates of auditory pacing. Thus there were no effects of sound rate in separate ANOVAs of maximal desynchronisation ($F_{2,14}$ = 0.044, p = 0.96) and maximal synchronization ($F_{2,14}$ = 2.48, p = 0.11) during auditory pacing by itself. In addition, maximal desynchronisation during auditory cues was -20.3 % $\pm$ 3.8 compared to -48.1 % $\pm$ 5.7 during paced tapping in the same subjects, averaged over all rates ($t_7$ = 6.4, p < 0.0001).

## 6.4 DISCUSSION

We observed two main task-dependent patterns of modulation in the beta-frequency band. First is a desynchronisation which was greatest at around 24 Hz, seen around the time of tapping, with an amplitude of desynchronization that was comparable across all tapping rates. Second is a relative rebound in synchronization which was greatest at around 20 Hz and which was only present for low and medium rates of tapping, coinciding with the time between taps when there was minimal movement of the finger. The defined separation between tapping rates captures major changes in beta activity but likely obscures a phenomenon that emerges gradually as movement rate increases. Nevertheless, the overall pattern of activity suggested a persistent beta desynchronisation of similar depth across tapping rates, and superimposed on this, a beta rebound synchronization only when tapping rates were slow enough to contain appreciable periods of

minimal movement. Although we focused on activity contralateral to the tapping hand, ipsilateral activity also displayed the same modulation, which is in line with previous reports demonstrating comparable beta reactivity in both hemispheres (Doyle et al., 2005; Androulidakis et al., 2007; Hebb et al., 2012)

These two components of beta-band modulation may be related to the features of discrete phasic movements. Firstly, it would seem reasonable to relate the desynchronisation, which reaches a maximal value at the time of tapping, with the desynchronisation that precedes and occurs during phasic movements. An important finding of this study is that the absolute level of beta suppression was similar despite varying velocities between the tapping tasks, suggest that it is not bound to any particular kinematic variable of the movement. The finding adds to the literature that movement related beta suppression does not directly relate to the motor processing underscoring biomechanical aspects of the response (Kempf et al., 2007; Brücke et al., 2012).

The second process, the synchronisation between taps at the lower two rates of tapping, may correspond to the beta rebound reported when a phasic voluntary movement comes to a stop. Both the resynchronization reported here and that previously reported following phasic movement tend to occur at lower frequencies in the beta band and are more variable between subjects (Alegre et al., 2004; Kempf et al., 2007). Although the beta

synchronization after each tap was less than the rebound seen after briefer movements, previous studies have also shown a decrease in beta rebound during sustained movements (Cassim et al., 2000; Alegre et al., 2003) as opposed to brief movements. The beta rebound following movement at the cortical level has been thought to reflect processes of active immobilization after movement or the termination of a motor plan (Salmelin et al., 1995; Alegre et al., 2004; Erbil & Ungan, 2007), analogous to the increases in beta activity seen when a motor act must be stopped or inhibited (Zhang et al., 2008; Ray et al., 2012). Alternatively, it has been thought to reflect movement related afferent feed-back and sensorimotor recalibration following a period of change (Cassim et al., 2000). The dependence of the relative rebound upon the duration of the static period in our study would argue against a simple, all or nothing, termination signal, although we cannot rule out a possible contribution from sensory re-afference.

There are three potential, but not mutually exclusive, explanations for the persistently suppressed beta activity found in the high-rate tapping condition. Firstly, as has been argued elsewhere (Jenkinson & Brown, 2011), a drop in beta levels could enable the predictive resourcing of motor actions. A major prediction of this hypothesis is that suppression of beta activity will be sustained under conditions of sequential movement, as the likelihood of imminent movement after each successive component is high. Here, the persistence of beta suppression for the entire sequence of movements at the higher rate of tapping, as well as the anticipatory nature of tapping at the

high rate whereby taps precede the auditory cues by about 25 ms, is consistent with the predictive and hence persistent suppression of beta activity. Secondly, the sustained suppression might represent a dynamic shift from discrete to continuous movement which is known to occur at around 2 Hz (Huys et al., 2008). The presence of a beta rebound with tapping at frequencies < 2 Hz, and its absence during tapping at frequencies ≥ 2 Hz has been previously reported at the level of the cortex - the disappearance of the rebound at higher tapping rates also led to a sustained suppression of beta activity (Toma et al., 2002) . These and other authors have argued that finger taps performed at < 2 Hz are programmed as independent movements timed to occur with the auditory cue, whereas tapping at ≥ 2 Hz becomes anticipatory or even syncopated, and is programmed as a continuous rhythmic movement (Mayville et al., 1999; Toma et al., 2002) . Indeed, a distinction has been made between an 'automatic' timing system controlling sub-second movement intervals and a 'cognitively controlled' system involved in the production of supra-second intervals and discrete movements (Lewis & Miall, 2003). The continuous reduction of beta activity observed here during high-rate tapping may reduce the resourcing required for sequential movements and contribute to the perceived automaticity under such conditions. This thinking is in line with the possible role of the basal ganglia in controlling the automatic output of entire behavioral sequences or representations (Graybiel, 1998; Jin & Costa, 2010). Lastly, and perhaps the most parsimonious explanation, is that during high rate tapping the beta rebound is partly canceled out by the beta

desynchronization of the next tap. Nevertheless, this simple effect could serve to maintain a consistent desynchronization and further promote continuous or sequential movement.

There are some limitations to the present study. Because our recordings were made in patients, any attempts to study normal physiology are necessarily confounded by the pathological state of PD. Dopaminergic therapy is known to suppress the heightened pathological beta activity in PD (Kühn et al., 2006). Nevertheless, our results may still have been influenced by the presence of motor impairment and pathological changes in the basal ganglia. Although the usual approach to addressing the role of pathology is to contrast OFF and ON medication recordings, the primary goal of our study was to examine the role of oscillations in the subthalamic nucleus during a tapping task under near-physiological conditions. The changes shown here are in line with studies of cortical activity in normal subjects (Toma et al., 2002), supporting a physiological, rather than pathological, basis to the observed activity. It is also important to stress that the evidence suggested our LFP signals were locally generated and were very unlikely to have represented volume conduction from the cortex.

We should also acknowledge that auditory pacing alone resulted in some rhythmic modulation of beta activity in the STN, although this was less than half of that occurring during paced finger tapping. It is possible that the modulation related to imagined movements as auditory pacing was not

specifically performed before tapping blocks, and motor imagery is known to induce substantial beta desynchronization in the STN (Kühn, et al., 2006). However, the basal ganglia have been implicated in timing and sequence learning (Lehéricy et al., 2005; Teki et al., 2011) and it is conceivable that the rhythmic modulation of beta activity with auditory pacing is physiological (Fujioka et al., 2012). As such, it may even underlie some of the performance benefits of external rhythmic cueing (Thaut et al., 1996; Baker et al., 2008; Rochester et al., 2009) through the promotion of additional beta suppression at the time of taps.

In conclusion, the beta oscillations recorded in the region of the subthalamic nucleus in medicated PD patients are modulated by finger tapping. The effects can be considered as twofold. First, beta desynchronisation becomes sustained for higher rates of tapping, in line with recent theories that suggest beta desynchronisation relates to the prospective resourcing of action (Jenkinson & Brown, 2011). Thus beta desynchronisation relates to the global sequence of movements rather than individual movement during high rate tapping. Second is a relative beta rebound the size of which depends in a graded fashion on the duration of static periods between taps. Together these different forms of beta modulation may facilitate the motor performance of tapping, as suggested by the fact that finger tapping is characteristically compromised when PD patients are withdrawn from their anti-dopaminergic medication, with beta activity exaggerated and its reactivity diminished (Doyle et al., 2005).

# 7. IMPAIRED RETENTION OF MOTOR MEMORIES IN PARKINSON'S DISEASE


## -Abstract-

In chapters 2-6, the role of the basal ganglia has been explored with respect to the production of simple discrete and repetitive movement. However, such temporally limited motor output does not capture the known plasticity of the basal ganglia and its posited role in motor learning. We therefore explored this latter aspect by testing PD patients during motor adaptation adaptation. Motor adaptation is a process in which a repeatable error drives the motor system to gradually adapt its output to reduce the error and to improve accuracy over time. Such adapted states can be stored as a motor memory. Recent evidence has demonstrated that people with Parkinson's disease (PD) have intact initial adaptation but impairment in subsequent re-testing. However, it is not clear whether the impairment in retention of the learned memory is due to a primary deficit in retention or a higher susceptibility to disruption of the motor memory over time. We sought to answer this question by testing people with PD using a visuomotor adaptation paradigm in two different experiments. In experiment 1, learning, short-term retention, de-adaptation were tested. In experiment 2 a different group of PD patients performed the same paradigm, this time with a competing interference task between learning and retrieval to disrupt retention of the motor memory. Our results in experiment 1 show that people

with PD have intact fast learning in the early part of the initial visuomotor rotation task but demonstrate deficient slow learning during both the late phase of the initial learning and de-adaptation sessions. However the largest impairment was seen at retrieval where the PD patients showed a marked lack of retention. However in experiment 2 PD patients show a paradoxical resistance to motor memory interference, with the interference task impeding retention in the PD group to a lesser degree than healthy controls. Our results from experiment 2 suggest that, like the initial adaptation task, the interference task was less well retained in PD, thereby reducing its disruptive effect on the first motor memory. We conclude that PD patients have a primary deficit in motor memory retention, rather than increased susceptibility to interference. Such a deficit in the ability to retain motor memory would impair processes central to rehabilitation and recovery of function compromised by neurodegeneration.

## 7.1 INTRODUCTION

Motor learning is a critical process in acquiring new skills, improving on existing abilities, recovering motor function after disease or injury, or simply adapting to changes imposed by growth. Successful learning, if undisturbed, can also lead to long-term, stable improvements in the associated task (Robertson et al., 2004). Such retention, retrieval, and improvement of motor memory is important is the long-term performance of learned tasks,

and thus plays a potentially fundamental role in rehabilitation and motor improvement after brain injury or neurological disease.

Various brain regions have been associated with the acquisition of motor memories. The cerebellum has been heavily implicated in the initial stages of learning and error reduction (Bédard and Sanes, 2009). Conversely, basal ganglia activity and motor cortical activity are often seen to increase later during the automatization of sequence learning (Virginia B Penhune and Julien Doyon 2002a; Seitz et al. 1994). Accordingly, some aspects of motor learning are impaired in patients with basal ganglia dysfunction, such as Parkinson's disease. Indeed, some studies have shown deficient overall motor learning, using tasks such as writing adaptation (Teulings et al., 2002), 90 degree visuomotor adaptation (Contreras-Vidal and Buch, 2003), or the serial reaction time task (Muslimovic et al., 2007). However, others have demonstrated intact initial learning of PD patients off levodopa (Messier et al., 2007; Paquet et al., 2008). Interestingly, two recent studies have shown normal adaptation but deficient retention using a visuomotor adaptation task (Marinelli et al., 2009; Bédard and Sanes, 2011, 2011). This supports other studies that suggest a reduction in the retention of learnt skills in PD (Doyon et al., 1998; Smiley-Oyen et al., 2003; Cohen and Pourcher, 2007). It may be that these deficits contribute to the limited benefit of rehabilitation programs for motor recovery in PD (Gage and Storey, 2004), in which case understanding these problems is of substantial clinical interest.

We sought to investigate motor adaptation and retention of adaptation in PD through use of a visuomotor rotation task. The task requires the remapping of a well-learned movements – in this case finger movement of a joystick - and a new spatial goal (Krakauer et al., 2000). During adaptation, the subject is exposed to a discrepancy between their own movements and the expected movement of the computer cursor being controlled. The discrepancy between hand and cursor movement requires the subject to adapt their motor output, with little explicit knowledge, in order to reach the target accurately. Re-testing the subjects after a period of rest, using the same discrepancy between joystick and cursor results in improved performance, which is termed 'savings' (Krakauer et al., 2005a). Savings has been described in two possible ways: as either a faster *rate* of readaptation (Kojima et al., 2004; Krakauer et al., 2005a), or a reduced error when re-tested, also known as aftereffect (Yamamoto et al., 2006), as compared with initial adaptation. Our focus in this study was on the latter form of savings, in which the adapted state is retained over time, as indexed by the level of error upon retrieval. Such improved performance at retrieval can be disrupted by an interference task (Krakauer et al., 2005a), in which the subjects learn a competing counter-rotation after initial learning, resulting in impaired future recall of the first learned rotation.

Our goal in this study was to determine whether the poor performance of PD patients at re-test (Marinelli et al., 2009; Bédard and Sanes, 2011) was due to i) reduced retention, ie. 'forgetting' of the learned motor memory, or ii) higher susceptibility of the motor memory to disruption. Such a distinction is

important, as an answer might guide rehabilitation strategies to minimize forgetting or interference, thereby enhancing future retrieval of a learned skill. We sought to answer this question with two experiments. In the first experiment, we tested PD patients and healthy controls on a visuomotor task, and then re-tested on the same task after 45 minutes We hypothesized that in the absence of any interference patients would show accelerated forgetting and impaired retention of the learned adaptation. In the second experiment, we imposed an interference counter-rotation task 5 minutes after initial learning. We reasoned that if learned motor memories were more susceptible to disruption in PD, then the interference task should impair PD patients more than controls upon retrieval of the first motor memory. Conversely, if the primary deficit is a lack of retention, then the interference task itself would also be less well retained, reducing its ability to disrupt the initial motor memory and thereby improving performance upon retrieval. Our results show a deficit in PD in retention on the primary task in experiment 1, and a paradoxical reduction in the effect of interference experiment 2. These effects were correlated with disease severity, suggesting that the basal ganglia are critical in the long-term retention of motor memories.

## 7.2 METHODS

### *7.2.1 Subjects*

All experimental procedures were in accordance with ethics approval by the Oxfordshire Research Ethics Committee and the Declaration of Helsinski.

Fifty patients with PD (66.1 $\pm$ 9.25 years of age, 20 females, mean H&Y score 1.91 $\pm$ 0.54, mean disease duration 8.15 $\pm$ 4.03 years) and 34 age-matched healthy controls (64.1 $\pm$ 7.0 years of age, abbreviated HCs) were recruited to the study. The diagnosis of PD was made according to the UK Parkinson's Disease Brain Bank criteria. Inclusion criteria were (i) no psychiatric disorders or neurological diseases other than PD, (ii) absence of moderate-to-severe tremor on testing day, defined as a score of 2 or more on item 20 or 21 of the UPDRS motor assessment, (iii) absence of dyskinesias on testing day (defined by clinical assessment). Four patients were excluded from the study, as two could not properly perform the task (did not move towards the target), and two had abnormal velocity profiles that could not be reliably assessed for analysis, leaving 46 patients. Patients received a Hoehn and Yahr (H&Y) staging from a neurologist on the same day. Patients were studied on their usual medication, which was converted (Tomlinson et al., 2010) to a mean levodopa equivalent daily dose (mean 619 $\pm$ 327 mg, range 70 to 1477 mg).

*7.2.2 Task*

Subjects sat in an armless chair 80 cm in front of a 42x36 cm size computer monitor, on which the task was presented. Subjects were asked to hold a joystick with their right hand, regardless of hand-dominance. An opaque shield covered the joystick so that the subjects could not see their hand or the joystick. Movement of the joystick controlled a green cursor (1x1 cm) on the computer screen, and was recorded at a sampling rate of 60 Hz. The goal

of the task was to follow a red target (1x1 cm) that was initially presented in the centre of the screen and then quickly jumped to one of eight points equidistantly located at the perimeter of a (13x13cm) visible circle once every 2 seconds (Figure 7.1). The sequence of target directions was random. They were instructed to move toward the target and back in a single striking motion without correcting for initial errors. Subjects were also reminded to move as quickly as possible in response to the cue. Examples of raw traces can be seen in Figure 7.2. We conducted two experiments to assess learning, retrieval, interference, and de-adaptation in patients and age-matched controls.

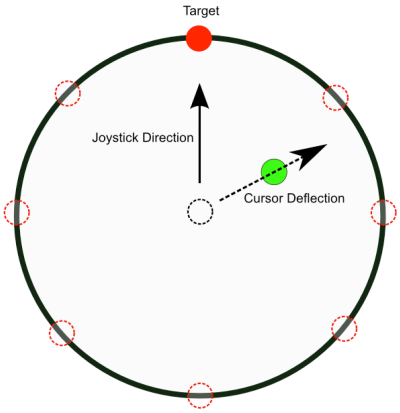


**Figure 7.1.** Schematic diagram of the display. One trial is shown, in which the red target jumps from the origin (dotted block line) to a point around the circle, and the green cursor is moved from the central position to the target. Attempted movement upwards is deflected 60 degrees clockwise. In any one trial only one target (solid red circle) is presented.

*7.2.3 Experiment 1 – Motor learning, retrieval, and de-adaptation*

28 Parkinson's patients (66.9 $\pm$ 8.9 years of age, 11 females, mean H&Y score 1.91 $\pm$ 0.49, mean disease duration 8.76 $\pm$ 3.97 years) and 18 age-matched healthy controls (63.2 $\pm$ 7.1 years of age, 10 males) were enrolled in experiment 1. The task began with a baseline phase (termed B1 subsequently) consisting of 50 trials in which joystick movement matched the movement of the green cursor on the screen. After a 1-minute break a learning phase (L1) was imposed, consisting of 150 trials, in which the relationship between the movement of the joystick and the cursor was altered so that the cursor moved with a 60 degree rotation relative to the joystick. Here, there were large initial errors (~ 60**°**) which decreased over the course of the session. Subjects were instructed not to allow the rotation to disrupt their response profile and to continue to make striking motions as in the baseline phase. Next, participants were afforded a 45 minute break. Participants were then retested in the retrieval phase (R1) with the same 60**°** rotation for 150 trials. The level of adaptation in this phase will subsequently be referred to as retrieval, and the difference between learning and retrieval as retention. Lastly, after a 1-minute break, a de-adaptation phase was conducted for 150 trials, restoring the veridical relationship between cursor and target (0**°**). Here, participants were initially perturbed from the target as a result of their previous motor learning and returned to baseline through de-adaptation (D1).

*7.2.4 Experiment 2 – Motor memory interference*

18 Parkinson's patients (64.5 ± 11.6 years of age, 7 females, mean H&Y score 1.91 ± 0.62, mean disease duration 7.6 ± 4.1 years) and 16 age-matched controls (65.1 ± 7.0 years of age, 10 males) were enrolled in experiment 2. These subjects had not taken part in experiment 1. Here, subjects were initially exposed to baseline (B2, 0°, 50 trials) and learning (L2, +60°, 150 trials) phases, as above. After learning however, participants were given a 5-minute break, and then exposed to an interference phase (I2), during which the relationship between cursor and target was switched to –60° for 150 trials. The interference task was therefore incongruent with learning phase (L2). After interference, the same 45-minute break was given as in experiment 1, followed by retrieval (R2, +60°, 150 trials) and de-adaptation phase (D2, 0°, 150 trials).

