INSIGHTS INTO THE NEURAL BASIS OF PARADOXICAL KINESIA IN PARKINSON'S DISEASE

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I, Anam Anzak, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Enhancements in peak motor performance have been demonstrated in response to intense stimuli both in healthy subjects and in the form of 'paradoxical kinesis' in patients with Parkinson's disease. Might the latter phenomenon thus reflect a physiological process? The first study outlined in this thesis suggests this may be the case, as maximal effort grips in healthy subjects undergo dramatic enhancements when the imperative visual cue is accompanied by an intense auditory tone.

Analogous enhancements in motor performance are demonstrated in a second study of patients with Parkinson's disease and age-matched healthy controls. Remarkably, the facilitating effect of loud auditory tones is similar whether patients are off or on dopaminergic medication, suggesting a potentially non-dopaminergic basis for the phenomenon.

A role of sub-cortical systems in the performance enhancements engendered by intense stimuli is next considered. Local field potentials recorded from the subthalamic nuclei of patients with Parkinson's disease, whilst they undertake the above established paradigm, identify both theta/alpha (5-12 Hz) and high gamma/high frequency (55-375 Hz) activity as exhibiting remarkable scaling with maximal motor responses to the visual cue alone, but having little explanatory influence on performance enhancements beyond this.

In the final study, a short-latency evoked potential in subthalamic nucleus local field potential recordings, which scales in amplitude with both stimulus intensity and corresponding enhancements in biomechanical measures of maximal handgrips, is identified. Interference with this potential through high frequency deep brain stimulation of the same nucleus, leads to a diminished behavioural effect of stimulus intensity. Recordings of a similar evoked potential in the related pedunculopontine nucleus – a key component of the reticular activating system – provide support for this neural signature as a physiological correlate of ascending arousal, propagated from the reticular activating system to exert an 'energizing' influence on motor circuitry through the subthalamic nucleus.

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِيْمِ

وَالضُّحٰى ۙ﴿۱﴾
وَالَّيْلِ اِذَا سَجٰى ۙ﴿۲﴾
مَا وَدَّعَكَ رَبُّكَ وَمَا قَلٰى ؕ﴿۳﴾
وَلَلْاٰخِرَةُ خَيْرٌ لَّكَ مِنَ الْاُوْلٰى ؕ﴿۴﴾
وَلَسَوْفَ يُعْطِيْكَ رَبُّكَ فَتَرْضٰى ؕ﴿۵﴾
اَلَمْ يَجِدْكَ يَتِيْمًا فَاٰوٰى ۪﴿۶﴾
وَوَجَدَكَ ضَآلًّا فَهَدٰى ۪﴿۷﴾
وَوَجَدَكَ عَآئِلًا فَاَغْنٰى ؕ﴿۸﴾
فَاَمَّا الْيَتِيْمَ فَلَا تَقْهَرْ ؕ﴿۹﴾
وَاَمَّا السَّآئِلَ فَلَا تَنْهَرْ ؕ﴿۱۰﴾

- Ad-Duha (The Morning Light)

Surah 93:The Glorious Qur'an

This work is dedicated to God

and

the three strong, beautiful women in my life:

my Little Sister - Nada

my Mum - Huma

and my Grandmother - Jamsheda

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Publications

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Anzak A, Gaynor L, Beigi M, Limousin P, Hariz M, Zrinzo L, Foltynie T, Brown P, Jahanshahi M (2011). *A gamma band specific role of the subthalamic nucleus in switching in verbal fluency.* **Exp Neurol**. 232 : 136-42

Tan H, Pogosyan A, **Anzak A**, Foltynie T, Limousin P, Zrinzo L, Hariz M, Ashkan K, Bogdanovic M, Green AL, Aziz T, Brown P (2013). *Frequency specific activity in subthalamic nucleus correlates with hand bradykinesia in Parkinson's disease.* **Exp Neurol [in press]**

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AD	analogue to digital conversion
ANOVAs	analysis of variance
AV	auditory-visual cue
CMVC	conventional maximal voluntary contraction
DBS	deep brain stimulation
DTI	diffusion tensor imaging
EEG	electroencephalography
EMG	electromyography
FMVC	functional maximal voluntary contraction
FOG	freezing of gait
GABA	gamma amino-butyric acid
GPe	globus Pallidus externa
GPi	globus Pallidus interna
KS	kolmogorov-smirnov test
L-DOPA	levodopa
LFP	local field potential
MEG	magnetoencephalography
MRI	magnetic resonance imaging
MSA	multiple system atrophy
MVC	maximal voluntary contraction
ON	on dopaminergic medication
OFF	off dopaminergic medication
PD	Parkinson's disease
PET	positron emission tomography
PF	peak force
PPNr	pedunculopontine nucleus region

PSP	progressive supranuclear palsy
PY	peak yank
RAS	reticular activating system
REM	rapid eye movement
RT	reaction time
SCM	sternocleidomastoid
SD	standard deviation
SEM	standard error of mean
SNpc	substantia nigra pars compacta
SNpr	substantia nigra pars reticulate
STNr	subthalamic nucleus region
UPDRS	Unified Parkinson's Disease Rating Scale
V	visual cue
ZI	zona incerta

Introduction

'... it is appropriate to speak of a physiologic and a psychologic limit. Capacity is the always undetermined measure of the former. Performance is always limited by the latter.'

– Ikai & Steinhaus, 1960.

1.1 The curious case of paradoxical kinesia in Parkinson's disease

'Paradoxical kinesia' was the term first coined by Souques (1921) to describe the remarkable normalisation of motor activity observed in patients with Parkinson's disease (PD), under circumstances of marked arousal. A wealth of anecdotal reports have since implicated eliciting stimuli as diverse as the sound of a car accident (Daroff, 2008), the sensation of an earthquake (Bonanni et al, 2010) or the sight of a fire or wall of flood-water (Schwab & Zieper, 1965), and yet obvious limitations in replicating such circumstances in controlled lab environments have meant that next to nothing is known of the phenomenon's underpinning. Nonetheless, the existence of neural systems that could override parkinsonian impairment remains a truly tantalising prospect, not least because identifying and manipulating these pathways may yield a novel and more effective therapy for motor impairment in PD. In this thesis I seek to clarify the neural basis of paradoxical kinesia, particularly in the context of PD. I will start by reviewing PD and its treatment, before considering the contributions of the basal ganglia to the control of movement and the means by which we may investigate this role still further.

1.2 Parkinson's disease: clinical features, pathophysiology and management

PD is a degenerative disorder of the central nervous system. Its clinical manifestations are primarily motor. Mean age of onset is early to mid 60s. However, in people with young-onset PD (affecting 5-10% of patients; Golbe, 1991), the initial symptoms can arise between 21-40 yrs. Juvenile-onset disease occurs before the age of 20 (Muthane et al, 1994). The disease affects approximately 1% of the world population aged over 60, with prevalence increasing to 4% of those over 80 years (de Lau & Breteler, 2006). The disease burden is thus likely to increase as a result of aging populations around the world. Indeed, in Europe, Gustavsson et al (2011) estimated the cost of PD in 2010 to be €13.9 billion.

1.2.1 Clinical features

The cardinal motor features of PD comprise tremor, bradykinesia, rigidity, postural instability and akinesia. These, as well as a number of non-motor manifestations of the disease, are outlined below:

1.2.1.1 Motor Symptoms

Resting tremor – which disappears with action and during sleep - is the most common symptom of PD, with most patients developing it as the disease progresses (de Lau & Breteler, 2006). In one study, 69% of patients were found to have tremor at rest at disease onset, with the prevalence increasing to 75% during the course of the disease (Hughes et al, 1993). Initially, distal parts of the limbs are most affected, with onset usually in a single arm or leg becoming bilateral later. The frequency of PD tremor is typically 4-6 Hz (cycles per second). Postural tremor is also present in many patients with PD (Jankovic et al, 1999). Parkinson's related postural tremor has also been termed re-emergent tremor because, unlike essential tremor, its appearance is often delayed after the patient assumes an outstretched horizontal position. The frequency of re-emergent tremor is the same as that of classical rest tremor. As it is additionally responsive to dopaminergic therapy, re-emergent tremor may be considered a variant of the latter (Jankovic, 2008). Clinical pathological studies in parkinsonian patients with and without tremor have attributed specific degeneration of a subgroup of neurons in the medial substantia nigra, especially the retrorubal area A8, to those parkinsonian individuals in which tremor is dominant (Jankovic, 2008).

Bradykinesia refers to slowness of movement, and has been posited to encompass difficulties with planning, initiating and executing movement, as well as with performing sequential and simultaneous tasks (Berardelli et al, 2001). However, the predicament of paradoxical kinesia, in which patients are reported to move 'normally' in response to intense stimuli, suggests intact cortico-muscular drives and argues against movement *execution* as the underlying disorder in PD. The symptom is described to initially manifest as a slowness in performing activities of daily living, such as buttoning, using utensils, and other tasks that require fine motor control, accompanied by a general slowing in movement and reaction times (Cooper et al, 1994; Giovanonni et al, 1999). Loss of spontaneous movements, drooling because of impaired swallowing (Bagheri et al, 1999), monotonic and hypophonic dysarthria, loss of facial expressions, decreased blinking, and reduced arm swing while walking, have also been reported (Jankovic, 2008). Assessment of bradykinesia by asking patients to perform rapid, repetitive, alternating movements of the hand typically identifies not only slowness, but also decrements in

the amplitude of movement. Of note, functional magnetic resonance imaging (fMRI) studies have reported impairment in the recruitment of both cortical and subcortical systems regulating kinematic motor parameters (Turner et al, 2003). In addition, positron emission tomography (PET) in patients with PD has demonstrated a correlation between the degree of bradykinesia and reductions in ^{18}F-fluorodopa uptake in the striatum and accumbens–caudate complex (Lozza et al, 2002).

Rigidity results from an increase in muscle tone, and can either manifest itself uniformly (lead-pipe) or be ratchety in nature (cog-wheel). Rigidity in PD can be seen throughout the passive movements of a limb (flexion, extension and rotation about a joint). It occurs in both proximal and distal joints. Rigidity is also often associated with pain, with painful shoulder being a frequent initial manifestation of the disease (Stamey et al, 2008).

Freezing of gait (FOG) is a common form of akinesia (loss of movement) in patients with PD. It may present itself as an inability to initiate movement, or a sudden and transient inability to continue locomotion (Moretti et al, 2011; Giladi et al, 1992). The situations in which it has been described include: when beginning to walk (start hesitation), whilst turning, or just before reaching a destination (destination hesitation; Schaafsma et al, 2003). FOG is also commonly precipitated in 'stressful' situations such as those that limit time or space, including walking through a narrow passage or crossing busy streets (Moretti et al, 2011; Okuma, 2006). The severity of freezing episodes is greater when patients are OFF dopaminergic medication (Jankovic, 2008). In one study, based on the responses of 6620 patient members of the German Parkinson's Association, 47% of these individuals reported freezing. The phenomenon was found to occur more frequently in men than in women, and less frequently in patients whose main symptom was tremor (Macht et al, 2007).

Loss of postural reflexes, leading to postural instability, is typically considered a feature of the late stages of PD. Along with freezing of gait, postural instability constitutes one of the commonest causes of falls, and contributes significantly to the risk of hip fractures in parkinsonian patients (Williams et al, 2006). Accordingly, the frequency of falls has been found to correlate with the severity of the disease (Koller et al, 1989). Unlike other neurodegenerative disorders such as progressive supranucelar palsy (PSP) and multiple system atrophy (MSA), however, a long latency to the onset of falls is observed in patients with PD (Wenning et al, 1999). In one study it was shown that the average time from onset of symptoms to the first fall was 108 months in patients with PD, compared with 16.8 and 42 months in patients with PSP and MSA respectively (Williams et al, 2006). Traditional treatments such as dopaminergic therapy, and deep brain

stimulation (DBS) of the subthalamic nucleus (STN) have not been shown to robustly improve this symptom. However, recent work has implicated the zona incerta (ZI) and pedunculopontine nucleus (PPN) as alternative and effective DBS targets for patients in which 'falling' is prevalent (Stefani et al, 2007; Thevathasan et al, 2011). It should be pointed out, however, that postural instability in patients with PD may be influenced by many other parkinsonian symptoms such as orthostatic hypotension and age related sensory changes (outlined below).

1.2.1.2 Non-motor symptoms

A number of non-motor symptoms are common in PD, including: cognitive and mood disorders, autonomic dysfunction, and sensory and sleep abnormalities.

Patients with PD are believed to have an almost six-fold increased risk of developing dementia (Aarsland et al, 2001). The Sydney Multicenter Study of PD identified cognitive decline in 84% of patients evaluated (Hely et al, 2005). In addition, 48% met the diagnostic criteria for dementia after 15 years of follow-up. PD related dementia has also been found to be associated with a number of other neuropsychiatric disturbances. In a study of 537 PD patients with dementia, depression (58%), apathy (54%), anxiety (49%) and hallucinations (44%) were also reported (Aarsland et al, 2007).

As alluded to above, depression constitutes the most common mood disturbance in PD, occurring in approximately 50% of patients (Dooneief et al, 1992). Mood fluctuations are more common in more advanced stages of the disease and demonstrate a strong correlation with motor fluctuations (Richard et al, 2004). Pychosis has also been reported in up to 30% of parkinsonian individuals (Naimark et al, 1996). Symptoms include visual hallucinations, delusions, agitation and occasionally aggression and paranoia. The loss of dopaminergic neurons in nigro-mesolimbic projections has been attributed to such symptoms (Davie, 2008).

Autonomic failure may be the presenting feature of PD. One study found that 47% of PD patients met the diagnostic criteria for orthostatic hypotension (Allcock et al, 2004). Other features commonly include sweating abnormalities (Senard et al, 1997), sphincter dysfunction and erectile dysfunction (Jankovic, 2008).

Rapid eye movement (REM) sleep behaviour disorder occurs in approximately 1 in 3 patients with PD (Gagnon et al, 2006; Jankovic, 2007). This disorder is now considered a pre-parkinsonian state (Borek et al, 2007), and is characterised by an increase in violent dream content. In remarkable contrast to the hypokinetic features of PD, punching, jumping and other potentially

violent motor activities have been described. Of interest, the potential to override the bradykinetic and hypokinetic features of PD during episodes of REM sleep behaviour disorder draws parallels with the phenomenon of paradoxical kinesia, and again points towards a *preservation* of pathways related to motor execution in the diseased state.

Sensory symptoms, including olfactory dysfunction (Stern et al, 1994), pain, and paraesthesia (Djaldetti et al, 2004; Tinazzi et al, 2006) are also common in parkinsonian patients. Olfactory dysfunction, in particular, has been implicated as an early marker of PD (Ponsen et al, 2004), and has been related to loss of dopaminergic neurons in the olfactory bulb, as well as neuronal loss in the corticomedial amygdala (Harding et al, 2002).

1.2.2 Pathophysiology

The motor symptoms of PD have long been attributed to the loss of striatal dopamine secondary to degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc; Fearnley & Lees, 1991; Ehringer et al, 1960). The rate of decline of striatal dopamine innervation has been shown to be faster in the initial years of disease evolution (Greffard et al, 2006), which is compatible with the idea of an acute or sub-acute onset followed by a slow, non-linear disease progression, that has been suggested to involve mechanisms including: inflammatory responses, glutamate mediated excitotoxicity, and reduced trophic support (Obeso et al, 2010).

The effect of the reduction of dopamine is typically described in the context of Albin and DeLong's classical model of basal ganglia circuitry (Albin et al, 1989; DeLong 1990). In this model (see **Figure 1.1**), cortical input to the system is received by the striatum (comprising the caudate nucleus and putamen), whilst the globus pallidus interna (GPi) and substantia nigra pars reticulate (SNpr) constitute the major output nuclei. Striatal activity can either be conveyed via its medium spiny neurons to the output nuclei through a mono-synaptic GABA (gamma**-**aminobutyric acid) -ergic projection (direct pathway) or a polysynaptic (indirect) pathway, which passes through the globus pallidus externa (GPe) followed by the STN. The output nuclei of the basal ganglia are believed to work by maintaining a tonic inhibitory control of thalamo-cortical projections. However, this tonic inhibition can be blocked by phasic inhibitory signals via the striato-nigral-pallidal projections of the 'direct pathway', thus allowing movement to proceed. On the other hand, the excitatory output of the 'indirect pathway' serves to increase the level of tonic inhibition, and subsequently arrest movement.

Dopaminergic input from the substantia nigra pars compacta (SNpc) has an excitatory influence on the pro-kinetic 'direct pathway' via D1 type dopaminergic receptors expressed on the striatal

spiny cells projecting to the GPi. Conversely, dopamine exerts an inhibitory influence on the anti-kinetic 'indirect' pathway, mediated by D2 receptors on cells projecting to the GPe. Thus, the overall effect of dopamine is to decrease the inhibitory outflow of the basal ganglia, and subsequently increase the excitability of upper motor neurons. In this framework, the death of dopamine-secreting SNpc cells, as occurs in PD, is thus proposed to lead to an increase in the inhibitory outflow of the basal ganglia, resulting in a decreased likelihood of thalamic activation of upper motor neurons, and subsequent hypokinetic and akinetic features of the disease.

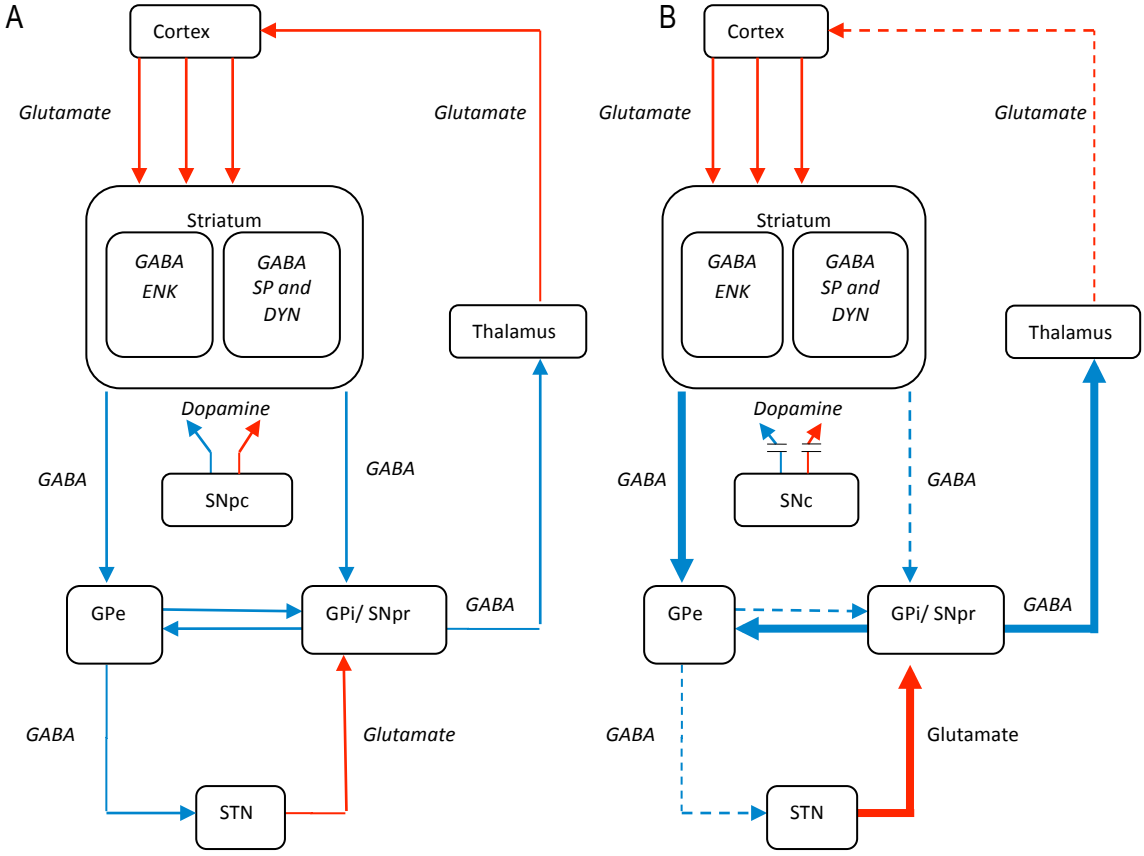


Figure 1.1 Basal ganglia circuitry according to Albin & DeLong's classical model in (A) normal conditions and (B) Parkinson's disease. In (B) dashed lines represent pathways that are hypoactive, and thickened lines represent those that are believed to be hyperactive. SNpc, substantia nigra pars compacta; SNpr, substantia nigra pars reticulate; Gpe, globus pallidus externa; GPi, globus pallidus interna; STN, subthalamic nucleus. Neurotransmitters are italicized. Blue and red arrows represent inhibitory and excitatory pathways respectively. DYN, dynorphins; ENK, enkephalins; GABA, gamma-amino butyric acid; SP, substance P. (Adapted from Michael-Titus, Revest & Shortland, 2007).

It should be pointed out, however, that whilst the 'direct' and 'indirect' pathways proposed in Albin & DeLong's classical model remain valid, a number of new anatomical, functional and clinical studies have thrown fresh light on our previous understanding of basal ganglia connectivity. In particular, multiple branching collateral fibres, which terminate sparsely in the GPe, have now been described as an additional feature of the direct pathway (from the striatum to the output nuclei; Wu et al, 2000; Matamales et al, 2009). In addition, multiple external afferents, from both cortical and subcortical structures, to the STN have been identified (Hartmann-von Monakow et al, 1978; Nambu et al, 2002; Coizet et al, 2009; Mena Segovia et al, 2004). The GPe is now understood to project not only to the STN and directly to the GPi and SNpr, but also to nigrostriatal dopaminergic neurons via a network of branched collaterals (Smith et al, 1998). Finally, moving onwards from the feed-forward nature of basal ganglia processing which is classically described, clear examples of reciprocal connectivity have been demonstrated between basal ganglia nuclei, in particular the STN and GPe (Shink et al, 1996), and GPe and the striatum (Bevan et al, 1998).

In addition, a number of major clinical paradoxes of the model are evident (Brown & Eusebio, 2008; Rodriguez-Oroz, 2009). First is the observation that lesioning or DBS of the motor thalamus does not result in prominent akinesia. Second, lesions or DBS of the STN or GPi have not been shown to lead to new deficits - as a consequence of loss of physiological functioning – but instead result in improvement of parkinsonian symptoms (The deep brain-stimulation for Parkinson's disease study group, 2001). Third, the amelioration of levodopa induced dyskinesias and dystonias by pallidotomy and pallidal DBS is further at odds with the model, which describes decreased tonic inhibition of the thalamus by the GPi, and subsequent uncontrolled facilitation of movement, as the underlying mechanism leading to the emergence of these side-effects.

Identification of the above paradoxes has led to the argument that it is the *pattern* of basal ganglia oscillatory activity – particularly the extent of synchronization over specific frequencies - which is disruptive in PD, rather than the net level of inhibition of thalamic cortical activation. Subsequent to the proposal of this 'noisy signal hypothesis' (Marsden & Obeso, 1994) several disease phenotype specific noisy patterns have been described in local field potentials (LFPs) recorded from various key basal ganglia nuclei. Indeed, in PD patients withdrawn from their antiparkinsonian medication, a synchronisation of 13-30 Hz LFP activity in both the STN and pallidum has been demonstrated. Of note, the degree of drug-induced improvement in bradykinesia and rigidity was shown to correlate with the degree of suppression of synchronization in this 13-30 Hz band in both the STN and cortex (Kühn et al, 2006; Silberstein et al, 2005b). More recently, DBS of the STN has been shown to progressively suppress peaks in

LFP activity over the 13-30 Hz range as stimulation voltage is increased beyond the median threshold for clinical efficacy (Eusebio et al, 2011).

Conversely, pathological activity across a 4-10 Hz (theta) frequency band has been associated with the 'hyper-kinetic' dyskinetic side effects of dopaminergic medication in patients with PD (Rodriguez-Oroz, 2011; Silberstein et al, 2003). In addition, several studies have now suggested that there is excessive oscillatory activity at <10 Hz in the LFP recorded in the pallidum in patients with primary dystonia (Liu et al, 2002; Silberstein et al, 2003). It has also been shown that tremor sides present predominant theta frequency oscillations in the most dorsal layers of the STN (Contarino et al, 2012).

Besides the loss of nigrostriatal dopaminergic melanised cells, an accumulation of alpha-synuclein protein in neuronal inclusions called Lewy bodies, is considered a further pathological hallmark of the disorder (Braak et al, 2003). Interestingly, novel insights into the mechanism of progression of PD have recently been afforded through post-mortem studies of these inclusions, in patients who died 13-16 years after transplantation of fetal nigral cells into the striatum (Li et al, 2008; Kordower et al, 2008a; Kodower et al, 2008b; Mendez et al, 2008; Kordower et al, 1995). Examination of these transplanted cells, revealed inclusion bodies almost identical in morphology and staining to Lewy bodies found in the host dopaminergic neurons. Indeed, three common Lewy body markers - α-synuclein, ubiquitin and thioflavin S—were all identified on staining. In addition, phenotypic alteration such as loss of dopamine transporters, were also evident in some cases. Such pathology was not encountered in those patients who survived less than 10 years after transplantation (Kordower et al, 1998), implicating a role of a progressive pathological process taking hold in older cells. On the basis of these remarkable observations, a prion-like process has been proposed as the mechanism by which α-synuclein parkinsonian pathology spreads (Olanow et al, 2009). In this model it has been posited that extracellular α-synuclein is taken up by neighbouring neurons by a process of endocytosis, leading to aggregation within the cell (Lee et al, 2005). However, the pathological significance of Lewy bodies still remains unclear.

Finally, a number of non-dopaminergic neurons have also been shown to undergo degeneration in PD, including: monoaminergic cells in the locus coeruleus and raphe nuclei (Zarow et al, 2003), cholinergic cells in the nucleus basalis of Meynert (associated with cognitive deficits; Hilker et al, 2005) the pedunculopontine tegmental nucleus (related to gait problems; Rinne et al, 2008), and hypocretin cells in the hypothalamus (believed to result in the sleep disorders common in Parkinson's disease; Thannickal et al, 2007). Indeed, it has been shown that approximately 30-50% of these non-dopaminergic cells have been lost by end stage PD (Obeso et al, 2010).

1.2.3 Medical management

Levodopa (L-DOPA) is the most commonly used drug in the medical management of PD. The drug is converted to dopamine by dopa-decarboxylase, leading to a partial correction of the dopaminergic deficiency of the diseased state and temporary amelioration of the motor symptoms. In order to prevent the metabolism of L-DOPA before it reaches the dopaminergic neurons, L-DOPA preparations commonly include peripheral dopa-decarboxylase inhibitors, such as carbidopa and benserazide, thus increasing bioavailability and reducing side-effects. The effects of L-DOPA can further be prolonged by administration of drugs such as entacapone, which inhibit the catechol-O-methyl transferase (COMT) enzyme that degrades dopamine. Several dopamine agonists have also been developed, including: bromocriptine, pergolide, pramipexole, ropinirole, cabergoline and apomorphine. These have been useful in reducing 'OFF-periods' in late PD, but are also commonly used as the initial therapy for motor symptoms, with the aim of delaying the motor complications of L-DOPA (NICE guidelines: Parkinson's disease, 2006). Finally, monoamine-oxidase B (MAO-B) inhibitors, such as selegiline and rasagiline, are also used to increase the level of dopamine in the basal ganglia by blocking its metabolism.

A number of major complications of long-term levodopa treatment do, however, exist. Motor fluctuations, in which patients report a 'wearing-off' effect of medication, and gradually become slower and more tremulous, are common. Switches between mobility and immobility can eventually become unpredictable, referred to as 'on-off phenomena'. Motor fluctuations have been shown to affect between 25-50% of patients after 5 years (Hely et al, 1994; Koller et al, 1999), and are even more prevalent in young-onset PD in which 90% of patients are affected at 5 years (Schrag et al, 1998). The emergence of dyskinesias is also a frequent complication. The most usual form of dyskinesia is peak dose chorea. Diphasic dyskinesias also occur, which are present or worse at the beginning and end of a dose-cycle. The development of drug-induced dyskinesias in PD has been associated with intermittent stimulation of dopamine receptors. As levodopa has a short half-life of 60–90 min, its pulsatile supply to a denervated striatum seems to be an important aetiological factor for this side-effect (Davie, 2008).

1.2.4 Surgical management

Early surgical options for treatment of PD focused on ablation strategies. Before the formulation of levodopa, pallidotomy was used to treat various motor symptoms in PD and thalamotomy was used to reduce contralateral tremor. With the introduction of levodopa in the 1960s, however, functional neurosurgery for PD was virtually abandoned. However, the emergence of motor

fluctuations and dyskinesias - with long-term levodopa treatment - led to a resurgence of interest in surgical management.

Deep brain stimulation (DBS) is now the surgical intervention of choice for PD. It is indicated in cases where long-term use of L-DOPA and dopamine agonists have resulted in uncontrollable motor complications such as fluctuations in the motor state ('wearing-off' and 'on-off' phenomena) and dyskinesias (Marsden & Parkes, 1976; Schrag & Quinn, 2000). The long-term efficacy of chronic high frequency stimulation of the STN in reducing both motor and non-motor symptoms of PD has now been widely documented (The deep brain-stimulation for Parkinson's disease study group, 2001; Rodriguez-Oroz et al, 2005; Deuschl et al, 2006; Fasano et al, 2010). Indeed, a ~50% long-term reduction in both UPDRS III scores (Krack et al, 2003) and levodopa dose (Benabid et al, 2009) has been reported. Whilst bilateral DBS of the GPi or STN has been shown to be effective in improving the symptoms of PD, the debate continues regarding the best stimulation target for the disorder.

1.3 Parkinson's disease as a disorder of motor control

It has previously been posited that the motor system can be described at three levels of control: computational, algorithmic and physical (Mazzoni et al, 2012). The computational level describes what the motor system does and *why.* For example, the choice of a straight trajectory in a reaching movement likely represents a strategy to minimize time or energy. The algorithmic level, on the other hand, dictates *how* the goals are accomplished. This may be achieved first by representation of the desired trajectory in space, followed by selection of the correct sequence of cortico- or reticulo-muscular drives to the required muscles, and of correct magnitudes, in order to keep the movement of the hand on the required path. Finally, the physical or implementation level describes the operation of the physical structures that perform the pre-computed movement, and the electrical and pharmacological substrates that connect and drive them.

A number of lines of evidence have now emerged implicating the algorithmic stage of motor control as the key level of dysfunction in PD. First, early studies by Flowers (1975) showed that whilst movements in patients with PD have a normal 'initial organization', their speed and amplitude is scaled down. In this study, the experimental paradigm required subjects to maintain a cursor on a visual target, which could randomly jump from position to position. Healthy subjects were able to move the cursor to the target in a single movement. However, the initial motor output of patients with PD was found to fall short of the target, and was subsequently followed by a series of additional corrective movements. The process of correction of movement, based on visual and proprioceptive feedback, has long been considered a physiological process, in-line

with Woodworth's two-component model for the control of goal-directed behaviour (Woodworth, 1899, Elliott et al, 2001). Thus the implication of this early work was that the first movement in PD is inadequately scaled, resulting in a greater amount of time being spent 'correcting' the initial undershooting.