*7.2.5 Outcome Measures*

Data were assessed on a trial-by-trial basis using semi-automated in-house code written in MATLAB (Mathworks Inc, Natick, USA). Joystick deflections (root-mean-square of the x and y coordinates) were taken to determine movement trajectory. The trajectory was then filtered with a 150 ms moving average. The start point of the movement was defined as the point where velocity reached 25% of maximal velocity after a minimum of 50 milliseconds from the beginning of the trial, and the end point defined as the point where velocity re-crossed this threshold on the downslope. Peak velocity was then taken as the maximum velocity between the start and end points, with time

to peak velocity also calculated. The main outcome measure was the absolute angular error between the initial outward movement of the cursor and the target angle. This was calculated as the angle between the origin and the point of maximal velocity in the response profile.

*7.2.6 Statistical analysis*

Trials were blocked in groups of 10, with trials exceeding 2 standard deviations of the mean from each block discarded. Errors were averaged over the first 2 blocks and last 2 blocks in each adaptation phase to measure early and late adaptation, respectively. 2x2 ANOVAs were to examine the main effect of group (PD or HC) and possible interactions between group and time point (early or late) in each individual phase, with post-hoc t-tests used to determine the time point in which groups differed. 'Retention' was also quantified by taking the difference in error between the end of the learning phase and the start of the retrieval phase. Mauchley's sphericity test was often significant, whereupon we applied Greenhouse-Geisser correction. Correlations between clinical parameters and outcome measures were performed using Pearson's product-moment correlation, with the exception of the H&Y scores in which non-parametric Spearman's rank correlation was used. Kolmogorov-Smirnov tests confirmed normality in all datasets except for H&Y scores.

## 7.3 RESULTS

### *7.3.1 Basic motor parameters*

There was no significant difference between the age of patients and controls in either experiment 1 ($p = 0.162$) or experiment 2 ($p = 0.890$). There was also no significant difference between patients across experiments 1 and 2 in terms of age ($p = 0.505$), H&Y score ($p = 0.995$) or disease duration ($p = 0.089$). Controls were also of similar age between experiments ($p = 0.462$).

To assess differences in basic motor performance, we analysed the kinematic measures of peak velocity and time to peak velocity. For peak velocity, PD patients had significantly lower peak velocities in both experiments (p-values $< 0.05$), with no main effect of phase and no interaction (p values $> 0.1$). When considering time to peak velocity, there was no significant main effect of group, phase, or interaction in either experiment (p values $> 0.18$). Thus, PD patients had lower peak velocities compared to HCs although this was not different between phases, confirming relatively consistent performance throughout.

### *7.3.2 Experiment 1: Intact adaptation, but impaired retrieval phase in Parkinson's disease*

We began by examining differences in learning, retrieval and de-adaptation in experiment 1 (when no interference was applied). Figure 7.2A and 7.2B demonstrate the raw trajectories and error histograms for a sample patient and control participant, respectively. Figure 7.3 displays the absolute errors

of all phases with de-adaptation reflected across the x-axis to highlight the reversed direction of adaptation.

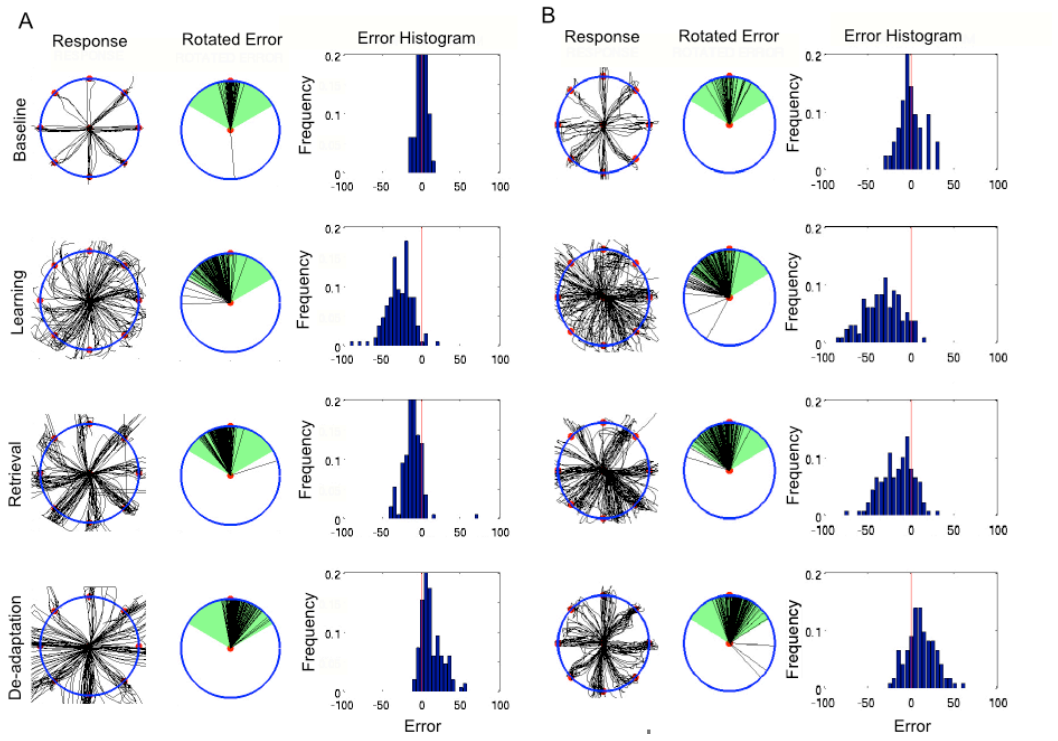


**Figure 7.2.** Raw data for two sample subjects in experiment 1. Data for healthy subject is demonstrated in (A). All trajectories to the 8 targets are plotted (response), and the relative error from the target (rotated error) as measured by angular deviation at point of maximal velocity (green areas represent 60° to either side of the target). Lastly, an error histogram demonstrates the distribution of response errors in the entire phase. A Parkinson's subject is displayed in (B). Of note is that both subjects have similar spread of movement trajectories and error profiles during the baseline and learning phases. However, during the retrieval phase a distinct tightening of the error around 0 is seen for the healthy subject, whereas the PD patient maintains a wider and more inaccurate spread. Similarly, a

tighter distribution for healthy controls during de-adaptation can be compared with the larger and more persistent errors in PD.

There was no difference between PD patient and healthy controls for the baseline phase ($t_{45}$ = -0.74, p = 0.46). We analyzed the first and last 2 blocks of each phase to assess initial and final performance on the adaptation phases (Figure 7.5A). A 2x2 ANOVA for the learning phase with factors group (PD vs HC) and time (early vs late) showed no effect of group ($F_{1,44}$ = 0.34, p = 0.62), an expected significant effect of time ($F_{1,44}$ = 536, p < 0.0001), but no significant interaction ($F_{1,44}$ = 2.9, p = 0.097).

For retrieval, PD patients had higher errors across the early and late blocks, as there was a main effect of group ($F_{1,44}$ = 13.81, p < 0.001), an effect of time ($F_{1,44}$ = 127, p < 0.0001), but no interaction ($F_{1,44}$ = 0.49, p = 0.49). Lastly, de-adaptation showed no effect of group ($F_{1,44}$ = 0.008, p = 0.93), an effect of time ($F_{1,44}$ = 317, p < 0.0001), and a significant interaction ($F_{1,44}$ = 13.5, p <0.001). This was accounted for by a trend towards less early errors for the PD group ($t_{44}$ = 2.0, p < 0.053), an expected effect based on the increased error at the end of retrieval, but there was also a significant increase in error in the late blocks ($t_{44}$ = -3.4, p < 0.002). In summary, PD patients had intact early adaptation but impaired retention and late de-adaptation. Further consideration of these data is afforded below when comparing Experiment 1 with Experiment 2.

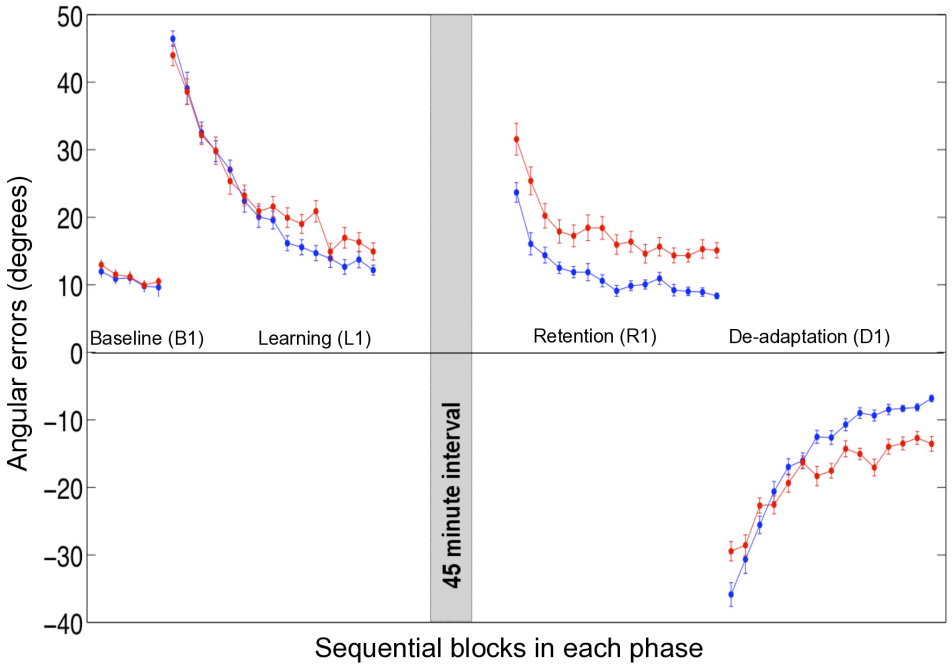


**Figure 7.3.** Adaptation curves for Experiment 1. Curves consist of sequential blocks of 10 trials and are shown for healthy controls (blue) and Parkinson's patients (red). Means and SEM for each block are shown. Note the large differences in the consolidation and de-adaptation phases. *Reflected about the x-axis for visualization.

*7.3.3 Experiment 2: Reduced effect of interference in PD*

Figure 7.4 displays all absolute errors for this task, with reversal and de-adaptation reflected across the x-axis to highlight directional difference. Figure 7.5B shows means of early and late blocks.

There was no difference in baseline between healthy controls and PD patients ($t_{45}$ = 0.53, p = 0.60). Examining the early and late blocks for learning, results were similar to experiment 1, with no effect of group ($F_{1,32}$ = 0.006, p = 0.94), an effect of time ($F_{1,32}$ = 486, p < 0.0001) and no interaction ($F_{1,32}$ = 2.9, p = 0.097). The interference phase had no significant effect of group ($F_{1,32}$ = 2.1, p = 0.16), an effect of time ($F_{1,32}$ = 199, p < 0.0001), and no significant interaction ($F_{1,32}$ = 3.5, p = 0.071). It is important that there was no difference in the final two blocks of interference ($t_{32}$ = -0.066, p = 0.95), so as to subsequently compare of the effect of interference on the retrieval phase.

Retrieval after interference (R2) showed no main effect of group ($F_{1,32}$ = 0.13, p = 0.72), an effect of time ($F_{1,32}$ = 157, p < 0.0001), and a significant interaction ($F_{1,32}$ = 19.5, p = 0.0001). Strikingly, errors were lower for the PD group in the early blocks ($t_{32}$ = 2.2, p = 0.036), whereas the final blocks demonstrated an increase in error similar to experiment 1 ($t_{32}$ = -2.1, p < 0.034). Lastly, de-adaptation had no effect of group ($F_{1,32}$ = 0.22, p = 0.64), an effect of time ($F_{1,32}$ = 131, p < 0.0001) and a significant interaction ($F_{1,32}$ = 5.8, p < 0.022). This was accounted for by reduced errors for the PD

group in the late blocks ($t_{32}$ = -2.4, p < 0.032) but not early blocks ($t_{32}$ = 1.4, p = 0.17).

In summary, PD patients were impaired in the late phases of learning, retrieval, and de-adaptation, as in experiment 1. Surprisingly, there was superior performance in PD relative to HC in the early blocks of the retrieval phase after interference (R2, Figure 7.4), in contrast to the large impairment in retrieval without interference (R1, Figure 7.4) seen in experiment 1.

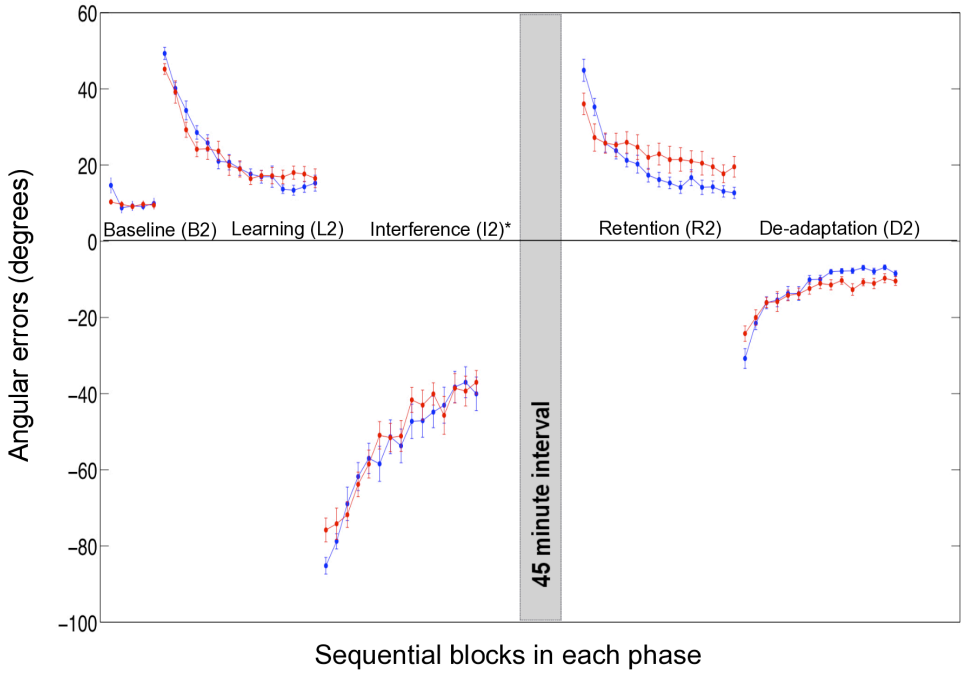


**Figure 7.4.** Adaptation curves for Experiment 2. Curves consist of sequential blocks of 10 trials and are shown for healthy controls (blue) and

Parkinson's patients (red). Means and SEM for each block are shown. *Reflected about the x-axis for visualization.

*7.3.4 Interference impairs the early retrieval phase in healthy controls more than in Parkinson's disease*

We confirmed that the interference task interrupted retrieval in both groups by comparing retrieval with and without interference, showing a significant increase in mean errors in the retrieval

phase when interference was imposed, for PDs (17.19° $\pm$ 0.26 without interference versus 23.57° $\pm$ 1.1 with interference, $t_{44} = -6.89$, $p < 0.0001$) and HCs (11.77° $\pm$ 0.18 versus 19.85° $\pm$ 0.47, $t_{34} = -16.78$, $p<0.0001$). This highlights the effect of interference in disrupting the retrieval of the learned motor memory, as errors increased for both groups at re-test following interference.

Paradoxically, the first two blocks at retrieval (R2) after interference actually showed improved performance in PDs compared to HCs (Figure 7.6A). Although interference had an impact on the starting point for both HC and PD groups in the retrieval phase, the learning curves indicated that controls were more severely affected, taking approximately 3 cycles (30 trials) to catch up to the PD group (Figure 7.6A). To confirm this effect, we took the difference in error between the first 2 blocks in the retrieval phase and the last 2 blocks in the learning phase to quantify retention with and without interference. Thus, a larger value indicated a more pronounced motor memory decay, or in other words less retention. We used this measure in an

ANOVA with factors group (PD and HC) and experiment (experiment 1 and 2), which showed no effect of group ($F_{1,32}$ = 1.8, p = 0.18), an effect of experiment ($F_{1,32}$ = 30, p < 0.0001), and an interaction ($F_{1,32}$ = 17, p < 0.0001). This revealed a remarkable double dissociation (Figure 7.6B). Thus, the large increase in error for PD patients between L1 and R1 was altered to a decrease in error when the original memory was disrupted by interference.

Altogether, we demonstrate a large impairment in retention in the PD group when no interference is applied. However, when acquired motor memory was challenged through the introduction of an interference phase, retention of the initial task was significantly worsened relative to experiment 1, but with a greater impact on HCs than PDs in the early blocks.

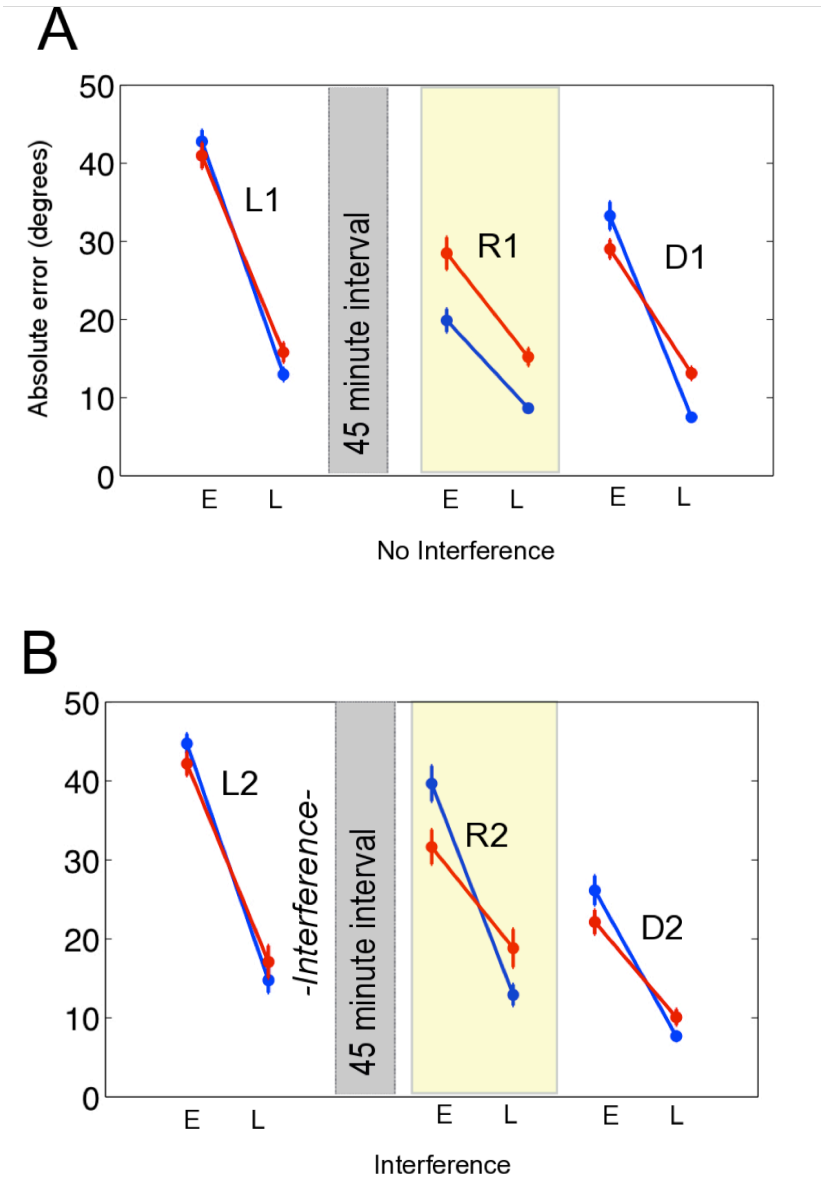


**Figure 7.5.** Mean errors of early and late blocks in all phases. The mean error across the early (first 2 blocks) and late (last 2 blocks) of each phase for HC and PD and shown for experiment 1 (A) and experiment 2 (B). Interference phase is excluded to maintain similar axis scaling (much higher errors). Retrieval phases are highlighted in yellow, showing the paradoxical reversal in performance on the first two blocks of R2 compared to R1 due to interference.

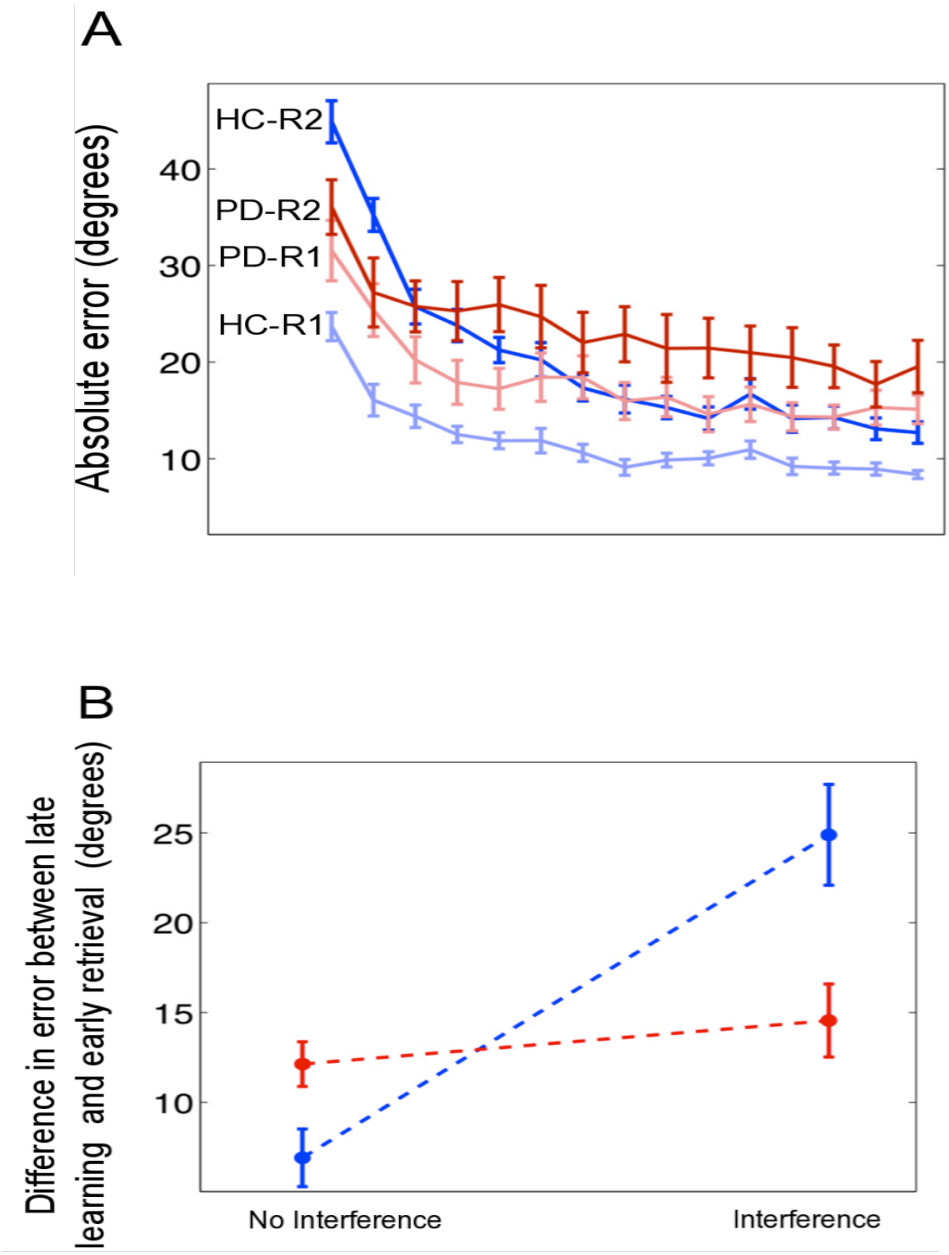


**Figure 7.6.** Effect of interference on retrieval. (A) shows the four retrieval adaptation curves overlayed, revealing an increased initial error for PD in R1 (no interference), and a decreased initial error for PD in R2 (interference). (B) displays the double dissociation in error between late learning and early

retrieval in both experiments. For experiment 1 (no interference), error in the PD group increases significantly more than the HC group between learning and retrieval, showing impaired retention of the learned adaptation. For experiment 2 (interference), error between learning and retrieval in the HC group increases significantly more than the PD group; PD patients were thus less affected by interference.

### *7.2.5 Retention and effect of interference correlate with clinical measures*

In experiment 1, there was a significant correlation between the mean retention and H&Y score ($r = 0.44$, $p = 0.020$), as well as disease duration ($r = 0.43$, $p = 0.024$, Figure 7.7A). As such, more advanced disease was related to a more motor memory loss, or less retention.

There was a significant negative correlation between effect of interference and H&Y score ($r = -0.61$, $p = 0.0067$), and disease duration ($r = -0.49$, $p = 0.037$, Figure 7.7B).

Age did not correlate with either retention in experiment 1 ($r = 0.17$, $p = 0.38$) or effect of interference in experiment 2 ($r = -0.31$, $p = 0.21$). Similarly, levodopa equivalent daily dose did not correlate with either retention in experiment 1 ($r = 0.19$, $p = 0.36$) or effect of interference in experiment 2 ($r = -0.13$, $p = 0.60$).

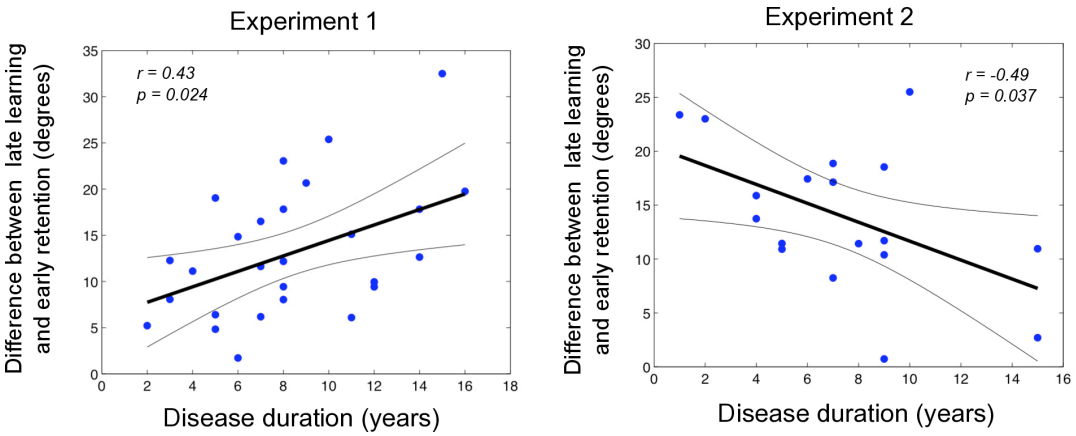


**Figure 7.7.** Correlation between disease duration and impaired retention. Linear regression (thick line) and 95% confidence intervals (thin lines) are shown. Disease duration is correlated with worse retention (more memory decay) (A), and decreased effect of interference (B).

## 7.3 DISCUSSION

We sought to determine if motor memories in Parkinson's disease are less well retained or more susceptible to disruption than those of healthy controls. Our main finding is that of a striking double dissociation in the ability of PD patients to retain a motor adaptation with and without interference. When no interference is applied PD patients have a profound deficit in short term retention of the visuomotor adaptation. In contrast, there is a significant reduction of the effect of interference compared to healthy control. These results show that a motor memory in PD undergoes accelerated decay even when undisturbed, but that the impact of an interference task is reduced.

We suggest these findings are due to a primary deficit in motor memory retention in PD.

PD patients had no significant impairments during initial adaptation to the rotation. This result is perhaps not surprising, given the known role of the cerebellum in the visual guidance of movement (Glickstein, 2000), and motor adaptation (Maquet et al., 2003; Smith and Shadmehr, 2005; Jenkinson and Miall, 2010), in particular visuomotor learning (Tseng et al., 2007; Galea et al., 2011) and the preservation of this structure in Parkinson's disease (Glickstein and Stein, 1991). The finding is in line with previous research showing relatively intact adaptation in PD during visuomotor adaptation (Marinelli et al., 2009; Bédard and Sanes, 2011).

Performance at retrieval exhibited higher errors than late adaptation in both groups, however this was far more prominent in PD patients, suggesting an accelerated decay of motor memory over time. Motor adaptation retention deficits have been previously demonstrated in PD (Marinelli et al., 2009; Bédard and Sanes, 2011). Marinelli et al. tested across days, leaving open the possibility that the deficit seen in their study was a result of the disruption of sleep-dependent processes. Bedard and Sanes tested within the same day and observed a deficit in savings, as measured by rate of adaptation after a learning and washout period. However in our experiment the focus was on the persistence of the adapted state during retrieval without an intervening washout (Yamamoto et al., 2006). Washout (or de-adaptation) can impair retention by interfering with the original task and this

effect may possibly have obscured the deficit in retention in Bedard and Sanes. This is plausible given the larger discrepancy in retention between controls and PD patients in our study. Here we definitively show a pronounced deficit in motor memory retention when re-tested after a short period in the absence of intervening washout. It has been suggested that the basal ganglia is implicated in the long-term retention of motor sequence learning (Penhune et al., 2002; Doyon et al., 1998). Our results from this experiment raise the possibility that the BG are similarly critical for retention of visuomotor adaptation, at least in the short term i.e. over hours.

In our second experiment we demonstrated that interfering with the original motor memory worsened HCs at re-test more than in the PD group. It must be noted that the mechanism by which this interference operates is not clear. Retrograde interference, where the second task disrupts consolidation of the motor memory, is a possibility (Krakauer et al., 2005a; Hinder et al., 2007). Another possibility is anterograde interference where the motor-memory of the previously experienced, but discordant task, interferes with the learning of the new task (Miall et al., 2004). This study was not designed to differentiate between these possibilities, however a unifying hypothesis proposes that the counter-rotation does not erase the original memory but competes with it for retrieval upon subsequent retesting (Krakauer at al 2009). The time at which interference was applied in this study, 5 minutes after the end of the first task, has been show to maximally disrupt subsequent retrieval of the motor memory (Krakauer et al., 2005a). Correspondingly our study reveals an impairment in retention following

interference in both groups. Strikingly, the deterioration was more pronounced in normal controls in the first two blocks of retrieval (fig. 7.4; phase C2), in line with the fact that interference is known to exert its main effect on re-test of a motor memory within the first few blocks (Miall et al., 2004; Krakauer et al., 2005b; Hinder et al., 2007). Thus, error of PD patients was now reduced compared to HCs. This unexpected reversal of adaptive state following interference suggests that interference had a smaller effect on PD patients. Indeed, after interference the retrieval curve of the HC group (Fig. 7.4; R2) resembles their original learning curve (Fig. 7.4; L2) much more-so than the PD group. Given the impairment of retention of the visuomotor task in experiment 1, this same impairment may prevent retention of the interfering counter-rotation task in PD. This would reduce the effect of interference on the original memory and preserve performance at retrieval.

Finally, PD patients were impaired in the late segment of the de-adaptation phase. In both experiments, PD patients quickly reduce aftereffect errors in tandem with healthy controls yet develop significantly higher error towards the end of the de-adaptation phase. Although de-adaptation is not very well understood, it may consist of a 'scaling down' of a previously learned motor memory (Miall et al., 2004; Krakauer et al., 2005b; Hinder et al., 2007). This in line with a deficit of 'task switching' in PD patients (Shook et al, 2005; Cools et al., 2001), as well as an observed impairment in negative transfer (Krebs et al., 2001) or task reversal (Messier et al., 2007) during adaptation. However, this raises the question of why there was no impairment during the

interference task. There were very large errors in the interference task, and thus subjects barely reached asymptotic performance. This 'fast' error-driven type of adaptation may be dependent on the cerebellum (Smith et al., 2006). In contrast, there is a visibly longer asymptotic period in de-adaptation as compared to interference or learning. Such 'slow', repetition-based automatization of adaptation may be more heavily reliant on basal ganglia mechanisms (Penhune et al., 2005; Orban de Xivry et al., 2011). This might also help to explain the small (but non-significant) increase in error near the end of the adaptation phase in PD patients, and the large and persistent increase in error even towards the end of the retrieval phases.

Previous studies have used small, early stage cohorts of patients (Marinelli et al., 2009; Bédard and Sanes, 2011). In this study, we tested a large cohort at various stages of disease severity, and found a significant positive correlation between error in the retrieval phase (R1) of experiment 1 and disease severity as measured with the H&Y scale and disease duration. Conversely, there was a significant negative correlation between the effect of interference and disease severity. These findings suggest that the paradoxical effects of decreased retention and increased resistance to interference are related to the underlying disease process, with its focus on the basal ganglia.

The development and maintenance of motor memories may be important in successful rehabilitation (Bastian, 2008). Unfortunately, systematic analyses

examining the effectiveness of rehabilitation for patients with Parkinson's disease have often proven insignificant or inconclusive at best (Gage and Storey, 2004). The relative disappointment in rehabilitation for Parkinson's disease may be in part due to the deficit observed here under experimental conditions, which allows for gains within session but no refinements or improvements across time. Worsening symptoms with disease progression may therefore be exacerbated by an increasing inability to improve performance through practice or training.

In summary, we demonstrate that retention of visuomotor adaptation is impaired in Parkinson's disease. Furthermore we reveal a previously un-described resistance to interference when a counter-rotation is applied. Our results lend strong support towards a role for the basal ganglia in the retention of learned adaptations. Additionally, we suggest that such increased 'forgetting' of motor memories in PD may restrict improvement through motor learning and underlie a relative lack of success in rehabilitation. Further understanding of the role of the basal ganglia in short and long term motor memory dynamics will be important in modelling effective rehabilitation regimes and designing interventions that might ameliorate this deficit.

# 8. TRANSCRANIAL DIRECT CURRENT STIMULATION IMPROVES VISUOMOTOR ADAPTATION IN PARKINSON'S DISEASE


**-Abstract-**

There is increasing evidence that patients with PD have deficits in motor adaptation, retention, and subsequent retrieval of learned tasks. Such deficits could have deleterious effect on rehabilitation and motor training after disease onset. Transcranial direct current stimulation (TDCS) has recently shown promise in improving motor learning in healthy controls and stroke patients. As chapter 7 demonstrated a selective deficit in retrieval in PD, we sought to determine whether application of TDCS during learning of a visuomotor adaptation could improve visuomotor learning or retrieval in PD patients. Accordingly, we conducted a double-blind study with 26 Parkinson's patients and 20 age-matched controls. Half of each group received sham stimulation, while the other half received real stimulation throughout baseline and learning phases of adaptation. We show that TDCS improves learning and retrieval of the visuomotor adaptation in both PD patients and healthy controls. However, there was no significant effect on clinical ratings or kinematics of movement. The results demonstrate a selective effect of TDCS on motor adaptation and raise the possibility of using TDCS as an adjunct therapy during rehabilitation in PD.

## 8.1 INTRODUCTION

Motor learning is a crucial part of our lives, often occurring implicitly and unnoticed but underlying a variety of important of activities. In the healthy state, motor learning allows the acquisition and long-term retention of motor skills, such as riding a bike, or typing on a keyboard. Motor learning is also thought to be crucial in rehabilitative processes during disease, such as recovery after stroke.

There is increasing evidence that individuals with PD have difficulties with motor adaptation. In particular, a recent set of papers using visuomotor adaptation paradigms has demonstrated that PD patients are relatively unimpaired in the initial learning phase. However, deficits are evident when re-testing after day-time rest (Bédard and Sanes, 2011), or overnight (Marinelli et al., 2009). We have shown here that deficits in retention are correlated with disease progression (see Chapter 7), raising the possibility that the basal ganglia dysfunction in PD may, in part, be responsible for the impairment in motor memory retention. Such a deficit would result in real world problems, and may be the reason that PD patients do not derive benefit from physical rehabilitation programs (Gage and Storey, 2004). Therefore, defining this deficit and divising interventions that can restore this deficit is of real clinical interest.

One promising avenue is non-invasive brain stimulation. Repetitive transcranial magnetic stimulation (rTMS) has shown some promising results in PD (Fregni et al., 2006; Grüner et al., 2010). Recently, TDCS has

emerged as an alternative brain stimulation technique, with the advantages of being less uncomfortable, cheaper, simpler, and allows induction of both excitation and inhibition (Sparing et al., 2008). In healthy controls, TDCS, has been shown to enhance cortical excitability (Nitsche and Paulus, 2001) and improve motor learning (Nitsche et al., 2003). Given this effect in the healthy population it has naturally been suggested as a therapeutic tool in disease, and has indeed been used to improve motor function in stroke with some success (Stagg et al., 2009). However evidence that TDCS may have beneficial effects in PD is limited to studies examining its effect on gross motor symptoms. In a cross-over study, anodal stimulation of M1 but not dorsolateral prefrontal cortex significantly improved motor function while off medication as assessed by unified Parkinson's disease rating scale (UPDRS) scores. However, in a small clinical trial Benninger (2011) failed to find any significant difference between TDCS and sham stimulation for most motor measures, including UPDRS, although gait and bradykinesia did benefit slightly. The small effects of TDCS on motor scores in PD dampen the enthusiasm for using this technique to improve gross motor symptoms. However, given its prominent effect on long-term plastic changes and motor learning (Nitsche et al., 2003), the possibility of applying TDCS as an adjunct therapy concurrent with rehabilitation or motor training has promise. Here, we test the hypothesis that TDCS can improve motor adaptation in PD by employing a well-known visuomotor adaptation paradigm. We have previously shown that PD patients have a pronounced deficit in retrieval of a learned visuomotor adaptation. We conducted a double blind, randomised,

sham controlled study to investigate whether TDCS can improve aspects of motor adaptation and retrieval.

## 8.2 METHODS

### *8.2.1 Subjects and UPDRS*

All experimental procedures were in accordance with ethics approval by the Oxfordshire Research Ethics Committee and the Declaration of Helsinski. 28 patients with PD (62.7 $\pm$ 9.0 (SD) years of age, 10 females, mean disease duration 6.6 $\pm$ 4.9 years) and 20 age-matched healthy controls (60.2 $\pm$ 8.9 years of age, abbreviated HCs) were recruited to the study. The diagnosis of PD was made according to the UK Parkinson's Disease Brain Bank criteria. Inclusion criteria were (i) no psychiatric disorders or neurological diseases other than PD, (ii) absence of moderate-to-severe tremor on testing day, defined as a score of 2 or more on item 20 or 21 of the UPDRS motor assessment, (iii) absence of dyskinesias on testing day (defined by clinical assessment). Two patients could not complete the task due to fatigue, and thus 26 patients used in the study. Patients were studied on their usual medication, which was converted to a mean levodopa equivalent daily dose (mean 704.9 $\pm$ 329 mg) (Tomlinson et al., 2010). The study was conducted in a double-blind fashion. Patients were randomly assigned to either sham or stimulation group and were not told of their assignment until after the experiment was completed. They were assessed on the UPDS motor sub-score (section III) before and after stimulation by a blinded rater. Healthy controls were also randomly assigned to either sham or stimulation group.