In a similar vein, Hallett & Khosbin (1980) noted that patients with PD appeared limited in their ability to increase the amount of EMG activity required for longer movements, resulting in additional cycles of muscle activation being used to accomplish longer movements. They subsequently suggested that a normal role of the basal ganglia is to 'energize' movement, so it is appropriately scaled, by selection of the appropriate sets of muscles and absolute amplitudes for the level of muscle activity. This 'energizing' process was described as distinct from a separate 'timing' program, involved in setting up programs of properly timed and sequenced muscle activity, which was proposed to remain intact in patients with PD. Thus, the suggestion of this work was that it was the algorithmic and not the computational aspects of motor control that were adversely affected in the diseased state. Indeed, the predicament of micrographia, another symptom of PD, further highlights a defect in energizing muscle which need not be accompanied by a defect in 'muscle timing'

On the basis of observations of patients with basal ganglia dysfunction, the proposal of a role of this network in providing a 'motor energy' (De Ajuriaguerra, 1975) has repeatedly arisen in the literature. As long ago as the early 1900s, Wernicke (1899;1906) described what he believed was a pathological change in patients' perceptions of the motor images of their whole bodies, such that *"the idea of a movement which has to be carried out is accompanied by the inhibiting thought of an effort that subjectively is very great"*, resulting in a suppression of the movement. Trousseau (1921) further wrote that *"it seems as though the patient has at his disposal only a fixed amount of incoming nervous energy, which in his case is not renewed as rapidly as it is in other men".* Moreover, early studies by Schwab (1959) showed that repetitive movements fatigued more rapidly in patients with PD than in healthy controls, a phenomenon which was described as a difficulty in 'elaborating' a motor plan or pattern (Schwab and Zieper, 1965; Joubert & Barbeau, 1969).

Over a century after Wernicke's original proposal, Mazzoni and colleagues (2007) have shown that PD patients are indeed less likely than healthy controls to self-select fast movements, even though both groups of subjects are able to achieve equal accuracy in the required velocity of movements for the task. In this paradigm, the total number of trials to reach twenty correctly performed movements was used as a measure of how much a subject was struggling in making a

movement at a required speed. For the same required speed, patients with PD tended to need a larger number of trials to meet the objective than healthy subjects, a phenomenon which increased in incidence to a greater extent in patients than in controls as the speed requirement increased. It was subsequently posited that although patients with PD were not limited in the maximum speed they could achieve, they selected lower speeds than normal. In line with Wernicke's proposal, it was posited that this selection was a result of a reduced 'motor motivation' as a result of a higher sensitivity to the effort required by faster movements in patients with PD.

The argument that some of the symptoms of PD can be attributed to a decrease in motor energy or 'vigor' is of importance in the search to determine the neural basis of paradoxical kinesia. The predicament of this phenomenon, in which arousing stimuli can improve motor performance over and above maximal effort of will, points to the lability of the both the bradykinetic and hypokinetic aspects of the disease. Such a suggestion was similarly put forward by Hallet & Khosbin (1980), on the basis of the observation of the variable number of cycles of bursts of EMG activity for the same required movement in successive trials, which they posited to result from changing amounts of emotional investment in the movement. Thus the implication is that algorithmic aspects of motor control, though scaled down as a result of dopaminergic deficiency and basal ganglia dysfunction in PD, are still normally influenced by motor motivation (Mazzoni et al, 2012) – which itself may be under control of pathways involved in the processing of emotion, incentive motivation, or arousal. Might intense or arousing stimuli thus exert their influence by providing an afferent input to 'energize' motor pathways?

1.4 Paradoxical kinesia: a physiological property of the motor system?

It is arguable that the predicament posed by such 'life-threatening' situations as are often implicated in paradoxical kinesia, is one which necessitates a patient's *maximal* effort of will to remove oneself from harm's way. As such, a parallel may be drawn between paradoxical movement in PD and simple reaction time (RT) tasks in which startling (Valldeoriola et al, 1998) or temporally pressing conditions (Majsak et al, 1998; Ballanger et al, 2006), have been shown to facilitate patients with PD to overcome their self-determined maximal reaction times.

However, it is of interest that even healthy subjects have been shown to have a considerably shortened reaction time in trials accompanied by a loud auditory stimulus, as in the so-called StartReact phenomenon (Valls-Solé et al, 1999; Carlsen et al, 2004; Carlsen et al, 2007). In view of such observations, whether paradoxical kinesia is a hallmark of PD or a physiological property of the motor system requires clarification. Evidence of a physiological process would fall in line

with the proposals of the previous section, implicating intense-stimuli induced modulation of 'normal' influences of arousal on motor processing, to bring about performance enhancement.

1.5 The contentious role of the dopaminergic system in paradoxical kinesia

As a decline in dopamine producing neurons is a key pathophysiological feature of PD (Fearnley & Lees, 1991), the evidence for paradoxical movement both in PD and healthy subjects calls into question the contribution of the dopaminergic system, if any, to the facilitatory effect observed in arousing situations. Here, the prospect of identifying a novel *non-dopaminergic* system for therapeutic manipulation in PD becomes particularly exciting.

Evidence from animal models of paradoxical kinesia certainly seems to favour a non-dopaminergic mechanism for this phenomenon. Indeed, it has been shown that rats rendered akinetic with intraventricular injections of 6-hydroxydopamine and subsequently treated with a combination of D1 and D2 receptor antagonists, were still able to escape from an ice bath and run away when confronted with a room full of cats (Marshall et al, 1976; Keefe et al, 1989).

On the other hand, it has been posited that sufficiently arousing stimuli may still be able to induce release of enough dopamine from endogenous reserves to briefly re-establish function in PD (de la Fuente-Fernández & Stoessl, 2002). Accordingly, it has been shown that dopaminergic neurons of the substantia nigra are able to increase their firing rate and subsequent release of dopamine in the presence of arousing stimuli (Chiodo et al, 1979; Keller et al, 1983; Horvitz et al, 2000). An alternative hypothesis draws on the suggested role of dopamine in reward circuitry (Ikemoto et al, 2007); in threatening situations, incentive motivation pathways involved in removing oneself from danger may play a role in enabling the release of reserved stores of dopamine, thus having a facilitatory effect on movement. In line with such a theory is the demonstration of a substantial increase in endogenous dopamine release in dorsal and ventral striatum in response to placebo, probably owing to an expectation of symptom relief (de la Fuente-Fernández et al, 2001). In summary, however, the role of dopamine in paradoxical kinesia remains enigmatic.

1.6 A role for basal ganglia oscillatory activity in driving motor enhancement?

A number of roles in the control of movement have now been ascribed to the basal ganglia (Turner & Desmurgert, 2010). As previously mentioned, this network of extensively interconnected deep brain nuclei located in the diencephalon and mesencephalon, has been traditionally described to comprise: the striatum (caudate nucleus and putamen), the GPi, GPe, STN, SNpc and substantia nigra pars reticulate (SNpr). More recently, an argument for the

inclusion in this network of a key component of the brainstem - the pedunculopontine nucleus (PPN) - situated caudal to the SN, has also been put forward on the basis of its close anatomical relationships with, and similarity in some aspects of function to, the basal ganglia (Mena-Segovia et al, 2004). These subcortical nuclei have been variously implicated in motor functions ranging from action selection and response inhibition (reviewed in Mink et al, 1996; Redgrave et al, 1999), to the online correction of motor error (Tunik et al, 2009) and motor learning (review in Doyon et al, 2009). Most importantly to this thesis, however, is the suggested role of this network in the scaling of movement (Brücke et al, 2012; Grafton & Tunik, 2011; Thobois et al, 2007; Turner et al, 2003). Might the basal ganglia thus also scale *enhancements* in motor performance, over and above maximal effort of will? Chapters 5 and 6 of this thesis focus on experimental recordings from the STN and PPN to try and answer this question.

1.6.1 The subthalamic nucleus

The STN is a small (120mm^3-175mm^3; Hardman et al, 1997, 2002; Levesque & Parent, 2005), bi-convex, glutamatergic nucleus situated at the diencephalo-mesencephalic junction. It is bounded superiorly and postero-medially by the zona incerta, anteromedially by preleminiscal radiations and postero-lateral hypothalamus, laterally by the cerebral peduncle, and infero-laterally by the superior aspect of the SNpr. The superior tip of the nucleus lies at the level of the posterior commissure, whilst the inferior tip lies with the mid-point of the red nucleus (Naidich et al, 2009; Lambert et al, 2011). Both primate work (Parent and Hazrati, 1995; Joel and Weiner, 1997) and diffusion tensor imaging (DTI) studies in healthy human subjects (Lambert et al, 2011) have provided evidence for the subdivision of the STN into limbic (anterior) and associative (mid), as well as sensorimotor (posterior) segments.

1.6.2 The pedunculopontine tegmental nucleus

The human PPN is bounded laterally by fibres of the medial leminiscus and medially by fibres of the superior cerebellar peduncle and its decussation. The anterior aspect of the PPN contacts the dorsomedial part of the postero-lateral substantia nigra rostrally, whilst dorsally it is bordered by the retrorubal field. The dorsal-most aspect of the PPN is bounded caudally by the pontine cuneiform and subcuneiform nuclei and ventrally by the pontine reticular formation. The most caudal pole of the PPN lies next to neurons of the locus coeruleus (Olszewski & Baxter, 1982; Pahapill et al, 2000).

The PPN is believed to constitute a key component of both the mesencephalic locomotor region (Skinner & Garcia-Rill, 1984), on the basis of its descending connections with the spinal cord (Skinner et al, 1990), and the ascending reticular activating system (RAS). The former function is posited to be sub-served by ascending cholinergic projections of the PPN to the thalamus, which subsequently modulate activation in thalamocortical systems, as indexed by the generation and maintenance of fast cortical rhythms which have been associated with wakefulness and REM sleep (Steriade, 2004). Extensive reciprocal connections between the PPN and basal ganglia have been described. In particular, a mixture of cholinergic, glutamatergic and GABAergic PPN projections to the STN have been demonstrated (Bevan et al, 1995; Hammond et al, 1983), with the PPN receiving excitatory glutamatergic innervations from the STN, in return (Lavoie et al, 1994).

1.6.3 Local field potential recordings

In characterizing the neural basis of paradoxical kinesia I will make use of local field potential (LFP) recordings. LFPs are believed to provide a measure of population neuronal activity in the vicinity of the electrode (Brown & Williams, 2005) with very high temporal resolution. The latter is a feature of tantamount importance when attempting to relate neural activity to short latency and high velocity behavioural parameters such as reaction time and rate of development of force, whilst avoiding the confound of peripheral afference which arises with alternative imaging techniques.

A number of lines of evidence provide support for the basal ganglia LFP as a marker of synchronous neuronal firing in the vicinity of the electrode. First, intraoperative microelectrode recordings, in patients undergoing implantation of deep brain stimulation electrodes, have consistently demonstrated the locking of neuronal spike activity to the LFP, both in the STN (Kühn et al, 2005, Trottenberg et al, 2006) and GPi (Chen et al, 2006). Close correspondence between STN LFP activity and synchronized neuronal activity, following cortical stimulation, has also been shown in single-unit recordings in healthy anaesthetized rats (Magill et al, 2004). The extracellular currents giving rise to the LFP, however, are believed to originate from the superimposition of a number of active cellular processes. Whilst synaptic activity is believed to provide the greatest contribution, Na^+ and Ca^+ spikes, spike after-hyperpolarizations, and intrinsic currents and resonances also play a part in generating the recorded potential (Buzsaki et al, 2012).

It has further been posited that the specific frequencies over which neurons fire play an integral role in the binding of neuronal assemblies (Fries, 2005; Schoffelen et al, 2005). Indeed, oscillatory activity in the STN has been described to originate both from intrinsic pace-maker properties (Nambu & LLinas, 1994; Stanford & Cooper, 1999; Bevan & Wilson, 1999), and interactions with other basal ganglia structures, as demonstrated by the coupling of oscillatory activity in the frequency domain between GPi and STN, and between these structures and the cortex (Brown et al, 2002; Williams et al, 2002). Changes in STN LFP power in particular, have been shown to occur over specific frequency bands in motor processing: theta/alpha (4-12 Hz; Rodriguez-Oroz, 2011), beta (13-30Hz; Kuhn et al, 2004), gamma (>30Hz; Alegre et al, 2005), and more recently very high frequency activity (Ray & Maunsell, 2011) have each been implicated.

The physiological role of low (4-12 Hz) frequency activities has long been related to attentional processes (Palva & Palva, 2007). A role in motor processing, however, has also been implicated. In a recent study by Singh and colleagues (2011), LFP recordings from the subthalamic nucleus of patients with PD and from the GPi of patients with dystonia revealed increases in contralateral alpha activity during fast movements as compared with rest, and during passive or active slow repetitive extension and flexion of the elbow.

Current evidence points towards the 13-30 Hz beta band being essentially anti-kinetic in nature and inversely related to motor processing (Brown & Williams, 2005). A number of studies have now demonstrated that such beta oscillations in the STN and GPi are reduced in PD patients prior to and during self and externally paced voluntary movements (Cassidy et al, 2002; Levy et al, 2002; Priori et al, 2002). Evidence against a pathological basis of such movement-related suppression in the beta band comes from the demonstration of a similar effect in the striatum of healthy monkeys (Courtemanche et al., 2003) and in the healthy human putamen (Sochurkova and Rektor, 2003). Most notably, the work of Kuhn and colleagues (2004) went some way in confirming the antikinetic nature of 13–30 Hz power in the STN. During a choice reaction time task an obvious drop in beta power, after the warning signal, and an even more marked drop following the go signal (but preceding the mean RT) was demonstrated. In addition, a remarkably strong correlation between the latency of onset of go cue-related desynchronisation and mean reaction time was identified. It has further been shown that when a ‘no-go’ signal is substituted for the usual ‘go’ signal, the usual post-imperative cue beta suppression is abbreviated and replaced by a premature increase in LFP power in the same band (Williams et al, 2003).

Increases in induced (non phase-locked) gamma activity have previously been ascribed a pro-kinetic function in the peri-movement period in the STN (Alegre et al, 2005), as well as in other key nodes in motor cortico-subcortical loops, including the thalamus (Kempf et al, 2004) and cerebral cortex (Crone et al,1998; Cheyne et al, 2008; Ball et al, 2008). The work of Kempf and colleagues (2004), in particular, showed sharply tuned activity centred at approximately 70 Hz in spectra of thalamic LFP recordings that was modulated not only by movement, but also aroused states such as rapid eye movement sleep and in response to startle-eliciting stimuli. A pro-kinetic function of very high frequency (>100 Hz) STN LFP power has further been alluded to on the basis of the increase in amplitude of this activity during voluntary movements, and in PD patients in the medicated state (Foffani et al, 2003). More recently, the *scaling* of gamma activity with movement amplitude has been described both at the cortical level (Muthukumaraswamy et al, 2010) and in the GPi (Brücke et al, 2012). Might induced frequency-specific components of basal ganglia oscillatory activities, over a gamma/ high frequency range, thus drive the motor enhancements observed in instances of paradoxical kinesia?

An alternative or complementary contribution of *evoked* activity (phase-locked to the stimulus) in response to arousing stimuli also merits further investigation. Indeed, evoked and induced components have previously been posited to reflect different neuronal processes. In particular, 'bottom-up' driving processes have been ascribed to evoked activities, whilst the functional role of frequency-specific induced responses (described above) has been posited to constitute 'top-down' modulation through backward connections and lateral interactions (Chen et al, 2012). Evoked responses have been suggested to employ mainly linear mechanisms, as has been demonstrated by the linear propagation of signals through cell layers of the cortex (Yamawaki et al, 2008). On the other hand, the underlying generative mechanisms of modulatory connections have been widely described as nonlinear (Chen et al, 2009, 2010; Salin and Bullier, 1995; Sherman and Guillery, 1998).

1.6.4 Deep brain stimulation as an investigative tool

As previously mentioned, neural synchrony in the beta (13-30Hz) band throughout the cortico-basal ganglia-thalamo-cortical network is now widely acknowledged as a likely contributor to the motor symptoms of PD (Kühn et al, 2006, 2009; Weinberger et al, 2006; Ray et al, 2008; Eusebio et al, 2011). According to Brown & Eusebio's (2008) extension of the 'noisy–signal hypothesis', high frequency stimulation represents a noise source that disrupts the pathological bursting behavior of the basal ganglia in PD. However, such a suppression or overriding influence is unlikely to discriminate between pathological and physiological processing in BG-cortical circuits

(Chen et al, 2006; Ray et al, 2009), which likely explains the many side-effects known to arise from this therapeutic approach (Limousin & Martinez-Torres, 2008). As a result, DBS presents itself as a useful investigative tool to interrupt physiological processing in the vicinity of the electrode. Indeed, any resultant behavioral deficits would go some way in supporting a causal relationship between activity in the targeted nucleus and the motor or non-motor parameters of interest.

A number of lines of evidence have now accumulated to suggest that DBS exerts it influence through interference with electrophysiological processing within the target nucleus, *and* its subsequent pathways. However, the mechanism by which this is achieved is still under debate. The similarity between the effects of DBS and those of lesioning of the same nuclei, have led some to argue that DBS may *silence* STN or GPi ouput. Indeed, both in vivo recordings in the parkinsonian primate (Meissner et al, 2005) and in vitro studies in slice preparations from parkinsonian rats have shown a frequency dependent decrease in neuronal activity during and after STN stimulation (Beurrier et al, 2001). Importantly, local decreases in neuronal activity have also been reported during STN and GPi stimulation in PD patients (Dostrovsky et al, 2000; Welter et al, 2004).

An alternative explanation that has been put forward is that DBS does not inhibit STN neurons, but changes their firing profile (Carlson et al, 2010). Indeed, therapeutic DBS has been associated with reduced spiking activity, reduced variability in spiking, and with overriding of disruptive oscillations, cumulatively resulting in changes in the underlying dynamics of the stimulated brain networks (McIntyre & Hahn, 2010). Xu et al (2008) showed that following STN DBS, pallidal neurons had a consistent pattern of response to STN DBS with peaks of increased activity in the post-stimulus time histogram occurring at 3 ms and 6.5 ms, resulting in a regularization of GPe and GPi activity organized by the stimulus timing (Hahn et al, 2008; Dorval et al, 2008).

Both theories of the mechanism of action of DBS have been neatly drawn together by Garcia et al (2003), in a model in which DBS inhibits spontaneous firing in the STN and simultaneously generates a new pattern of activity. Consistent with this, is evidence that DBS does not have the same impact on the neuronal soma and axon, suggesting that STN DBS may uncouple somatic and axonal activity (Holsheimer et al, 2000; McIntyre et al, 2004).

1.7 Thesis objectives

The work outlined in the following chapters aims to address the issues highlighted in the Introduction through a study of maximal hand grips executed in response to intense auditory stimuli delivered on random trials. Specifically, the objectives of the proceeding studies are:

1. To determine whether an intense auditory stimulus delivered in combination with an imperative visual cue can improve peak force and rate of development of force, as well as reproduce previously reported reductions in reaction time in response to intense cuing (Chapter 3).
2. To ascertain whether increasingly intense stimuli can lead to *progressive* enhancements in motor performance, over and above a subject's maximal effort of will (Chapter 6).
3. To establish whether enhancements in peak motor performance are achievable both in healthy subjects and in patients with a relative dopaminergic deficiency (ie. in patients with PD) (Chapter 4).
4. To determine the influence, if any, of dopaminergic medication on this phenomenon (Chapter 4).
5. To describe signatures of basal ganglia activity which may constitute significant determinants of an individual's motor performance at maximal effort of will (Chapter 5).
6. To investigate whether induced frequency-specific oscillatory activities in the basal ganglia may drive motor enhancements, over and above maximal effort of will (Chapter 5).
7. To investigate whether evoked activity in the basal ganglia, and related subcortical nuclei, may drive motor enhancement (Chapter 6).
8. To finally propose the electrophysiological and anatomical substrates which mediate intense-stimulus induced energizing influences on motor performance (Chapter 6).

Chapter 2

Materials & methods

In this chapter the details of techniques and principles common to the investigations described in Chapters 3-6 are outlined. Additional elements, specific to each study, are considered in their respective chapters.

2.1 Subjects

Experiments were conducted with the understanding and written consent of each participant in accordance with the Declaration of Helsinki, and were approved by the local ethics committees at each hospital. The demographic features of study subjects are outlined in the relevant chapters.

2.2 Common protocol

To complete the recordings in one morning, and limit intrusion on our easily fatigable patients with PD (Chapters 4-6), recordings were always made first after overnight withdrawal of anti-parkinsonian medication (OFF L-DOPA), and then again ~1 h after taking their usual morning dose. Improvement with medication was confirmed through assessment of tremor, rigidity and finger tapping using the corresponding items of the motor UPDRS (items 20, 22 & 23 respectively; Fahn & Elton, 1987). In accordance with this scale, tremor in the head, upper and lower extremities was assessed, and the most severe resting tremor was considered one that was marked in amplitude and present most of the time. Rigidity was judged on passive movement of major joints. The most severe rigidity was where the range of motion was achieved with difficulty. An inability to perform the finger-tapping task, in which the patient was asked to tap their thumb with their index finger in rapid succession, was considered a marker of severe bradykinesia/ hypokinesia.

2.2.1 Chapters 3-5

Subjects were presented with a series of imperative visual cues (V), separated by 11-13s, and instructed to squeeze a force dynamometer *"as fast and hard as you possibly can when the light comes on, and maintain this for the duration of the light"* (red light-emitting-diode illuminated for 5 s). In half of these trials, randomly selected, a loud auditory-visual stimulus (AV cue, 0.3 s duration, 1kHz, 96dB) was delivered binaurally through headphones, with onset simultaneous with that of the V cue. Subjects were however asked to just focus on responding to the V cues.

In requesting subjects to grip both as strongly and *quickly* as possible, we aimed to incorporate a RT component to the paradigm which would enable confirmation of the well-documented improvement in this movement parameter with loud auditory stimuli (Valls-Solé et al, 1999; Carlsen et al, 2004; Carlsen et al, 2007; Reynolds & Day, 2007), and thus provide evidence that the auditory stimulus had been strong enough to affect behaviour in each individual.

The choice of sound pressure level and duration was influenced by considerations for safety and tolerability for each subject when repeatedly receiving this stimulus through headphones. Pilot experiments confirmed that this stimulus profile, which fell within the range of sound intensities used in previous studies (Blumenthal et al, 1996; Coombes et al, 2007; Carlsen et al, 2007), provided a sufficiently high intensity to elicit the effects of interest, as effects do not seem to be critically dependent on the presence of an overt startle (Reynolds & Day, 2007) and likely depend on both duration and intensity at the ear.

Trials were approximately equally divided (allowing for the randomization process in each session) into those with V & AV cues and randomly interspersed in blocks. Left and right hand recordings were performed in separate blocks and counterbalanced across subjects. The number of trials collected in each experimental run is outlined in the individual study chapters.

2.2.2 Chapter 6

Subjects were presented with a series of imperative visual (V) cues, separated by 8.0 ± 0.5 s, and instructed to squeeze a force dynamometer “as fast and hard as you possibly can when the light comes on and maintain this for the duration of the light” (red light-emitting-diode illuminated for 3 s). A loud auditory stimulus (40 ms duration, 1 kHz), at one of five different randomly selected intensities (82, 88, 94, 100, 105 dB) was delivered binaurally through headphones, with onset simultaneous with that of the V cue. However, subjects were asked to just focus on responding to the V cues. Fifteen cues of each intensity (75 trials in total) were delivered in each experimental run.

2.3 Recordings

2.3.1 Grip force

Grip force was measured one hand at a time in each subject using an isometric dynamometer (G100, Biometrics Ltd, Cwmfelinfach, Gwent), with standard Jamar design and its handle in the second position. Subjects were seated with their shoulders adducted, their elbows flexed at about

90^0 and their forearms in neutral, as recommended by the American Association of Hand Therapists (Fess, 1992).

2.3.2 Surface electromyography (sEMG): technical aspects

In Chapters 3 & 4, evidence of an overt startle response characterised by short latency sternocleidomastoid (SCM) EMG activity (Brown, 1991), was sought. A number of technical strategies were employed in order to maximise the signal to noise ratio of EMG recordings from ipsilateral sternocleidomastoid. First, in order to reduce transducer noise generated at the electrode-skin junction, the skin was cleaned with alcohol prior to application of conducting jelly (Sigma, Parker Laboratories, New Jersey, USA) to the base of the Ag-AgCl electrodes. EMG was grounded to an electrode attached in the above manner to the wrist. Secondly, a bipolar electrode arrangement was used with a differential amplifier (D360 amplifier, Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK). In this way the potential at one electrode could be subtracted from the other, and the difference amplified. Thus noise common to both sites, whether from power sources, electromagnetic devices or EMG signals from more distant source muscle, would be suppressed. Finally, signals were band-pass filtered at 10-1000 Hz using the D360 amplifier. High pass filtering aimed to remove movement artifact comprised of low frequency components (<10Hz), whereas low pass filtering aimed to remove high frequency components which may have led to signal aliasing at the analogue-digital conversion stage.

2.3.3 STN LFP recordings

2.3.3.1 Surgical procedure

Implantation of bilateral STN DBS electrodes was performed either under local or general anaesthesia in all patients, after overnight withdrawal of their antiparkinsonian medication. The DBS electrodes used were model 3389 (Medtronic Neurological Division, Minneapolis) with four platinum–iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and a centre-to-centre separation of 2 mm. Contact 0 of each electrode was the lowermost, contact 3 being the uppermost. Fast acquisition T2 weighted axial and coronal stereotactic MRI scans were performed using Leksell's Frame (Elekta, Sweden), with contiguous slices of 2 mm thickness, which allowed visualisation of the STN, especially the medial border (Hariz et al, 2003). The centre of the STN, which formed the anatomical target point, was defined as lying at the level of the anterior border of the red nucleus on the axial image showing the largest diameter of the red nucleus (Bejjani et al, 2000). This is the point where contact 1 of each electrode was intended to reach. Calculations of Cartesian co-ordinates of the target point were performed both manually on

enlarged MRI film copies and using Framelink software (Medtronic, Minneapolis). At two of the four surgical centres, intra-operative high frequency test stimulation and clinical evaluation of patients (operated on under local anaesthesia) were carried out during the surgical procedure, in order to help identify the best functional target. Once the optimum anatomical and functional target point for stimulation had been identified, the electrode was advanced 1–2 mm to 'encompass' this optimal target point before it was fixed in position with either the Medtronic burr hole cap or the Navigus system (Image Guided Neurologics, FL, USA). The same procedure was repeated on both STN sides. Finally, implanted electrodes were attached to extension cables that were externalised. Immediate post-operative stereotactic MRI was carried out on all patients, with the Leksell frame still in place on the head, to confirm correct positioning of the DBS electrode (Foltynie and Hariz, 2010). Data collection for Chapters 5 & 6 was carried out prior to connection of the electrodes to a battery-operated programmable pulse generator (Kinetra 7428, Medtronic).

2.3.3.2 LFP Recordings

Recordings were made 3–6 days after surgery. LFPs were recorded bipolarly from adjacent contacts of each deep brain stimulation electrode (0–1, 1–2, 2–3) using either a D360 amplifier (Digitimer Ltd) in combination with a 1401 A/D converter (Cambridge Electronic Design) and sampled onto a computer using Spike 2 software (Cambridge Electronic Design), or TMSi porti (TMS international) and its respective software. All recordings were originally sampled at 2048 Hz.

2.3.4 Analogue-Digital conversion

Analogue correlates of the visual and auditory stimuli and dynamometer output were recorded and digitized in the same way as LFPs. Choice of sampling rate was based on Nyquist theorem, which states that the critical sampling rate must be at least twice the highest frequency to be resolved (Marks, 1991). In this way, aliasing was prevented and a higher resolution of the waveform could be recorded in a digital format.

2.4 Data Analysis

2.4.1 Behavioural data

Analysis was performed in MATLAB. Peak yank (PY; where yank is defined as the rate of change of force, calculated by differentiation of the force signal) and peak force (PF) were the primary variables of interest, and had the advantage that they could be estimated trial by trial without re-alignment to compensate for differences in premotor reaction times (RTs). Two further variables

derived were time to reach PF and time to reach PY, which necessarily required realignment of trials to response onset, in order to maintain an independence of these parameters from variability in premotor RT. In Chapters 3 & 4, response onset was defined as the point at which force exceeded three standard deviations of the baseline over the 0.5 s prior to presentation of the visual cue. A slight variant of this definition has been used in Chapters 5 & 6 (see respective chapters). Premotor RT was further defined as the time interval between cue onset and this point. Grand averages of PF, PY, premotor RT, time to reach PF and time to reach PY in V and AV trials were estimated after deriving each of these variables from the individual grips made by a subject, and calculating averages for that subject, before averaging across subjects. Group mean percentage changes in variables were estimated as the average of the mean percentage changes in each subject.

The method described above provided unbiased estimates of the average peak yank and peak force, independent of the average time to reach peak yank and average time to reach peak force, respectively. However, in order to graphically display the average grip trace for both force and yank, averages across individual grips at each millisecond time point were taken**.** Note that force and yank traces for recordings from individual's hands were first normalized prior to averaging across subjects (normalization techniques used in each study are described in their respective chapters). In this way, any potential skew which may have been introduced by particularly strong individuals or by dominance of hands, when averaging across all subjects, was limited.

2.4.2 EMG data

Evidence of a short latency startle response in sternocleidomastoid (SCM) was identified by comparing maximal rectified SCM activity occurring within the first 100ms in young healthy subjects, and 150 ms in patients with PD and age-matched healthy controls, after onset of the AV cues, with the mean maximal SCM activity occurring within the same time period after V cues. A startle response was considered present if the former index exceeded the latter by over 3 standard deviations. In analysing SCM activity up to these time periods from cue presentation, we aimed to avoid SCM responses related to co-activation once the grip had been initiated (before average premotor reaction time of the respective subject groups).

2.4.3 LFP Data

2.4.3.1 Derivation of evoked and induced LFP power

In Chapters 5 & 6, LFP recordings were first converted off-line to a bipolar montage between adjacent contacts (three bipolar channels per side) to limit the effects of volume conduction from distant sources. The line noise artifacts at 50 Hz and 100 Hz were removed using notch filters (5th order zero-phase Butterworth filters). For analyses in Chapter 6, evoked activity was derived by averaging across trials. Induced LFP power (Chapters 5 & 6) was subsequently calculated by subtraction of the average LFP power across trials from the original local field potential measurement of each trial, to avoid contamination from evoked potentials. A time-frequency decomposition based on the continuous wavelet transform was then applied to each (average-subtracted) trial to analyze changes in induced LFP activity in the time-frequency domain. The wavelet function was convolved with the observed data at each time point across the range of frequencies, allowing the identification of specific frequency components over time. In the present work the Morlet wavelet function was used, where a sinusoidal oscillation ($e^{i\omega t} = \cos(\omega t) + i\sin(\omega t)$) is modulated by a Gaussian bell curve (e^{-t^2}) to give a brief oscillation localized in both time and frequency (Weinberger et al, 2009). The absolute value of the transform was squared to give a continuous time-frequency representation of the power content of the signal. The ensuing power was averaged across trials to estimate induced activity.