*8.2.2 Task*

See Chapter 7.

6 patients in the current had previously performed the visuomotor paradigm in Chapter 7 (without TDCS) approximately 1 year prior. Thus we used an opposite rotation (-60 degrees) for those individuals to minimize any carry-over effect. Furthermore, these 6 patients were equally distributed between the groups.

8.2.3 TDCS

TDCS was delivered using a DC-Stimulator Plus (NeuroConn, Ilmenau, Germany) via sponge electrodes soaked in saline in a bi-polar configuration. We placed the target electrode (area 5x7 cm) on the scalp overlying the hand area of the left motor cortex, as identified by single monophasic pulses of TMS (MagStim 200, Whitland, Dyfed, Wales, UK) and the reference electrode (5 x 10 cm) on the contralateral supraorbital area. All subjects were naïve to TDCS. In the stimulation group, anodal TDCS (2 milliamps) was delivered throughout the baseline and learning phases, and for 10 minutes afterwards while the subject rested while remaining seated. Stimulation was ramped up and ramped down over 30 seconds, to avoid discomfort. Altogether, patients received stimulation for approximately 17 minutes (7 minutes for task plus 10 minutes rest). In the sham group, the same procedure was followed, except stimulation was maintained only for 30 seconds, and then was discontinued. UPDRS measurements were done immediately before and immediately after stimulation.

*8.2.4 Outcome Measures*

UPDRS was assessed as above.

Angular deviation during adaptation was calculated as per Chapter 7.

*8.2.5 Statistical analysis*

Trials were blocked in groups of 10, with trials exceeding 2 standard deviations of the mean from each block discarded. Errors were averaged over each subject and phase. As well, to determine the rate of learning, individual trials from each subject's adaptation curves were fit with a single exponential function, taking the form:

$y = C_1 * \exp(-\text{rate} * x) + C_o$

where $C_1$ and $C_o$ are constants, x is the trial number, and y is the error.

For each phase, 2x2 ANOVAs were used to examine the main effects of group (PD or HC) and stimulation. The same analysis was performed to compare subjects between groups. To assess the impact of stimulation on UPDRS, a repeated measures 2x2 ANOVA was conducted with group (PD and HC) and time point (before and after stimulation).

Where Mauchley's sphericity test was significant we applied Greenhouse-Geisser correction. There were no significant interactions and therefore no post-hoc tests were employed. Kolmogorov-Smirnov tests confirmed normality in all datasets.

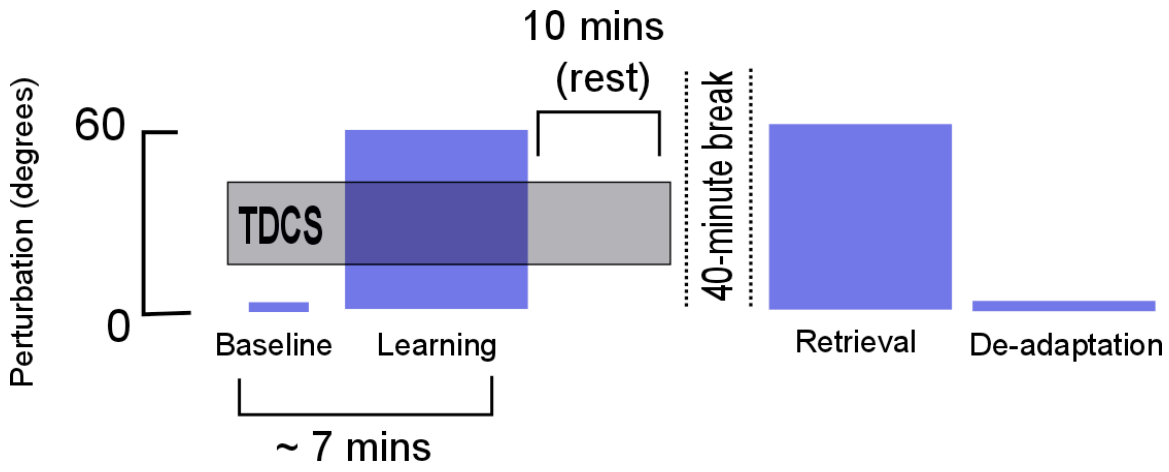


**Figure 8.1.** Experimental design. Subjects completed baseline and learning phase while TDCS or sham was being applied. Subjects then rested for 10 minutes with stimulation ongoing (or pads in place in the sham condition), and then a 40-minute break after pads had been removed. Lastly, subjects re-adapted in the retrieval phase (no stimulation) the subjects were finally tested again in the initial, normal condition in the de-adaptation phase (no stimulation).

## 8.3 Results

*8.3.1 Baseline parameters*

There was no significant difference in age between any of the groups. A 2x2 ANOVA with factors group (PD and HC) and condition (sham and stim) showed no significant effect of group ($F_{1,42}$ = 0.49, p = 0.49), condition ($F_{1,42}$

= 0.67 p = 0.42), or interaction ($F_{1,42}$ = 0.015, p = 0.90). Furthermore, there was no difference between PD stimulation and sham groups in terms of disease duration ($t_{25}$=1.4, p = 0.19) and levodopa equivalent daily dose ($t_{25}$ = 0.39, p = 0.71).

A 2x2 ANOVA for each phase showed that PD patients had lower maximal velocity in all phases (p < 0.05). There was no effect of stimulation or interaction with any phase. Reaction time showed no effect between groups, stimulation, or interaction. Thus, PD patients had lower maximal velocity than normal subjects across all phases, but stimulation did not have any significant effect on baseline motor parameters.

*8.3.2 UPDRS*

We first assessed the impact of stimulation on UPDRS (see Figure 8.1). A repeated measures ANOVA with factors condition (sham or stim) and time (before and after stimulation) revealed no significant effect of condition ($F_{1,24}$ = 0.07, p = 0.79), time ($F_{1,24}$ = 0.25 p = 0.62), or interaction ($F_{1,42}$ = 0.49, p = 0.49).

*8.3.3 Effect of stimulation on adaptation*

All adaptation curves are shown for healthy controls (Figure 8.2) and PD patients (Figure 8.3). We assessed the effect of stimulation on each adaptation phase. For baseline a 2x2 ANOVA with factors group (PD and HC) or condition (sham or stim) show no effect of group ($F_{1,42}$ = 3.8, p = 0.057), stimulation ($F_{1,42}$ = 0.49, p = 0.49), or interaction ($F_{1,42}$ = 2.7, p = 0.11).

For learning, there was a main effect of stimulation ($F_{1,42}$ = 4.50, p = 0.04) but no effect of group ($F_{1,42}$ = 0.47, p = 0.50), or interaction ($F_{1,42}$ = 0.24, p = 0.63). For the retrieval phase, there was similarly a main effect of stimulation ($F_{1,42}$ = 6.6, p = 0.014), a non-significant trend for group ($F_{1,42}$ = 3.6 p = 0.063), and no interaction ($F_{1,42}$ = 0.17, p = 0.68). Lastly, for de-adaptation there was no effect of group ($F_{1,42}$ = 1.9, p = 0.18), stimulation ($F_{1,42}$ = 0.1.4, p = 0.25), or interaction ($F_{1,42}$ = 0.91, p = 0.35). See Figure 8.4.

*8.3.4 Effect of stimulation on rate of learning*

The improvement in error reduction during the learning phase raised the possibility that this was mediated through an improvement in the actual rate of learning. For the learning phase, there was a main effect of stimulation on rate ($F_{1,42}$ = 5.9, p = 0.019), but no effect of group ($F_{1,42}$ = 0.36, p = 0.55), or interaction ($F_{1,42}$ = 1.0, p = 0.32). For the retention phase, there was no main effect of stimulation ($F_{1,42}$ = 0.002, p = 0.96), no effect of group ($F_{1,42}$ = 0.32, p = 0.57), or interaction ($F_{1,42}$ = 0.022, p = 0.88).

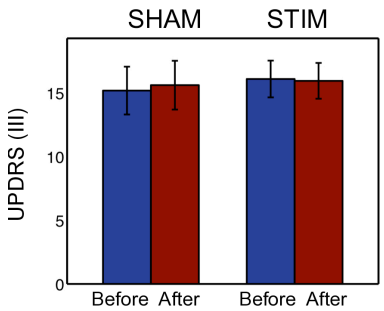


**Figure 8.1.** UPDRS. There is no significant effect of sham or real stimulation on motor scores.

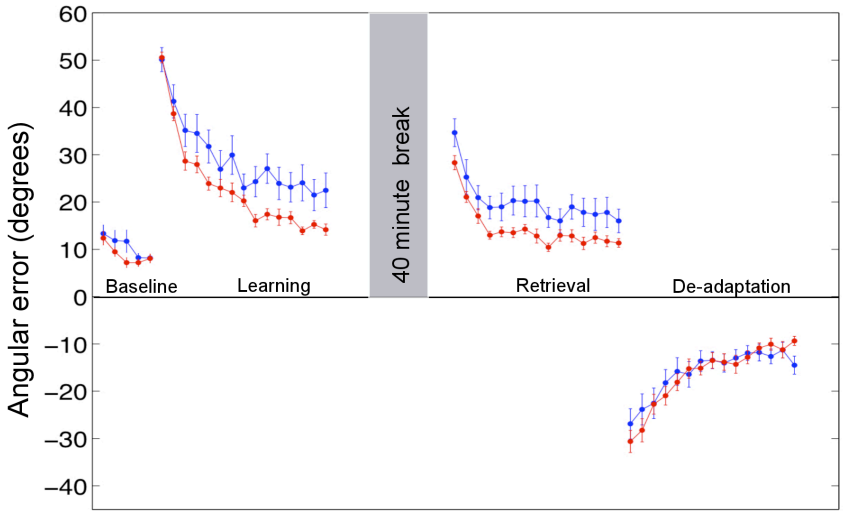


**Figure 8.2.** All phases of adaptation for Parkinson's patients, for sham (blue) and stimulation (red) groups.

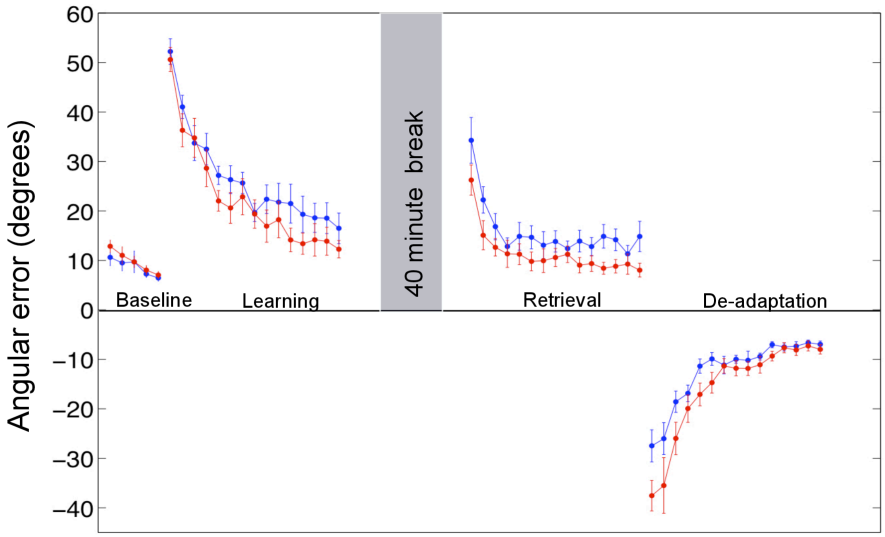


**Figure 8.3.** All phases of adaptation for healthy controls, for sham (blue) and stimulation (red) groups.

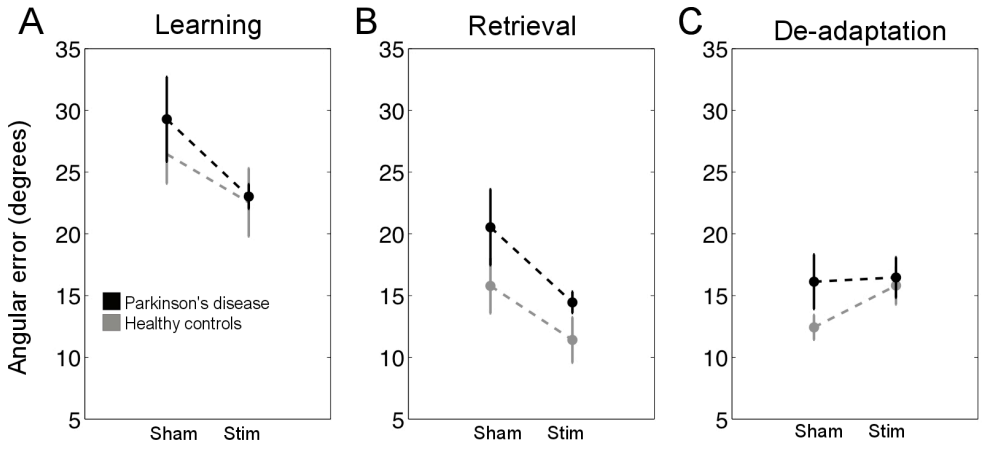


**Figure 8.4.** Average error for each phase of adaptation. Healthy controls are shown in grey and Parkinson's patients in black. Stimulation had a main effect of decreasing error in both the learning and retrieval phases. There was no effect for de-adaptation.

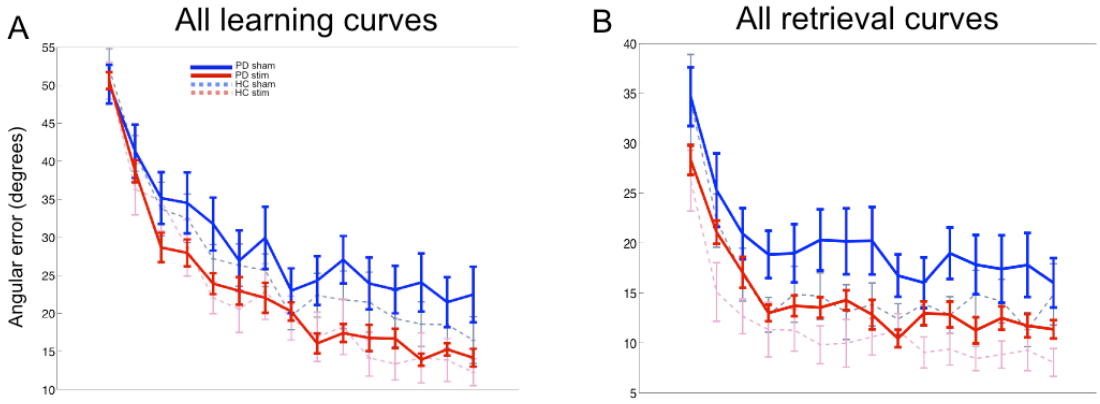


**Figure 8.5.** All adaptation curves overlaid for learning (A) and retrieval (B). Stimulation in PD patients improves adaptation to the level of non-stimulated healthy controls.

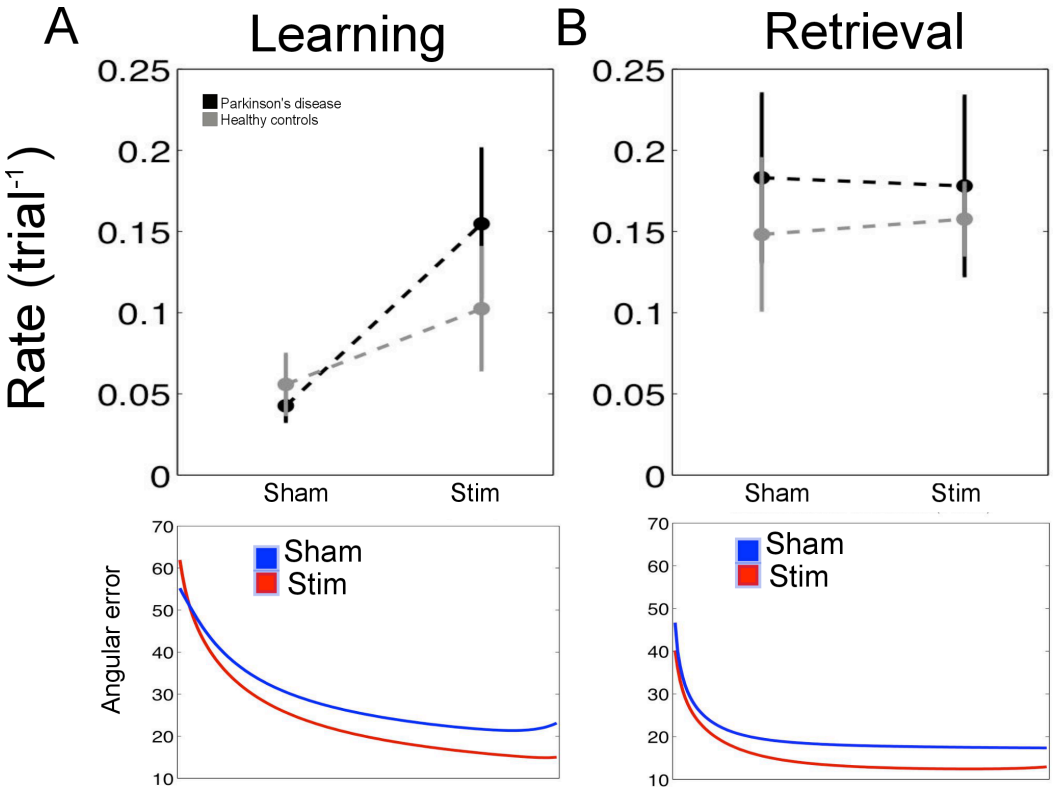


**Figure 8.6.** Rate of adaptation, as measured by fitting single exponential curves to the data. Top figures show means and SEM for rate of learning for sham and stimulation groups during learning (A), and retrieval (B). Bottom figures show averages of curve fits.

## 8.4 Discussion

Our study shows that TDCS can improve motor adaptation for both PD patients and age-matched healthy individuals. This was through an effect on the rate of learning, which resulted in more adaptation during learning; this improvement carried over intro the retrieval phase. There was no differential effect between the two groups. These results show, for the first time, a

beneficial effect on adaptation in PD patients, and implicates the primary motor cortex in both the learning and retrieval of a visuomotor adaptation, in both healthy individuals and PD patients.