2.4.3.2 Derivation of event-related synchrony

Event related LFP power was subsequently derived by normalizing the power at each time point against the average power between two seconds and one second before the cue, so that a value higher than zero indicated power higher than before cue and *vice versa*. The normalized power induced at different frequencies and at different time points was aligned to cue presentation, and averaged across trials of a given type and subsequently across the three bipolar contacts for each STN electrode contralateral to the gripping hand. Averages across all the contact pairs in a given electrode were calculated so as to avoid selection bias.

2.4.3.3.Selection of frequency bands

Frequency-specific STNr LFP activity was subsequently segregated into discrete bands. These were selected separately in Chapters 5 & 6 so as to best capture the features in the group average time-frequency plots, derived for each experimental condition, in the time period between cue onset and time taken to reach PY. The latter was at a shorter latency and more consistent than the time to reach PF. In initial analyses in Chapter 5, LFP power was averaged over this

time period for analyses related to PF or PY, but for correlates of RT, only the time period up to movement onset was analyzed. In a further sub-analysis, however, simple and multiple regression analyses for PY and PF taking LFP power changes from cue onset to response onset were used, in recognition that the latter methodology was more likely to avoid contamination by activities related to peripheral afference. This approach was subsequently retained for analyses related to induced frequency-specific LFP power in Chapter 6. Frequencies near line-artifact and its first harmonic were avoided throughout (higher harmonics were far less prominent, and their effects further attenuated by our normalization).

In the V cue, ON L-DOPA condition in Chapter 5, three frequency bands were identified over which increases or decreases in power could be distinguished from the pre-cue baseline and from frequency bands with an absence of reactivity to cue. These were the theta/alpha (5-12Hz), high beta (25-30Hz), and high gamma/high frequency (55-375Hz) ranges. Inspection of time-frequency spectra derived for the three manipulations of experimental condition, however, identified frequency-specific LFP reactivity across two further bands compared to those defined in the baseline condition (V cue, ON L-DOPA), which lay in the time period between cue onset and time to peak yank. These bands were low beta (13-23Hz) activity, on the basis of the increased synchrony prominent in this band in the OFF L-DOPA state, and low gamma (31-45Hz) in which an increased reactivity relative to baseline was evident in response to AV cues. At this stage of the analysis, we also divided high gamma (55-95Hz) and high frequency (105-375Hz) activity into individual bands, as they have previously been considered separately in the literature (Belluscio et al, 2012). This allowed us to determine whether changes were frequency selective or broad-band over this range (Ray & Maunsell, 2011). In Chapter 6, five frequency bands reactive to the AV stimulus (independent of auditory tone intensity) were discerned: theta/alpha (5-12Hz), low beta (13-19 Hz), intermediate beta (20-25 Hz), high beta (26-33 Hz), and broad gamma (34-375 Hz*).*

2.4.3.4 Data transformation

Frequency-band specific averages of induced STNr LFP power were found to be closely clustered around zero. Thus a transform that created a greater spread in the data was required. To this end, the square root of the absolute average LFP power was taken, whilst preserving the polarity of the data.

2.5 Statistical considerations

Statistical analyses were performed in Microsoft Office Excel 2003, MATLAB and SPSS Statistics 17 (SPSS Inc., Chicago). Means ± standard error of the means (SEM) are specified throughout the text.

Data analysis in the studies presented largely relied on parametric statistical testing. An assumption of parametric statistics is that the data is normally distributed; this requires that the variance must be uniform. Thus, normal distributions are defined as having the mean and standard deviation (SD) independent of one another, and 95% of sample values falling within 2 SDs of the mean. Kolmogorov-Smirnov goodness-of-fit tests were first applied to the sample data to confirm this assumption was met.

2.5.1 Kolmogorov- Smirnov (K-S) tests

The one-sample Kolmogorov-Smirnov test can be used to compare a test sample with a standard normal distribution. This is achieved by attempting to use the test distribution to define the normal distribution, which changes the null distribution of the test statistic.

In Chapters 3 & 4, two-sample K-S tests have been used to determine whether two underlying probability distributions of hand grips, with V and AV cueing, significantly differ from each other. The skewness, which is a measure of the asymmetry of the probability distribution, has been calculated subsequent to the confirmation of a significant two-sample K-S test.

2.5.2 Student's t-tests

The student's t-test is used for comparing the means of two samples. Paired t-tests were used to compare the mean motor parameters of the same study subjects under different conditions, thus offsetting variability in kinematic profiles between individuals. Two-tailed t-tests were performed as the direction of the difference was not known. The null hypothesis (that there is no difference between conditions) was rejected if the P-value was <0.05.

2.5.3 Analysis of variance (ANOVAs)

ANOVAs determine whether the variance of group means is greater than would be expected by chance alone. The assumptions of the test are that the sample is drawn from a normally-distributed population, there is homogeneity of variance, and for within-subjects designs there is sphericity of data (see below).

The test statistic that is generated by performance of an ANOVA is denoted by **F**, which represents the ratio of between and within group differences. The null hypothesis estimates such a ratio as being equal to 1, thus the greater the value of F the greater the evidence that the two group means differ. Statistical significance of the F value can be derived taking into consideration the degrees of freedom for the sample.

In Chapter 4, when comparing the effect of stimulus and drug state/experimental run *within* the patient group, a straight-forward repeated measures ANOVA was applied. This was similarly the case in Chapters 5 & 6. However when comparing across PD and Control groups in Chapter 4, a *mixed* design repeated measures ANOVA was used, in which PD and Control were defined as independent groups, and subjected to repeated measures. STIMULUS (V & AV) formed the within-subjects variable, whereas GROUP (PD & Control) formed the between-subjects variable.

Sphericity (homogeneity of variance of differences) was determined using Mauchly's test (performed in SPSS). If the data were found not to be spherical, based on a positive Mauchly's test, the Greenhouse-Geisser correction factor was applied.

2.5.4 The problem of multiple testing and the Bonferroni correction

As multiple post-hoc testing was undertaken to elucidate significant differences highlighted by ANOVAs, a correction factor had to be applied to the significance level, in order to minimise the likelihood of Type I error (the error of rejecting a null hypothesis when it is actually true). The Bonferroni correction is a multiple-comparison correction which can be used when several statistical tests are being performed simultaneously. Here, the alpha value (P-value below which the null hypothesis is rejected, taken as P=0.05, throughout this thesis) is lowered to account for the number of comparisons being performed, by straightforward division by the number of statistical comparisons made. In Chapter 4, those ANOVA results that have been emboldened in the tables are those that remained significant when force and temporal parameters were

separately corrected for multiple comparisons using the Bonferroni correction (Curran-Everett, 2000).

2.5.5 Pearson's correlation coefficient (r)

Pearson's correlation coefficient is a parametric test which was used as the measure to test the strength of the association between changes in the different parameters of movement recorded with V & AV stimuli. It was also used in Chapters 5 & 6 to test the strength of associations between percentage increments/decrements in motor parameters and frequency specific LFP power.

2.5.6 Multiple regression and multi-level multivariate regression modelling techniques

Multiple regression analysis enables an estimation of the contribution of a predictor variable to the response variable, after controlling for the influence of all other predictors (Brace, Kemp & Snelgar, 2002). In Chapter 5, the predictor variables constituted mean STNr LFP power in the different frequency ranges whilst the response variable was one of the three performance measures of interest. Between subject multiple regression was performed for our baseline task, grips made in response to V cues with the patient ON medication.

Multi-level multivariate regression modelling, on the other hand, was used to identify the unique contribution, if any, of the average LFP activity in several frequency bands to the *change* in motor performance from our baseline condition. The approach was advantageous in that it enabled the estimation of group effects simultaneously with the effect of group-level predictors, so that the contributions of experimental condition (cue type, V or AV, and drug state, OFF or ON medication) could be considered simultaneously with any predictive effects of LFP activities in different frequency bands recorded within that condition. This afforded experimental condition specific regression equations linking significant predictor variables (average LFP power across defined frequency bands) and % increments/decrements in measures of motor performance.

As mentioned above, we aimed to model percentage change in data relative to the baseline condition. To this end, all frequency-specific LFP averages and behavioral data, related to individual grips, were normalized as a percentage of the respective average response to V cues in the ON medication state. In this way, our analysis modelled *within*-subject effects of experimental condition and focused on induced LFP power-behavior relationships, over and above those found to be contributing to between-subject variance in performance measures attained in the baseline condition.

The statistical software – R (R Development Core Team, version 2.13.2) – was used for modeling (Bliese, 2009). The approach began with definition of all explanatory variables (cue, medication and transformed power in candidate LFP frequency bands) as independent fixed effects. In doing so, we assumed that the gradient between the explanatory variables and the dependent variable was fixed across subjects and intercepts were allowed to vary randomly across subjects. If a given explanatory variable did not have a significant independent effect, then its two-way and three-way interactions with cue and medication were included in the model. If neither a significant independent effect nor interaction with cue or medication was determined for the explanatory variable, then this variable was removed from the model. This process was iterated for the remaining variables. Eventually, therefore, the model only included variables that had either significant independent effects, and/or interactions with cue or medication. Maximum likelihood estimation, using the 'lme' function in R, was used to derive estimates of the mean and standard error of the model parameters. These were then used in significance testing by computing the test statistic t-value: t = mean/SEM, and corresponding P-value from the student's t-distribution. In this way, separate models for each peak motor parameter of interest, were fitted (see **Figure 2.1**).

$$y = \Sigma_{i=1}^{k} (\beta_i + \beta_{cue_i} * \text{cue} + \beta_{med_i} * \text{med}) * x_i + \mu_1 * \text{cue} + \mu_2 * \text{med}$$

If V cue, cue = 0 OFF L-DOPA, med = 0

AV cue, cue = 1 ON L-DOPA, med = 1

Figure 2.1 General multi-level multivariate regression model for peak motor parameters.

Here, y represents % increments or decrements in the peak motor parameters of interest, relative to maximal effort grips executed in response to V cues when patients were ON L-DOPA. β is the regression coefficient linking activity in a given frequency band *x* (*i* to *k* bands) to *y*. Interactions between cue type or medication with frequency specific LFPs contributed to the overall β coefficient, as indicated by separate β_{cue_i} and β_{med_i} components. The model was also extended to test three-way interactions. In addition, an experimental condition dependent intercept shift (μ) comprises response variable increments independent of frequency specific oscillatory activity, as a result of cue type (AV cue) and medication (OFF L-DOPA). As the response to V cue when patients were ON L-DOPA was set as the baseline, an intercept of zero, equated to ~100% of the response achieved in the latter condition.

Chapter 3

Loud auditory stimulation yields improvements in maximal voluntary force in healthy subjects

3.1 Introduction

The innate capacity of humans to strengthen and expedite response execution in aversive or highly arousing situations has undoubtedly offered an evolutionary advantage since times immemorial. In a contemporary context, such a phenomenon is frequently translated to championship games, where emotional arousal evoked by the large audiences could conceivably contribute to the boosting effect, which allows sportsmen to routinely exceed their personal best performance, to effectively perform 'better than their best'. Decoding the nature of the facilitating stimuli, and aiming to harness the power of the neural circuitry related to such behavioural energisation, could have useful applications not only to professionals required to regulate arousal status such as surgeons and military personnel, but have important therapeutic implications for those suffering motor impairment (e.g. Parkinson's disease and stroke).

A common experimental paradigm used to explore performance optimisation is to ask subjects to react as quickly or contract as forcefully as possible. The subject is instructed to do their best, and yet performance can be improved through manipulation of cues. One of the most remarkable of such effects is the striking reduction in reaction time when an imperative cue is accompanied by a loud auditory stimulus, as in the so-called StartReact phenomenon (Valls-Solé et al, 1999; Carlsen et al. 2004, 2007). Healthy subjects have a considerably shortened reaction time in trials accompanied by a loud auditory stimulus, despite their willed intention to move as fast as possible irrespective of any noise.

Could loud sounds also have a beneficial effect on force when subjects are asked to grip as strongly as possible? Auditory stimuli can augment response force when these are submaximal (Miller et al, 1999; Jaśkowski et al, 1995; Coombes et al, 2007). Although augmentation of reaction time and response force need not go hand-in-hand and may relate to different processes (Stahl and Rammsayer, 2005), a recent report has described improvement in both the reaction time and amplitude of corrective movements made during gait when the appearance of obstacles is accompanied by a loud sound (Queralt et al, 2008). These observations of the effects of loud sounds on submaximal contractions prompted us to see whether loud auditory stimuli can improve response force over and above that possible through maximum effort of will.

3.2 Materials and methods

3.2.1 Subjects

Eighteen healthy subjects (mean age 26, range 20–36 years, 9 males) were recruited to the study. Experiments were conducted with the understanding and the written consent of each participant and were approved by the local ethics committee. Grip force was measured one hand at a time in the eighteen subjects (n = 36 hands) using an isometric dynamometer (G100, Biometrics Ltd, Cwmfelinfach, Gwent), with standard Jamar design and its handle in the second position. Subjects were seated with their shoulders adducted, their elbows flexed at about 90˚ and their forearms in neutral, as recommended by the American Association of Hand Therapists (Fess, 1992).

3.2.1 Experimental paradigm

At the outset of each experiment, subjects were instructed to "squeeze the force dynamometer as hard as you possibly can" to produce three of their 'very best' maximal contractions per hand in response to illumination of a red light emitting diode, and maintain the grip for the duration of each cue (5 s). These three visually triggered grips (without simultaneous auditory stimulation) were always elicited prior to the main experiment, in order to minimise any fatigue effects, and were separated by relatively long intervals (minimum of 40 s). By averaging these initial grips, an estimate of each individual's conventional maximal voluntary contraction (CMVC) could be derived (Langerström and Nordgren, 1998; Bohannon et al, 2006).

Next, subjects were presented with the same imperative visual cue (V) as before, in all trials, and again instructed to "squeeze as fast and hard as you possibly can and maintain this for the duration of the visual cue." In half of these trials, randomly selected, a loud auditory stimulus (0.3 s duration, 1 kHz, 96 dB) was delivered binaurally through headphones, with onset simultaneous with the V cue. Subjects were, however, reminded to just focus on responding to V cues. Successive visual cues were separated by 11–13 s. Forty trials were collected in total, which were approximately equally divided (allowing for the randomization process in each session) into those with visual cues alone (V) and those in which visual cues were combined with auditory stimulation (Auditory-Visual, AV). Trials were carried out in a blocked design, and left and right hand recordings were counterbalanced across subjects.

3.2.2 Recordings and analysis

EMG was recorded from the sternocleidomastoid ipsilateral to the tested hand and amplified and band-pass filtered (10–1,000 Hz) using a D360 amplifier (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK). Analogue correlates of the visual and auditory stimuli, EMG and dynamometer output were then digitised through a 1401 A-D converter (Cambridge Electronic Design, Cambridge, UK) and sampled at a rate of 2,048 Hz onto a computer using Spike 2 version 5 software (Cambridge Electronic Design).

Analysis was performed in MATLAB. V and AV trials were represented as a percentage CMVC, thus eliminating any potential skew which may have been introduced by particularly strong individuals when averaging across subjects. The term CMVC acknowledges that within a given trial MVC may not be reached due to variations in factors like arousal or fatigue, even though this is the subject's intention. Indeed, the large number of trials that were averaged in our study meant that although subjects were making grips as quickly and as forcefully as they could manage, their average force was less than CMVC. Here, we will use the term functional maximal voluntary contraction (FMVC) to describe grip performance in subsequent trials and to clearly distinguish it from CMVC.

Peak force and peak yank (where yank is defined as the rate of change of force, calculated by differentiation of the force signal) were the primary variables of interest, and had the advantage that they could be estimated trial by trial without re-alignment to compensate for differences in premotor reaction times. Two further variables derived were time to reach peak force and time to reach peak yank, which necessarily required re-alignment of trials to response onset, in order to maintain an independence of these parameters from variability in premotor reaction time. Response onset was defined as the point at which force exceeded three standard deviations of the baseline over the 0.5 s prior to presentation of the visual cue. Premotor reaction time was further defined as the time interval between cue onset and this point. Grand averages of peak force, peak yank, premotor reaction time, time to reach peak force and time to reach peak yank in V and AV trials were estimated after deriving each of these variables from the individual grips made by a subject, and calculating averages for that subject, before averaging across subjects. Group mean percent changes in variables were estimated as the average of the mean percent changes in each subject.

In contrast, in graphically presenting our data, we plotted the average profile of grip traces for both force and yank, by averaging across individual grips at each time point. As mentioned

earlier, average values presented in the text were derived by a different method than that used to construct the illustrated average grip traces. This provided estimates of the average peak forces and peak yanks that were independent of the average time to peak force and average time to peak yank.

Evidence of an overt startle response characterised by short-latency sternocleidomastoid (SCM) activity (Brown et al, 1991) was also sought. We identified such activity by comparing maximal rectified SCM activity occurring within the first 100 ms after onset of the AV cues, with the mean maximal SCM activity occurring within the first 100 ms after V cues. A startle response was considered present if the former index exceeded the latter by over 3 standard deviations. In analysing SCM activity up to only 100 ms from cue presentation, we aimed to avoid SCM activity related to a co-activation effect once the grip had been initiated. However, in using this narrow time-window (0–100 ms) we may have derived relatively conservative estimates of the number of trials in which startle activity was elicited.

3.2.3 Statistics

Kolmogorov–Smirnov tests confirmed that data were normally distributed. Variability in kinematic profile between individuals was offset by always performing paired comparisons of trial types within subjects. Means ± standard error of the means are specified. ($P < 0.05$; Microsoft Office Excel 2003, MATLAB & SPSS Inc., Chicago).

3.3 Results

3.3.1 Force parameters in healthy subjects

Mean peak force was increased by 7.2 ± 1.4 % in AV (19.3 ± 1.2 kg) compared to V trials (18.2 ± 1.1 kg, two tailed paired t-test, P<0.0001). Peak force as a % of each individual's CMVC also showed a significant improvement in AV (66.6 ± 2.2 %) as compared to V trials (62.4 ± 2.1 %, P<0.0001; **Figure 3.1**). A significant improvement in mean peak yank of 17.6 ± 2.0 % in AV (143.0 ± 13.0 kg/s) compared to V trials (122.3 ± 11.1 kg/s, P<<0.00001) was also observed. Similarly, peak yank expressed as a % of that in CMVC showed a significant improvement in AV (71.1 ± 4.1 %) as compared to V trials (61.2 ± 3.8 %, P<<0.00001; **Figure 3.2**).

In order to further investigate the manner by which V and AV trials differed for the above-mentioned variables, the distributions of CMVC normalized peak forces and peak yanks elicited in each subject were plotted (**Figure 3.3)**. Two-sample Kolmogorov-Smirnov tests identified significant differences (P<0.00001) between the V and AV distributions for both peak force and

peak yank. Inspection of the frequency histograms in **Figure 3.3** confirms that the range of values of V and AV trials are similar, but that the distribution of AV trials is more positively skewed. Accordingly, the peak force distribution skew increased from 0.217 for V trials to 0.419 for AV trials and the peak yank distribution skew increased from 0.889 for V trials to 1.269 for AV trials.

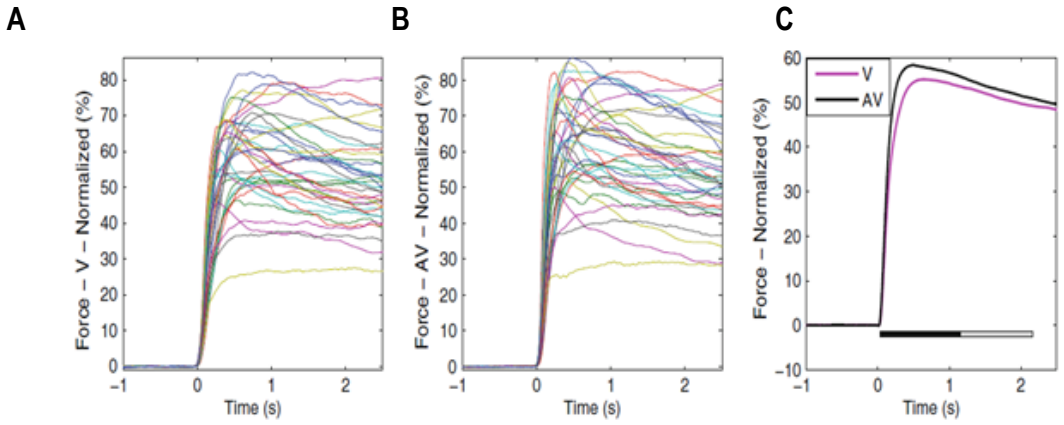


Figure 3.1 Grip forces averaged after re-alignment to response onset in young healthy subjects. (A) Each subject's normalized mean force from visual cue only (V) trials, in left and right hands. **(B)** Each subject's normalized mean force from trials in which a loud auditory stimulus was delivered as the visual cue came on (AV). Each subject is colour coded with the same colour in A and B. **(C)** Group average of V and AV trials across 18 healthy subjects (n=36 hands). The black and grey bar combined indicate those timings over which the two traces were different at the 5% significance level. The black bar on its own denotes those timings over which the two traces were different at the 1% significance level.

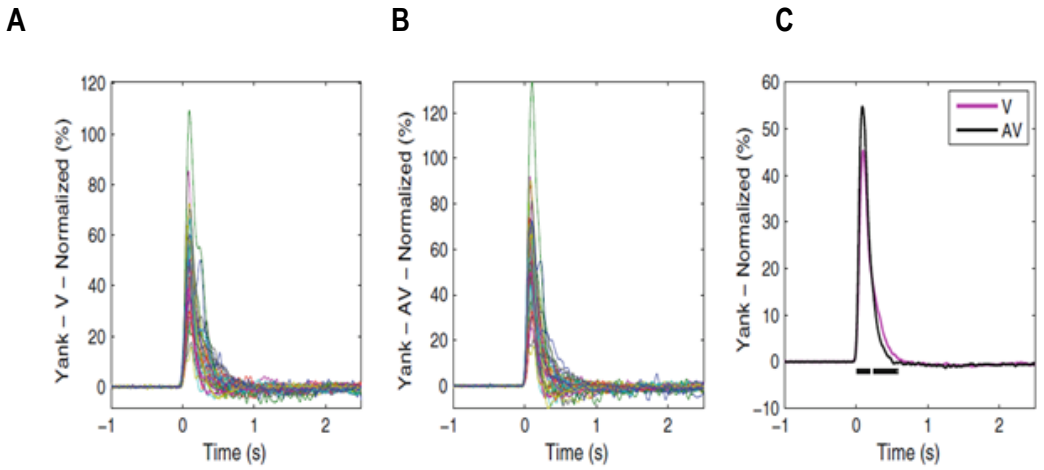
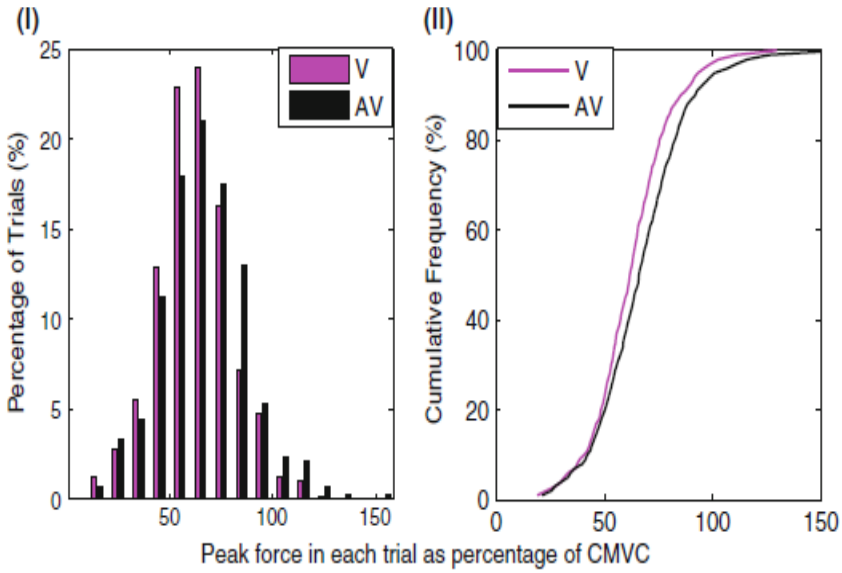


Figure 3. 2 Yank (rate of force development) averaged after re-alignment to response onset in young healthy subjects. (A) Each subject's normalized mean yank from visual cue only (V) trials, in left and right hands. **(B)** Each subject's normalized mean yank from trials in which a loud auditory stimulus was delivered as the visual cue came on (AV). Each subject is colour coded with the same colour in **A** and **B**. **(C)** Group average of V and AV trials across 18 subjects (*n* = 36 hands). The horizontal bars denote those timings over which the two traces were different as in **Figure 3.1**.

A



B

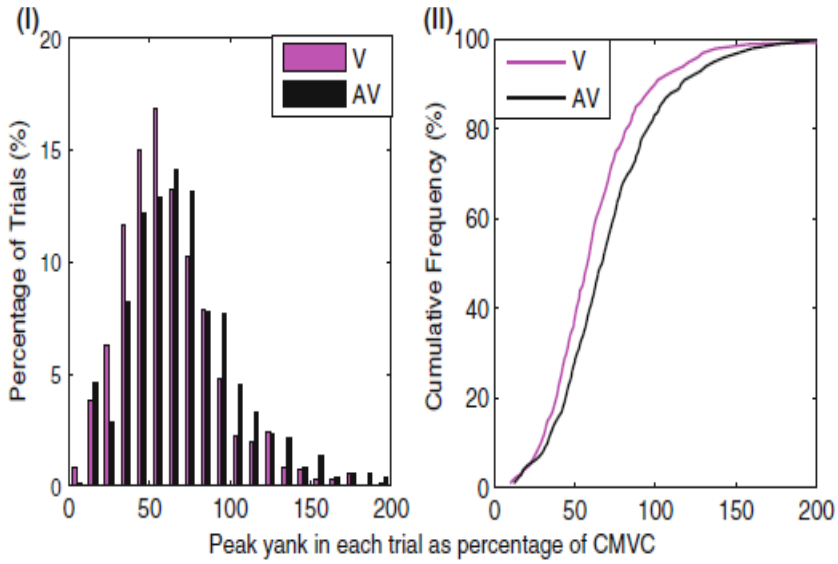


Figure 3.3 Peak force and yank distributions in young healthy subjects. (A) i) Histogram and ii) cumulative frequency plot, to show distributions of peak forces generated in each V and AV trial across 18 subjects, represented as a % of each hand's CMVC. **(B)** i) Histogram and ii) cumulative frequency plot to show distributions of peak yanks generated in each V and AV trial across 18 subjects (n=36 hands), represented as a % of that in each hand's CMVC. AV trials have similar ranges of peak force and peak yank as V trials, but their distributions in the histograms are more skewed to the right, suggesting that loud auditory stimuli enable more of the trials with greater peak force and peak yank to be achieved.

3.3.2 Temporal parameters in healthy Subjects

In line with the improved peak yank in AV trials, the time to reach peak force was 10.0 ± 3.6 % shorter in AV (770 ± 67 ms) as compared to V trials (850 ± 67 ms, *P*=0.0059). The mean time to reach peak yank also decreased by 8.9 ± 2.9 % in AV (53 ± 3.4 ms) compared to V trials (60 ± 3.8 ms, *P*=0.0028). As expected, mean premotor reaction time was reduced by 28.7 ± 1.3 % in AV (220 ± 7 ms) compared to V trials (310 ± 8 ms, *P*<<0.00001). There was however no significant correlation between improvement in premotor reaction time and % change in any of the other variables investigated.

3.3.3 Duration of effect

The above findings pertain to the initiation phase of the grip (Household et al. 2004). However our results suggest that AV cues also had a significant effect on the grip profile that extended to the maintenance phase, with peak force remaining significantly (*P*<0.05) greater in AV compared to V trials up to 2.1 s into the grip **(Figure 3.1)**. Yet the boosting effect of the loud auditory stimulus did not persist in to subsequent trials, as paired t-tests between average normalized peak forces elicited in V trials preceded by V trials (61.8 % ± 2.1 %), and those V trials preceded by AV trials (63.0 % ± 2.1 %), across subjects, did not show a significant difference (*P* =0.083).

3.3.4 Fatigue

Fatigue was clearly evident in the peak forces elicited as the experiment progressed. We were interested to see whether the loud auditory stimulation in AV trials could off-set such an effect. Accordingly we estimated the % change in peak force in the average of the first three AV as compared to the first three V trials and that in the last three AV as compared to the last three V trials. These % changes were averaged across subjects. There was a trend for the AV-V differential in peak force to fall from the beginning (14.1% ± 2.5 %) to the end of trial runs (7.0% ± 2.3 %; *P*=0.054, paired t-test). Likewise, there was a significant fall in the AV-V differential in peak yank from the beginning (29.2% ± 3.6 %) to the end of trial runs (10.3% ± 4.0 %; *P*=0.010). Together, these data suggest, if anything, a negative impact of fatigue on AV induced improvements in response force.

3.3.5 Startle

Startle activity occurred in SCM at least once in 10 out of the 36 experimental runs (recordings from left and right hands in 18 subjects). Trials in which startle activity was seen were not significantly stronger (P=0.169, paired t-test) or faster (P=0.486), nor was the rate of development of force greater (P=0.297) than the average of AV trials in which startle was not evident, within the same experimental run. However this result should be treated with caution, given that in those experimental runs in which startle activity was observed, it occurred only in response to an average of 2.1 of the ~20 AV cues delivered each run.

3.4 Discussion

The principal finding in this study was that peak force was stronger and rate of force development greater in FMVC when preceded by a loud auditory stimulus. Premotor reaction time, time to reach peak force and time to reach peak yank were also significantly improved with the loud auditory stimulation delivered in AV trials.

The nature of our AV stimulus was such that effects may have been engendered by any one of a number of well described physiological phenomena: intersensory facilitation (Woodworth 1938, Dufft and Ulrich, 1999; Miller et al, 1999), intensity effects (Angel 1973; Jaśkowski et al,1995), and the StartReact phenomenon (Valls-Solé et al,. 1999; Carlsen et al, 2004). However, the relative scarcity across trials and subjects of short latency responses in SCM, which are considered to be the most sensitive hallmarks of the generalised startle response (Brown et al, 1991), certainly argues against the latter phenomenon having a key role. Indeed, even those AV trials without short-latency startles had elevated peak forces and peak yanks, as well as shortened premotor reaction times. In line with our results, it has recently been suggested that even shortening of reaction time is not contingent on an overt startle response (Reynolds & Day, 2007). Thus our findings firstly make it unlikely that increased force was the result of summation of the voluntary response with a reflex startle response. Although loud sounds can cause subliminal excitation at the spinal cord, as evidenced by the audiospinal reflex, it is also unlikely that increased force was the result of summation of the voluntary response with the audiospinal reflex (Liegeois-Chauvel et al, 1989), as the latter lasts no more than about 200 ms and yet force was increased for up to 2100 ms in our paradigm. Secondly, the absence of a correlation between improvement in premotor reaction time and the % change in peak force or peak yank with loud sound, further corroborates the view that these effects may be underscored by relatively different processes altogether (Stahl and Rammsayer 2005).

Ultimately, however, some or all of the effects attributed to intersensory facilitation, stimulus intensity and startle may relate to increased arousal. Arousal has been proposed as the underlying mechanism for force increases in other 'redundant-signal' tasks whereby auditory and visual cues are presented independently or alone (Dufft and Ulrich 1999; Giray and Ulrich 1993; Mordkoff et al, 1996). These latter studies build on the hypothesis that a cue not only instigates specific processing related to stimulus analysis and response execution, but also "immediate arousal" (Sanders, 1983) or "automatic alertness" (Posner et al, 1976). Arousal (or alertness) could then, in turn, exert its influence by improving activation of motor areas (Baumgartner et al, 2007; Jepma et al, 2009) and hence amplify the effects of the specific processing stream (Miller et al,. 1999; Stahl and Rammsayer 2005). This could conceivably result in a more consistent optimum performance. Emotional stimuli may also increase arousal and thereby optimise motor performance (Baumgartner et al, 2007; Coombes et al, 2009; Schmidt et al, 2009).

Indeed, analysis of the distributions of the peak forces and peak yanks generated in V and AV trials by the 18 subjects, suggested that the increased average peak force in AV compared to V cued grips was not due to a systematic shift of the distribution to stronger grips, but rather an increase in the proportion of stronger grips selected from a similar range of movement capabilities present with V and AV cueing. The term 'motor vigor' has been used to describe just such a likelihood of selecting faster *speeds* to move at from a distribution of speed capabilities (Mazzoni et al, 2007). Framed in this way the arousing nature of the loud stimulus might improve motor vigor, over and above any considerations of force or speed-energetic cost trade-offs (Mazzoni et al, 2007), thus bringing about a more consistent 'best' performance. This optimisation did not seem to simply involve an attenuation of the effects of fatigue across trials (see Results). The influence of auditory stimuli of differing intensity was not tested, but this would be of interest for future experimentation.

In conclusion, our core finding is that force development can be accelerated and force increased by a loud auditory stimulus over and above that achieved during FMVC. The implication is that the auditory stimulus allows additional motor pathways to be accessed or existing motor pathways to be more effectively and consistently activated than through voluntary will alone. Together with literature on paradoxical kinesis in Parkinson's disease (see Chapter 1), the above observations raise the interesting possibility that there may be brain circuits that are ordinarily difficult to fully engage through effort of will, but which can be relatively preserved in disease, so that indirect activation of these circuits by sound, or potentially through direct stimulation, might over-ride parkinsonian and other deficits.

Chapter 4

Improvements in rate of development and magnitude of force with intense auditory stimuli in patients with Parkinson's disease

4.1 Introduction

It has long been known that intense stimuli can shorten the reaction time and increase the rate of development and magnitude of response force in healthy subjects (Woodworth, 1938; Angel, 1973). Indeed, this effect can be so marked that it leads to shorter reaction times and faster and stronger responses than can be achieved through maximal effort of will alone (Chapter 3). Interest in this phenomenon is heightened by the existence of a similar effect, traditionally called paradoxical kinesis (Souques, 1921), in patients with Parkinson's disease (PD). This disease is dominated by dopaminergic denervation of the basal ganglia and, as a consequence, patients make slow and small voluntary movements. Paradoxical kinesis describes the remarkable normalisation of motor activity in PD patients that may follow intense stimuli as diverse as the sound of a car accident (Daroff, 2008), the sensation of an earthquake (Bonanni et al, 2010a) or the sight of a fire or bolting horse (Glickstein & Stein, 1991). The phenomenon suggests the existence of neural systems that can override parkinsonian impairment, systems that, if identified and manipulated, might yield novel and more effective therapies for motor impairment in PD.

So could reports of paradoxical kinesis in fact be florid examples of an essentially physiological process, precipitated by intense stimulation, which remains preserved in PD? There is already evidence to suggest that this is at least partly true in that startling stimuli are able to elicit reactions in PD that have a dramatically shortened reaction time (RT), just as in healthy subjects (Valldeoriola et al,1998). Here we test whether, under similar conditions, patients with PD also retain the ability to make responses with increased magnitude and rate of development of force, over and above that possible through maximal effort of will alone. Two former studies have demonstrated that PD patients are able to overcome their self-determined maximal speeds under temporally pressing conditions (Majsak et al, 1998; Ballanger et al, 2006), but the results of these are ambiguous as the response benefit might have arisen through anticipatory increases in attention and visuomotor processing speeds. Here we use a simpler paradigm that obviates anticipatory effects (Chapter 3) and, moreover, we address the novel and important question of the effect of dopaminergic state on any improvements in the magnitude and rate of development of force following intense auditory stimuli. Paradoxical kinesia has previously been attributed to

behavioural energization through the release of 'dopamine reserves' by intense stimuli (de la Fuente-Fernández & Stoessl, 2002), but any independence of the phenomenon from dopaminergic state would heighten the relevance of the underlying neural systems as a potential novel target for therapeutic manipulation in PD.

4.2 Materials & methods

4.2.1 Subjects

Nine patients with PD (mean disease duration 11 years, mean age 61 years, range 51–75 years; eight males) and nine age-matched healthy controls (mean age 63 years, range 49–73 years; seven males), were recruited to the study. Clinical details of the patients are available in **Table 4.1**.The mean percentage improvement in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) on treatment with levodopa (L-DOPA) was 42.7 ± 2.9% ($P < 0.0001$). Note that whilst the motor UPDRS scores of Patient 8 suggest only a modest amelioration whilst taking (ON) L-DOPA, the patient exhibited significant improvements in peak force, peak rate of development of force and respective times to reach these two parameters ON as opposed to whilst not taking (OFF) drugs (two-tailed Student's *t*-tests between OFF and ON drug recordings in visual (V) and combined audiovisual (AV) cue conditions independently; $P < 0.05$). Accordingly, and so as not to introduce retrospective selection of cases, the patient's results are included in the study. Experiments were conducted with the understanding and written consent of each participant in accordance with the Declaration of Helsinki, and were approved by the local ethics committee.

4.2.2 Experimental paradigm

Grip force was measured one hand at a time in each subject using an isometric dynamometer (G100; Biometrics Ltd, Cwmfelinfach, Gwent, UK), with standard Jamar design and its handle in the second position. Subjects were seated with their shoulders adducted (so that elbows rested against the trunk), their elbows flexed at ~90° and their forearms in neutral, as recommended by the American Association of Hand Therapists (Fess, 1992).

Table 4.1 Clinical details of patients with PD. UPDRS= Unified Parkinson's Disease Rating Scale.

Patient Number	Age/yrs	Disease duration/yrs	Morning medication	Daily L-DOPA equivalent dose/mg	UPDRS part III OFF/ON
1	75	12	100 mg L-DOPA	300	30/ 20
2	60	12	100 mg L-DOPA 1 mg Rasagiline 200 mg Entacopone 8 mg Ropinirole XL	600	23/ 11
3	67	17	200 mg L-DOPA 0.7 mg Pramipexol 10 mg Selegeline	800	19/ 11
4	71	7	100 mg L-DOPA	400	21/12
5	57	4	100 mg L-DOPA	300	24/13
6	61	17	100 mg L-DOPA 5 mg Bromocriptine	300	12/ 6
7	51	10	100 mg L-DOPA 200 mg Entacapone 10 mg Selegeline 100 mg Amantadine	300	15/ 8
8	70	8	200 mg L-DOPA 0.7 mg Pramipexol	400	24/ 18
9	52	12	200 mg L-DOPA 100 mg Amantadine	800	15/ 8

Subjects were presented with a series of imperative visual cues (V), separated by 11–13 s, and instructed to 'squeeze as fast and hard as you possibly can when the light comes on and maintain this for the duration of the light' (red light-emitting-diode illuminated for 5 s). In half of these trials, randomly selected, a loud auditory stimulus (0.3 s duration, 1 kHz, 96 dB) was delivered binaurally through headphones, with onset simultaneous with that of the V cue, to give the AV cue. Stimulus intensity was measured with a Brüel and Kjaer 2260 Observer (Brüel and Kjaer, Nærum, Denmark). Subjects were, however, asked to just focus on responding to the V cues. In requesting subjects to grip both as strongly and quickly as possible, we aimed to incorporate an RT component to the paradigm. The intention here was to provide confirmation of the loudness of the auditory stimulus, as it is well-documented that such stimuli lead to a significant shortening of RT (Valls-Solé et al*,* 1999; Carlsen et al*,* 2004, 2009; Reynolds & Day, 2007; Chapter 3).

The choice of sound pressure level and duration was influenced by considerations of safety and tolerability for each subject when receiving this stimulus through headphones ~40 times (when summating recordings across experimental runs in both hands and in the OFF and ON medication states). Note that loudness is a subjective measure and should not be confused with sound pressure level or intensity as the human auditory system integrates the effects of sound pressure level (SPL) over any window shorter than 600–1000 ms. Hence, although our SPL was somewhat less than that used in most startle studies, the duration of our stimulus was longer.

Twenty trials were collected in each experimental run. Trials were approximately equally divided (allowing for the randomization process in each session) into those with V and AV cues. Both the number of trials executed and the inter-trial interval were decided upon given the necessity to collect a sufficient number of trials whilst keeping the experiment tolerable for our patients with PD when OFF medication. Inter-trial intervals were similar to those previously used in investigations of the StartReact phenomenon (Valls-Solé et al, 2005; Carlsen et al, 2009). Trials were carried out in a blocked design, and left- and right-hand recordings were counterbalanced across subjects. Patients with PD were always recorded OFF medication first, then again ~1 h after taking their usual morning dose of antiparkinsonian medication (average L-DOPA equivalent dose administered, 133 mg; range, 100–200 mg). Improvement with medication was confirmed through assessment of finger tapping, wrist rigidity and tremor (using the corresponding items of the motor UPDRS). Healthy controls were also asked to undertake two experimental runs, with a 45- to 60-min break in between, in order to match any practice, habituation or fatigue effects in the patients.

4.2.3 Recordings and analysis

EMG was recorded from sternocleidomastoid (SCM), and amplified and bandpass-filtered (10–1000 Hz) using a D360 amplifier (Digitimer Ltd, Welwyn Garden City, Hertfordshire, UK). Analogue correlates of the visual and auditory stimuli, EMG and dynamometer output were then digitized through a 1401 A-D converter (Cambridge Electronic Design, Cambridge, UK) and sampled at a rate of 2048 Hz onto a computer using Spike 2 version 5 software (Cambridge Electronic Design).

Analysis was performed in Matlab. Peak yank (where yank is defined as the rate of change of force, calculated by differentiation of the force signal) and peak force were the primary variables of interest, and had the advantage that they could be measured trial by trial without realignment to compensate for differences in premotor reaction times. Two further variables derived were time to reach peak force and time to reach peak yank, which necessarily required realignment of trials to response onset in order to maintain an independence of these parameters from variability in premotor reaction time. Response onset was defined as the point at which force exceeded 3 SD of the baseline over the 0.5 s prior to presentation of the visual cue. Premotor reaction time was further operationally defined as the time interval between cue onset and this point. Premotor reaction time is more usually considered to be the interval between cue presentation and EMG onset (Botwinick & Thompson, 1966). However, we found the use of EMG to be suboptimal in the context of maximal grips because of movement artifact and sampling error, given that many muscles are activated in this task. Grand averages of peak force, peak yank, premotor reaction time, time to reach peak force and time to reach peak yank in V and AV trials were calculated after deriving each of these variables from the individual grips made by a subject, and calculating averages for that subject, before averaging across subjects. Group mean percentage changes in variables were calculated as the average of the mean percentage changes in each subject.

The method described above provided unbiased calculations of the average peak yank and peak force, independent of the average time to reach peak yank and average time to reach peak force, respectively. However, in order to graphically display the average grip trace for both force and yank, we averaged across individual grips at each millisecond time point **(Figures 4.1 and 4.2)**. Note that force and yank traces for each individual's hand were first normalized to the average of each subject's peak force and peak yank, respectively, in each hand in the V condition. In this way, any potential skew which may have been introduced by particularly strong individuals or by dominance of hands, when averaging across all subjects, was limited.

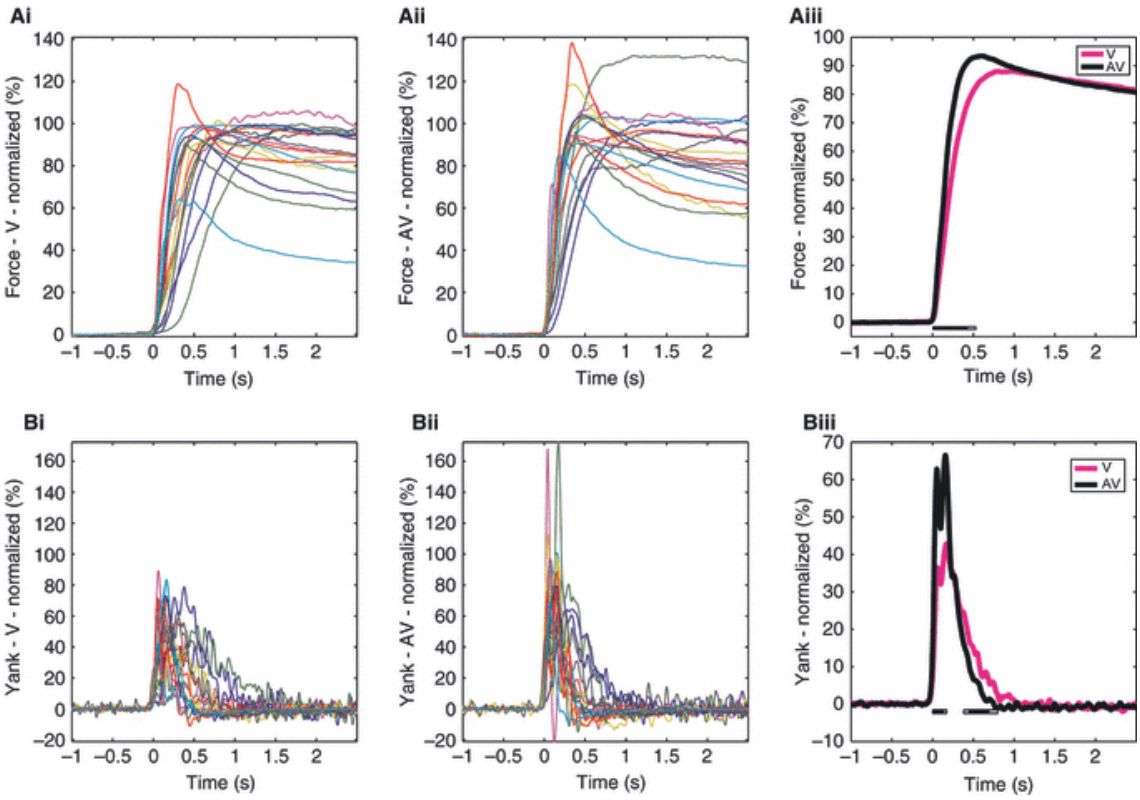


Figure 4.1 (A) Grip forces averaged after realignment to response onset in patients with Parkinson's disease OFF medication. (Ai) Each patient's normalized mean force from visual cue only (V) trials, in left and right hands. (Aii) Each patient's normalized mean force from trials in which a loud auditory stimulus was delivered as the visual cue came on (AV). Each patient is colour-coded with the same colour in Ai and Aii. (Aiii) Group average of V and AV trials across nine patients (n = 18 hands). **(B) Yank (rate of force development) averaged after realignment to response onset off medication.** (Bi) Each patient's normalized mean yank from V trials, in left and right hands. (Bii) Each patient's normalized mean yank from AV trials. Each patient is colour-coded with the same colour in Bi and Bii. (Biii) Group average of V and AV trials across nine subjects (*n* = 18 hands). The black and grey bars combined indicate those timings over which the two traces were different at the 5% significance level. The black bar on its own denotes those timings over which the two traces were different at the 1% significance level.

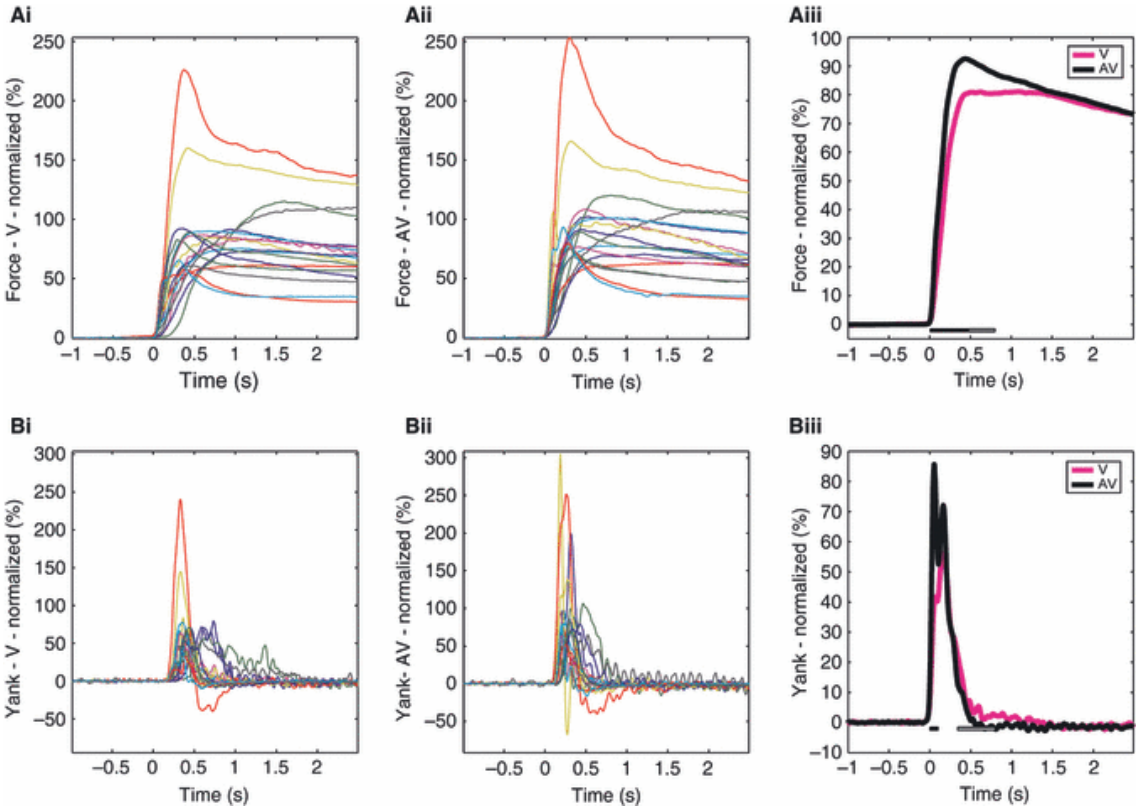


Figure 4.2 (A) Grip forces averaged after realignment to response onset in patients with Parkinson's disease ON medication. (Ai) Each patient's normalized mean force from visual cue only (V) trials, in left and right hands. (Aii) Each patient's normalized mean force from trials in which a loud auditory stimulus was delivered as the visual cue came on (AV). Each patient is colour-coded with the same colour in Ai and Aii. (Aiii) Group average of V and AV trials across nine patients (n = 18 hands). **(B) Yank (rate of force development) averaged after realignment to response onset ON medication.** (Bi) Each patient's normalized mean yank from V trials, in left and right hands. (Bii) Each patient's normalized mean yank from AV trials. Each patient is colour-coded with the same colour in Bi and Bii. Note the prominent action tremor in one patient. (Biii) Group average of V and AV trials across nine subjects (n = 18 hands). The black and grey bars combined indicate those timings over which the two traces were different at the 5% significance level. The black bar on its own denotes those timings over which the two traces were different at the 1% significance level.

Evidence of an overt startle response characterised by short latency SCM activity (Brown et al, 1991) was also sought. Here, we had to avoid contamination of our results with SCM responses related to coactivation once the maximal grip had been initiated. We avoided this confound by comparing maximal rectified SCM activity occurring within the first 150 ms after onset of the AV cues across trials, with the maximal SCM activity occurring within the first 150 ms after V cues across trials. A startle response was considered present if the former index exceeded the latter by > 3 SD in a given subject. Coactivation related to the grip would have been expected to be similar between trial types. Moreover, we aimed to ensure our latency of interest for SCM responses was shorter than the mean latency to co-activation (average AV premotor reaction time in patients with PD ON medication, 156 ms; healthy controls in first experimental run, 152 ms).

4.2.4 Statistics

Statistical analyses were performed in microsoft office excel 2003, matlab and SPSS Statistics 17 (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov tests confirmed that data were normally distributed. Variability in kinematic profiles between individuals was offset by always performing paired comparisons of trial types within subjects. When comparing the effect of stimulus and drug state or experimental run within the patient group, a repeated-measures anova was applied. However, when comparing across PD and Control groups, we used a mixed-design repeated-measures anova in which PD and Control were defined as separate groups. Those statistical tests that reached significance ($P < 0.05$) and, where appropriate, survived correction for multiple comparisons using the Bonferroni correction (Curran-Everett, 2000), are indicated with an asterisk (*) in the text. Means ± SEM are specified.

4.3 Results

4.3.1 Force parameters in patients with PD

Mean peak yanks across subjects increased from 106.5 ± 15.7 kg/s in V trials to 121.7 ± 17.4 kg/s in AV trials, in the OFF drug state. Similarly, increases from 105.4 ± 11.5 kg/s in V trials to 123.1 ± 13.9 kg/s in AV trials were observed in the ON drug state. Subsequent application of a repeated-measures anova with factors Drug state (OFF and ON L-DOPA) and Stimulus (V and AV) to mean peak yanks generated on each side by each of our patients with PD (18 hands) identified a main effect of Stimulus ($F_{1,17} = 9.16$, $^*P = 0.008$) which was independent of the dopaminergic state (Drug state × Stimulus interaction, $F_{1,17} = 0.230$, $P = 0.638$). There was no overall effect of Drug state ($F_{1,17} = 0.00$, $P = 0.985$). Thus, averaging across drug states for

each stimulus type, a mean increase in peak yank of 20.0 ± 7.1% (*P = 0.008, two-tailed paired t-test between V and AV stimuli) with AV cueing was observed (Figure 4.3).

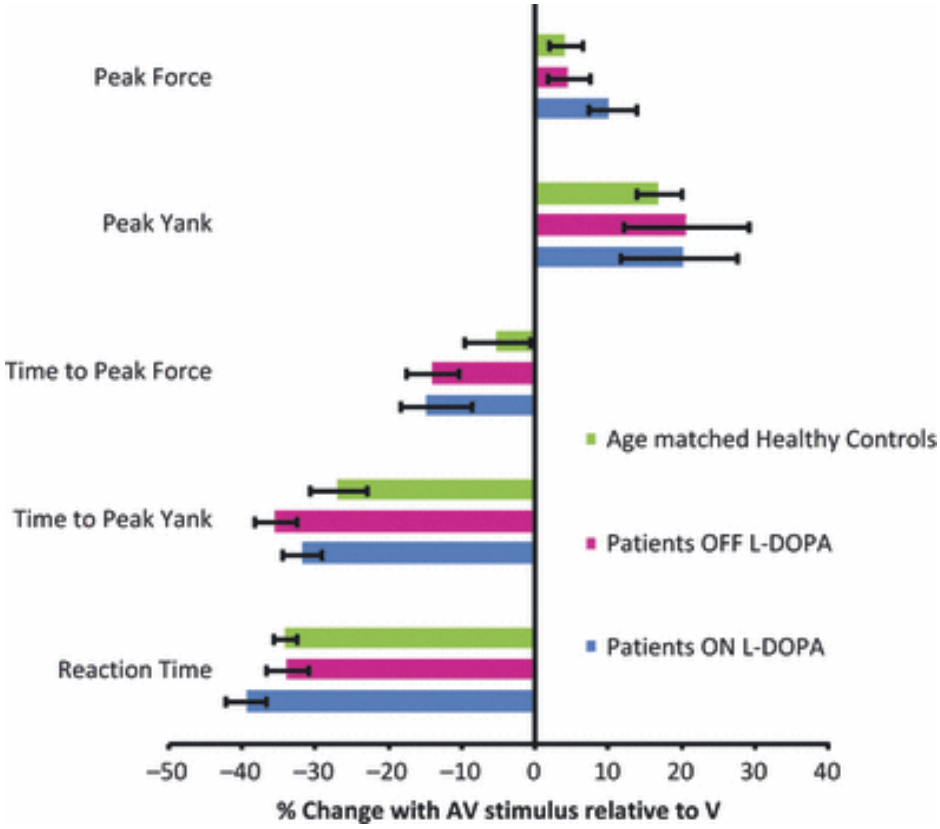


Figure 4.3 Average percentage changes with AV relative to V stimuli, in patients with Parkinson's disease OFF and ON their usual antiparkinsonian medication and in age-matched healthy controls averaged across experimental runs 1 and 2. A percentage increase means that the measure is greater in AV trials than in V trials.

Mean peak force increased from 17.0 ± 1.5 kg in V trials to 17.7 ± 1.5 kg in AV trials in the OFF drug state. Increases from 15.1 ± 1.0 kg in V trials to 16.1 ± 1.0 kg in AV trials were observed in the ON drug state. Application of a further repeated-measures anova to mean peak forces similarly identified a main effect of Stimulus ($F_{1,17}$= 7.23, **P* = 0.016) but no Drug state × Stimulus interaction ($F_{1,17}$= 0.695, *P* = 0.447) or effect of Drug state ($F_{1,17}$= 2.52, *P* = 0.131). The mean increase in peak force with AV cueing across drug states was 6.1 ± 2.1% (**P* = 0.016, paired *t*-test).

In order to further investigate the manner in which V and AV trials differed for the above-mentioned variables, the distributions of normalized (see Materials and methods) peak yanks and peak forces elicited in each patient across drug states were plotted (Figure 4.4). This figure suggests that, although the range of movement capabilities was similar in the two conditions, AV trials were associated with an increased proportion of stronger grips selected from within this range, as also occurs in healthy subjects (Chapter 3). Application of two-sample Kolmogorov–Smirnov tests identified significant differences between the V and AV distributions for peak yank (**P* < 0.0001) and peak force (**P* = 0.0026), which was manifest as a skew of the AV relative to V distributions towards higher forces and yanks. The peak yank distribution skew increased from 2.239 for V trials to 2.369 for AV trials and the peak force distribution skew increased from 2.414 for V trials to 2.454 for AV trials.

4.3.2 Temporal parameters in patients with PD

In line with the improvements in peak yank with AV cueing, time to reach peak force from movement onset also decreased, from 873 ± 115 ms in V trials to 786 ± 105 ms in AV trials in the OFF drug state. Decreases from 738 ± 107 ms in V trials to 638 ± 93 ms in AV trials were observed in the ON drug state. Application of repeated-measures anova to mean time to reach peak force further identified a trend towards an effect of Stimulus ($F_{1,17}$= 4.29, *P* = 0.054) independent of dopaminergic state (Drug state × Stimulus interaction, $F_{1,17}$= 0.075, *P* = 0.788). The mean reduction in time to peak force, averaged across drug states, was 7.6 ± 6.2% with AV compared to V cueing (*P* = 0.054, paired *t*-test). There was an additional main effect of Drug state ($F_{1,17}$= 6.50, **P* = 0.021), which was consistent with the expected amelioration of bradykinesia with L-DOPA. The reduction in time to peak force, averaged across V and AV trials, was 14.2 ± 5.2% (**P* = 0.021, paired *t*-test) on compared to off medication.

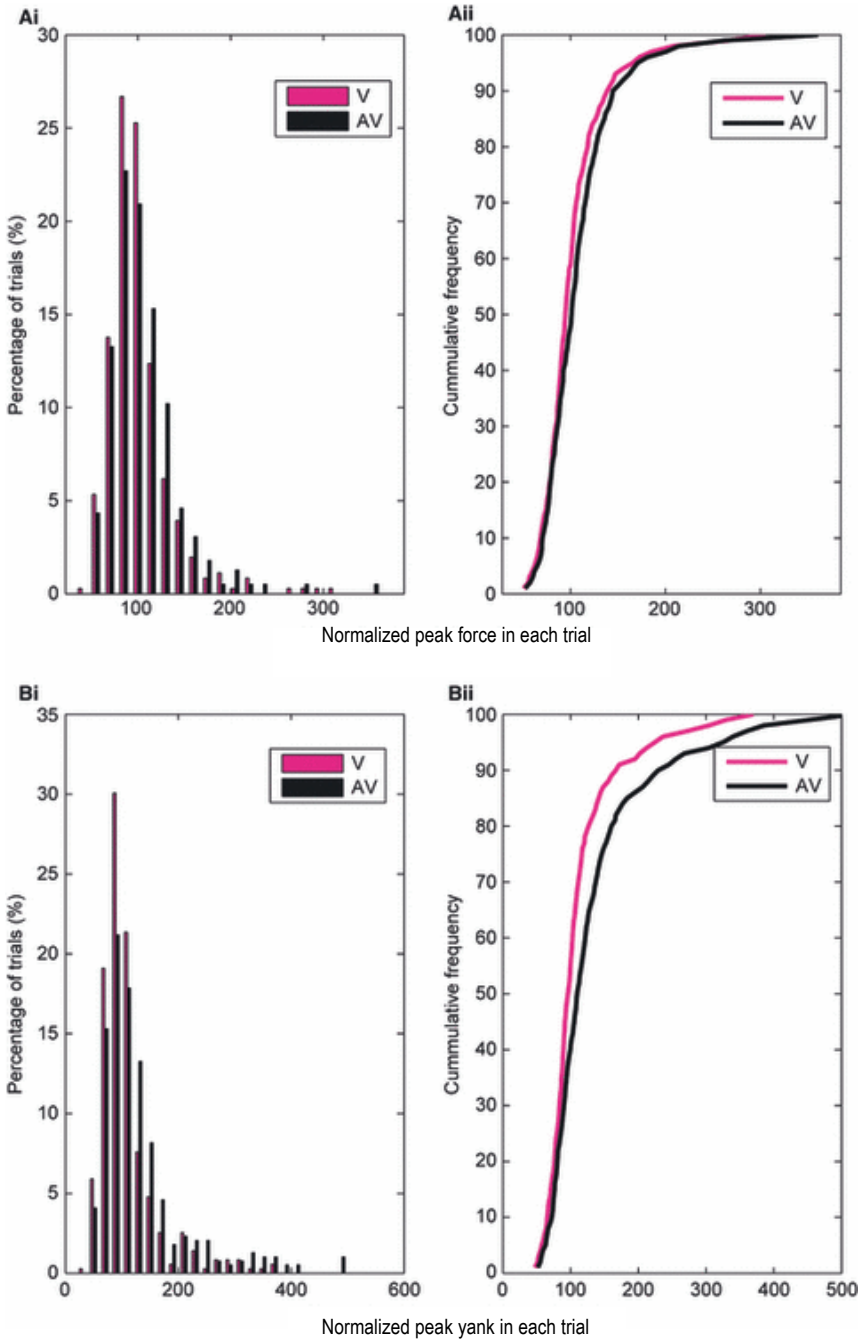


Figure 4.4 Peak force and yank distributions in patients with Parkinson's disease. (A) (i) Histogram and (ii) cumulative frequency plot, to show distributions of peak forces generated in each V and AV trial across nine patients with Parkinson's disease (PD) in the OFF and ON L-DOPA states combined, represented as a percentage of each hand's average in the V condition. (B) (i) Histogram and (ii) cumulative frequency plot to show distributions of peak yanks generated in each V and AV trial across nine patients with PD (18 hands) in the OFF and ON L-DOPA states combined, represented as a percentage of each hand's average in the V condition. AV trials have similar ranges of peak force and peak yank as V trials but their distributions in the histograms are more skewed to the right, suggesting that loud auditory stimuli facilitated more of the trials with greater peak force and peak yank to be achieved.