The motor cortex has been the target of non-invasive stimulation for improvement in motor learning in several previous studies. In one study, when TMS is applied to the motor cortex during adaptation trials, adaptation itself is not affected but there is a quicker de-adaptation, which the authors interpret as a more fragile motor memory due to TMS (Hadipour-Niktarash et al., 2007). The finding is similar to another study showing reduced consolidation of sequence learning after M1 TMS (Cohen et al., 2009). An effect on motor memory strength but not acquisition has also been observed in M1 TDCS studies. Hunter et al. (2009) applied anodal TDCS to M1 and observed no difference in the learning phase of a force-field adaptation task. However, there was increased reaching error in the TDCS group when the force-field was removed. Increased after-effect has also been observed after TDCS in a 'broken escalator' adaptation task (Kaski et al., 2012). Lastly, M1 TDCS over the course of the learning phase of a visuomotor adaptation significantly improved the retention of a learned task when the rotation was removed (ie. increased aftereffect), however had no effect on the learning the adaptation itself (Galea et al., 2011). In contrast, stimulation of the cerebellum resulted in a faster learning phase but no effect on retention. This is in line with another study demonstrating increased locomotor adaptation with cerebellar stimulation (Jayaram et al., 2012). Taken together, the above results indicate that the motor cortex may be less

involved in on-line evaluation and correction of movement during motor adaptation, but mediate retention of the learned task over the long-term. In contrast, the cerebellum has a preferential role in initial adaptation.

Here, TDCS improves both the learning and retrieval phases of visuomotor adaptation in Parkinson's disease and healthy controls. The result is seems at odds with the specific role of M1 in retention – but not learning – previously reported. However, Smith et al. (Smith et al., 2006) have proposed a two-state model of adaptation, in which a fast module, which responds strongly to error but has poor retention, and a slow module, which responds weakly to error but retains information well. It may be that slow learning and retention are underpinned by similar mechanisms. Where the fast error-based learning phase is thought to be mediated by the cerebellum (Smith et al., 2006), the substrates for the slow phase are unknown – however the basal ganglia and cortex have been implicated in the automatization of movement in sequence learning (Penhune and Doyon, 2002) and force-field adaptation (Orban de Xivry et al., 2011). Orban et al., (2011) suggest that the motor cortex is involved with the late stage repetition-based learning in force-field adaptation (Orban de Xivry et al, 2011), and Huang et al. (Huang et al., 2011) have shown repetition can enhance savings in a visuomotor reaching paradigm. This suggests that improved learning in the slow phase could result in improved retention due to enhanced reward-based repetition. Finally, two main differences must be noted between our study and that of Galea et al., (Galea et al., 2011) which showed no difference in learning with M1 TDCS. Firstly, our studied

population was different (elderly controls and Parkinson's patients) and secondly we used a most difficult rotation (60 degrees in our study versus 30 degrees in Galea et al.). These differences may have contributed to slower learning which would be amenable to cortical stimulation-induced improvement.

TDCS has also been effective at improving motor learning in modalities other than visuo-motor adaptation. Anodal TDCS has shown improvements in serial reaction time (Nitsche et al., 2003; Tecchio et al., 2010; Stagg et al., 2011), visuomotor skill (Antal et al., 2004), as well as a visual force grip skill (Fritsch et al., 2010). In the latter task, TDCS had no effect on skill acquisition but improved performance when tested across days – with the performance benefit even remaining after 3 months. The wide-array of tasks in which a benefit effect of TDCS is seen raises the possibility that it may be useful for the general improvement in motor function after stroke or disease. Studies testing the effect of TDCS are limited, however preliminary results are promising. Lindenberg et al., (2010) demonstrated that anodal TDCS to the ipsilesional M1 and cathodal TDCS or contralesional M1 concurrent with 5 days of rehabilitation therapy improved motor performance in stroke patients. Other studies have also shown beneficial effects on similar rehabilitation paradigms in stroke (Kim et al., 2010).

As previously discussed motor learning studies in PD have produced conflicting results. Some studies have shown deficient overall motor learning, using tasks such as writing adaptation (Antal et al., 2004), 90

degree visuomotor adaptation task (Contreras-Vidal and Buch, 2003), or serial reaction time task (Muslimovic et al., 2007). However, others have demonstrated intact initial learning of PD patients off L-dopa (Messier et al., 2007; Paquet et al., 2008). Two recent studies have shown normal adaptation but deficient retention using a visuomotor adaptation task (Marinelli et al., 2009; Bédard and Sanes, 2011). We recently demonstrated that this is due to reduced retention of learned skills, and not increased interference (see Chapter 7 of this thesis). Furthermore this deficit correlated with disease progression, in keeping with the suggestion that basal ganglia degeneration may be responsible for the deficit.

Improvement during the retrieval phase of adaptation with anodal TDCS may be due to three possibilities. Firstly, retention itself may have been improved due to stimulation, similar to other studies showing a specific effect on consolidation with stimulation (Reis et al., 2009). Improvement in task performance is known to occur during the off-line period as soon as 5 minutes after adaptation (Hotermans et al., 2006), and thus our maintained stimulation until 10 minutes after learning may have enhanced plasticity during this window. Secondly, it must be noted the effects of excitability from anodal TDCS could theoretically have lasted until the retrieval phase. However, a study of MEPs after anodal TDCS has shown that excitability is increased post-TDCS but decreases to control levels when tested 40 minutes afterwards (Lang et al., 2004). Thus, whereas the effect in learning may have been due to excitability only, the longer-lasting effects imply long-term plastic processes over simple changes in excitability. Lastly, the performance

in retrieval was not dramatically different from error during the end of learning, raising the possibility that improvement retrieval is carry-over effect from previous learning. Nevertheless, a functional improvement in learning which is preserved over time could be a potential intervention by which to improve rehabilitation and long-term skill learning, regardless of mechanism.

In our paradigm there was no change in UPDRS due to stimulation. One study has shown improvements in UPDRS after anodal stimulation, however patients were off medication (Fregni et al., 2006). Our results are in keeping with Benninger et al., (2011) who show no effect of TDCS on UPDRS measures while the patients were medicated. In that study, there were improvements in bradykinesia and gait over time, which the authors suggest may be due to learning mechanisms. Given the improvements in adaptation here, it may be that TDCS coupled with motor training could boost improvement of motor skills and abilities for PD patients. Future studies should address whether such adaptation can be preserved over the course of days and weeks, and investigate measures more readily related to rehabilitation in Parkinson's disease.

# 9. General Discussion

## 9.1 Implications of findings on basal ganglia function

### *9.1.1 Role of the STN and motor cortex in driving ballistic movement*

Chapter 2 demonstrated that DBS of the STN improves velocity of ballistic movements in Parkinson's disease. However the mechanism underpinning this improvement is unclear. Perhaps the most plausible explanation for the effects of DBS is the alteration of aberrant pathological activity (McIntyre et al., 2004). Accordingly, it has been shown that DBS suppresses beta oscillations in the STN (Eusebio et al., 2011). Such suppression of beta activity could facilitate movement. In support of such a mechanism, it was shown in chapter 3 that beta oscillations in the subthalamic nucleus may underpin motor preparation by desynchronizing during cue presentation, especially when a ballistic movement will be required.

The basal ganglia have long been implicated in the inhibition, disinhibition, and general gating of upcoming movement (DeLong and Wichmann, 2007). Accordingly, beta oscillations and evoked activity in the STN modulate in relation to the behavioral significance of an external cue (Williams et al., 2003; Sauleau et al., 2009; Leventhal et al., 2012). Such a mechanism would presumably exploit relevant signals to prepare a forthcoming movement, and accordingly earlier decreases of beta activity are related to quicker reaction times (Doyle et al., 2005; Williams et al., 2005). Another study demonstrated a more pronounced desynchronization in beta activity before an upcoming double movement as compared to a single movement

(Kempf et al., 2007). In chapter 3, we demonstrated that earlier desynchronization occurred in response to the fast cue, suggesting that the fast cue acts as a salient signal that predicts high upcoming motor demands, to which beta activity is reactive. This argues against an all-or-none desynchronization in beta activity prior to movement, but rather one that is dependent on future task to be performed and as such confers motor readiness. Such a mechanism could help enable the necessary resourcing prior to a demanding task, and further supports the role of the basal ganglia in the preparation and initiation of movement (Jaeger et al., 1993; Jenkinson and Brown, 2011).

On the other hand, gamma activity (70-90Hz) increased in correspondence with the speed of movement. In the motor system, high frequency oscillations have been detected in the primate motor cortex between 30-60 Hz (Donoghue et al., 1998), and in the striatum of awake, behaving rats, (Berke et al., 2004) where dramatic increases in speed were associated with increases in 50 Hz synchrony (Masimore et al., 2005). Recordings of gamma activity from cortex (Crone et al., 1998, Gonzalez Andino et al., 2005; Ball et al., 2008), and basal ganglia of humans (Androulidakis et al., 2007; Kempf et al., 2009; Brücke et al., 2012) supports the notion that gamma occurs in a frequency range of 70-90 Hz, is predominantly lateralized to the contralateral side during movement, and bears a tighter temporal relationship to movement than beta activity (Muthukumaraswamy, 2010). This is consistent with our results, which show gamma range activity between 70-90 Hz, with a peak at around 75 Hz, occurring around the onset of movement.

Our results from chapter 3 are in line with a recent study demonstration a similar relationship between gamma oscillations and movement in the globus pallidi of dystonic patients (Brücke et al., 2012). In the latter study gamma activity scaled simultaneously with both amplitude and velocity, but not direction. However the study was not fully able to disentangle the contributions of amplitude and velocity. Here we kept amplitude constant and observed an increase in gamma with speed alone. This raises the possibility that the basal ganglia may drive movement parameters subsequent to initiation. Single unit activity in the basal ganglia can scale with aspects such as direction, movement duration, amplitude, and speed (Georgopoulos et al., 1983; Mitchell et al., 1987; Turner & Anderson, 1997; Turner et al., 2003).

Despite the clear indication that gamma increases with movement difficulty, our study was not designed to explicitly differentiate between speed, force, or effort. Lastly, although proprioceptive feedback around the time of movement may also have influenced gamma synchronization, it is unlikely as we demonstrate that oscillatory activity increased significantly in the fast condition even before onset of the reach. Furthermore, previous studies have shown minimal synchronization in the gamma band in response to passive movement (Brücke et al., 2012; Liu et al., 2008; Muthukumaraswamy, 2010). Future studies should aim to disambiguate these parameters to better understand the specific role of gamma in motor performance.

In summary of chapter 3, whereas beta oscillations desynchronized during preparation, gamma oscillations increased during actual movement. Both of these processes are heightened by task demands. Our results provide strong evidence that the basal ganglia modulate functionally specific oscillations at different frequencies to facilitate both the initiation and the driving of motor output. This raises the possibility that the concurrent increase in beta and decrease in gamma activity in the STN of PD patients without dopaminergic medication (Androulidakis et al., 2007) may prevent voluntary increases in the speed of movement and thus contribute to the cardinal symptom of bradykinesia.

Despite the strong indications above for the role of oscillatory synchrony in motor performance, they are nonetheless correlational. Therefore, in chapter 4, we sought to establish a causal link between oscillatory activity and motor performance. Using a brain stimulation technique intended to influence neural oscillations, we demonstrate a frequency selective way of modifying rate of force development during maximal performance. Due to a specific effect on force-rate in go trials, rather than reaction time or other parameters, we can suggest that the effect is specific for motor, rather than attentional, processing. We show that 70 Hz oscillatory activity can improve force-rate, with a particular effect on the initial rising slope. This suggests that gamma activity may be specifically involved in the early, dynamic phases of movement or force development. This is corroborated by the time course of gamma activity in the cortex recorded using MEG during force production (Muthukumaraswamy, 2010). In the latter study, gamma occurs

as a short burst which often terminates before the end of the movement, in contrast to beta activity, which continues throughout.

We chose 70 Hz as our stimulation frequency as it has been observed commonly in ECoG, MEG and EEG studies over the motor cortex and emerges quite specifically during periods of subthalamo-cortical coherence (Williams et al., 2002). Although gamma activity has been correlated with reaction time in the human (Fründ et al., 2007), this was recorded over central and posterior areas, and therefore may indicate a different subsystem for high frequency activity. Indeed, the frequency range for observed gamma activity is much broader than other frequencies, and therefore might serve different functions in the motor and cognitive domains across different brain areas and frequencies. The effect of gamma stimulation is important, as it shows for the first time an actual improvement in maximal motor performance induced by TACS, and underscores a role for gamma in the motor domain. Because the effect of other high frequencies was not systematically probed, we can only speculate that 70 Hz oscillations are specifically important in motor function. However, the more likely scenario that a range of oscillations in the gamma range would have produced this effect remains to be tested.

The suppression of no-go trials with beta stimulation provides a compelling corollary to gamma-mediated improvement of go-trials, and demonstrates a functionally enhancing role for beta oscillations. Previously, correlative evidence has shown that corrective movements can be enhanced during periods of increased beta synchrony (Androulidakis et al., 2006). Here we

show that similar results may be produced by stimulation at beta frequency. During trials where *not going* is the task goal, beta synchrony can *improve* task performance. This is in line with recordings showing increased beta activity during no-go trials in the inferior frontal cortex and STN (Swann et al., 2009; Kühn et al., 2004), and in the STN during stop-trials in the stop-signal-reaction-time task (Ray et al., 2012). It also lends support to the idea that beta is the natural resonating rhythm in the motor system, as evidenced by the 20Hz response from TMS in the motor cortex (Van Der Werf, 2006), resonance between STN and cortex at 20 Hz (Eusebio et al., 2009) and a recent study showing highest MEP values after 90s of 20 Hz TACS as compared to other control frequencies (Feurra et al., 2011). Under this schema, tonic beta levels might contribute to maintaining the current motor set and resisting new movement, whereas bursts of gamma activity would facilitate novel, dynamic motor output.

Directed methods of optimizing the motor system can help not only to further understand the mechanisms of movement, but may also be important in developing more targeted approaches in diseases where poverty of movement (i.e. Parkinson's disease) or inappropriate movement (ie. myoclonus), may be controlled and potentially exacerbated by pathological oscillatory activity (Salenius and Hari, 2003; Brown, 2007)

### *9.1.2 Role of STN in motor timing*

In chapters 5 and 6 of this thesis, repetitive finger tapping behavior in PD was explored in an electrophysiological and interventional perspective. In

chapter 5, it was demonstrated that DBS of the STN at therapeutic settings (>130 Hz) in PD patients significantly decreased the variability of tapping, without affected the mean interval between taps. As a secondary analysis, we used the Wing-Kristofferson model (1973) to separate the variability into motor and central variance – and demonstrated a selective effect on the central variance alone. The obvious improvements in motor function with DBS have made it challenging for researchers to assess motor timing in a pure manner. Here, we tried to standardize tap sizes and instructed patients to generate relatively small, easy movements. Additionally, there was no significant difference in either IRI or goniometer amplitudes between on and off stimulation, and thus we find it unlikely that the change in variance was due to the general motor improvement seen with STN-DBS. This selective improvement in variability, particularly central-variability, with stimulation, causally implicates the basal ganglia in generation of motor timing.

The substantial improvements in timing performance raise the question of how such non-specific high frequency (~130 Hz) stimulation would affect timing function of the basal ganglia. The striatal beat frequency model is a prominent framework for the basal ganglia's role in motor timing (Matell and Meck, 2004; Buhusi and Meck, 2005). This proposes that detection of coincident neural activity in the striatum encodes temporal duration. This could occur via oscillations among basal ganglia nuclei that are synchronized at a certain frequency by dopaminergic activity from the substantia nigra (Matell and Meck, 2004). However, heightened pathological oscillatory activity is known to occur in the basal ganglia of PD patients (Jenkinson and

Brown, 2011). Such aberrant oscillations could disrupt functional oscillators, or prevent physiological rhythms from being set up, thereby perturbing the underlying basis for timing activity. High-frequency stimulation, which is known to suppress these pathological oscillations (Eusebio et al., 2011), could in part allow physiological rhythms to re-emerge in the basal ganglia.

However, it is likewise conceivable that stimulation could actually disrupt the normally functioning rhythms, thus impairing performance. In our study, there was a quantitative dependence of the effect of stimulation on baseline performance, suggesting that the stimulation is impacting performance by interacting with underlying residual basal ganglia function. Indeed, a few of the best performers in this study had an *increased* variance with stimulation. It may be the case that patients with more aberrant rhythms in the basal ganglia (worse performers) have more to gain from stimulation-induced suppression of pathological activity, whereas in those patients with relatively spared activity (best performers), stimulation would interference with normal functioning. Similar dissociations have been observed in rapid finger movements (Chen et al., 2006), force production (Chen et al., 2011), and stop-signal reaction time (Ray et al., 2009), though it is likely that the mechanisms supporting such singular cue driven responses are different from those that are required to produce rhythmic tapping.

The patterning of sequential rhythmic movements is required to perform a variety of important behaviors in daily life. The basal ganglia and supplementary motor cortex are thought to play pivotal roles in the

execution of sub-movements within a sequence. This is especially the case when the pattern of movements is well learned and requires few attentional resources, such as gait or speech. In PD, basal ganglia dysfunction gives rise to a disruption in rhythmic movement performance. For example, PD patients are known to have abnormalities of timing and rhythmic stability in repetitive hand and finger movements (Yahalom et al., 2004), speech (Skodda et al., 2010) and gait (Blin et al., 1990; Morris et al., 1994). The above effect of deep brain stimulation on variability could explain its beneficial effect on repetitive behaviors such as gait (Hausdorff et al., 2009).

The above study demonstrates the involvement of the STN in the production of repetitive movements, but does not provide many clues as to the underlying mechanisms mediating such behavior. Thus, in the second tapping study (Chapter 6) we sought to reveal the neural basis for repetitive tapping in the basal ganglia. Due to the pathological changes in the basal ganglia, we recorded from the STN of Parkinson's disease patients while on their dopaminergic medication in order to study the most normal physiological state possible. We demonstrated that STN oscillatory activity in the beta range is modulated in a task-dependent manner depending on the rate of finger movement. In particular, mean beta rebound is dramatically suppressed when moving at 2 Hz as compared to slower rates. Firstly, this demonstrates that beta activity is selectively modulated in tapping and seems to serve a facilitatory role in promoting sequential movement. Secondly, the striking differential modulation of oscillatory activity due to

frequency of tapping, despite similar amplitudes, lends support to the role of STN beta synchrony in the feedforward organization of movement.

We observed a decrease in the size of rebound for 1 Hz and 2 Hz movements, although this was most pronounced for the 2 Hz condition. There are two potential implications for these changes in beta activity. Firstly, a reduced beta rebound could facilitate subsequent movement processing by eliminating the otherwise prolonged desynchronization which is observed prior to discrete movements. Such desynchronization is observed as early as 2 second before a movement (Pfurtscheller, 1981; Kühn et al., 2004) and presumably allows the necessary resourcing for a motor act to take place. Thus a lower starting point would require less desynchronization, given that the trough desynchronization in the beta band remains the same, which is the case in our study. Secondly, a continuously depressed beta band might promote a heightened motor state – one that is preferential towards sequential, repetitive, or continuous movement.

Given the similarity with EEG studies, we suggest our finding may be a general phenomenon in the motor system that facilitates repetitive movement processing. Though the function of beta oscillations in motor control is controversial, an emerging view is that desynchronization in this band serves a facilitatory, or gating role (Brown, 2007; Engel and Fries, 2010; Brücke et al., 2012, Chapter 3 of this thesis). Attenuation of beta band synchrony might be necessary for neuronal populations to engage in more detailed and task-specific parameterization of the movement (Brown,

2003). A final possibility is that beta activity is modulated by tonic dopamine to set a running index for the likelihood of voluntary movement (Jenkinson and Brown, 2011). Under conditions of higher tapping rates, sequential movements would be closer together and thus more predictable, thereby increasing the likelihood of imminent movement and suppressing beta activity in a feedforward manner.

These potential mechanisms could help to facilitate continuous motor performance. Interestingly, gait and speech deficits in Parkinson's disease can be partially alleviated through the use of external rhythmic cueing (Thaut et al., 1996; Baker et al., 2008; Rochester et al., 2009). Our results raise the possibility that such externally cued continuous movement at fast tempos could facilitate motor performance through the sustained reduction in beta oscillatory activity.

*9.1.3 Role of BG and motor cortex in motor adaptation*

In chapter 7 we investigated the ability of PD patients to perform a visuomotor adaptation task. PD patients had no difficulty in learning the initial task, but were markedly impaired when tested 45 minutes later. This complements previous studies showing a lack of retention of visuomotor adaptation (Bédard & Sanes, 2009a; Marinelli et al., 2009). Here, we additionally show a reduced impact of interference in PD. Taken together, chapter 7 provides good evidence that motor memories can be acquired but retention is impaired in PD.

It is apparent that brain plasticity is fundamental to motor learning. Motor learning is thought to be due to plastic processes dependent on long-term changes in underlying neural activity and synaptic properties. Various brain regions have been associated with the acquisition and retention of motor skills and procedural memories, including the cortex (Seitz et al., 1990; Friston et al., 1992; Grafton et al., 1992), the cerebellum (Albert et al., 2009), and the basal ganglia (Graybiel et al., 1994; Doyon et al., 2003). The cerebellum has been heavily implicated in the initial stages of learning and error reduction (Penhune & Doyon, 2005). Conversely, basal ganglia activity, localised mostly to the putamen, and motor cortical activity, predominantly the supplementary and pre-motor areas, are often seen to increase later during the automatization of a motor task (Friston et al., 1992; Seitz et al., 1994). However, there is evidence of cerebellar involvement in skill consolidation as well as skill learning (Imamizu et al., 2000; Albert et al., 2009). Nevertheless, the idea that early motor sequence learning requires cerebellum with basal ganglia and cortex more involved with later automatization phase, and delayed recall (Seitz et al., 1990; Friston et al., 1992; Grafton et al., 1992) is consistent with the present data. Given this model, the retention of a motor memory through basal ganglia plasticity after its acquisition by the cerebellum would be compromised in the PD group, due to pathology within the basal ganglia.

One possibility for the retention deficit in PD is a deficit in plasticity in the cortico-basal system. Thus, the fast error-corrective mechanisms of the cerebellum may be normally functioning, whereas the subsequent long-term

plastic changes that require normal basal ganglia physiology are disrupted. The deficit in retention was found in patients on dopaminergic therapy. This suggests that the underlying impairment in plasticity was not adequately corrected by L-dopa therapy. Although dopaminergic medication is known to increase some forms of plasticity in the substantia nigra (Prescott et al., 2009) and motor cortex (Morgante et al., 2006), there was no correlation between the levodopa equivalent dose and the consolidation deficit in our study. It remains to be seen whether the impairment in retention is due to altered plasticity related to non-dopaminergic processes, or to phasic dopamine release as opposed to tonic dopamine levels (as manipulated by levodopa or dopamine agonists). An explicit comparison of learning and retention in the same patients on treatment and following withdrawal of treatment would help inform on this point, although the comparison will remain challenging due to differences in baseline performance. Likewise, it would be interesting to contrast impairments in consolidation in patients with and without levodopa induced dyskinesias, given that synaptic plasticity is thought to be impaired in the latter situation (Picconi et al., 2003; Huang et al., 2011).

The striking difference in retention of the 60 degree rotation in PD patients points to an important role for the basal ganglia in retention of visuomotor memories. However, the results from chapter 8 suggest that the motor cortex also plays a significant role. Here, we studied patients on the same 60 degree adaptation-retention task, this time applying either sham stimulation or real stimulation to the motor cortex during the baseline and

learning phase. Stimulation improved adaptation in both healthy controls and PD patients, an improvement which carried over to the retention phase. Given that an increase in excitability in the motor cortex induced improvements in learning may argue against the distinct functional separation between cerebellum, motor cortex, and basal ganglia. For example, Galea et al. (2011) showed stimulation of the cerebellum results in improved learning of a visuomotor task (but not retention), and stimulation of the motor cortex resulting in improved retention (but not learning). The differences may have been due to the more difficult task employed here (60 degree compared to 30 degree rotation) or different populations (older individuals and PD patients compared to healthy young controls). However, this result does support the role of the motor cortex in the automatization of learned task. Indeed, the difference between groups did not emerge until the 3$^{rd}$ block of the learning phase, when the steepness of the curve began decreasing. The motor cortex may act as an intermediary between cerebellar and basal ganglia processes. As error-based cerebellar-driven adaptation proceeds, the motor cortex might slowly increase its activity and ultimately take over during the repetition-based asymptotic phase. Therafter, interactions between motor cortex and basal ganglia might mediate retention and retrieval of the learned task.

Rehabilitation sessions will always involve initial learning but also continuous remodelling, alterations, and improvements on learned tasks. The relative disappointment in rehabilitation for Parkinson's disease (Gage and Storey,

2004) may be in part due to an inability of PD patients to carry over learned tasks and improvements from one session to the next.

*9.1.4 Insights into the general role of the basal ganglia*

The basal ganglia network has traditionally been viewed as a system that regulates the 'gating' of movement; This is particularly the case in the influential Albin-Delong model (Albin et al., 1989; DeLong 1990), where persistent inhibition of output nuclei is punctuated by transient disinhibition that allows firing rates to increase and movement to proceed. In this thesis, we have shown support for the gating model in three main ways: i) beta desynchronization in the STN occurs prior to a movement and is maintained throughout movement (Chapter 3), ii) the level of early beta desynchronization is more pronounced when a demanding movement is expected (Chapter 3) and iii) the level of maximal desynchronization during movement is the same regardless of task demands (Chapter 3 and Chapter 5). On the one hand, the dynamics of beta oscillations might suggest a role for the basal ganglia network as an all-or-none regulator of movement. However, this thesis has further shown that the basal ganglia network has a crucial role in the organization of movement parameters even *after* initiation and onset of movement, in the context of discrete movement, repetitive movement, and long-term representations of movement. Firstly, gamma oscillations in the STN, which occur predominantly after movement onset, were correlated with the speed of movement (Chapter 3). Stimulation of the STN was also shown to increase speed of movement (Chapter 2).

Furthermore, stimulating the motor cortex of healthy subjects at beta and gamma frequency reduced and increased peak force generation, respectively (Chapter 4). Although in the latter study only the motor cortex, and not basal ganglia, was stimulated, oscillations are thought to have analogous functional roles in both systems (Lalo et al, 2008), and previous work has demonstrated the reduction of grip force rate with 20 Hz stimulation of the STN (Chen et al., 2011). Thus, this points to a role for oscillations and the basal ganglia during the ongoing parameterization of movement. Secondly, this thesis demonstrates that the basal ganglia are not only critical in the production of single, discrete movement, but also in the repetitive and continuous generation of motor output. Stimulation of the STN can improve repetitive tapping performance (Chapter 5), and beta oscillations maintain desynchronization during a train of repetitive finger taps (Chapter 6). This suggests that the basal ganglia system is a likely candidate for the promotion of movements that are linked in sequence or rhythm. Lastly, this thesis extends basal ganglia involvement into the longer-term representation of movements. Patients with Parkinson's disease are shown to have impaired retention of a learned adaptation over 45 minutes. This implies an important role for the basal ganglia in preserving the integrity and future expression of learned motor memories. These three motor roles (discrete movement, repetitive movement, retention of learned movement) may not be exclusive of one another. Rather, acquired improvements in discrete and repetitive motor performance may depend on optimal basal ganglia function for retention of those gains. Impaired retention in Parkinson's disease could

impart on the future performance of simple movements such as reaching or repetitive movements such as gait. Such a process could exacerbate ongoing degeneration in Parkinson's disease through disruption of the normal retention and expression mechanisms in the basal ganglia. In summary, it is clear that a simple 'gating' role for the basal ganglia does not adequately encompass the true nature of their dynamic functionality in organizing and maintaining more complex motor programs.

It must be noted that these functions are likely not limited strictly to the basal ganglia. Strong anatomic connections have been identified between basal ganglia and motor cortical structures (Akkal et al., 2007), however the functional interactions remain unclear. Here we show that the basal ganglia and motor cortex may perform complementary roles. Firstly, the effect of stimulation of the motor cortex at beta and gamma frequencies (Chapter 4) were as predicted from recordings (Chapter 3) and stimulation (Chen et al. 2007; Chen et al, 2011) of the STN (ie. beta as 'anti-kinetic' and gamma as 'pro-kinetic'). This implies that such oscillatory frequencies have similar roles across motor structures, and may serve as a method of communication between them (Lalo et al., 2008), although the details of such an interaction remain to be elucidated. Secondly, we show that DC stimulation of the motor cortex can improve motor adaptation. This is in contrast to the proposed role of the basal ganglia system in retention (Chapter 7). One possible scenario might implicate the motor cortex in the learning and the basal ganglia in the internalization of that learning and retention across a longer period of time, in line with previous proposals (Penhune et al, 2002).

A deeper understanding of the pathological mechanisms of Parkinson's disease and potential treatments may thus necessitate a better understanding of dynamic cortico-subcortical interactions.

## 9.2 CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

### *9.2.1 Oscillations and TACS*

Our recordings from the STN have revealed distinct roles of beta and gamma oscillations in ballistic movements. In particular, both correlational and experimental evidence was presented for the anti-kinetic and pro-kinetic roles of beta and gamma oscillations, respectively. Although recordings were obtained from people with PD, the medicated state of the patients and similarity with cortical recordings from healthy subjects suggests that these signals represent physiological function. This position is further supported by the TACS experiment, where driving oscillations at beta and gamma frequencies in the cortex of healthy humans altered motor performance. The latter experiment opens up possible therapeutic options that could be taken in two main directions:

1) Disorders with poverty of movement, such as PD. In these conditions, enhancing gamma activity at the cortex might improve speed of motor output and relieve bradykinesia. Although the effect size was small with healthy normals, the impairment in Parkinson's disease may allow further

improvement, simply because their impoverished motor state leaves them with more to gain.

2) Disorders with excessive movement, such as tics or tourette's. The large effect of beta stimulation in suppressing no-go trials may aid in preventing unwanted or excessive movement in these disorders. Individuals with tourette's are known to have lower resting beta levels and more desynchronization during movement (Franzkowiak et al., 2010; Marceglia et al., 2010) (this the opposite pattern compared with PD). Thus stimulation may increase beta levels and enhance inhibition, thereby suppressing tics.

### *9.2.2 Repetitive movement and timing*

Given PD patients' deficient ability to generate internal motor programs and their reliance on external cues, cuing could be used as a compensatory mechanism to bypass the problem with internal motor generation. Chapter 6 shows that persistent beta suppression may underlie the effect of repetitive cues in improving rhythmic performance. Anecdotal evidence suggest many individuals with PD notice improvements in bradykinesia, akinesia, and gait when moving rhythmically – i.e. dancing, tai chi, or even listening to music or thinking about a beat. Although there is little 'hard evidence' for improvements due to such activities, some reviews indicate overall positive benefit of music therapy on aspects such as gait (de Dreu et al., 2012). The suppression of beta activity with repetitive cues offers an intriguing insight into the possible mechanisms of these processes, and indicates a potential avenue that may be exploited in order to improve symptoms in PD. It should

be noted that such suppression may be restricted to when patients are off their dopaminergic medication, thereby impairing sequential movement (Moreau et al., 2007). It would be informative to study the activity of beta oscillations during rhythmic movement while patients are off medication to clarify this possibility.

### *9.2.3 Motor adaptation and TDCS*

The improvements in motor adaptation with TDCS indicate an obvious route for possible therapeutic intervention. Improvements have already been noted in stroke patients (Stagg et al., 2012). However, the large heterogeneity in stroke patient populations may pose challenges for a generic treatment such as TDCS. For Parkinson's disease, stimulation of the motor cortex may be a more functionally relevant approach. Rehabilitation generally has poor outcomes in PD (Gage and Storey, 2004). An adjunct therapy that could 'boost' the effect of rehabilitation through an effect on learning and retention could potentially enhance long-term gains. This study shows preliminary promise for TDCS but further studies are required. Firstly, longer-term performance should be tested (on the order of weeks or months). Secondly, timing of the TDCS for maximal effectiveness could be determined. Lastly, the improvements on motor adaptation tasks must be transferred over to real life benefits. Thus, TDCS should be tested on more realistic measures in PD such as learning to improve gait performance, reaching, or rhythmic movement.

## 9.3 CONCLUSION

In this thesis, the enhancement of motor performance is investigated in two main ways. Firstly, the neural correlates of motor enhancement are determined. This line of work identified beta and gamma oscillations as important mediators of motor control. Secondly, methods of electrical stimulation, namely DBS, TDCS, and TACS, are used to enhance motor performance in healthy individuals and people with PD. Taken together, this thesis demonstrates that knowledge of underlying neural substrates and behavioral deficits can be coupled with stimulation paradigms to selectively enhance aspects of motor performance. The thesis further challenges the limited traditional schema of the basal ganglia as a 'gate', in demonstrating a wide range of motor parameterizations, from discrete, to repetitive, to long-term movement representations. Future research should seek to further understand the precise neural underpinnings of motor deficits in PD, as such knowledge will be critical in designing smarter and more effective therapeutic techniques.

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# 11. APPENDIX I: EFFECT OF BDNF VAL/MET POLYMORPHISM ON VISUOMOTOR ADAPTATION

**-Abstract-**

Brain-derived neurotrophic factor (BDNF) has been implicated a wide-variety of cognitive and motor processes. Individuals with a val(66)met polymorphism have lower levels of BDNF and demonstrate diminished short-term plasticity and motor learning, although its role in the latter is unclear. The current study examines the effect of the BDNF polymorphism on visuomotor adaptation in two separate experiments. In the first experiment, 21 subjects with the val/met polymorphism and 21 matched controls performed a 60-degree visuomotor rotation task testing learning, retention, and de-adaptation. Val/met subjects demonstrated a slower rate of initial learning and a deficit in de-adaptation. In a second experiment we tested 13 val/met subjects and 13 matched controls on a more difficulty 80-degree rotation. This resulted in a more pronounced deficit as compared to the 60-degree rotation. We conclude that BDNF regulates processes important for visuomotor adaptation.

## 11.1 INTRODUCTION

Brain-derived neurotrophic factor (BDNF) is a key regulator of activity dependent synaptic neuroplasticity in the human brain, thereby influencing memory and learning (Lu and Gottschalk). Its involvement in these processes is in part underpinned by its regulation of vital synaptic functions, such as transmission, survival, differentiation, and development (Huang et al., 1999; Gorski et al., 2003). In particular, BDNF is known to play a critical role in long-term potentiation (LTP) and long-term depression (LTD) within several brain regions(Figurov et al., 1996; Huang et al., 1999; Meis et al., 2011). Such a role in memory and learning also extends to the motor domain, as BDNF is elevated in the cortex in response to motor practice and learning in both monkeys (Ishibashi et al., 2002) and humans (Klintsova et al., 2004).

The effect of BDNF in humans has in large part been revealed through studying individuals with a single nucleotide polymorphism (SNP) of the BDNF gene, which results in a valine-to-methionine substitution at codon 66 (val66met). It is relatively common (65% Val66Val to 35% Val66Met in the Caucasian population), and confers an 18% decrease in activity-dependent BDNF secretion (Chen et al., 2003; Egan et al., 2003). This genetic difference has been associated with episodic memory impairments (Egan et al., 2003), reduced hippocampal activity as measured by fMRI (Hariri et al., 2003) and abnormal cortical morphology (Pezawas et al., 2004). Differences are also present in the motor domain, in line with the evidence that plasticity

in the motor cortex is in part genetically determined. For example, val/met subjects show a smaller expansion in motor map (Missitzi et al., 2011) size after training as revealed by transcranial magnetic stimulation (TMS) (Kleim et al., 2006). Moreover, they demonstrate reduced short-term plasticity in response to a variety of non-invasive brain stimulation protocols (Cheeran et al., 2008), and smaller activation volume in cortical areas after motor training (McHughen et al., 2010).

Despite the physiological differences in plasticity, it is unclear what functional impact BDNF polymorphism has on motor behavior. There is little consistency between studies examining motor learning; whereas some studies have shown no significant difference, such as a speeded movement task (Li Voti et al., 2011), a marble navigation task (McHughen et al., 2011), or a hand-movement task (Kleim et al., 2006). Other studies have reported behavioral differences on a driving task (McHughen et al., 2010) and visual pinch grip task (Fritsch et al., 2010). Here, we used a joy-stick controlled visuomotor adaptation task to further understand the role of BDNF polymorphism in motor learning. In experiment 1, we sought to determine if val/met subjects would be impaired in the adaptation, retention, or de-adaptation of a 60 degree rotation, and if this would persist over long periods of training. In a follow-up experiment we focused only on the early learning phase but applied a more difficult rotation, and hypothesized that a larger rotation would induce a more pronounced behavioral deficit in val/met subjects. Our results shed light on the possible functional impact of BDNF polymorphism on motor behavior.

## 11.2 METHODS

### *11.2.1 Subjects and genotyping*

The study was approved by research ethics committees in Seville (S), London (L) and A Coruna (AC). Subjects were recruited at a single site (AC) as part of a larger ongoing Stimulation Genomics study. The study was completed over a 10-month period. Genotyping for the BDNF Val66Met SNP (rs6265) was performed using commercially available primers and standard techniques by PGG and PM in Seville.

In total, 139 Caucasian subjects were genotyped for this study. Each subject was allocated a 4 digit alpha-numeric study ID to enable effective blinding. Only 2 subjects with the BDNF Met66Met genotype (AA genotype) were found and have been excluded. 21 subjects with the BDNF Val 66 Met polymorphism were invited to participate in the Experiment 1. 12 subjects with the BDNF Val 66 Met polymorphism were invited to participate in Experiment 2. An equal number of Val66Val subjects, selected to provide the closest possible age and sex matching, were also invited for each experiment. 6 subjects in each group of Experiment 2 had previously participated in experiment 1. Cohort selection was performed by BC to ensure age and sex matching.

RJ and VL, blinded to subject genotype, performed data collection for experiment 1. Analysis for experiment 1 was subsequently performed by RJ, with subjects identified only as 'Group 1' and 'Group 2', prior to designing experiment 2. AL and VL performed data collection for experiment 2 and

remained blinded to genotype, "group" and results of Experiment 1 throughout. Genotype was revealed to RJ by BC only once all statistical analyses were completed.

*11.2.2 Task*

See Chapter 7 for visuomotor task.