Time to reach peak yank also decreased from 238 ± 35 ms in V trials to 143 ± 19 ms in AV trials in the OFF drug state. Decreases from 196 ± 27 ms in V trials to 135 ± 16 ms in AV trials were observed in the ON drug state. Application of a repeated-measures anova to the mean time to reach peak yank also showed a main effect of Stimulus ($F_{1,17}$ = 15.36, *P = 0.001), a trend towards an effect of Drug state × Stimulus interaction ($F_{1,17}$ = 4.28, P = 0.054) and an effect of Drug state ($F_{1,17}$ = 5.51, *P = 0.034). The reduction in time to peak yank with AV cueing averaged across drug states was 31.7 ± 4.3% (*P = 0.001, paired t-test). The reduction in time to peak yank, averaged across V and AV trials, was 7.6 ± 6.3% (*P = 0.034, paired t-test) ON compared to OFF medication.

RTs also decreased from 252 ± 14 ms in V trials to 163 ± 8 ms in AV trials in the OFF drug state. Similarly decreases from 236 ± 11 ms in V trials to 156 ± 6 ms in AV trials were observed in the ON drug state. An anova of mean premotor reaction times showed a main effect of Stimulus ($F_{1,17}$= 127.3, *P < 0.001) independent of dopaminergic state (Drug state × Stimulus interaction, $F_{1,17}$= 0.317, P = 0.581), and no effect of Drug state ($F_{1,17}$= 2.59, P = 0.126). The mean reduction in premotor RT was 33.7 ± 1.9% (*P < 0.001 paired t-test).

4.3.3 Comparisons with age-matched healthy controls

We applied a mixed design repeated-measures anova with factors Stimulus (V and AV), Group (patients with PD and age-matched healthy controls) and Drug state/Experimental run (OFF L-DOPA in patients with PD/ first experimental run in controls and ON L-DOPA in patients with PD/ second experimental run in controls). This confirmed a significantly improved response to the AV stimulus in all parameters of movement measured in both patients with PD and age-matched healthy controls (i.e. main effect of Stimulus but no Stimulus × Group interactions). The differential behaviour in V and AV trials was retained across the two groups despite differences in absolute values due to better baseline performance in healthy controls, as demonstrated by the main effects for Group in peak yank (114.2 ± 7.3 kg/s in patients with PD and 162.6 ± 9.7 kg/s in healthy controls; $F_{1,34}$= 5.972, *P = 0.049) and time to peak yank (178 ± 13 ms in patients with PD and 117 ± 6 ms in controls; $F_{1,34}$= 6.76, *P = 0.014) and a trend towards an effect for Group in peak force (16.5 ± 0.6 kg in patients with PD and 20.7 ± 1.0 kg in healthy controls; $F_{1,34}$= 3.127, P = 0.086). There was an absence of significant group interactions for the remaining temporal and force parameters. The Drug state/Experimental run factor was significant, with net increases in peak force for the first set of stimulus presentations (eg OFF state in patients and first run in healthy subjects), and decreases in time to peak force and time to peak yank across groups in the second set of stimulus presentations. Note that the factor Drug state/Experimental run

includes drug and fatigue effects, which cannot be disambiguated given that the OFF drug state in patients was always tested first. However, the fact that there was a main effect of Drug state/Experimental run, whereby peak force was higher in the first run regardless of group, suggests that fatigue effects may have dominated over any drug effects. Conversely, the lower peak force in the second run may have contributed to the decreased time to reach (lower) peak force and yanks (see Table 4.2).

4.3.4 Habituation to the performance-boosting effects of AV trials

We next assessed whether the performance-enhancing effect of the loud sound declined with trial presentation. Application of an anova to peak yanks generated by each of our subjects, with factors Group (PD patients and healthy controls) and Trial position (average percentage change between first two V and AV trials and average percentage change between last two V and AV trials) identified no significant effect of Trial position ($F_{1,34}$= 3.141, P = 0.085) nor a Trial position × Group interaction ($F_{1,34}$= 0.574, P = 0.454). There was also no effect of Group ($F_{1,34}$= 0.398, P = 0.532). However, application of a similar anova to peak forces generated by each of our subjects did identify a significant effect of Trial position ($F_{1,34}$= 7.74, *P = 0.009) but no Trial position × Group interaction ($F_{1,34}$= 0.158, P = 0.693). There was again no effect of Group ($F_{1,34}$= 1.766, P = 0.193). Thus there was no habituation to the performance-boosting effects of loud sounds on peak yank, although there was such an effect on peak force. The latter effect was similar in PD patients and healthy controls.

4.3.5 Startle

Startle responses (defined in Materials & methods) were rare in subjects with PD, occurring in only 10 of 197 AV trials in the off medication state and four out of 198 trials in the on medication state across patients. In healthy controls the startle response was observed slightly more frequently (21 out of 184 AV trials in the first experimental run and 21 out of 195 AV trials in the second experimental run).

Table 4.2 Patients with PD compared with age-matched healthy controls in mixed design repeated measures ANOVAs. Factors include: GROUP (PD or age-matched healthy controls), STIMULUS (V or AV), L-DOPA/Experimental run (ON or OFF L-DOPA recordings in patients with PD compared to experimental run 1 or 2, respectively, in healthy controls).

Peak Force	*Within subject effects:* STIMULUS $F_{1,34}$ =9.0, P**=0.005** STIMULUS x GROUP $F_{1,34}$ =0.120, P=0.731	L-DOPA/ Experimental run : $F_{1,34}$ =12.4, P=**0.001** L-DOPA/ Experimental run x GROUP: $F_{1,34}$ =0.247, P=0.622 L-DOPA/ Experimental run x STIMULUS: $F_{1,34}$ =0.881, P= 0.355 L-DOPA/ Experimental run x STIMULUS x GROUP: $F_{1,34}$ =0.043, P=0.838
		Between subject effects: GROUP $F_{1,34}$ =3.127, P=0.086
Peak Yank	*Within subject effects:* STIMULUS $F_{1,34}$ =38.0, P**<0.001** STIMULUS x GROUP $F_{1,34}$ =1.64, P=0.209	L-DOPA/ Experimental run : $F_{1,34}$ =2.28, P= 0.140 L-DOPA/ Experimental run x GROUP : $F_{1,34}$ =2.38, P=0.132 L-DOPA/ Experimental run x STIMULUS : $F_{1,34}$ =0.211, P=0.649 L-DOPA/ Experimental run x STIMULUS x GROUP: $F_{1,34}$ =0.056, P=0.815
		Between subject effects: GROUP $F_{1,34}$ =5.972, P**=0.049**
Time to Peak Force	*Within subject effects:* STIMULUS $F_{1,34}$ =6.94, P**=0.013** STIMULUS x GROUP $F_{1,34}$ =0.553, P=0.462	L-DOPA/ Experimental run : $F_{1,34}$ =7.33, P=**0.011** L-DOPA/ Experimental run x GROUP : $F_{1,34}$ =1.19, P=0.283 L-DOPA/ Experimental run x STIMULUS : $F_{1,34}$ =1.29, P=0.264 L-DOPA/ Experimental run x STIMULUS x GROUP: $F_{1,34}$ =2.16, P=0.151
		Between subject effects: GROUP $F_{1,34}$ =0.276, P=0.603
Time to Peak Yank	*Within subject effects:* STIMULUS $F_{1,34}$ =31.44, P**<0.001** STIMULUS x GROUP $F_{1,34}$ =3.538, P=0.069	L-DOPA/ Experimental run : $F_{1,34}$ =12.4, P=**0.015** L-DOPA/ Experimental run x GROUP : $F_{1,34}$ =1.57, P=0.218 L-DOPA/ Experimental run x STIMULUS : $F_{1,34}$ =2.38, P=0.132 L-DOPA/ Experimental run x STIMULUS x GROUP: $F_{1,34}$ =2.67, P=0.112
		Between subject effects: GROUP $F_{1,34}$ =6.76, P**=0.014**

Premotor Reaction Time	*Within subject effects:* STIMULUS $F_{1,34}$ = 335.0, P**<0.001** STIMULUS x GROUP $F_{1,34}$ = 0.020, P=0.888	L-DOPA/ Experimental run : $F_{1,34}$ =0.073, P=0.788 L-DOPA/ Experimental run x GROUP : $F_{1,34}$ = 4.12, P=0.050 L-DOPA/ Experimental run x STIMULUS : $F_{1,34}$= 0.174, P=0.680 L-DOPA/ Experimental run x STIMULUS x GROUP: $F_{1,34}$=0.183, P=0.672 *Between subject effects:* GROUP $F_{1,34}$ =0.048, P=0.827

4.4 Discussion

The findings from our study are three-fold. We observed a significant facilitation of the onset, peak and rate of hand grip force production in our patients with PD in response to loud auditory stimulation, over and above that achieved with maximum effort of will. The effect was observed whether or not patients were treated with dopaminergic medication. Moreover, the phenomenon was reproduced in age-matched healthy controls, corroborating the view that paradoxical kinesia, in so far as it is captured by the present paradigm, may not be a unique hallmark of PD but rather an essentially physiological property of the motor system (Ballanger et al, 2006).

The finding that the facilitatory effect of loud auditory stimuli was present in patients regardless of whether they were on or off medication is a key one. Importantly, our patients were all DOPA-responsive and demonstrated improvements in the time taken to reach peak force and peak yank during the grip task following medication. Despite this, there was no change in the facilitatory effect of loud auditory stimuli between the off and on medication states. Could we have missed a dopaminergic role in the shortening of reaction time and the increasing of the rate of development and magnitude of response force elicited by loud auditory stimuli? In particular, it could be argued that treatment with L-DOPA would be unlikely to promote any phasic release of dopamine with loud auditory stimuli. This, however, seems unlikely. First, if the facilitatory effect really were dopamine dependent, we should have found an attenuation of the phenomenon in PD patients withdrawn from their antiparkinsonian medication compared to age-matched controls. This was not the case. Second, L-DOPA has been shown to increase stimulation-induced phasic dopamine release in the striatum of intact and parkinsonian rats, suggesting that L-DOPA might be successfully converted to dopamine in remaining nigral neurons (Keller et al, 1988; Wightman et al, 1988). In line with this, L-DOPA decreases [^{11}C]raclopride binding in the striatum of parkinsonian patients, which is indicative of increased levels of synaptic dopamine, and this effect increases with progression of the disease (de la Fuente-Fernández et al, 2004). Third, evidence

from animal models of paradoxical kinesia also seems to favour a nondopaminergic mechanism. Rats rendered akinetic with intraventricular injections of 6-hydroxydopamine and subsequently treated with a combination of D1 and D2 receptor antagonists are still able to escape from an ice bath and run away when confronted with a room full of cats (Marshall et al, 1976; Keefe et al, 1989).

Several nondopaminergic systems could potentially underlie the facilitatory effect of loud auditory stimuli demonstrated here. Noradrenergic activation as part of the fight-or-flight response to aversive stimuli remains a candidate mechanism and is supported by studies showing that animals treated with haloperidol are able to overcome their motor difficulties during a stressful situation, during which they also develop high plasma levels of noradrenaline (Yntema & Korf, 1987). In addition, glutamatergic mechanisms in the inferior colliculus, a structure which has been demonstrated to process auditory information and send output to motor centres which induce defensive behaviors such as arousal and escape responses (Melo et al*,* 2010), may play a role. Important among these centres may be the brain stem reticular formation, which also has multiple cholinergic projections and has long been known to contribute to rapid behavioural responses to abrupt startling or arousing stimuli (Grillon & Baas, 2003).

It is, however, worth considering precisely how closely our results might relate to paradoxical kinesis as reported in patients with PD. Obvious ethical constraints in inducing frightening or life-threatening situations mean that the direct and systematic study of this phenomenon is practically impossible. The intense stimulus used in the current study was markedly more brief than those described in anecdotal reports of paradoxical kinesis (Schwab & Zieper, 1965; Marshall et al*,* 1976; Schlesinger et al*,* 2007; Bonanni et al*,* 2010a,b). Nevertheless, the stimulus used still had a remarkable effect on all the examined force and temporal parameters related to a maximal hand grip. An important question is whether these improvements in performance would also occur in a more complex series of movements, such as those more commonly described in case reports of paradoxical kinesis. Future experiments investigating the effect of stimulus intensity and duration on a more complex motor paradigm would certainly be of interest.

Another issue is the precise stimulus features which might have precipitated the facilitatory effect observed in our study, and that in anecdotal reports of paradoxical kinesia. Several features could be invoked, including intersensory facilitation (Woodworth, 1938; Dufft & Ulrich, 1999; Miller et al., 1999) and stimulus intensity effects (Angel, 1973; Jaśkowski et al, 1995). The StartReact phenomenon may also have played a role (Valls-Solé et al, 1999; Carlsen et al, 2004, 2009; Reynolds & Day, 2007; Chapter 3). This is the dramatic shortening of reaction times in trials

accompanied by a startling stimulus. However, against a role of this phenomenon is the scarcity of a short-latency response in SCM in our subjects, which is considered to be the most sensitive hallmark of the generalised startle response (Brown et al*,* 1991). Indeed, the startle response has previously been described as reduced in PD (Miller et al*,* 2009), and substantial improvements in RT and force parameters may be elicited by loud auditory stimuli without elicitation of an overt startle response (Chapter 3).

A number of studies have now shown that emotional stimuli can shorten reaction time and increase response force (Baumgartner et al*,* 2007; Coombes et al*,* 2007; Schmidt et al*,* 2009). This raises the possibility that it is phasic arousal or alertness which may play a key role in motor improvement, given that the latter is precipitated by both emotional and loud auditory stimuli. Phasic arousal or alertness should be distinguished from tonic arousal or alertness. The former is the ability to increase response readiness for a short period of time subsequent to external stimuli (Sturm & Willmes, 2001). Phasic arousal or alertness also forms a plausible mechanism for both intersensory facilitation and intensity effects, and has been proposed as the underlying mechanism for force increases in other 'redundant-signal' tasks by which auditory and visual cues are presented independently or alone (Dufft & Ulrich, 1999; Giray & Ulrich, 1993; Mordkoff et al, 1996). Specifically, it has been posited that a cue not only instigates specific processing related to analysis of the stimulus and execution of the response, but also 'immediate arousal' (Sanders, 1983) or 'automatic alertness' (Posner et al, 1976; Posner, 2008). Phasic arousal or alertness could in turn exert its influence by improving activation of motor areas (Baumgartner et al, 2007; Jepma et al, 2009) and amplifying the effects of the specific processing stream (Miller et al, 1999; Stahl & Rammsayer, 2005). In this way a more consistent optimum performance could be achieved.

Analysis of the distributions of the peak forces and peak yanks generated in V and AV trials in patients with PD supported just such an effect, evident as an increase in the proportion of stronger grips selected from a similar range of movement capabilities present in both conditions. A similar effect has previously been described in healthy subjects (Chapter 3). It has been hypothesised that movement parameters are 'selected' from an underlying range of capabilities so as to optimise the use of neuromuscular energy; this concept, describing the likelihood of selecting a certain speed of movement, has been termed 'motor vigor' by Mazzoni et al (2007). It has further been suggested that in an arousing or temporally pressing situation the system is forced to adopt a more 'expensive' trade-off (Ballanger et al*,* 2006). Thus in our paradigm the arousing or alerting nature of the loud auditory stimulus might improve motor vigor, over and

above any considerations of force or speed–energetic cost tradeoffs, thus bringing about a more consistent 'best' performance. Accordingly, we have shown that whilst PD patients cannot produce as large forces and rates of development of force as control subjects, an intense and presumably arousing stimulus may still produce improved task performance. Nevertheless, the role of phasic arousal or alertness remains speculative and further studies are necessary to confirm that our loud auditory stimuli were actually accompanied by phasic activation.

To summarise, loud auditory stimulation in patients with PD resulted in a significant facilitatory effect on peak force, peak yank, time to reach peak force, time to reach peak yank, and RT, over and above that achieved with maximum effort of will. Similar improvements in age-matched healthy controls suggest that paradoxical kinesia, as captured in the current paradigm, may be a physiological property of the motor system. Moreover, the potential independence of the mediating pathways from the dopaminergic system provides impetus for further investigation as it may yield a novel nondopaminergic target for therapeutic manipulation in PD.

Chapter 5

Subthalamic nucleus activity optimizes maximal effort motor responses in Parkinson's disease

5.1 Introduction

To what extent might the basal ganglia dictate the speed and the force of our maximal motor responses? Some contribution might be expected given that the basal ganglia have recently been implicated in the scaling of movement (Turner et al., 2003; Thobois et al., 2007; Muthukumaraswany, 2010; Turner and Desmurget, 2010; Grafton and Tunik, 2011; Brücke et al., 2012), although whether the same relationship holds true at the limits of voluntary performance remains unclear. Moreover, what is achieved by our maximal 'effort of will' is known to vary according to the context, with paradoxical enhancements of 'best' performance reported in response to intense stimuli both in healthy subjects (Woodworth, 1938; Angel, 1973; Chapter 3) and, most notably, in the form of the brief amelioration of motor impairment, termed 'paradoxical kinesis' (Souques, 1921), described in patients with Parkinson's disease (Valldeoriola et al, 1998; Chapter 4). So, if activity in the basal ganglia is involved in achieving our 'best' performance, is it also modulated by experimental challenges like the introduction of intense stimuli? Or, are the performance improvements associated with such challenges achieved relatively independently of the basal ganglia? Indeed, understanding how fastest and strongest movements are achieved, and how their performance can be enhanced still further, are important goals which may inform the search for treatments for movement disorders such as Parkinson's disease (PD).

One of the difficulties in determining which brain activities may be instrumental in achieving optimal motor performance relates to the confound of peripheral afference, so that techniques like electrophysiological recording, which have high temporal resolution, have a unique contribution to make. Here, we recorded directly from deep brain stimulation electrodes implanted bilaterally in the region of the subthalamic nucleus of patients with PD whilst they executed handgrips as fast and as strongly as possible in response to a visual cue. By delivery of a loud auditory tone simultaneous with the visual cue, on random trials, we further aimed to relate subthalamic nucleus local field potential (LFP) activity to any changes in force parameters and reaction time observed in response to intense stimuli. Finally, by testing patients ON and OFF dopaminergic medication, we could investigate the role, if any, of dopaminergic processes in performance of the task.

5.2 Materials and methods

5.2.1 Subjects

Ten patients with PD (mean disease duration 10 years, mean age 58 years, range 42–65 years; seven males) gave informed consent to take part in this study, which was approved by the local ethics committees at our recording sites in Oxford and London, UK. Patients underwent bilateral implantation of deep brain stimulation electrodes into the subthalamic nucleus, as a prelude to therapeutic high-frequency stimulation for advanced idiopathic PD with motor fluctuations and/or dyskinesias. Techniques to target and implant electrodes in the subthalamic nucleus have previously been described (Foltynie and Hariz, 2010). No microelectrode recordings were made, although the effects of direct stimulation were confirmed intra-operatively at surgical sites 1 and 3 **(Table 5.1)**. The locations of the electrodes were additionally confirmed with immediate postoperative stereotactic imaging. Nonetheless, in acknowledgement of the fact that not all electrode contacts could be expected to lie in the subthalamic nucleus *per se*, we term the area sampled by the contact pairs as the subthalamic nucleus region. Electrodes were attached to extension cables 'externalized' through the scalp to permit recordings before connection to a subcutaneous deep brain stimulation pacemaker, implanted in a second operative procedure up to 7 days later. Clinical details of the patients are given in **(Table 5.1)**. The mean percentage improvement in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) ON treatment with L-DOPA was $59.9 \pm 5.7\%$ ($P < 0.0001$) across subjects, indicating good responsiveness to L-DOPA in our study participants.

5.2.2 Experimental paradigm

Subjects were presented with a series of imperative visual cues, separated by 11–13 s, and instructed to squeeze a force dynamometer 'as fast and hard as you possibly can when the light comes on and maintain this for the duration of the light' (red light-emitting diode illuminated for 5 s). In half of these trials, which were randomly selected, a loud auditory stimulus (0.3 s duration, 1 kHz, 96 dB) was delivered binaurally through headphones, with onset simultaneous with that of the visual cue (auditory–visual cue). However, subjects were asked to just focus on responding to the visual cues.

Table 5.1 Clinical details of patients with PD and externalized DBS electrodes (a). Surgical sites: (1) John Radcliffe Hospital, Oxford; (2) National Hospital for Neurology and Neurosurgery, London; (3) Kings College Hospital, London, United Kingdom.

Site	Patient no.	Age (yrs)	Disease duration (yrs)	Daily L-DOPA equivalent dose (mg)	Pre-operative UPDRS part III	
					OFF	ON
1	1	64	13	500	33	6
1	2	65	17	150	29	8
1	3	42	6	500	50	38
1	4	63	7	400	76	16
2	5	62	8	950	64	25
2	6	46	7	600	43	10
2	7	57	9	625	60	27
3	8	62	9	750	38	20
3	9	57	7	100	40	20
3	10	59	15	750	33	16

Twenty trials were collected in each experimental run. Trials were approximately equally divided (allowing for the randomization process in each session) into those with visual and auditory–visual cues. Trials were carried out in a blocked design, and left- and right-hand recordings were counterbalanced across subjects. The rationale for the number of trials executed, and the inter-trial interval, as well as stimulus intensity and decision to include a reaction time component into our paradigm has previously been described (Chapter 4). Stimulus intensity was measured with a Brüel and Kjaer 2260 Observer.

Grip force was measured one hand at a time in each subject using an isometric dynamometer with standard Jamar design, and its handle set in the second of the five discrete grip diameter adjustments possible (G100; Biometrics Ltd, Sancho-Bru et al, 2008). Subjects were seated with their shoulders adducted (so that elbows rested against the trunk), their elbows flexed at ~90° and their forearms in neutral, as recommended by the American Association of Hand Therapists (Fess, 1992).

5.2.3 Recordings and analysis

Recordings were made 3–6 days after surgery. To complete the recordings in one morning, and limit intrusion on our easily fatigable postoperative patients, recordings were always made first after overnight withdrawal of anti-parkinsonian medication (OFF L-DOPA), and then again ~1 h after taking their usual morning dose [average L-DOPA dose administered, 155 ± (SEM) 25 mg, although Cases 4 and 10 also received subcutaneous apomorphine]. Improvement with medication was confirmed through assessment of finger tapping, wrist rigidity and tremor (using the corresponding items of the motor UPDRS). Although this sequence of recordings may have introduced a confound in that ON medication performance may have been affected by fatigue, our results suggest that any such effects were relatively minimal, as medication was still able to reduce reaction time.

LFPs were recorded bipolarly from adjacent contacts of each deep brain stimulation electrode (0–1, 1–2, 2–3) using either a D360 amplifier (Digitimer Ltd) in combination with a 1401 A/D converter (Cambridge Electronic Design) and sampled onto a computer using Spike 2 software (Cambridge Electronic Design), or TMSi porti (TMS international) and its respective software. All recordings were originally sampled at 2048 Hz. Analogue correlates of the visual and auditory stimuli and dynamometer output were recorded and digitized in a similar way.

Analyses of both behavioural and LFP data were performed in Matlab (version 7.10). Peak yank (where yank is defined as the rate of change of force, calculated by differentiation of the force signal) and peak force were the chosen biomechanical variables of interest, and had the advantage that they could be measured trial by trial without realignment to compensate for differences in premotor reaction times. Premotor reaction time was operationally defined as the time interval between cue onset and the point at which force exceeded 5% of peak force (taken as response onset). We acknowledge that premotor reaction time is more usually considered to be the interval between cue presentation and EMG onset (Botwinick and Thompson, 1966). However, we found the use of EMG to be suboptimal in the context of maximal grips because of

movement artifact and sampling error, given that many muscles are activated in this task. The process of derivation of average induced frequency-specific LFP power, over discrete frequency bands, from contralateral subthalamic nuclei to the gripping hand, is described in Section 2.4.3

5.2.4 Statistics

For behavioural data, grand averages of peak force, peak yank and premotor reaction time for visual and auditory–visual trials were calculated after deriving each of these variables from the individual grips made by a subject, and calculating averages for that subject, before averaging across study participants. Group mean percentage changes in variables were calculated as the average of the mean percentage changes in each subject.

Our approach to statistical analysis of subthalamic nucleus region LFP power relationships with motor performance is summarized in **Figure 5.1**. We first sought to characterize frequency band-specific oscillatory activities in the subthalamic nucleus region that might independently predict between-subject differences in maximal handgrip performance under standard/baseline conditions. This was achieved by means of multiple regression analysis applied to behavioural and LFP responses to visual cues alone, retrieved from experimental runs where visual and auditory–visual cues were delivered at random, when patients were ON medication. The continuous black regression line, labelled 'RL' in **Figure 5.1**, describes the expected relationship of motor performance with any given frequency band-specific activity identified as a significant independent predictor of peak motor parameters, across subjects, in this baseline (visual cue, ON L-DOPA) condition.

Next, we used a multi-level multivariate regression modelling approach (Hox, 2002) to identify any contribution of frequency-specific subthalamic nucleus region LFP activity to the change in motor performance with experimental manipulations, relative to our baseline condition (thus effectively removing the baseline relationship between LFP amplitude and performance given by the line labelled 'RL', and concentrating on those dependencies described by the interrupted black line, labelled 'MLM' in **Figure 5.1**). The multi-level multivariate regression modelling approach used here had the advantage that each trial executed by every subject under the different experimental conditions was considered. The resulting high degrees of freedom meant that very small effects could be identified with relatively narrow confidence limits. Further details of both the multiple regression and multi-level modelling technique are described 2.5.6.

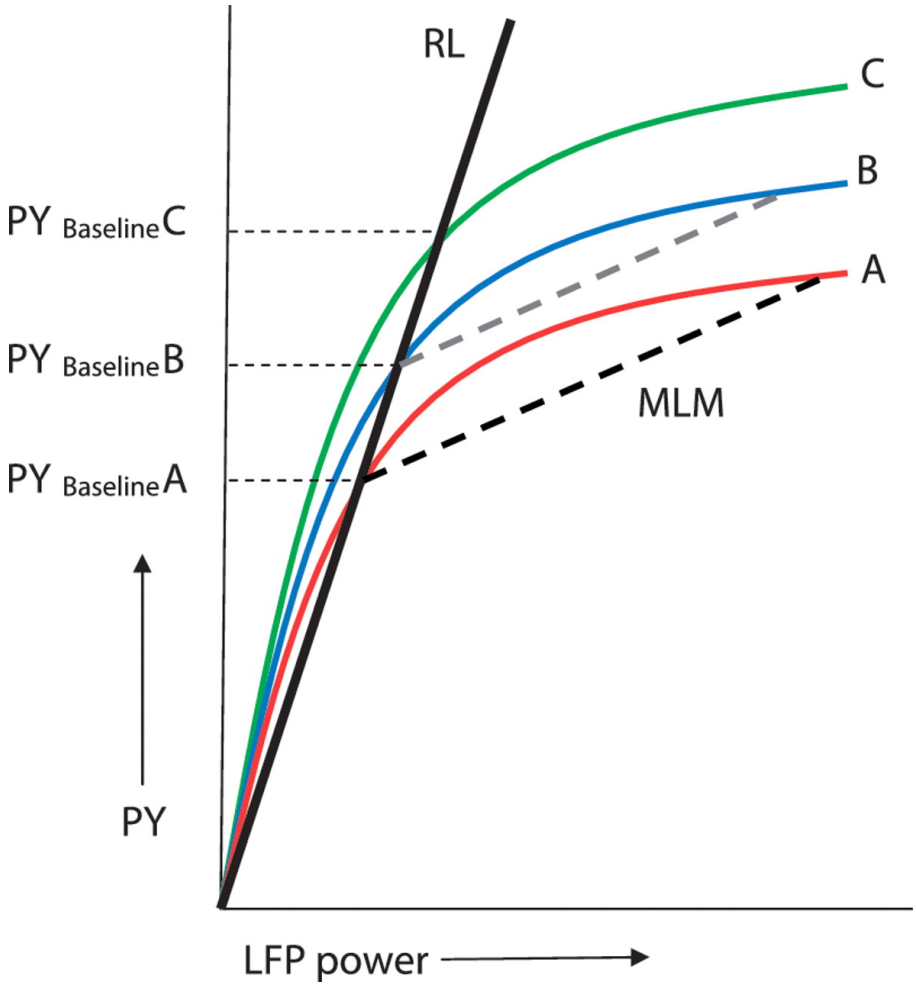


Figure 5.1 Putative relationship between frequency-specific LFP power and peak yank (PY), shown for three hypothetical individuals (Cases A, B and C). The continuous black line labelled 'RL' is the regression line fitting the LFP power relationship with peak yank, under baseline conditions (response to visual cues, when patients ON L-DOPA), across subjects. The interrupted black line, labelled 'MLM' is estimated by multi-level modelling on the basis of experimental condition-specific regression coefficients between frequency-specific LFPs and peak yank, corrected to each individual's baseline performance. It thus models 'within-subject' effects of experimental manipulations from standard conditions. An average experimental condition-specific intercept shift of the MLM line from baseline would implicate increments or decrements in motor performance independent of frequency-specific subthalamic nucleus LFP power. Such an average shift would equate to the shift of curve A to curve B, whilst maintaining the gradient of the MLM line (translation of interrupted black line to the position of the interrupted grey line).

Statistical analyses were performed in SPSS Statistics 19 (SPSS Inc.) and R (for multi-level modelling; R Development Core Team, version 2.13.2). Kolmogorov–Smirnov tests were applied to confirm that both transformed LFP data and behavioural measures were normally distributed, before further parametric testing. Where Mauchly's test of sphericity was significant ($P < 0.05$) in repeated-measures ANOVAs, Greenhouse–Geisser corrections were applied. Mean ± SEM are presented throughout the text, unless otherwise specified.

5.3 Results

Our aim was to identify the role of basal ganglia activity, as indexed by the subthalamic nucleus region LFP, in the generation of grips made as fast and as strongly as possible, under standard conditions and in the setting of the performance enhancements engendered by intense auditory stimuli (Chapters 3 & 4). To this end, we first identified those frequency bands in the subthalamic nucleus region LFP that underwent a change when grips were triggered by simple visual cues. We chose to consider recordings made in the ON L-DOPA state as our starting point and then define how LFP responses differed when triggered by intense stimuli (combined auditory and visual cues) and with or without overnight withdrawal of anti-parkinsonian medication.

5.3.1 Maximal effort grips are associated with frequency-specific changes in subthalamic nucleus region local field potential activity that correlate with peak motor performance across subjects

Three motor parameters of interest were derived from handgrips executed as quickly and strongly as possible, in response to visual cues in the ON L-DOPA state: premotor reaction time, peak yank and peak force. Average reaction time across subjects was 358 ± 21 ms. Average peak force and peak yank were 12.3 ± 1.5 kg and 72.8 ± 13.6 kg/s, respectively ($n = 20$ hands). The average force and yank traces for the hand contralateral to each subthalamic nucleus are represented in **Figure 5.2.**

Time-evolving power spectra of changes in subthalamic nucleus region LFPs induced by visual cues, relative to a pre-cue baseline, were derived by averaging across all visual-cued trials in an experimental run, for each patient undertaking the task when ON medication. These were then averaged across subjects **Figure 5.3**. In this way, three frequency bands were identified over which increases or decreases in power, in the period from cue onset to average time to peak yank, could be distinguished from the pre-cue baseline and from frequency bands with an

absence of reactivity to cue. These were the theta/alpha (5–12 Hz), high-beta (25–30 Hz) and high-gamma/high-frequency (55–375 Hz) ranges.

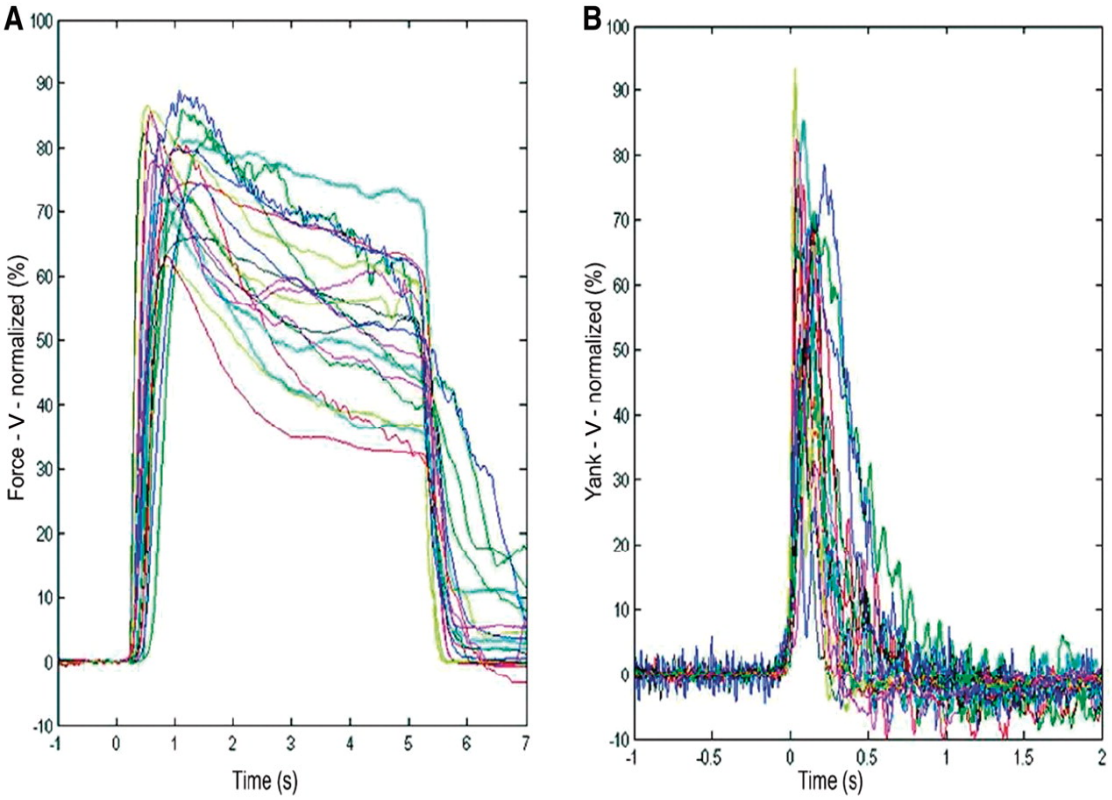


Figure 5.2 (A) Sustained maximal force grips, in response to a visual (V) cue illuminated for 5 s, when patients with Parkinson's disease – with externalized DBS electrodes - were ON dopaminergic medication. In this panel, time zero represents cue onset, so that each individual's average reaction times can be discerned. Average grip traces for left and right hands are presented and are normalized as a percentage of the maximal voluntary contraction achieved, by each hand, respectively, under this condition. Note, as can be seen in the figure, those trials in which subjects were slow in releasing the maximal grip were not excluded from further analysis, as the motor parameters of interest in this study fell at much earlier latencies. (**B) Yank (rate of development of force), averaged after realignment to response onset following a visual cue, when patients with Parkinson's disease – with externalized DBS electrodes - were ON dopaminergic medication.** Traces have been normalized as in **A**. Each patient is colour-coded with the same colour in **A** and **B**.

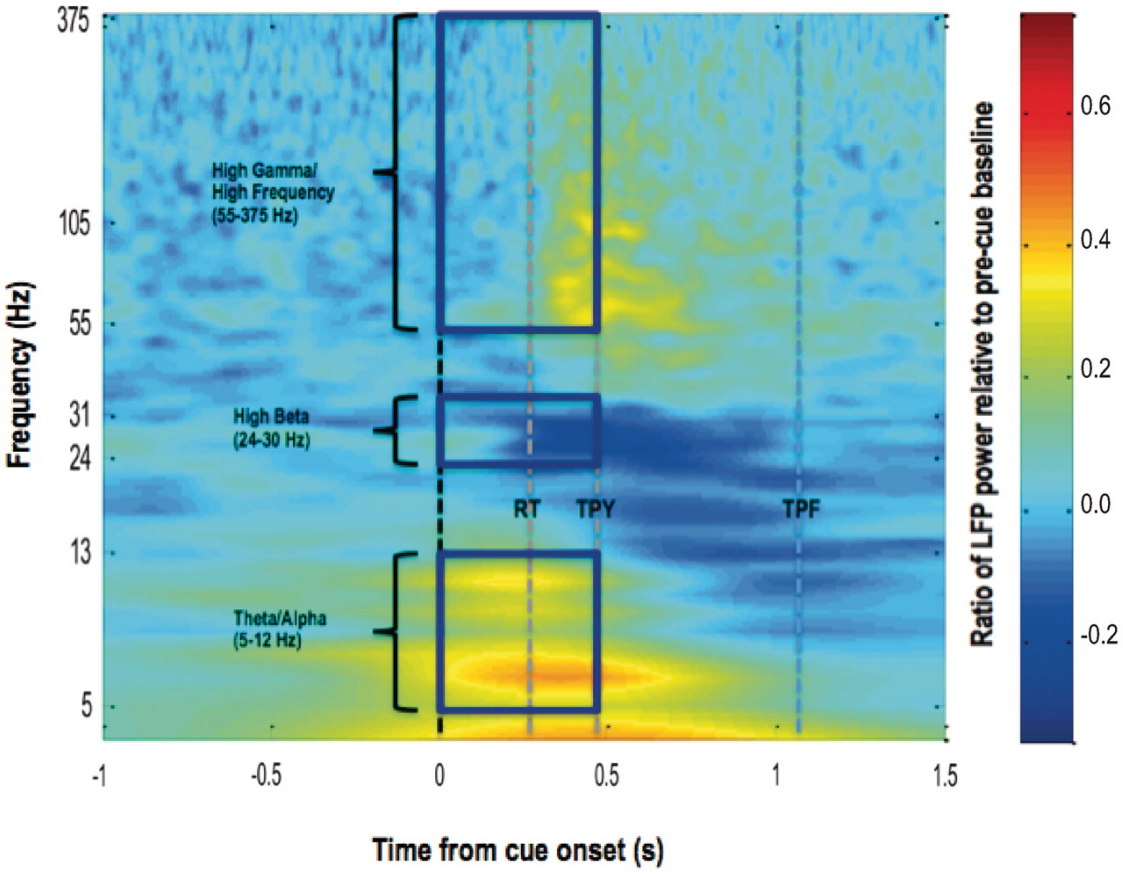


Figure 5.3 Average time–frequency plot of change in induced spectral power - in response to the imperative visual (V) cue - in 20 subthalamic nuclei contralateral to sustained maximal handgrips, relative to a pre-cue baseline. Time zero represents onset of the imperative V cue. Patients were recorded ON their normal dopaminergic medication. Colour gradient represents ratio of post-cue LFP power to average LFP power 1–2 s before cue onset. Lines labelled RT, TPY and TPF demarcate the average premotor reaction time, time to peak yank and time to peak force, under this condition, respectively. Frequency is plotted on a log axis.

Evidence of a relationship between performance and average LFP power in the earlier defined frequency bands, was then sought. Simple linear regression analysis identified significant correlations between performance and LFP activity in theta/alpha and high gamma/high frequency, but not beta bands. The significant associations are shown as scatter plots fitted by simple regression in **Figure 5.4**. However, whether activity in these frequency bands made an independent contribution to the motor parameters of interest, over and above the influence of other frequency-specific activities, remained to be clarified. To address this question, multiple regression analysis was performed, using each subject's mean LFP in the three reactive frequency bands identified earlier as the predictive variables, and each motor parameter of interest as the response variable.

Both increases in theta/alpha and high-gamma/high-frequency LFP power were found to be predictive of (i.e. could explain some of the variance in) increases in peak yank ($\beta = 0.486$, $P = 0.003$ and $\beta = 0.594$, $P = 0.001$, respectively). Beta activity was of no independent predictive value. The overall fit of the regression model was excellent ($F = 15.662$, $P < 0.001$, $R^2 = 0.698$) and the intercept was non-significant.

The overall model fit for the multiple regression model for peak force was also very strong ($F = 13.700$, $P < 0.001$, $R^2 = 0.667$), and similarly identified significant contributions of theta/alpha ($\beta = 0.505$, $P = 0.003$) and high-gamma/high-frequency ($\beta = 0.600$, $P = 0.001$) power in predicting peak force. The intercept was non-significant and beta activity was of no independent predictive value. Thus, the results suggest that had a given subject been able to achieve a greater mean increase in LFP activity in either the theta/alpha or high-gamma/high-frequency bands, their mean peak yank or peak force would also have improved. Furthermore, the strong fits of the regression models, as indexed by large R^2 values, and the insignificant intercepts suggest that subthalamic nucleus region LFPs were able to predict the majority of the variance in peak force and peak yank between subjects.

Conversely, only increases in theta/alpha LFP power were found to be predictive of reductions in reaction time ($\beta = -0.490$, $P = 0.035$). Neither beta nor high-gamma/high-frequency activity made an independent predictive contribution. The model fit was moderate, only approaching significance ($F = 3.106$, $P = 0.056$, $R^2 = 0.250$), and the regression model had a significant intercept of 465 ms ($P < 0.001$), suggesting that the greater part of the reaction time was dictated by processes that were independent of, at the very least, any linear relationship with induced subthalamic nucleus region LFP activity.

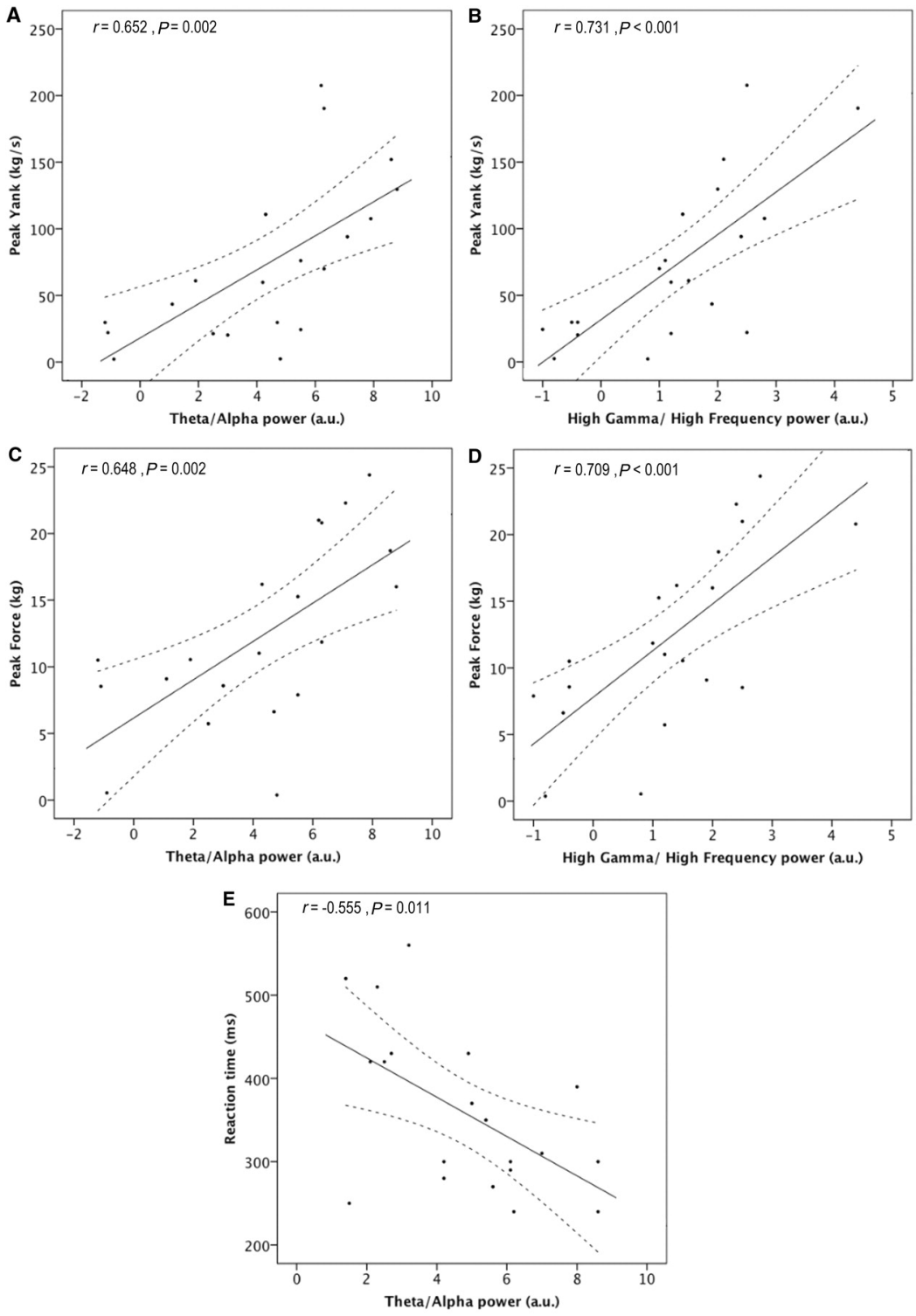


Figure 5.4 Scatter-graphs relating induced LFP power to performance at maximal effort. Continuous and interrupted lines represent the best fit and corresponding 95% confidence limits estimated by linear regression. Significant correlations with peak yank, peak force and reaction time were found in the theta/alpha (5–12 Hz) band, and with peak yank and peak force in the high-gamma/high-frequency (55–375 Hz) range. No correlations were found in the beta (13–30 Hz) band. Non-significant correlations are not illustrated.

5.3.2 Frequency specific changes in STNr LFP activity correlate with peak motor performance across subjects, irrespective of peripheral afferance.

Earlier in the text, we considered LFP power changes from cue onset to response onset in the case of reaction time, and from cue onset to the moment of development of peak yank in the case of peak yank and peak force. However, the latter allows sufficient time for peripheral afference to contribute to the correlations. We therefore repeated the previous simple and multiple regression analyses for peak yank and peak force taking LFP power changes from cue onset to response onset and confirmed the same relationships despite the fact that the greatest gamma increases developed after response onset .

As before, significant correlations between theta/alpha and high gamma/high frequency LFP power with both PY and PF were again identified **(Figure 5.5)**. Multiple regression analysis (with theta/alpha, high beta, and high gamma/high frequency power as predictive variables) identified a strong model fit for PY ($F=12.96$, $P<0.001$, $R^2=0.708$), with a non-significant intercept. Both increases in theta/alpha and high gamma/high frequency LFP power were found to be predictive of increases in PY ($\beta = 0.486$, $P= 0.004$ and $\beta = 0.576$, $P=0.003$, respectively), with no significant contribution from high beta power. Similarly, the overall multiple regression model fit for PF was also very strong ($F=9.720$, $P=0.001$, $R^2=0.646$) and identified significant contributions of theta/alpha ($\beta = 0.539$, $P = 0.004$) and high gamma/high frequency ($\beta = 0.463$, $P = 0.019$) power in predicting PF. The intercept was non-significant and beta activity was of no independent predictive value.

5.3.3 Within-subject scaling of frequency band specific LFP power with performance under baseline conditions.

Finally, in a small number of cases, we were also able to identify a scaling effect of frequency band-specific LFP power with performance at the within-subject level **(Figure 5.6).**

Spearman's rank correlation coefficients were calculated to investigate the expected monotonic but non-linear relationships between frequency-specific LFPs and variations in peak motor parameters around the limits of performance, at the within-subject level and under baseline conditions (responses to V cues when ON L-DOPA). Significant correlations ($P<0.05$) were found between PY and high gamma/high frequency power in two cases (rho=0.943, p=0.005; rho=0.683, $P=0.042$) and with theta/alpha power in one case (rho=0.810, $P=0.015$). In addition, a significant correlation between PF and high gamma/high frequency activity was found in one case (rho=0.829, $P=0.042$), and between RT and theta/alpha power (rho=-0.850, $P=0.004$) in one

further case. The scatterplots identifying the strongest correlations between frequency-specific LFPs and each performance measure, within the ten subjects, are shown in **Figure 5.6**.

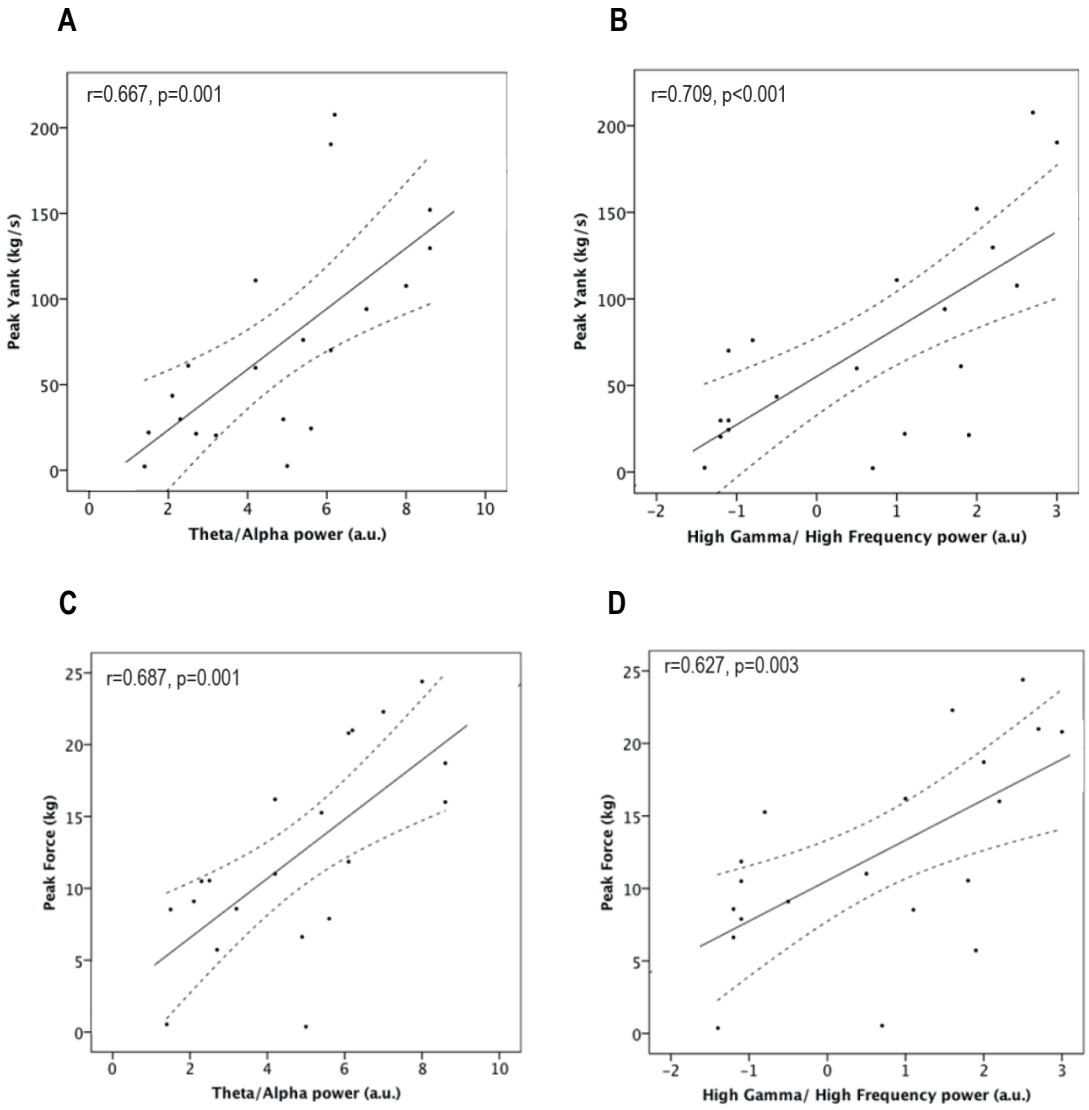


Figure 5.5 Scatter-graphs relating LFP power (over the time period from cue onset to response onset) to performance. Continuous and interrupted lines represent the best fit and corresponding 95% confidence limits estimated by linear regression.

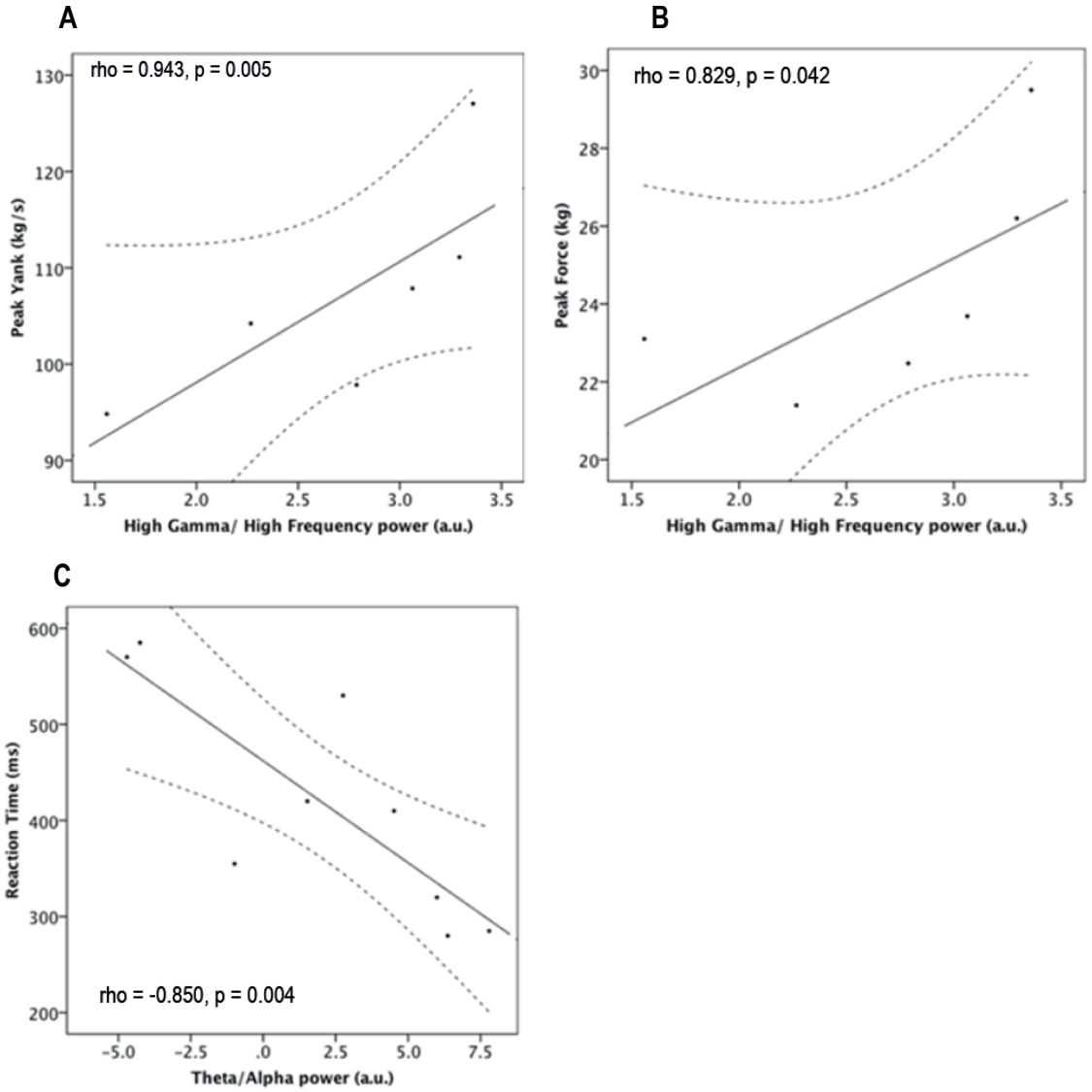


Figure 5.6 Scatter-plots demonstrating the strongest correlations between frequency-specific LFPs and each performance measure, identified within the ten subjects, in response to the V cue when ON medication. Each point represents data from an individual trial in an experimental run in that subject (trials in which patient failed to make a response or LFP activity was contaminated by signal artifact were rejected prior to further statistical analyses). Peak Force and Yank correlations are derived from Patient 1, Reaction Time correlations are derived from Patient 7 in **Table 5.1**.

5.3.4 Intense auditory stimuli enhance mean peak yank and reaction time, whereas L-DOPA only reduces reaction time and does so without interacting with the effects of loud auditory cues

The delivery of brief 96-dB auditory tones at the same time as visual cues, improved average peak yank and reaction time in our subjects. A repeated-measures ANOVA applied to peak yank data identified an effect of cue type ($F_{1,19} = 6.464$, $P = 0.020$), but no effect of dopaminergic medication ($F_{1,19} = 2.695$, $P = 0.117$) or dopaminergic medication × cue-type interaction ($F_{1,19} = 3.333$, $P = 0.084$). Peak yank increased by 11.8 ± 3.5% with auditory–visual cues (82.0 ± 16.1 kg/s) as compared with visual cues (71.8 ± 13.0 kg/s), when averaging across OFF and ON medication recordings.

A repeated-measures ANOVA applied to reaction time data identified an effect of cue type ($F_{1,19} = 64.919$, $P < 0.001$) and dopaminergic medication ($F_{1,19} = 5.597$, $P = 0.029$), but no dopaminergic medication × cue-type interaction ($F_{1,19} = 3.465$, $P = 0.078$). Reaction time reduced by 35.4 ± 2.2% with auditory–visual cues (239.3 ± 13.8 ms) compared with visual cues (380.6 ± 26.3 ms), when averaging across OFF and ON medication recordings. Reaction time decreases from 322.5 ± 22.2 ms OFF L-DOPA to 297.4 ± 17.2 ms ON L-DOPA were further observed ($P = 0.029$, paired *t*-test averaged across cue types). The lack of dopaminergic medication × cue-type interactions for both peak yank and reaction time data suggested that improvements in performance with auditory–visual cues, were independent of dopaminergic therapy (Chapters 3 & 4)

In the current study, however, there were no significant effects of cue or drugs on peak force so that this measure of performance was not considered further (cue type, $F_{1,19} = 0.212$, $P = 0.650$; medication state, $F_{1,19} = 0.985$, $P = 0.333$; medication × cue-type interaction. $F_{1,19} = 2.462$, $P = 0.133$). Group average force and yank traces, in response to visual and auditory–visual cues, are shown in **Figure 5.7.**

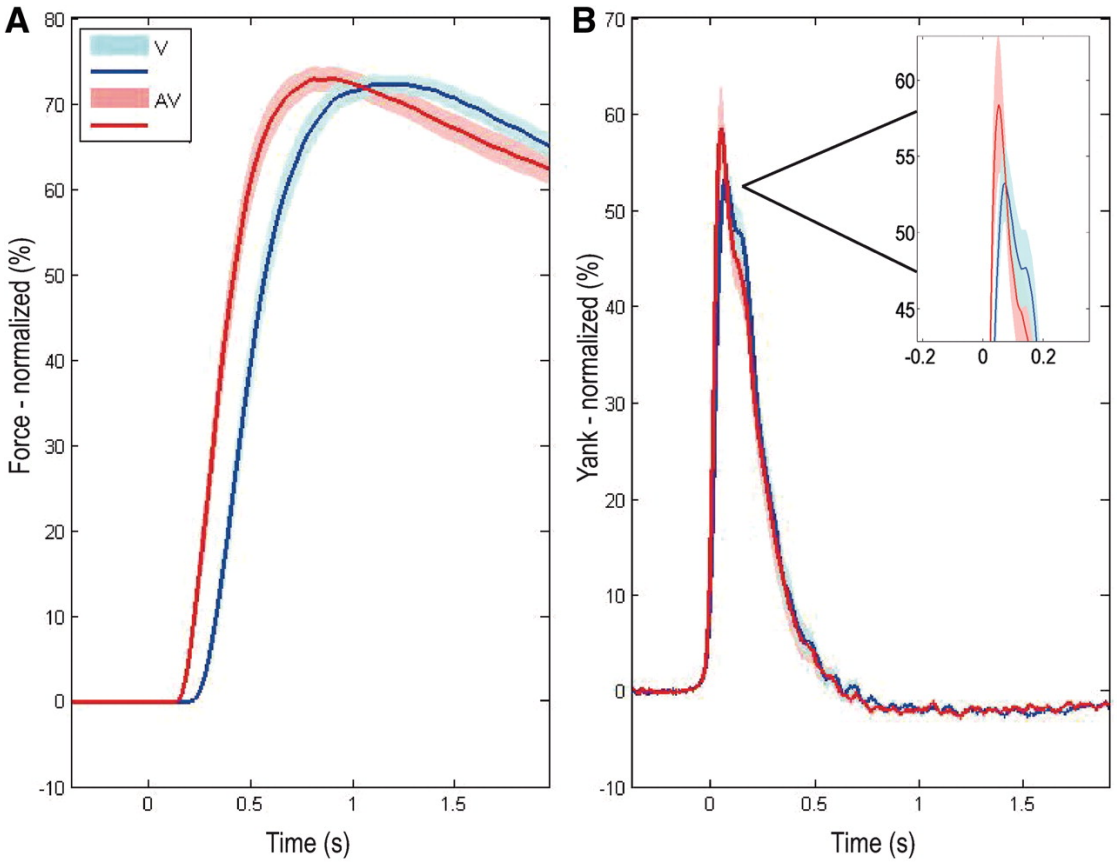


Figure 5.7 (A) Group average grip force achieved in visual (V) and auditory–visual (AV) trials across STN DBS patients (no stimulation; n = 20 hands), averaged across OFF and ON L-DOPA conditions. Time zero represents cue onset. For the purposes of graphical representation only, group average traces have been derived as the mean of the average responses of each gripping hand to visual and auditory–visual cues, normalized as a percentage of the average maximal voluntary contraction achieved in the visual condition when patients were ON and OFF L-DOPA. Shaded area represents SEM. of the trace. (**B) Group average yank (rate of development of force) achieved in visual and auditory–visual trials, averaged across OFF and ON L-DOPA conditions.** Traces have been averaged after realignment to response onset. Significant reductions in reaction time and enhancements in peak yank (see boxed expansion of the peak difference), but no change in peak force, are evident in response to auditory–visual as compared with visual cues.