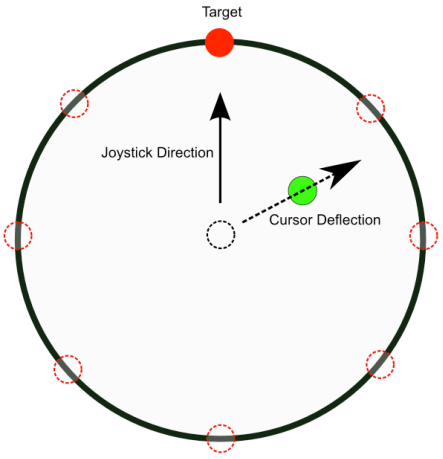


**Figure 11.1.** Schematic diagram of the task. One trial is shown, in which the red target jumps from the origin (dotted block line) to a point around the circle, and the green cursor is moved from the central position to the target. Attempted movement upwards is deflected 60 degrees clockwise. In any one trial only one target (solid red circle) is presented.

In experiment 1, the task began with a baseline phase consisting of 48 trials in which joystick movement matched the movement of the green cursor on the screen. After a 1-minute break a learning phase ($Learning_{60}$) was imposed, consisting of 152 trials, in which the relationship between the movement of the joystick and the cursor was altered so that the cursor moved with a +60 degree rotation relative to the joystick. Here, there were large initial errors (~ 60**°**), that decreased over the course of the session. Subjects were instructed not to allow the rotation to disrupt their response profile and to continue to make striking motions as in the baseline phase. Next, participants were afforded a 45 minute break. Participants were then retested (Retention-1) with the same 60**°** rotation for 152 trials. There was a second break lasting 24 hours, in which the subjects engaged in their normal activities. Another set of 152 trials with 60 rotation (Retention-2) was performed. Lastly, a de-adaptation phase was conducted for 152 trials, restoring the veridical relationship between cursor and target (0**°**). Here, participants were initially perturbed from the target as a result of their previous motor remapping and returned to baseline through de-adaptation.

In experiment 2, we wished to focus specifically on the early component of learning and therefore limited adaptation phases to 80 trials. All subjects began with 24 trials of a baseline phase in which joystick movement matched the movement of the green cursor on the screen, followed by adaptation to an angular deviation of -80 degrees ($Learning_{80}$). The angular deviation was opposite to that employed in Experiment 1 (+60 degrees) in order to preclude any carry over effects, as 12 subjects performed both experiments.

However the de-adaptation phase at the end of Experiment 1, coupled with the long period of time between experiments (8 months), likely mitigated any such effect.

### *11.2.3 Analysis*

#### *11.2.3.1 Outcome Measures*

See Chapter 7

#### *11.2.3.2 Statistical analysis*

Trials exceeding two standard deviations of the mean from each block of 8 tials were rejected. We then analyzed the adaptation data in two ways. Firstly, individual trials from each subject's adaptation curves were fit with a single exponential function, taking the form:

$$y = C_1 * \exp(-\text{rate} * x) + C_o$$

where $C_1$ and $C_o$ are constants, x is the trial number, and y is the error. Using the rate variable, we conducted a 4x2 mixed model ANOVA with

factors `group' and `phase'. We used post-hoc t-tests to assess group differences for each phase after an interaction was found.

However, such analysis of rate of learning would obscure an overall increase in error across a particular phase. Trials were blocked in groups of 8, with the mean error across blocks 2-10 (similar to Krakauer et al.) taken as the 'early' component, and blocks 11-19 the 'late' component for each adaptation phase. Thus there were 9 blocks for each of early and late adaptation phase. For each phase in experiment 1, a 2x2 mixed model ANOVA was applied to test for a main effect or interactions across early and late learning. Mauchley's sphericity test was often significant, whereupon we applied Greenhouse-Geisser correction. If an interaction was found, post-hoc independent t-tests were used to test for group differences at each phase, with significant p value $< 0.05$.

In experiment 2, errors across blocks 2-10 were averaged for each subject and independent t-tests used to assess group differences. For both experiment 1 and experiment 2, similarity in baseline performance was assessed with t-tests between groups for the mean error over the baseline phase. Lastly, to examine differences in adaptation to 60 degree and 80 degree rotations, a 2x2 ANOVA was used with factors group (val/val and val/met) and rotation (60 and 80 degree rotation). Kolmogorov-Smirnov tests confirmed normality in all datasets.

## 11.3 RESULTS

### *11.3.1 Baseline Measures*

There were no differences in peak velocity, time to peak velocity, or reaction time between val/val and val/met subjects in either experiment 1 or experiment 2 ($p>0.05$ for all phases). Thus kinematic measures were similar across groups.

### *11.3.2 Experiment 1*

We first analyzed rate of learning across all adaptation phases. A single exponential function was fit to each subject's data, which estimated the rate of error-reduction (Huang et al.). The average curve fits overlayed on the mean of the individual trial are shown in Figure 11.2A. An ANOVA across groups and phases had no significant effect of group ($F_{1,40} = 3.7$, $p = 0.063$), an effect of phase ($F_{3,120} = 7.1$, $p = 0.0002$), and a significant interaction ($F_{3,120} = 4.4$, $p = 0.015$). Post-hoc t-tests showed a significant difference in rate for the learning phase ($t_{20} = -2.6$, $p = 0.016$, Figure 11.2B), and for 24-hour retention ($t = -2.5$, $p = 0.017$), but not for 45-minute retention ($p = 0.4$) or de-adaptation ($p = 0.3$).

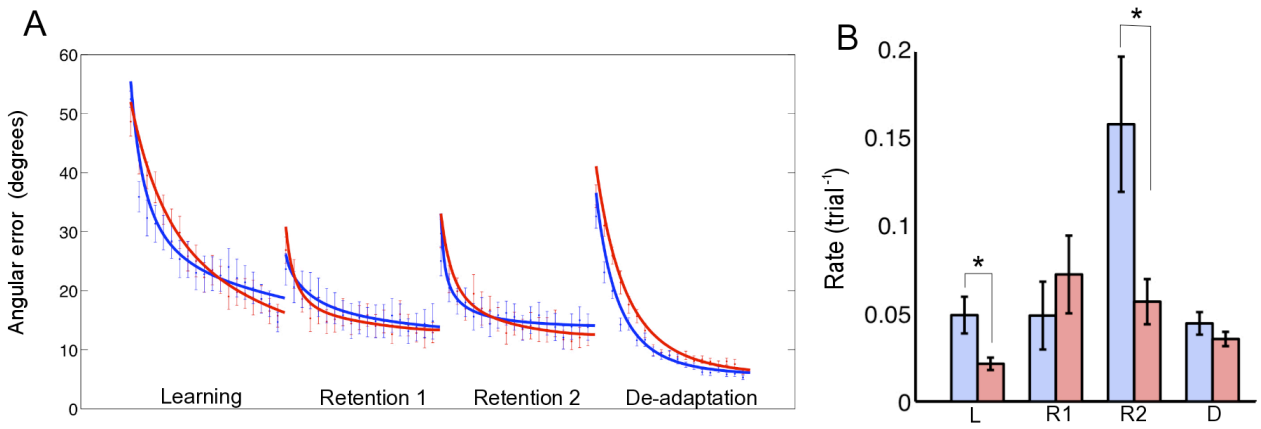


**Figure 11.2.** Rate of learning. A) shows the average of the single exponential adaptation curves fitted to individual data for each phase overlayed on average blocks. B) shows mean rates of adaptation taken from the fitted curves. Val/met subjects have significantly slower rates of adaptation in the learning (L) and 24-hour retention phase (R2). * $p < 0.05$

We secondly analyzed mean error across the adaptation phases. All blocks of 8 trials in experiment 1 are shown in Figure 11.3A for phases: Baseline, $Learning_{60}$, Retention 1, Retention 2, and $De\text{-}adaptation_{60}$. Both groups clearly decrease their error substantially with all phases of adaptation. There was no significant difference in mean error of the baseline phase between groups ($t_{20} = -1.1$, $p = 0.29$).

Figure 11.3B shows mean errors across early and late adaptation for all phases. In the learning phae, a 2x2 ANOVA with factors time (early and late) and group (val/val and val/met) showed no significant effect of group ($F_{3,120} = 0.13$, $p = 0.723$), and expected effect of time due to the decreased

error during adaptation ($F_{3,120}$ = 172, p < 0.0001), and a significant interaction ($F_{3,120}$ = 9.9, p = 0.003). Although there was a visibly higher error in the val/met as compared to the val/val group during the early part of learning, post-hoc t-test between groups did not reveal a significant difference for early ($t_{19}$ = -1.03, p = 0.31) or late learning ($t_{19}$ = 0.38, p = 0.71).

During Retention 1, there was no main effect of group ($F_{3,120}$ = 0.25, p = 0.62), an effect of time ($F_{3,120}$ = 20, p < 0.0001), but no interaction ($F_{3,120}$ = 0.066, p = 0.80).

Similarly for Retention 2, there was no effect of group ($F_{3,120}$ = 0.011, p = 0.92, an effect of time ($F_{3,120}$ = 41.9, p < 0.0001), and no interaction ($F_{3,120}$ = 2.3, p = 0.13).

Lastly, for de-adaptation there was a main effect of group ($F_{1,40}$ = 7.46, p = 0.009), an effect of time ($F_{1,40}$ = 202, p < 0.0001), and a significant interaction ($F_{1,40}$ = 4.6, p = 0.037). This interaction was due to a larger impairment in de-adaptation for val/met subjects during the early segment ($13.7^{o} \pm 0.77$ val/val versus $17.06 \pm 0.97$ val/met, $t_{19}$ = -2.7, p = 0.010) compared to the late segment ($6.59^{o} \pm 0.31$ val/val versus $7.97^{o} \pm 0.51$ val/met, $t_{19}$ = -2.3, p = 0.028).

In summary, val/met subjects showed a significantly slower rate of learning during initial testing and also 24 hours later. Furthermore, val/met subjects had higher mean errors during the de-adaptation phase.

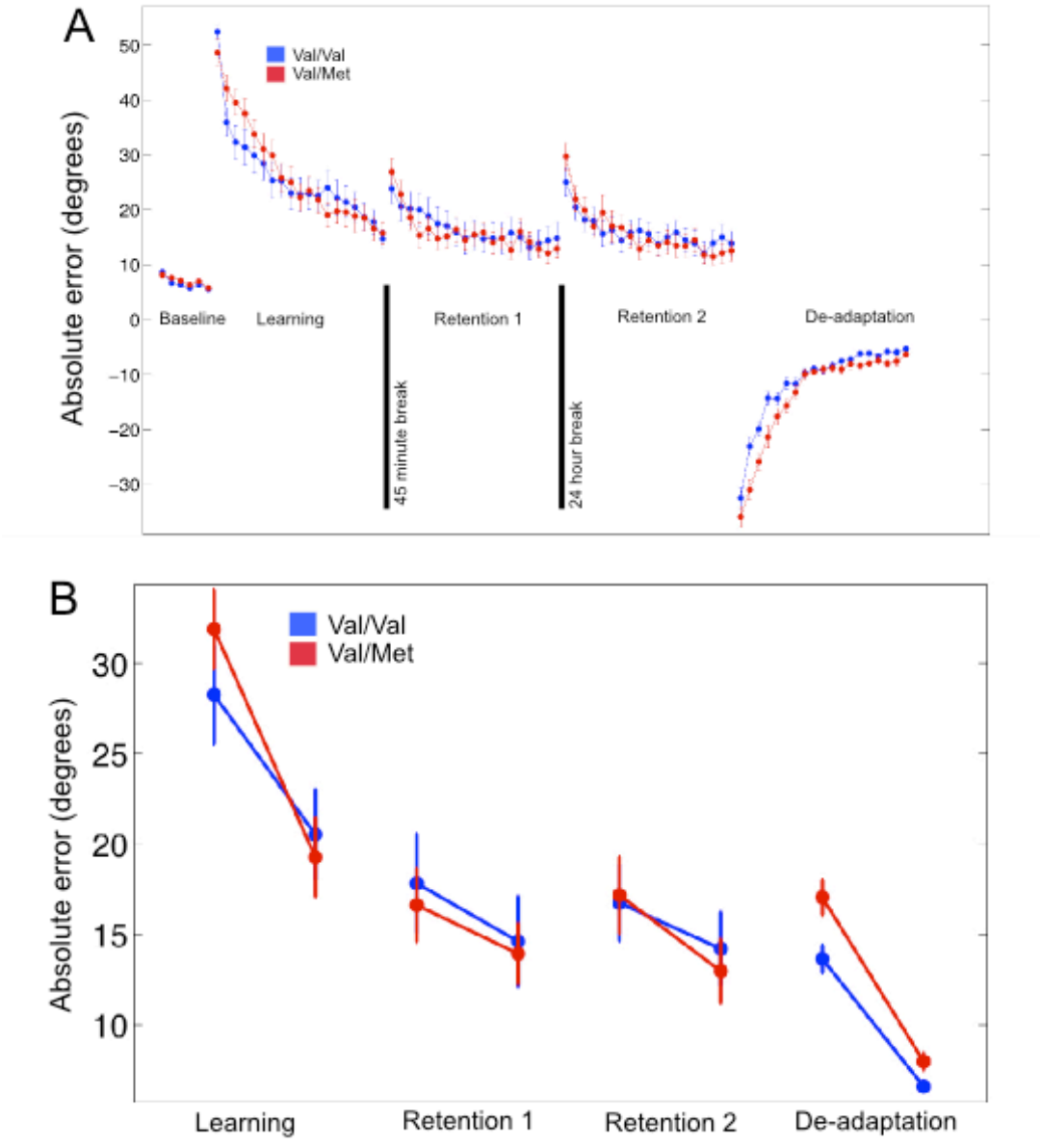


**Figure 11.3**. Experiment 1. A) All phases are displayed in sequence for val/val (blue) and val/met (red) subjects, in blocks of 8 trials. Higher error in the val/met group can be observed in the early parts of learning and de-adaptation. B) Mean errors are displayed for early and late adapation for each phase. De-adaptation errors are significantly higher in val/met subjects, particulary during the early segment.

*11.3.3 Experiment 2*

All blocks of experiment 2 are shown in Figure 11.4. There was no difference in the baseline phase ($t_{11}$ = 0.44, p = 0.66).

For the 80-degree learning phase (blocks 2-10), there was a significant difference between groups (43.1° ± 2.6 val/val versus 59.1° ± 3.4 val/met, $t_{11}$ = 3.7, p = 0.0012).

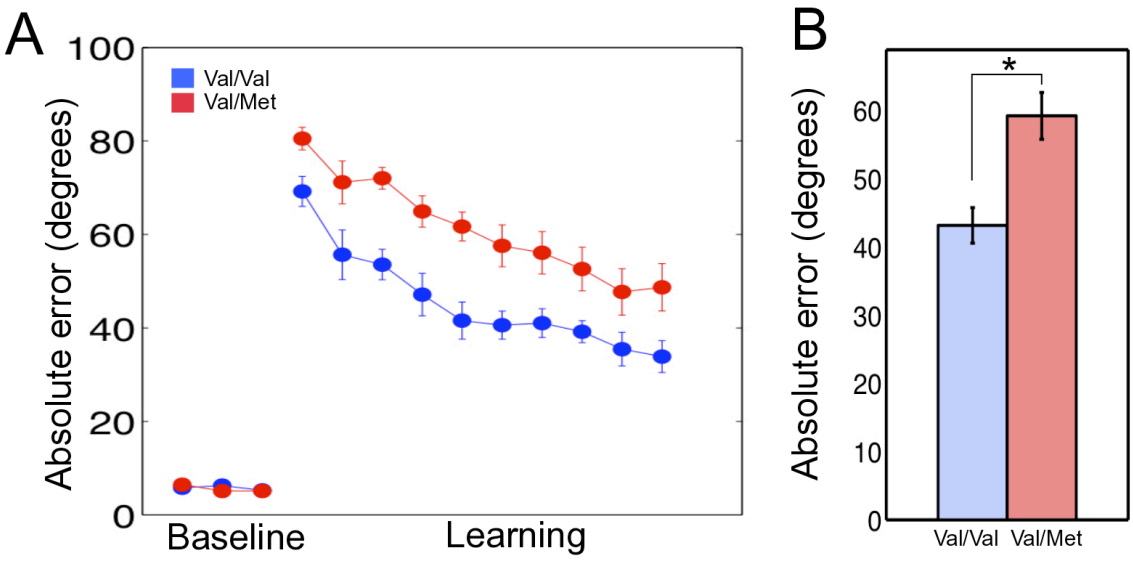


**Figure 11.4.** Experiment 2. A) Baseline and learning phases are displayed for val/val (blue) and val/met (red) subjects, in blocks of 8 trials. B) Val/mets have significantly higher error for 80 degrees rotation. * p < 0.05

*11.3.4 Larger rotation induces bigger deficit in val/mets*

Given the larger and significant difference in mean error in the 80 degree as opposed to 60 degree rotation, we compared the performance of groups between both degrees of rotation to assess a dependency on task difficulty. We took the mean of the early component of $Learning_{60}$ (blocks 2-10) and compared with the same blocks in $Learning_{80}$ (blocks 2-10). A 2x2 ANOVA with factors group and rotation (60 or 80) was significant for group ($F = 819.6$, $p < 0.0001$), time ($F = 12.0$, $p < 0.001$), and interaction ($F_{1,62} = 4.8$, $p = 0.032$, Figure 11.5). Thus, val/met subjects had an overall increase in error across both tasks, but this effect was significantly larger with the 80 degree rotation.

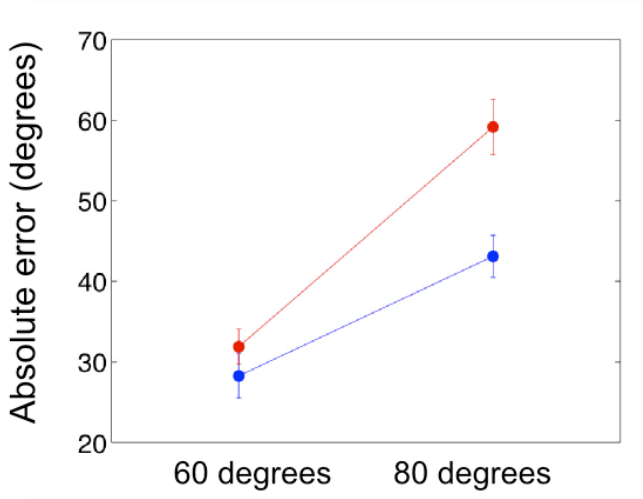


**Figure 11.5.** Effect of error amplitude on val/met deficit. There is a larger difference between val/val and val/met due to 80 degree rotation as compared to 60 degrees.

## 11.4 DISCUSSION

In this study we sought to understand the impact of BDNF polymorphism on visuomotor adaptation in humans. We show that individuals with the val/met polymorphism have a reduced rate of learning a 60 degree rotation initially and also after a 24-hour gap period compared to val/val subjects. Val/met subjects also showed a significant deficit in de-adaptation from a 60 degree rotation. In all cases this difference was reduced or normalized with further training. Additionally when testing on a more difficult 80-degree rotation, we revealed a larger deficit in adaptation than 60 degrees. Our results suggest a role for BDNF in the adaptation and de-adaptation to an environmental perturbation.