5.3.5. Changes in peak yank and reaction time are accompanied by frequency-specific mean changes in local field potential power with experimental condition

We next defined how LFP responses differed when triggered by combined auditory and visual cues with or without overnight withdrawal of anti-parkinsonian medication. To this end, we aimed to group activity over frequencies with similar reactivity to either cue type or L-DOPA into discrete bands, contiguous with neighbouring bands which differed in their average response to experimental condition. Time–frequency spectra of cue-induced subthalamic nucleus region LFPs in the three additional experimental conditions (OFF L-DOPA visual cue, OFF L-DOPA auditory–visual cue, and ON L-DOPA auditory–visual cue) revealed prominent differences in power at frequencies ≤30 Hz between OFF and ON L-DOPA recordings, and at frequencies >30 Hz between visual and auditory–visual cues **Figure 5.8**. We therefore performed separate ANOVAs of percentage change in LFP power (relative to a pre-cue baseline) in activities across the three frequency bands ≤30 Hz (5–12, 13–23 and 24–30 Hz) and for the three frequency bands >30 Hz (31–45, 55–95 and 105–375 Hz), to see which, if any of these bands, might be influenced by cue type and medication status (refer to 2.4.3.3 for rationale for selection of frequency bands). The results of these ANOVAs are presented in **Table 5.2**. *Post hoc* exploration of significant main effects and interactions is described below.

Table 5.2 Separate repeated-measures ANOVAs of percentage change in LFP power (relative to a pre-cue baseline) applied to activities ≤30 Hz (5–12, 13–23, 24–30 Hz bands) and >30 Hz (31–45, 55–95, 105–375 Hz bands). Additional factors included cue type (visual or auditory–visual) and medication (OFF or ON L-DOPA). Significant results are in bold.

Within-subject effects	**(A) ≤ 30 Hz frequency bands**	**(B) > 30 Hz frequency bands**
Frequency	**$F_{2,38}$ = 56.099, *P*<0.001**	**$F_{2,38}$ = 11.493, *P*<0.001**
Cue type	$F_{1,19}$ = 0.282, *P* = 0.602	**$F_{1,19}$ = 15.000, *P* = 0.001**
Medication	$F_{1,19}$ = 3.585, *P* = 0.074	$F_{1,19}$ = 0.059, *P* = 0.811
Frequency x Medication	**$F_{2,38}$ = 3.503, *P* = 0.041**	**$F_{2,38}$ = 7.777, *P* = 0.002**
Cue type x Frequency	$F_{2,38}$ = 0.094, *P* = 0.865	$F_{2,38}$ = 0.632, *P* = 0.500
Cue type x Medication	$F_{1,19}$ = 0.047, *P* = 0.830	$F_{1,19}$ = 0.658, *P* = 0.427
Frequency x Cue type x Medication	$F_{2,38}$ = 0.160, *P* = 0.843	$F_{2,38}$ = 0.785, *P* = 0.432

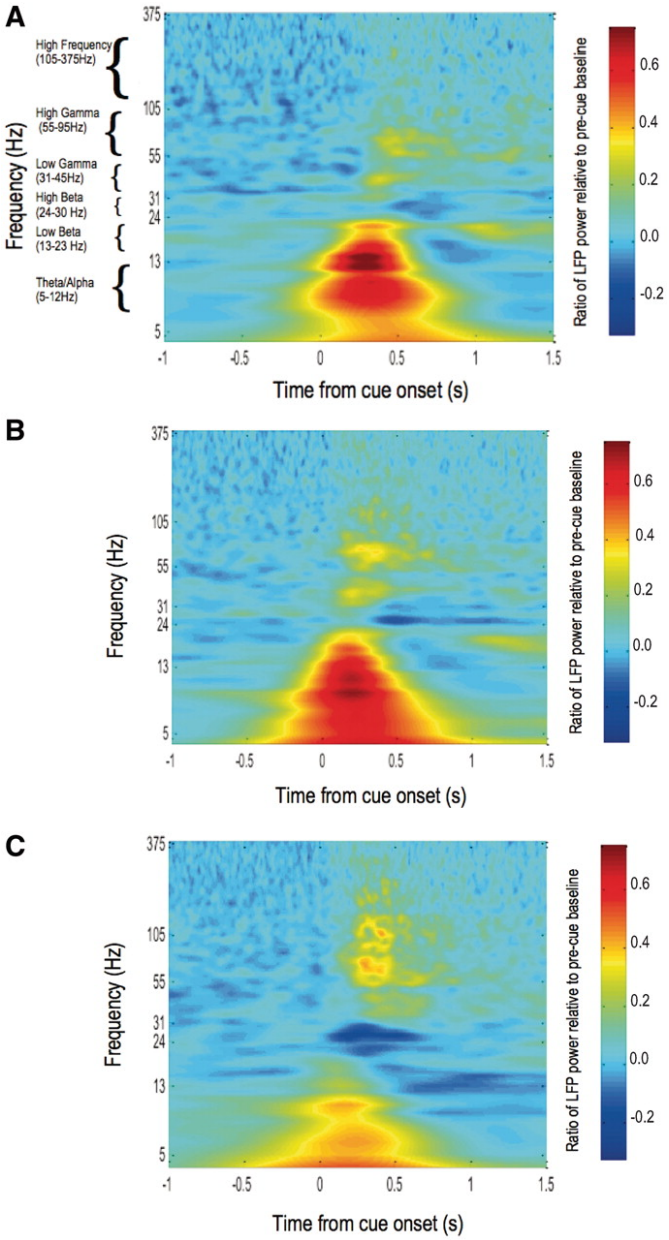


Figure 5.8 Matrices of average time–frequency plots of change in induced spectral power in 20 subthalamic nuclei contralateral to sustained maximal hand grips, relative to a pre-cue baseline, under different experimental manipulations. Time zero represents onset of the imperative visual or loud auditory–visual cue. Colour gradient represents ratio of post-cue LFP power to average LFP power 1–2 s before cue onset. Spectral changes under three different experimental conditions are represented as (**A**) OFF L-DOPA, visual cue; (**B**) OFF L-DOPA, auditory-visual cue and (**C**) ON L-DOPA, auditory–visual cue. The spectral changes in the baseline condition, ON L-DOPA, visual cue state are shown in Figure 5.3. Power changes common to each experimental condition occurred over six frequency bands: theta/alpha (5–12 Hz), low beta (13–23 Hz), high beta (24–30 Hz), low gamma (31–45 Hz), high gamma (55–95 Hz), and high frequency (105–375 Hz). Frequency is plotted on a log axis.

The repeated-measures ANOVA applied to activities ≤30 Hz identified a significant effect of frequency and a significant medication × frequency interaction. *Post hoc* paired *t*-tests confirmed a significant reduction in power in the low beta band ($P = 0.020$) and trend towards a similar effect on high-beta activity ($P = 0.077$), but no effect on theta/alpha power ($P = 0.774$) with L-DOPA, when averaging across responses to different cue types.

Conversely, the ANOVA of percentage change in activities >30 Hz identified a significant effect of cue type, but no cue type × frequency interaction, suggesting a similar magnitude of response to auditory–visual cues in each frequency band. An overall effect of frequency reflected only differences in the average power across each frequency band relative to baseline. A significant medication × frequency interaction, resulted solely from an increase in low gamma activity ($P = 0.015$, paired *t*-test when averaging across cue type; high gamma, $P = 0.284$; high frequency, $P = 0.180$). Given these results recordings from OFF and ON dopaminergic medication were averaged across the three frequency bands, and *post hoc* paired *t*-tests were performed that demonstrated higher power in a broad gamma (31–375 Hz) band following auditory–visual as opposed to visual cues (low gamma, $P = 0.027$; high gamma, $P = 0.006$; high frequency, $P \ll 0.001$). Thus, auditory–visual cues promoted cue-related power increases in frequency bands >30 Hz. This broad gamma band was used for all subsequent analyses.

5.3.6 Frequency-specific subthalamic nucleus region local field potential activity contributes to the facilitation of peak motor performance with experimental condition

Multi-level modelling was used to derive general regression equations for percentage increments/decrements in peak yank and reaction time, relative to our baseline condition of maximal effort grips executed in response to visual cues when patients were ON medication. Within the model, regression coefficients afford an estimate of the degree to which the change in performance from baseline scales with LFP activity, whereas intercepts represent the portion of the change from baseline performance that is independent of subthalamic nucleus region LFPs.

The models only identified broad gamma power (31–375 Hz) as a significant predictor of the response variables **(Tables 5.3 & 5.4)**. Auditory–visual cues were found to induce a scaling of broad gamma activity with peak yank, in both OFF and ON L-DOPA states, which was not present in response to visual cues alone. On the other hand, a consistent scaling of broad gamma activity with reaction time was present independent of experimental condition. There were also large shifts in intercepts relative to the baseline condition; those due to withdrawal from dopamine included an improvement in peak yank that most probably related to the lack of fatigue

rather than drug state, as OFF drug recordings were necessarily conducted before ON drug experiments. Moreover, no significant difference was identified between peak yank attained in OFF and ON drug recordings, in an earlier analysis of the performance data alone (see earlier text).

Given the relatively large intercept shifts with auditory–visual cues, we lastly evaluated the quantitative contribution of broad gamma activity in predicting auditory–visual-induced changes in peak yank and reaction time from the baseline visual ON L-DOPA condition. This was achieved by multiplying coefficients by the mean level of broad gamma band activity in the corresponding condition. Averaging across drug states, broad gamma activity contributed to 13.2 ± 8.0% (95% confidence interval) of the enhancement in peak yank, but only 1.1 ± 0.1% of the reduction in reaction time with loud auditory cues. Thus, changes in broad gamma activity contributed to improvements in peak yank, but barely affected reaction time. Even in the case of peak yank, the larger proportion of motor enhancement with auditory–visual cuing was independent of synchronous oscillatory activities in the subthalamic nucleus, or, at the very least, independent of a linear relationship with the LFPs.

Table 5.3 Experimental condition specific regression coefficients (β) and intercept shifts (μ) for regression models derived for Peak Yank and Reaction Time. Intercept shifts represent the % increments/decrements from maximal grips made in response to visual (V) cues when patients were ON L-DOPA, which also formed the baseline condition for our multi-level multivariate regression modelling approach. AV = auditory–visual.

Experimental condition		(A) Peak Yank			(B) Reaction Time		
		Broad gamma regression coefficient (β)	Intercept shift (μ)		Broad gamma regression coefficient (β)	Intercept shift (μ)	
			AV cue	OFF L-DOPA		AV cue	OFF L-DOPA
OFF L-DOPA	V cue	----	----	8.57	-0.101	----	4.38
	AV cue	0.223	11.38	8.57	-0.101	-36.46	4.38
ON L-DOPA	V cue	----	----	----	-0.101	----	----
	AV cue	0.223	11.38	----	-0.101	-36.46	----

Table 5.4 Detailed multi-level multivariate regression modelling output for (A) Peak Yank and (B) Reaction Time. Values derived for 'AV cue' and 'OFF L-DOPA' conditions represent intercept shifts from baseline, of the regression line relating any frequency-band specific LFP power to motor performance under the respective conditions (see line labelled 'MLM' in **Figure 5.1**). Those values attributed to frequency bands or frequency band- experimental condition interactions (*), represent the regression coefficients for the condition specific LFP power-performance best fit lines. The baseline constituted LFP power-performance relationships during maximal grips in response to V cues when patients with PD were ON L-DOPA. Significant values are emboldened. SE is standard error. DF is degrees of freedom.

A. Peak Yank Model					
	Value	SE	DF	t-value	*P-value*
AV Cue	**11.38156**	2.436769	759	4.670757	**0.0000**
OFF L-DOPA	**8.57415**	2.421700	759	3.540551	**0.0004**
Broad Gamma	-0.07665	0.065249	759	1.174801	0.2404
Theta/Alpha	0.24400	0.128297	759	1.901854	0.0576
Broad Gamma *OFF L-DOPA	-0.10961	0.059026	759	1.856919	0.0637
AV cue * Broad Gamma	**0.22329**	0.068037	759	3.281859	**0.0011**
B. Reaction Time Model					
	Value	SE	DF	t-value	P-value
AV Cue	**-36.46863**	1.4916246	762	24.44893	**0.0000**
OFF L-DOPA	**4.38373**	1.4776935	762	2.96660	**0.0031**
Broad Gamma	**-0.10110**	0.0352781	762	-2.86572	**0.0043**

5.3.7 Local field potential activity reflects local processing in the subthalamic nucleus region

LFP recordings from the subthalamic region were highly focal, as indexed by steep percentage drops in power when comparing the 'best' contact pair, with the highest absolute power, to the mean power recorded by the two remaining contact pairs on each electrode. **Figure 5.9** shows the power drop for each frequency band used in multi-level modelling analysis. In this, we have averaged across experimental conditions and drug states. There is a clear drop in all frequency bands, albeit less pronounced in the theta–alpha band.

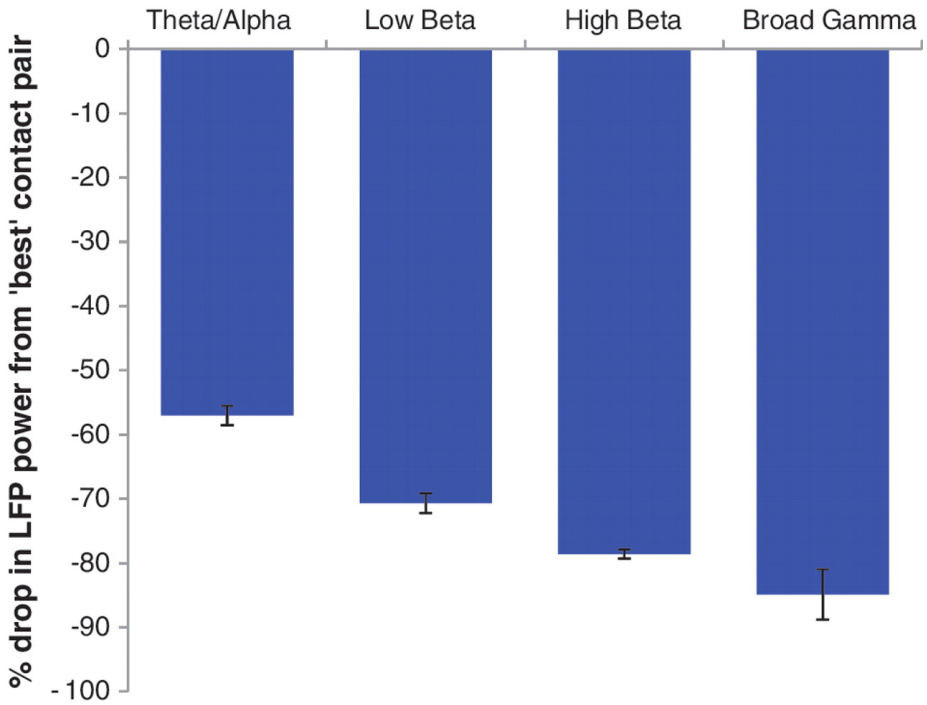


Figure 5.9 Mean ± SEM percentage drop in LFP power from the contact pair recording the greatest power change from baseline, for each frequency band, averaged across experimental condition.

5.4 Discussion

The findings of our study are 2-fold. We first report a striking correlation between both theta/alpha (5–12 Hz) and high-gamma/high-frequency (55–375 Hz) activities in the subthalamic nucleus region LFP and average peak force measures attained, in response to visual cues when patients were ON L-DOPA (baseline condition). These spectral features were able to independently predict close to 70% of the variance in peak yank and peak force across subjects. The relationship with reaction time, however, was limited to the theta/alpha band, and less substantial, suggesting a larger influence of a different neural source, or at the very least a non-linear effect of LFP activity, on this parameter. Second, we describe an increase in broad gamma (31–375 Hz) subthalamic nucleus region LFP power, over and above those activities encoding maximal effort grips in the baseline condition, which was found to make a modest but significant 13.2% contribution to enhancements in peak yank, but only a trivial contribution to reaction time shortening, with auditory–visual cues. Although reaction time shortening was also observed in response to administration of L-DOPA, independent of cue type delivered, no frequency-specific components of subthalamic nucleus region LFP activity could be attributed to this effect.

5.4.1 Theta/alpha and high-gamma/high-frequency subthalamic nucleus region local field potential activity predicts average peak force measures attained by an individual

The results of our study ascribe a novel function to frequency-specific subthalamic nucleus region LFP activity, as having substantial explanatory influences on the peak motor parameters attainable by a subject at maximal effort. A similar, albeit weaker, phenomenon has previously been described whereby subthalamic nucleus region LFP measures have been found to correlate with motor UPDRS across patients (Chen et al*,* 2010; Pogosyan et al*,* 2010). These subthalamic nucleus LFP-force correlations are in line with the hypothesized role of the basal ganglia in the scaling of movement, although this role is largely deduced from activities related to a range of submaximal motor responses (Turner and Desmurget, 2010). Indeed, both PET (Turner et al*,* 2003) and functional MRI studies (Vaillancourt et al*,* 2004, 2007; Prodoehl et al*,* 2009; Grafton and Tunik, 2011) have identified correlations between basal ganglia activity and a range of amplitudes, velocities and forces with which healthy subjects were required to execute movement. In particular, subthalamic nucleus activity has been associated with the generation of force pulses in precision grip tasks (Vaillancourt et al*,* 2007).

With respect to the correlation between high-gamma/high-frequency (55–375 Hz) activity in the subthalamic nucleus LFP and force measures reported in our study, high-gamma (35–100 Hz)

activity in the globus pallidus interna LFP has also recently been implicated in the scaling of movement in patients with segmental dystonia, although the correlations with movement velocity were much weaker than those shown here (Brücke et al*,* 2012). In addition, a similar role has been suggested for gamma (60–90 Hz) synchronization in the motor cortex of healthy subjects (Muthukumaraswamy, 2010). A prokinetic function of subthalamic nucleus LFP activity at very high frequencies (>100 Hz), has further been proposed, on the basis of the increase in amplitude of high-frequency oscillations accompanying voluntary movements, and following treatment with dopaminergic medication in patients with Parkinson's disease (Foffani et al*,* 2003). However, the latter is contentious as Lopez-Azcarate and colleagues (2010) reported high-frequency oscillations of a similar amplitude both OFF and ON dopaminergic medication, but showed marked movement-related amplitude modulation of this activity when liberated from beta coupling when ON dopaminergic medication. A further study has suggested that it is the ratio of slower (200–300 Hz) to faster (300–400 Hz) high-frequency oscillations that correlates with UPDRS motor scores (Özkurt et al*,* 2011). As with Lopez-Azcarate et al, (2010), we found that our high-gamma/high-frequency band (which included oscillatory activity >100 Hz) was of similar amplitude with or without dopaminergic medication, although in considering a wide frequency range we could not address the question of a frequency shift in the high-frequency activity. The very wide spectral range of the high-frequency oscillations in this and other studies also raises the possibility that some of the activity could reflect neuronal spiking in the electrode vicinity, as has been suggested at the cortical level (Ray and Maunsell, 2011).

Oscillatory activity in the theta/alpha range, which was found to correlate with our peak force measures, has generally been associated with mechanisms of attention (for review see Palva and Palva, 2007). In particular, alpha activity (7–13 Hz) in the subthalamic nucleus of patients with Parkinson's disease at rest is coherent with parietotemporal cortex in a circuit that has been proposed to subserve attentional functions (Hirschmann et al*,* 2011; Litvak et al, 2011). More apposite to the present results, LFP recordings from the subthalamic nucleus of patients with Parkinson's disease and from the globus pallidus interna of patients with dystonia have shown that contralateral alpha activity increases in fast movements compared with rest, and passive or active slow repetitive extension and flexion of the elbow (Singh et al, 2011). In the latter study, the increased synchronization in the alpha range was concurrent with the period of elevated acceleration in the fast movement. As this was seen in both patient groups, it was considered to be primarily physiological and task specific, rather than disease related.

The lack of an independent contribution of beta band oscillations to the prediction of force measures was conspicuous. Elsewhere, it has been argued that suppression of population synchrony in the beta frequency range is necessary to allow task-related rate coding and more focal neuronal assemblies to engage in task-specific processing related to voluntary movement (Brown and Williams, 2005). Indeed, recordings in non-human primates confirm an inverse relationship between oscillatory LFP activity in the beta band and local task-related rate coding in the striatum (Courtemanche et al, 2003). Our finding of a suppression of beta activity following imperative visual cues, which did not scale with behavioural performance, is thus consistent with a binary gating function of beta (Kempf et al, 2007; Brücke et al, 2012).

Finally, whether theta/alpha and high-gamma/high-frequency activities in the basal ganglia relate to a phenomenon that parameterizes force or a higher order process that regulates the scaling of movement (Turner and Desmurget, 2010) is unclear. It has previously been suggested that movement parameters are essentially 'selected' from an underlying range of physiological capabilities, so as to optimize the use of neuromuscular energy; the likelihood of selection of faster or stronger movement parameters, based on such implicit cost-benefit assessments, has been termed 'motor vigor' (Mazzoni et al, 2007). In the current paradigm, it is plausible that even under instruction to execute maximal handgrips, individuals continued to select grips from the previously described distribution, and it is, thus, the motor vigor or effort invested in selection of the optimal motor parameters, that frequency-specific oscillatory activity in the basal ganglia encodes. Further work in this area would be of great interest.

5.4.2 Broad gamma subthalamic nucleus region local field potential activity makes a significant but modest contribution to motor enhancement with intense stimuli

Our multi-level multivariate regression modelling approach identified the induction of a novel (over and above that in the baseline state) but small scaling factor between broad gamma (31–375 Hz) activity and peak yank, with auditory–visual cuing. Such an influence of frequency-specific subthalamic nucleus LFP activity on motor enhancement with intense stimuli provides further support for the previously proposed role of the subthalamic nucleus in 'energizing' movement. Indeed, it has previously been proposed that 'motor vigor' itself can be subject to modulation by temporally pressing situations, whereby the system is forced to adopt a more expensive trade-off, thus leading to a more consistent optimum performance (Ballanger et al, 2006).

Nonetheless, it was the contribution of experimental condition-specific 'intercept shifts' of the best-fit line relating broad gamma LFP power to motor performance, which dominated over

changes in regression coefficients for both performance measures. Broad gamma activity was found to account for only 13.2 ± 8.0% of the enhancement in peak yank, when considering the induced scaling factor together with the increase in amplitude of LFP activity in this frequency band, following auditory–visual cues. Moreover, the effect of changes in broad gamma LFP power on the marked shortening of reaction time with auditory–visual cuing was near inconsequential. Thus, we conclude that enhancement of peak motor performance with auditory–visual cues was achieved largely independently of frequency-specific subthalamic nucleus region LFP activity, or at the very least, independent of a linear relationship of this activity with the performance increments observed.

What then might be the neural substrate mediating performance enhancements with auditory–visual cuing? We have previously posited that the intense or arousing nature of our auditory–visual cue implicates a role of phasic arousal (Sturm and Willmes, 2001) in driving the phenomenon (Chapter 4). The brainstem reticular activating system, in particular, is a largely non-dopaminergic network that has been implicated in cortical activation or arousal (Dringenberg and Vanderwolf, 1998). Its involvement would fall in line with the dopamine independence of the behavioural effect observed. Within this network, a role of the pedunculopontine nucleus, known to be tightly coupled to the subthalamic nucleus (Aravamuthan et al, 2009), is conceivable, but whether alerting cholinergic projections from the brainstem reticular activating system (Steriade et al*.,* 1990, 1991; Munk et al, 1996) can bypass those basal ganglia components dependent on dopaminergic input deserves further investigation. In addition, a role of the left parasagittal and lateral cerebellar hemisphere, as well as bilateral sensory motor cortices, has also been suggested in sensory stimulus-elicited improvements in performance (Thobois et al*,* 2007).

5.4.3 Caveats and concluding remarks

Two possible limitations of the present study are worth highlighting. First, our study participants were necessarily patients with Parkinson's disease, so inferences regarding normal functioning must be circumspect (Williams et al, 2002). That said, and as discussed previously, the core relationship between subthalamic nucleus region LFPs and force measures in our baseline task had much in common with the behaviour of cortical and pallidal activities in healthy subjects and patients with cranial dystonia, without obvious upper limb involvement (Muthukumaraswamy, 2010; Brücke et al, 2012). The latter, however, introduces the second issue—could the power changes picked up at the bipolar contacts of the deep brain stimulation electrode be the product of volume conduction from another, possibly cortical, source? Against this, we report a steep gradient in LFP power between those bipolar contact pairs recording the highest absolute power

and the two remaining contact pairs, independent of the frequency of the oscillatory activity, which is consistent with a local generator (Kühn et al, 2004, 2006). Moreover, a number of studies have now demonstrated the locking of discharge of neurons in the subthalamic nucleus to the LFP (Levy et al, 2002; Kühn et al, 2005; Pogosyan et al, 2006; Trottenberg et al, 2006; Weinberger *et al*., 2006). Finally, it should be pointed out that involvement of the subthalamic nucleus in motor control has been suggested to extend well beyond the scaling of movement, as discussed here, to include motor learning, action selection and response inhibition, and the online correction of motor error (Turner and Desmurget, 2010).

To conclude, we provide strong correlative evidence (accounting for ~70% of the intersubject variance) linking subthalamic nucleus region oscillatory activity over the theta/alpha and high-gamma/high-frequency ranges to the average peak force and peak rate of development of force attained by individuals, in voluntary grips performed as fast and as strongly as possible in response to a visual cue. Frequency-specific oscillatory activity, however, was found to make only a small contribution to the additional improvement in peak yank and reaction times engendered by intense auditory stimuli, independent of dopaminergic state. Our findings provide insight into the relationship between oscillatory activity in the subthalamic nucleus region and contractions made with maximal effort and raise the possibility that such activity encodes motor vigor. At the same time the suggestion that non-dopaminergic processes (which are also independent of frequency-specific oscillatory activity in the subthalamic nucleus region) underscore the additional performance improvements following intense stimuli, encourages the search for alternative, non-dopaminergic, systems that may beneficially influence motor behaviour.

Chapter 6

Manipulation of subcortical evoked activity enhances peak motor performance in Parkinson's disease

6.1 Introduction

A brief enhancement of motor performance in response to intense, alerting, or arousing stimuli, is a commonly experienced phenomenon. Under such circumstances, experimental evidence has now shown that even peak motor responses can undergo augmentation, over and above the effects of maximal effort of will, both in healthy subjects (Chapter 3; Angel, 1973; Woodworth, 1938) and in patients ordinarily hindered by the bradykinetic symptoms of Parkinson's disease (PD) (Chapters 4 &5; Ballanger et al, 2006; Valldeoriola et al, 1998). Indeed, anecdotal reports of a comparable effect – termed 'paradoxical kinesis' (Souques, 1921) - have described patients with advanced PD suddenly being able to jump up and run at the sound of a car accident, the sensation of an earthquake, or sight of a fire (Daroff, 2008; Bonanni et al, 2010; Glickstein & Stein, 1991). However, the neural mechanisms underlying this remarkable phenomenon have remained enigmatic. Our goal in the current study is thus to define the mechanisms underlying the augmentation of peak motor performance by arousing stimuli. Characterization of the candidate activities mediating such facilitation of peak motor performance is a critical step if interventions are to be developed to modulate them, with potential applications ranging from military personnel to a novel therapeutic approach for patients suffering from hypokinetic disorders such as PD.

A number of studies have now implicated a role of the basal ganglia in the scaling of voluntary movement (Brücke et al, 2012; Grafton & Tunik, 2011; Turner & Desmurget, 2010; Muthukumaraswany, 2010; Thobois et al, 2007; Turner et al, 2003), including that at maximal effort (Anzak et al, 2012; Joundi et al, 2012). Here we test the hypothesis that activity in this network responsible for movement scaling also helps mediate additional enhancements in motor performance with arousing stimuli. To this end we capitalize on the unique opportunity afforded by therapeutic deep brain stimulation to record from and stimulate key subcortical nuclei.

6.2 Materials and methods

6.2.1 Subjects

All subjects gave their informed consent to take part in the study, which was approved by the local ethics committees at our recording sites in Oxford, London and Bristol, United Kingdom.

Eight patients with PD (mean disease duration 11.6 years, mean age 57.1 years, range 32–70 years, six males) underwent bilateral implantation of DBS electrodes into the STN, as a prelude to therapeutic high frequency stimulation for advanced idiopathic PD with motor fluctuations and/or dyskinesias. Techniques to target and implant electrodes in the STN have previously been described (Foltynie and Hariz, 2010). No microelectrode recordings were made, although the effects of direct stimulation were confirmed intra-operatively in those patients who underwent surgery at the John Radcliffe Hospital, Oxford and King's College Hospital, London **(see Table 6.1)**. In addition, the locations of the electrodes were confirmed with immediate post-operative stereotactic imaging carried out at all surgical centres. Nonetheless, in acknowledgement of the fact that not all electrode contacts could be expected to lie in the STN *per se*, we term the area sampled by the contact pairs the STN region, STNr. DBS electrode extension cables were externalized through the scalp to enable recordings prior to connection to a subcutaneous DBS pacemaker, implanted in a second operative procedure up to seven days later. Clinical details of the patients are available in **Table 6.1.** The mean percentage improvement in the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) on treatment with levodopa (L-DOPA) was 70.0 ± 5.6% (P = 0.002, paired t-test between ON and OFF L-DOPA scores; data missing in one case) across subjects, indicating good responsiveness to L-DOPA in our study participants. A further PD patient was implanted in the pedunculopontine region (PPNr) and STNr/ zona incerta, bilaterally, for freezing of gait (see last case in **Table 6.1**). The PPNr electrodes were placed using a transventricular trajectory so that all four electrode contacts were intended to lie within the PPN. The STNr electrodes were placed in the caudal zona incerta, with the central two electrode contacts lying adjacent to or clipping the STN. Details of the surgical procedure are outlined in Khan et al, 2011. In a further sub-study, 10 patients with PD, under the care of the National Hospital for Neurology & Neurosurgery, London, and undergoing chronic high frequency DBS of the STN for an average of 20 months, were recruited (mean age 53.2 years, range 33-65 years, 7 male, average daily L-DOPA dose 671mg, 64.0% average improvement in UPDRS scores with DBS ON compared to OFF, when ON dopaminergic medication).