Val/met subjects had a decreased rate of learning when tested on 60 degree rotation. Although at short-term retesting (45 minutes) there was no longer any difference in rate of adaptation, at 24 hours later this deficit re-emerged. The general enhancement of rate of learning after a time period, referred to as 'savings', has previously been observed (Krakauer et al., 2005). Such savings may be partly due to the development of an internal model of the learned task (Huang et al., 1999). In our study valmets were impaired at 24 hours despite an having learned to an equal level previously, and starting with the same error on block 1, implying a deficit in savings. Taken together, these results are in line with previous demonstrations that val/met subjects have impaired visuomotor adaptation and retention abilities (Fritsch et al., 2010; McHughen et al., 2010) . McHughen et al. used a driving-based motor

learning task and show higher error across all blocks of the learning period, as well as impaired retention when tested 5 days later (McHughen et al., 2010). Another study by Fritsch et al. showed no difference in initial learning of a complex force grip skill - deficits emerged only when re-tested at later days. However, this type of skill learning task requires days to master (Fritsch et al., 2010) and thus the differences may take longer to present. In contrast, in a sudden visuomotor perturbation subjects have to return to a 'baseline' levels of performance and reach asymptotic performance within minutes.

In this study, asymptotic performance was very similar across groups. Although there was a decreased rate of learning the 60 degree rotation, there was no significant difference in late errors. Similarly, the difference between val/val and valmet subjects was significantly reduced from the early to the late segment of de-adaptation. The reduction of behavioral differences due to the val/met polymorphism with training is in line with recent evidence showing that intense training on a task over 5 days could overcome differences in motor map plasticity (McHughen et al., 2010). The val/val subjects showed significant increases in cortical map plasticity after 30 minutes of training on the first day, whereas val/met subjects showed no such increase. In contrast, the behavioral differences in adaptation in our study were overcome within minutes, rather than days, of training. This may be accounted for by differences in task, as McHughen et al. used a marble navigation task quite different than visuomotor adaptation tested here. Furthermore, there were no differences in actual behavioral performance of

the marble navigation task (McHughen et al., 2011). Nevertheless, this suggests a preferential role for BDNF in fast error-based rather than slow asymptotic adaptation. Alternatively, BDNF may be important for the entire course of learning, but adaptation may induce an activity-dependent increase in BDNF that presumably helps to normalize BDNF levels and improve performance. Although sustained training is known to increase BDNF gene expression at longer time scales (Neeper et al., 1995; Gómez-Pinilla et al., 2002; Berchtold et al., 2010), BDNF also undergoes activity-dependent release in 4-30 minutes (Balkowiec and Katz, 2002; Zhang and Poo, 2002; Egan et al., 2003). As BDNF is known to increase even during motor practice and exercise (Rasmussen et al., 2009), performance of the baseline phase may have allowed the necessary time for BDNF levels to increase and assist in normalizing performance mid-way through adaptation (6-7 minutes from first joystick movement).

During de-adaptation, there was larger increase in error for val/mets in the early part of the de-adaptation phase. However despite a reduction in the de-adaptation difference over time, mean error was still significantly higher for val/met subjects in the late segment. De-adaptation may in part involve learning, however the significant difference in error as well the persistence of the deficit in val/met over an extended period of time seem to distinguish this process from initial learning. Although de-adaptation is not very well understood, it may consist of a scaling down or deactivation of a previously learned motor memory (Davidson and Wolpert, 2004). A deficiency in 'un-learning' in this case may be underpinned by a known role of BDNF in the

synaptic de-potentiation and long-term depression (Woo et al., 2005; Foltynie et al., 2009). This may also analogous to previous findings showing that the val66met snp impaired homeostatic plasticity - Cheeran et al. studied the effect of preconditioning with cathodal TDCS (inhibitory effect on corticospinal exctability) on subsequent 1 Hz rTMS (also inhibitory on its own): the Val/Val subjects showed the expected reversal of corticospinal excitability towards facilitation (maintaining homeostatsis), whereas MEPs remained suppressed in the non-Val/Val individuals (Cheeran et al., 2008). Although speculative, such reversal of excitability may be necessary when switching from an adapted to de-adapted state, further accentuating the deficit in val/met subjects during de-adaptation.

In experiment 1, there was small but non-significant increase in the mean errors between blocks 2-10 for val/met subject. However in Experiment 2, there was a large deficit between groups. This effect was significantly more pronounced that the 60 degree rotation. An explanation of this difference may be drawn from the known deficit in error processing of met carriers (Beste et al., 2010). Subjects with val/met genotype were shown to have a decreased error-induced potential in EEG activity, and reduced behavioral slowing after an error. Such altered error processing may impact performance on a visuomotor task, which requires trial-by-trial adaptation dependent on visual feedback of the rotated error. This is made more likely by the fact that rotated feedback during visuomotor adaptation induces an error-related signal in EEG, the magnitude of which corresponds to the degree of rotation (Anguera et al., 2009). In this study, the 80 degree

rotation in experiment 2 revealed significantly larger difference in performance between groups. This raises the possibility that a smaller error-related signal in val/met subjects may promote less evaluation and on-line correction of subsequent movements, thereby impairing adaptation.

The val66met polymorphism is relatively common (35% Val66Met in the Caucasian population), and thus the differences in adaptation here are potentially significant and may be representative of subtle functional variations in motor learning that occur in daily life. For example, individuals with the polymorphism may take longer to adapt their movements in learning a new skill or recovering from injury, depending on the degree of difficulty. On the other hand, the known reduction in adaptation and plasticity (Cheeran et al., 2008) may also confer an increased in stability and maintenance of the current motor or cognitive set. Indeed, the val66met polymorphism has been reported to have a beneficial effect on cognitive status in a variety of neurological disorders (Alberch et al., 2005; Oroszi et al., 2006; Zivadinov et al., 2007; Foltynie et al., 2009). The deficiency in de-adaptation or 'un-learning' seen here may be representative of this increased stability and resistance to downscaling a previously learned motor set.

In summary, this study demonstrates that subjects with the val/met polymorphism are significantly impaired during de-adaptation of a 60 degree rotation, and during learning of a more difficult 80 degree rotation. Our results demonstrate that differences in adaptation between val/val and val/met subjects are dependent on the amount and difficulty of adaptation as

well as task demands, and point to possible functional consequences of BDNF during motor learning in health and disease.

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# Appendix II:

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Short communication

## Rapid tremor frequency assessment with the iPhone accelerometer☆

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ABSTRACT

The physician is often seeking more efficient ways of performing patient assessments. Currently, measuring tremor frequency requires expensive and bulky equipment. We propose the use of the in-built accelerometer of the iPhone via the iSeismo application for rapid measurement of tremor frequency. We use this device in a series of 7 different tremor cases, and show that the frequency measurements on the iSeismo graph closely match the more sophisticated EMG analysis during tremor. This is a preliminary confirmation of the usefulness of this device in the clinical setting for quick assessment of the dominant frequency component in a variety of tremors.



### 1. Introduction

Tremor, a 'rhythmical, involuntary oscillatory movement of a body part' [1] is the most common movement disorder. Tremor can appear alone as in essential tremor (ET) or as part of other conditions, such as Parkinson's disease, multiple sclerosis, or cerebellar damage.

Frequency as a property of tremor has been studied for quite some time; Holmes in 1904 identified that tremor frequencies were characteristic to certain conditions, and thought that this might be linked to their pathophysiology [2]. Tremor can be found in a wide variety of frequencies and amplitudes. For example, the frequency of classical rest tremor in Parkinson's disease is between 4 and 7 Hz with large variations in tremor amplitude [1]. Essential tremor and dystonic tremor have a frequency between 4 and 12 Hz, multiple sclerosis between 2 and 10 Hz, and orthostatic tremor between 13 and 18 Hz [3].

Although clinical rating scales are quite useful for a rough assessment of tremor amplitude, assessing frequency by observation is by definition approximate and inaccurate. Clinical assessments then, are often combined with EMG measurements and accelerometry to determine tremor amplitude and frequency [4].

The ways of measuring tremor range dramatically. Innovative methods that have been used to measure tremor include an electromagnetic tracking device [5], a mechanical linkage device on the fingertip [6], lasers [7], and digitizing tablets [8], to name a few.

Although these various techniques are interesting and useful in their own right, they have demonstrated limited usability in a clinical setting, where flexibility, efficiency, and accuracy are paramount. The use of portable triaxial accelerometers is perhaps the easiest way to assess tremor [9], however this also involves purchase and transportation of necessary equipment from patient to patient. All in all, the existing methods for tremor assessment are quite cumbersome and expensive.

The challenge is finding a universally accessible, easily used device that can give a quick, accurate representation of tremor characteristics. Here, we present the use of the iPhone® seismograph application (iSeismo by ObjectGraph LLC) in tremor detection and measurement. The freely available application uses the in-built accelerometer of the iPhone (or iPod Touch®) to measure movement in the X, Y, and *Z* axes relative to the device. These data are then displayed graphically showing the three axes and their predominant frequency band.

Although originally developed as an earthquake detector, here we show the iSeismo application can act as an easily accessible way for clinicians who own this popular device to measure pathological tremor simply and accurately.

#### 1.1. Patients and methods

The local research ethics committee approved methods in this study, and written informed consent was obtained from all

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**Table 1**
Comparison of tremor frequency peaks between EMG and iPhone.

| Tremor type, Gender, Age | EMG peak (Hz) | iPhone peak (Hz) |
|---|---|---|
| Essential 1, M, 38 | 5.6 | 5.5 |
| Essential 2, (OFF stim), M, 41 | 5.8 | 5.7 |
| Essential 2 (ON stim) | 0 | 0.4 |
| Parkinson's, M, 65 | 4.7 | 4.7 |
| Multiple Sclerosis, F, 38 | 3.8 | 3.9 |
| Post-stroke, M, 48 | 3.8 | 3.6 |
| Dystonic, F, 53 | 7.4 | 7.3 |
| Orthostatic, M, 71 | 14.7 | 15.3 |

patients. A total of 7 patients were used in this study, with the following conditions: Essential tremor (2 cases, 1 with implanted deep brain stimulator) Parkinson's tremor, multiple sclerosis tremor, post-stroke tremor, dystonic tremor, and orthostatic tremor. This allowed comparison of the iPhone with the EMG analysis at various tremor frequencies.

The iPhone was strapped securely to the tremorous limb (either forearm or lower leg) and tremor was recorded using the iSeismo application for 30 s concurrently with EMG recordings. On-screen spectral analysis of tremor in three dimensions was saved as a screen capture for later comparison with the EMG.

Electromyograms (EMG) were recorded from disposable adhesive Ag/AgCl electrodes (H 207 PT; Kendall, Tyco International, Germany) placed roughly 1 cm apart on the belly of the muscle utilising a bipolar configuration. The muscles studied included *flexor carpi radialis* and *extensor carpi radialis* for all patients except orthostatic tremor where *tibialis anterior* was used. Parkinson's, post-stroke, and dystonic tremors were captured at rest, while essential tremor and multiple sclerosis tremors were with arms straight out (postural position), and orthostatic tremor was with the patient standing. Signals were amplified (×1,000) using isolated CED 1902 amplifiers (Cambridge Electronic Design, Cambridge, UK), filtered (0–500 Hz) and digitised at 16 bit resolution using CED 1401 mark II analogue-digital converter (Cambridge Electronic Design, Cambridge, UK) at a sample rate of 2.5 kHz. Recordings were displayed online on a personal computer using Spike 2 (Cambridge Electronic Design, Cambridge, UK) and saved to disk for off-line analysis.

Data were analysed off-line using custom written software in the MatLab (Mathworks Inc., Natick, MA, USA) numerical simulation environment. A 30 s data segment free from large movement artefact, recorded during tremor, was exported at a sample rate of 1 kHz. Prior to further analysis data was bandpass filtered between 2 and 300 Hz. The signal was then full-wave rectified and the power

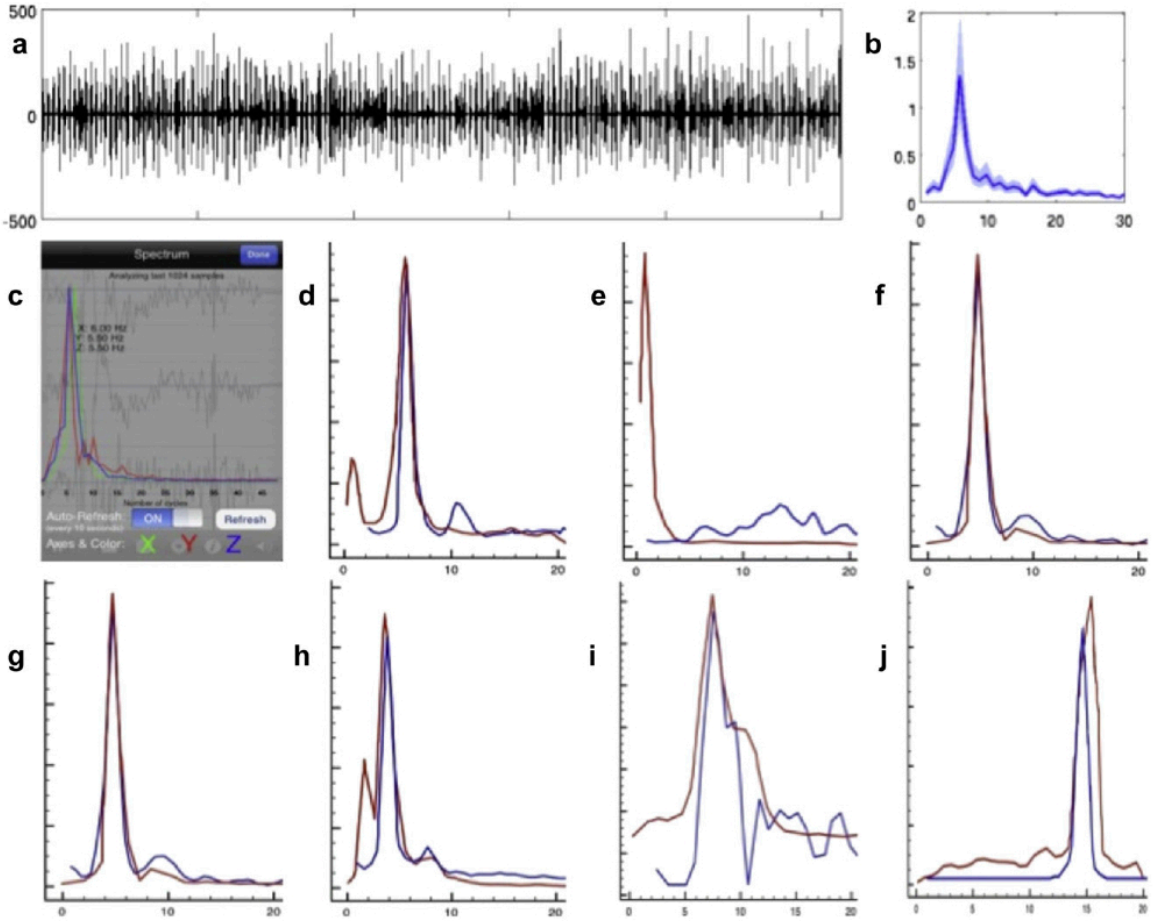


**Fig. 1.** Comparative illustrations from iPhone accelerometer and EMG analysis for all tremor cases. (a) Example 30s segment of EMG activity taken from essential tremor. (b) Corresponding EMG analysis, showing PSD and tremor peak. (c) Corresponding iSeismo screen capture. Subsequent graphs show data from EMG analysis (blue) and iSeismo data (red) for (d) essential tremor without deep brain stimulation, (e) essential tremor with deep brain stimulation showing tremor peak suppression, (f) Parkinson's tremor, (g) multiple sclerosis tremor, (h) post-stroke tremor, (i) dystonic tremor, and (j) orthostatic tremor.

spectral density (PSD) calculated using Welch's modified periodogram approach utilising a Hanning window over 2 s disjointed sections [10]. Each PSD generated was evaluated for the frequency of tremor by identifying the highest amplitude peak and comparing this to the iPhone recording, which generates a frequency peak on-screen. The axis which best corresponded to the direction of movement was selected for this analysis. We focused only on the predominant frequency, as iSeismo does not properly measure amplitude, which allowed easy comparison across tremors and methods.

## 2. Results

The results of off-line EMG analysis matched well with the online iPhone tremor plots. Data are summarized in Table 1 and Fig. 1. Fig. 1 illustrates the compatibility of tremor assessment across these conditions. Individual plots for EMG and iPhone data are shown for the first case (essential tremor). For all subsequent cases, raw values were extracted and re-plotted on the same graph for direct comparison. Both methods produced similar bands of activity for the given tremor, and nearly identical peaks. The range of increased frequency power was also visibly quite similar. Table 1 shows tremor peak frequency for all tremors tested. For multiple sclerosis, essential tremor, post-stroke, dystonic and Parkinson's tremor, the difference in tremor peak between the two methods was marginal, between 0 and 0.2 Hz. The higher frequency orthostatic tremor had a slightly larger difference (0.5 Hz).

## 3. Discussion

The above cases demonstrate that the iPhone accelerometer, through the iSeismo interface, can be a useful way of quickly isolating the dominant tremor frequency in the clinical setting. This is perhaps the simplest method available for the quick assessment of tremor frequency, and as seen here can be applied to a variety of disease pathologies. All tremors were well detected by the iPhone and matched well with the EMG assessment. Even suppression of tremor with deep brain stimulation was demonstrated neatly as the abolishment of the previous tremor peak. The data presented in this paper are not intended to provide a thorough or rigorous analysis for the accuracy of the iPhone, but rather to show that it is generally accurate and reliable at displaying the same tremor frequency bands as the EMG analysis.

One main problem with this technique is that amplitude is not reliably measured. However, amplitude itself is much more variable than frequency and is a poor diagnostic measure compared to frequency, for example in differentiating between essential tremor and Parkinson's tremor [11]. There is, of course, considerable overlap in tremor peak frequencies across conditions [1]. This makes it difficult to assign definitive diagnostic value to a frequency peak, except in the case of orthostatic tremor, where the tremor peak is unique to the condition and cannot be appreciated clinically. Although this condition is not often confused with other tremors, a confirmation of the frequency of tremor is important in making a final diagnosis, especially when psychogenic tremor is suspected.

Using the iPhone to measure frequency is a less informative method than commercial accelerometers or EMG analysis. However, the using of these established techniques is often expensive, technically cumbersome, and time consuming; clinicians often seek more efficient ways of obtaining a quick general impression. Many physicians already own an iPhone, and use it for obtaining important on the-go reference information. As well, there are now accelerometers included in many handheld devices and cellular phones. This opens the possibility of using similar applications for these devices to exploit the in-built accelerometer.

Devices such as the iPhone are also increasingly being used as easy, flexible methods of collecting and storing data in the laboratory [12]. From a research perspective this method could be valuable, for example in taking a survey of tremor frequencies in a given population at low-cost, without the need for more sophisticated equipment.

We have shown here that the iPhone can act as an easily accessible way for clinicians who own this popular device to measure tremor frequency simply and reliably.

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