6.2.2 Experimental paradigm

Subjects were presented with a series of imperative visual (V) cues, separated by 8.0 ± 0.5 s, and instructed to squeeze a force dynamometer "as fast and hard as you possibly can when the light comes on and maintain this for the duration of the light" (red light-emitting-diode illuminated for 3 s). A loud auditory stimulus (40 ms duration, 1 kHz), at one of five different randomly selected intensities (82, 88, 94, 100, 105 dB) was delivered binaurally through headphones, with

onset simultaneous with that of the V cue. However, subjects were asked to just focus on responding to the V cues. Fifteen cues of each intensity (75 trials in total) were delivered in each experimental run. Trials were carried out in a blocked design, and left- and right-hand recordings were counterbalanced across subjects. Inter-trial intervals were similar to those previously used in investigations of the StartReact phenomenon (Valls-Solé et al, 2005; Carlsen et al, 2004), but shorter than in our previous studies (Chapters 3, 4 & 5) to allow for a greater number of trials to be executed prior to correlative analysis, whilst avoiding an excessively lengthy paradigm in our patients with PD.

Grip force was measured one hand at a time in each subject using an isometric dynamometer (G100; Biometrics Ltd, Cwmfelinfach, Gwent, UK), with standard Jamar design and its handle set in the second of the five discrete grip diameter adjustments possible (Sancho-Bru et al, 2008). Subjects were seated with their shoulders adducted (so that elbows rested against the trunk), their elbows flexed at about 90° and their forearms in neutral, as recommended by the American Association of Hand Therapists (Fess, 1992). Stimulus intensities were measured in a sound-proofed room with a Brüel and Kjaer 2260 Observer (Brüel and Kjaer, Nærum, Denmark) via an artificial ear and headphone adapter.

Table 6.1 Clinical details of patients with PD and externalized DBS electrodes (b). Surgical sites: (1) National Hospital for Neurology & Neurosurgery, London, (2) John Radcliffe Hospital, Oxford, (3) Kings College Hospital, London, (4) Frenchay Hospital, Bristol. UPDRS scores for Patient 8 were not available.

Site	Bilateral targets	Patient No.	Age/yrs	Disease duration/yrs	Daily L-DOPA equivalent dose/mg	Pre-op UPDRS OFF/ON Levodopa
1	STN	1	59	15	700	28/5
1	STN	2	60	17	1725	63/7
1	STN	3	32	10	875	52/13
1	STN	4	56	10	400	40/12
2	STN	5	70	12	1100	62/29
2	STN	6	60	7	200	25/13
3	STN	7	56	10	900	26/7
3	STN	8	64	12	300	n/a
4	STN& PPN	9	68	12	475	38/20

6.2.3 Recordings

In our nine patients with externalized DBS electrodes (8 bilateral STN, 1 bilateral PPN & STN/ZI), LFP recordings were made 3–6 days after surgery. In order to complete the recordings in one morning, and limit intrusion on our easily fatigable post-operative patients, recordings were always made first after overnight withdrawal of anti-parkinsonian medication (OFF L-DOPA), and then again approximately 1 h after taking their usual morning dose (average morning L-DOPA dose administered = 186 ± 62 mg). Improvement with medication was confirmed through assessment of finger tapping, wrist rigidity and tremor (using the corresponding items of the motor UPDRS).

LFPs, and surface EEG from Fz and Cz were recorded monopolarly with respect to a linked earlobe reference using a TMSi porti (TMS international) and its respective software. EMG was recorded from orbicularis oculi. All recordings were band-pass filtered between 0.5 and 500 Hz and sampled at 2048 Hz. Analogue correlates of the visual and auditory stimuli and dynamometer output were recorded and digitized in a similar way. Monopolar LFP recordings were subsequently converted off-line to a bipolar montage between adjacent contacts (three bipolar channels per side) to limit the effects of volume conduction from distant sources. Bipolar Fz-Cz was also created offline. The line noise artifacts at 50 Hz and 100 Hz were removed using notch filters (5th order zero-phase Butterworth filters).

In an additional sub-study, 10 patients with DBS electrodes chronically connected up to the DBS pacemaker were asked to undertake the above-outlined gripping paradigm OFF and ON DBS, in a randomized order. A 20 minute ‘wash-out’ period between ON and OFF DBS experimental runs was instigated. Likewise, the same period of time was allowed in order for the full benefits of STN DBS to manifest, once the stimulator had been turned on. These 10 patients were studied ON their usual anti-parkinsonian medication.

6.2.4 Data analysis

Analyses of both behavioral and LFP data (in 19 and 9 patients, respectively) were performed in Matlab (version 7.10). Peak yank (PY; where yank is defined as the rate of change of force, calculated by differentiation of the force signal) and peak force (PF) were the chosen biomechanical variables of interest, and had the advantage that they could be measured trial by trial without realignment to compensate for differences in premotor reaction times. Premotor reaction time was defined as the time interval between cue onset and the point at which force exceeded 5% of the PF (taken as response onset). We acknowledge that premotor reaction time is more usually considered to be the interval between cue presentation and EMG onset (Botwinick & Thompson, 1966). However, as in previous studies (Chapters 3,4 & 5) we found the use of EMG to be suboptimal in the context of maximal grips because of movement artifact and sampling error, due to activation of multiple muscles in this task. Note too that the cortical EEG, whether examined as monopolar or bipolar signals, was contaminated by auditory blink reflexes to the intense stimuli and so was not analyzed further.

STNr LFP activity recorded from externalized DBS electrodes was decomposed into two components: evoked potentials, which are typically characterized as phase-locked to stimulus onset, and induced frequency-specific components, which are not (David et al, 2006). We sought to derive both these constituents in order to investigate whether STNr activity in either domain preceded and correlated with enhancements in motor performance. Evoked activity was derived from bilateral DBS electrodes by averaging across trials. The *absolute* peak amplitudes of evoked potentials (lying between 50-100ms), were derived as an average over a 10ms window centered around the peak. Induced power was derived by subtracting the average across trials from the original local field potential measurement of each trial to avoid contamination from evoked potentials. A time-frequency decomposition based on the continuous wavelet transform was then applied to each (average-subtracted) trial to analyze changes in induced LFP activity in the time-frequency domain. The wavelet function was convolved with the observed data at each time point across the range of frequencies, allowing the identification of specific frequency components over time. See Section 2.4.3.

Event related LFP power was calculated by normalizing the power at each time point against the average power between two seconds and one second before the cue, so that a value higher than zero indicated power higher than before cue and *vice versa*. The normalized power induced at different frequencies and at different time points was aligned to cue presentation, and averaged across trials of a given type and subsequently across the three bipolar contacts for each STN electrode contralateral to the gripping hand. Averages across all the contact pairs in a given electrode were calculated, so as to avoid selection bias. The resultant time-evolving power spectra of changes in STNr LFPs induced by cues at each intensity, relative to a pre-cue baseline, enabled five frequency bands to be identified over which increases or decreases in power (in the time period from cue onset to response onset) were distinguishable from the pre-cue baseline and from neighbouring bands. The five frequency ranges identified as responsive to the imperative auditory-visual cues, under all experimental conditions, were thus: theta/alpha (5-12Hz), low beta (13-19 Hz), intermediate beta (20-25 Hz), high beta (26-33 Hz), and broad gamma (34-375 Hz). As a data-driven approach - specific to the power spectra derived from this study - was adopted, the precise definitions of the reactive frequency bands differ slightly from that in our previous work (Chapter 5). Most notable is the presence of synchrony over a narrow intermediate beta band in OFF L-DOPA recordings, and a high beta desynchrony that extends to marginally higher frequencies than previously described.

6.2.5 Statistics

Grand averages of PF, PY and premotor reaction time (henceforth termed RT) in response to each stimulus intensity were calculated after deriving each of these variables from the individual grips made by a subject, and calculating the mean values for that subject, before averaging across study participants.

For within-subject correlation and regression analysis, behavioural and LFP data - in response to each stimulus intensity - was normalized as a proportion of responses to the lowest intensity (82 dB) stimulus. In order to achieve a more uniform spread of the data, behavioral parameters and peak evoked potential amplitudes were log transformed, whilst mean induced power over specific frequency bands benefited the most from a square root transform of the absolute amplitude of the activity (preserving the polarity of the data). Extreme outliers (defined here as data points lying >3 times the interquartile range from the nearest quartile) were excluded from further analysis.

In graphical representations of evoked activity, the time-evolving power of the group mean absolute evoked potential traces, for each stimulus intensity, was plotted as z-scores calculated for the average evoked potential profiles derived from all contact pairs on each DBS electrode in

an individual, before collapsing across subjects. Z-scores were derived for the absolute amplitude of the evoked potential at each millisecond interval by subtraction of the mean LFP power 1-2 seconds prior to the cue, followed by division of this value by the standard deviation of the power of the 1-2 second pre-cue baseline.

Statistical analyses were performed in SPSS Statistics 19 (SPSS Inc, Chicago, IL, USA). Kolmogorov-Smirnov tests were applied for confirmation of normal distributions, where required, prior to parametric testing. Where Mauchly's test of sphericity was significant (P<0.05) in repeated measures ANOVAs, Greenhouse-Geisser corrections were applied. Mean ± standard error of mean (SEM) are presented throughout the text.

6.3 Results

6.3.1 Progressive enhancements in peak motor performance with increasing stimulus intensit Group average RTs and the average shape of the maximal grip profile in n=16 gripping hands, with increasing stimulus intensity, are shown in **Figure 6.1**. PF and PY increased with stimulus intensity, with the exception that the response to the highest two sound intensities was indistinguishable. RTs decreased in a monotonic fashion with increasing stimulus intensity. Application of repeated measures ANOVAs to PF, PY and RT data confirmed significant ($p<0.05$) effects of stimulus intensity on each movement parameter (see **Table 6.2**). The absence of an interaction of stimulus intensity with medication, confirmed an independence of the motor enhancements observed from dopaminergic manipulations (Chapters 3,4 & 5). Note, group average reduction in PF with dopaminergic medication (16.7 ± 1.6 kg ON medication, as compared to 19.4 ± 2.0 kg OFF medication, when averaging across responses to all stimulus intensities) likely reflects greater fatigue in ON drug recordings as compared to OFF, as the latter were necessarily conducted prior to the former (see Methods). Group average PF, PY and RT across dopaminergic states changed from 17.7 ± 1.8 kg, 148.6 ± 18.0 kg/s and 211.9 ± 9.4 ms in response to the lowest intensity stimulus, to 18.5 ± 1.7 kg, 163.4 ± 17.8 kg/s and 188.3 ± 7.9 ms in response to the highest intensity stimulus.

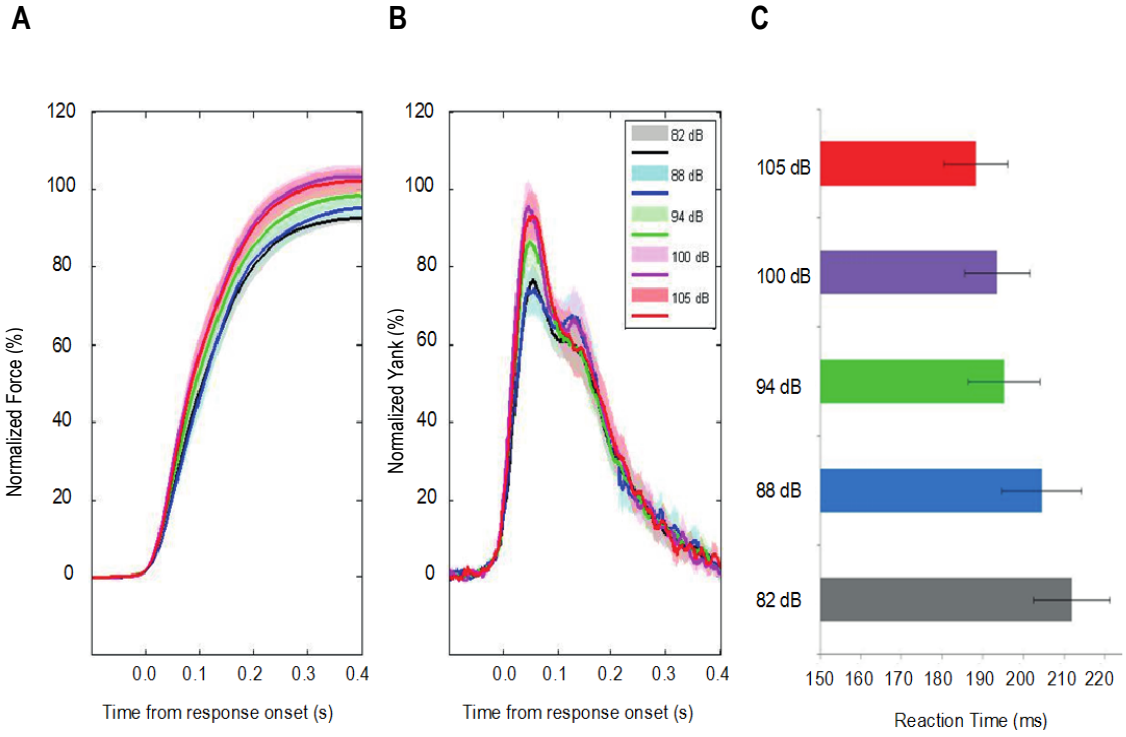


Figure 6.1 Normalized group average (A) grip force (B) yank (rate of development of force) realigned to response onset, and (C) group average RTs, in response to five different cue intensities averaged across OFF and ON L-DOPA recordings. n=16 gripping hands. Traces in (A) and (B) have been normalized as a percentage of the maximal peak force and peak yank attained amongst different trials by an individual in response to the lowest intensity stimulus, before collation across subjects. Shaded area corresponding to each cue intensity represents the 95% confidence interval (CI) of the force and yank traces. Note, where the CIs overlap, the CI of the greater amplitude trace is shown. Group mean RTs are shown with SEM.

	Peak Force	Peak Yank	Reaction Time
Cue Intensity	$F_{4,60}$=3.369 ***P*=0.015**	$F_{4,60}$=3.643 ***P*=0.010**	$F_{4,60}$=4.487 ***P*=0.003**
Medication state	$F_{1,15}$=5.357 ***P*=0.035** (Off>On)	$F_{1,15}$=1.431 *P*=0.250	$F_{1,15}$=0.004 *P*=0.951
Cue intensity * Medication state	$F_{4,60}$=0.584 *P*=0.675	$F_{4,60}$=0.367 *P*=0.831	$F_{4,60}$=0.382 *P*=0.821

Table 6.2 Results of repeated measures ANOVAs with factors (1) cue intensity (82, 88, 94, 100 and 105 dB) and (2) medication state (OFF and ON dopaminergic medication), applied to peak force, peak yank and reaction time data. n=16 gripping hands. Significant values are emboldened. The greater peak forces attained by subjects OFF medication compared to ON, likely reflects a fatigue effect in ON drug recordings which were undertaken second.

6.3.2 A short latency evoked potential, with focal origin in the STNr, increases in amplitude with increasing stimulus intensity

Analysis of STNr LFP activity revealed an evoked potential which scaled in amplitude with stimulus intensity **(Figure 6.2)**. Repeated measures ANOVAs applied to mean peak evoked potential amplitudes (averaged across all contact pairs on each DBS electrode, and derived separately for OFF and ON L-DOPA recordings), with factors stimulus intensity (5 levels) and hemisphere (left and right DBS electrodes), revealed main effects of stimulus intensity, but no effects of STNr side, nor STNr side x stimulus intensity interactions in either OFF or ON L-DOPA states (see **Table 6.3**). Importantly, a further repeated measures ANOVA applied to the average of the bilateral evoked potentials for each stimulus intensity identified an independence of the peak amplitude from dopaminergic state (significant effect of stimulus intensity, $F_{4,60}$ =9.390, P<0.001; but no effect of dopaminergic medication, $F_{1,15}$= 0.00, P=0.999, nor stimulus intensity x dopaminergic medication interaction, $F_{4,60}$=0.410, P=0.800).

Thus, averaging across recordings from all contact pairs in left and right sided DBS electrodes, and across OFF and ON L-DOPA experimental runs, the mean onset latency - defined here as the latency of a z-score (see Methods) >1 - of this evoked potential in response to all stimulus intensities was 42.4 ± 2.7 ms. Peak latencies fell between 50-100ms, with mean peak latency (averaged across L-DOPA states, left and right sided DBS electrode contact pairs, and all stimulus intensities) falling at 83.3 ± 1.2 ms. Of note, the imperative visual cue alone resulted in an evoked potential with a peak latency of > 100ms **(see Figure 6.3)**.

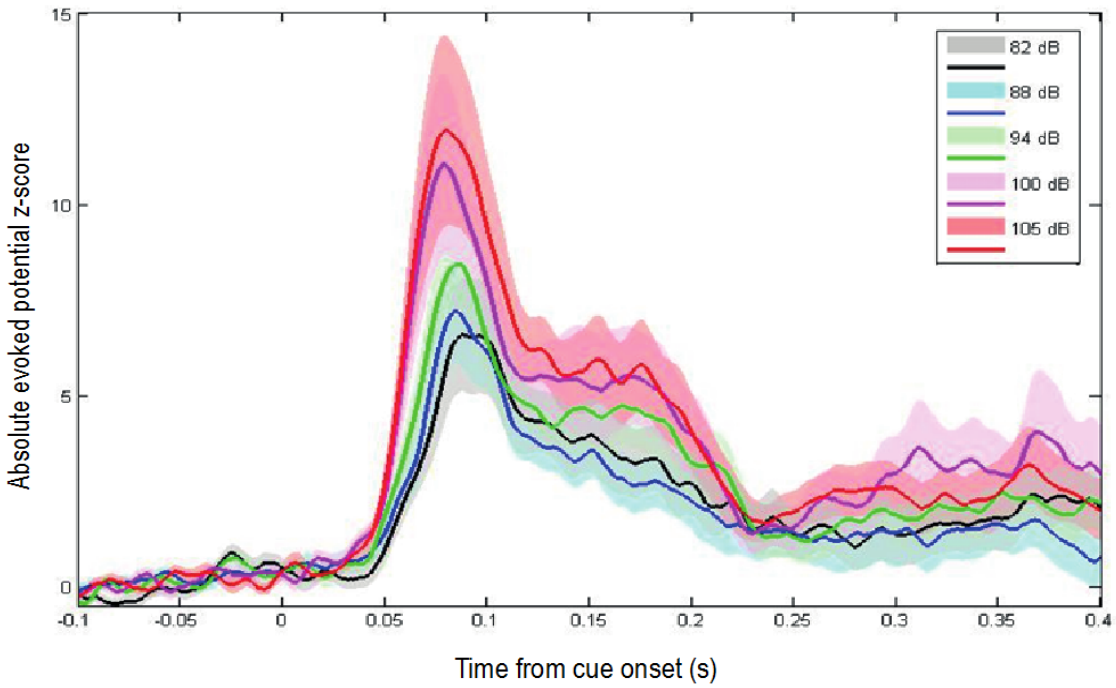


Figure 6.2 Group average STNr short latency evoked potentials in response to five different cue intensities, averaged across OFF and ON L-DOPA recordings. n=16 STNr. Shaded area corresponding to each cue intensity represents the 95% CI of the evoked potential, and where the CIs overlap, the CI of the greater amplitude trace is shown. The absolute amplitude of the evoked potential is shown as a z-score (see Section 6.2.5).

	OFF L-DOPA	ON L-DOPA
Cue Intensity	$F_{4,60}$=7.365 ***P*=0.001**	$F_{4,60}$=5.766 ***P*=0.003**
STNr side	$F_{1,15}$=0.441 *P*=0.517	$F_{1,15}$=0.002 *P*=0.963
Cue intensity * STNr side	$F_{4,60}$=0.660 *P*=0.513	$F_{4,60}$=1.484 *P*=0.218

Table 6.3 Results of separate repeated measures ANOVAs for OFF and ON L-DOPA recordings applied to each individual's mean peak evoked potential amplitudes, with factors (1) cue intensity (82, 88, 94, 100 and 105 dB) and (2) hemisphere (left versus right STN), (n=16 experimental runs). Significant values are emboldened.

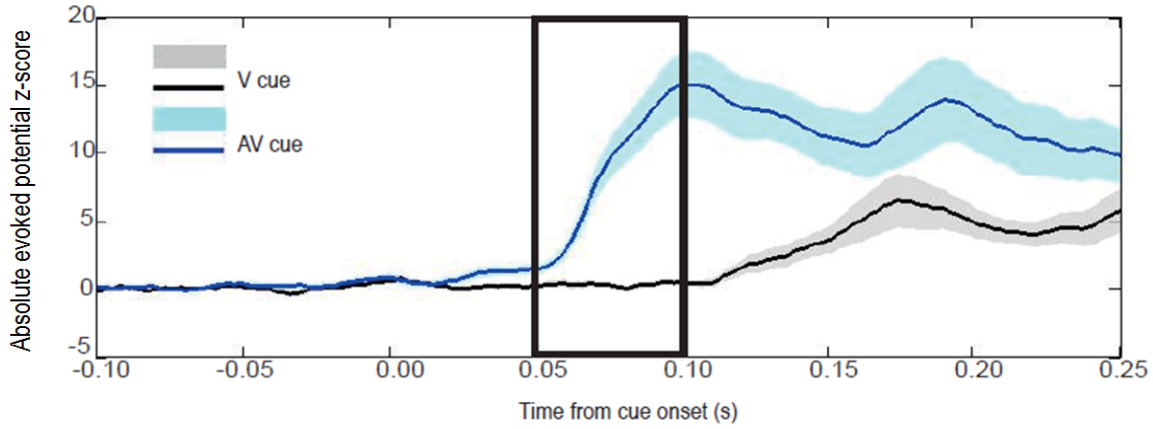


Figure 6.3 Group mean STN evoked responses to a Visual (V) and combined 96dB Auditory and Visual (AV) cue in n=20 STN. AV cue evoked potentials reach peak amplitude between 50-100ms (boxed region). Evoked responses to V cues alone peak at longer latencies (>150ms). See Chapter 5 for experimental paradigm and patient details.

In the current study, local generation of the evoked potential was confirmed by the steep gradient in the peak amplitude of the evoked potential between the contact pair in which it was maximal and the remaining contact pairs (56.0 ± 2.1 % averaged across responses to all sound intensities in 8 subjects). The contact pair recording the greatest amplitude evoked potential was 0-1 in 39% of cases, 1-2 in 31% of cases and 2-3 in 30% of cases.

6.3.3 *Induced frequency-specific components of LFP activity are not associated with increases in stimulus intensity*

Derivation of time-evolving power spectra of changes in STNr LFPs separately for both OFF and ON L-DOPA recordings, identified five frequency bands reactive to cue **(see Methods; Figure 6.4**). However, application of repeated measures ANOVAs to the average induced power retrieved from each frequency range identified an absence of an effect of stimulus intensity on any of the induced activities identified **(Table 6.4)**.

6.3.4 Enhancements in peak motor performance correlate with amplitude of the STNr short latency evoked potential

Potential relationships between the amplitude of the short latency evoked potential and motor enhancement, were next investigated. Both the evoked potentials and peak movement parameters were normalized to the average response to the lowest stimulus intensity, so that relationships were investigated at the within-subject level. Simple regression analysis (applied to log transformed data) identified significant relationships between the STNr evoked potential amplitude and PF (r=0.603, P<0.001), PY (r=0.477, P<0.001) and RT (r=-0.354, P=0.004) **(Figure 6.5)**.

In line with the absence of effect of stimulus intensity on induced frequency specific components of LFP activity, no significant correlations were found between these and any of the movement parameters of interest. Accordingly, three separate multiple regression models that included both peak evoked potential amplitude and transformed (see Methods) mean LFP power of induced components over the five identified frequency bands (ie. six predictive variables in total) revealed that only evoked potential amplitude, and not induced frequency-specific activities, contributed to PF (β = 0.613, P <0.001) and PY (β = 0.485, P = 0.001). The model fit in each case was good: F = 7.264, P <0.001, R^2 = 0.439 for PF; F = 3.078, P=0.014, R^2 = 0.206 for PY. In agreement with the weaker correlations identified with simple regression analysis in the case of RT, the model fit for this parameter with multiple regression analysis was poorer (F= 1.187, P = 0.332, R^2 = 0.023

for RT) and the contributions of neither evoked (β = -0.278, *P*=0.082) nor any induced STN LFP components reached significance, when all six predictive variables were simultaneously included.

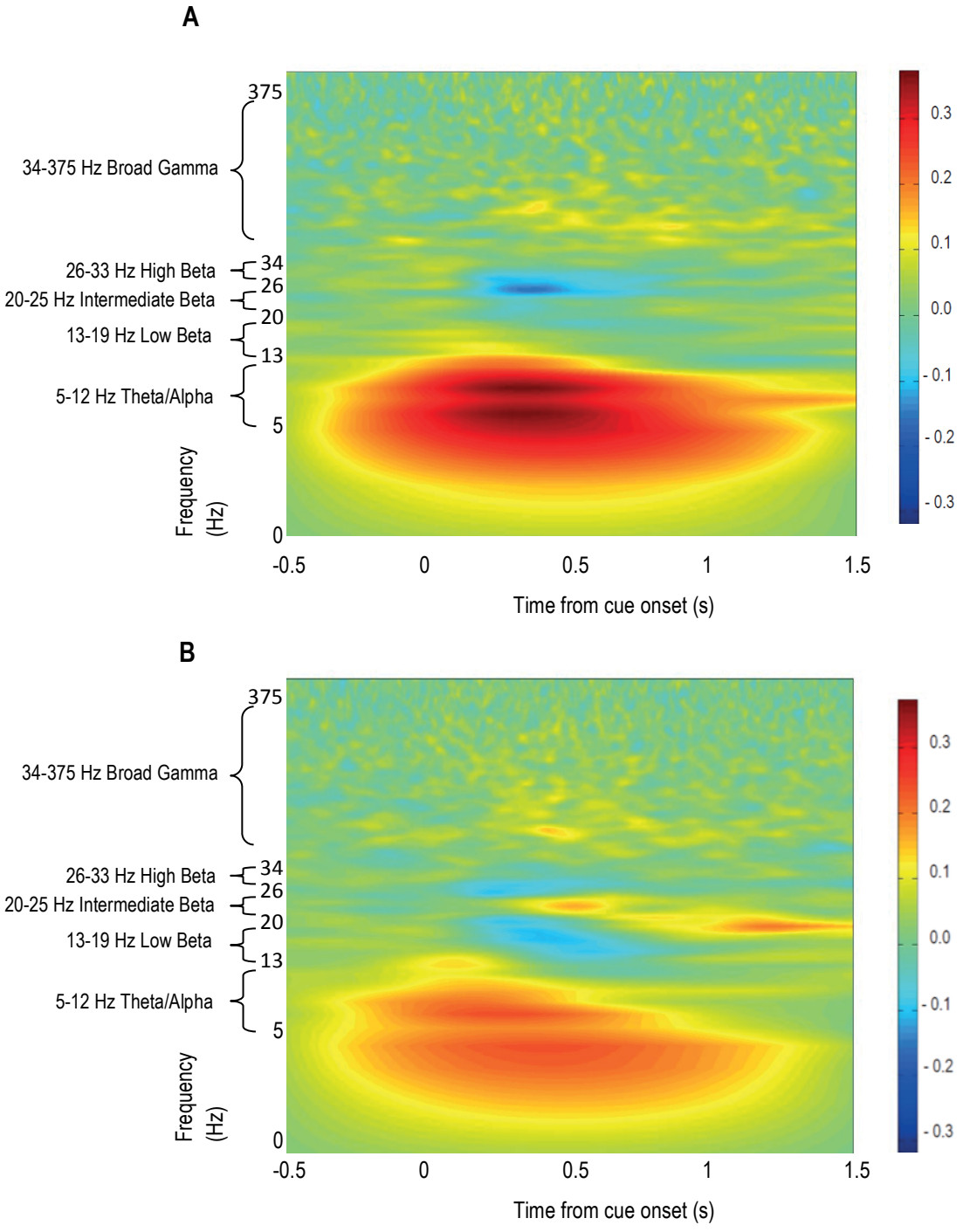


Figure 6.4 Average time-frequency plots of *change* in induced spectral power – in response to an 82 dB auditory stimulus combined with a visual cue - in 16 STN contralateral to sustained maximal handgrips, relative to a pre-cue baseline under A) ON L-DOPA and B) OFF L-DOPA conditions. Time zero represents onset of the imperative visual cue in combination with the auditory stimulus. Colour gradient represents ratio of post-cue LFP power to average LFP power 1-2 s before cue onset. Frequency is plotted on a log axis.

	Cue Intensity	**Medication status**	**Cue intensity x medication status**
5-12Hz Theta/Alpha	$F_{4,60}$= 0.266, *P*=0.755	$F_{1,15}$= 0.889, *P*=0.361	$F_{4,60}$= 0.764, *P*=0.492
13-19Hz Low Beta	$F_{4,60}$= 0.807, *P*=0.432	$F_{1,15}$= 0.670, *P*=0. 426	$F_{4,60}$= 1.157, *P*=0.332
20-25 Hz Intermediate Beta	$F_{4,60}$= 1.405, *P*=0.261	$F_{1,15}$= 5.659, ***P*=0. 031**	$F_{4,60}$= 1.157, *P*=0.339
26-33 Hz High Beta	$F_{4,60}$= 1.557, *P*=0.197	$F_{1,15}$= 3.720, *P*=0.073	$F_{4,60}$= 2.022, *P*=0.103
34-375 Hz Broad Gamma	$F_{4,60}$= 1.049, *P*=0.348	$F_{1,15}$= 0.010, *P*=0.922	$F_{4,60}$= 2.160, *P*=0.151

Table 6.4 Repeated measures ANOVAs applied to log transformed mean induced LFP power derived from the time period between cue onset and time to movement onset, separately for the five reactive frequency bands identified. Factors included: cue intensity (5 different levels) and medication status (OFF vs ON L-DOPA). The time period analyzed was selected to minimize the inclusion of activities related to peripheral afferance during the movement phase. No significant effect of cue intensity was identified.

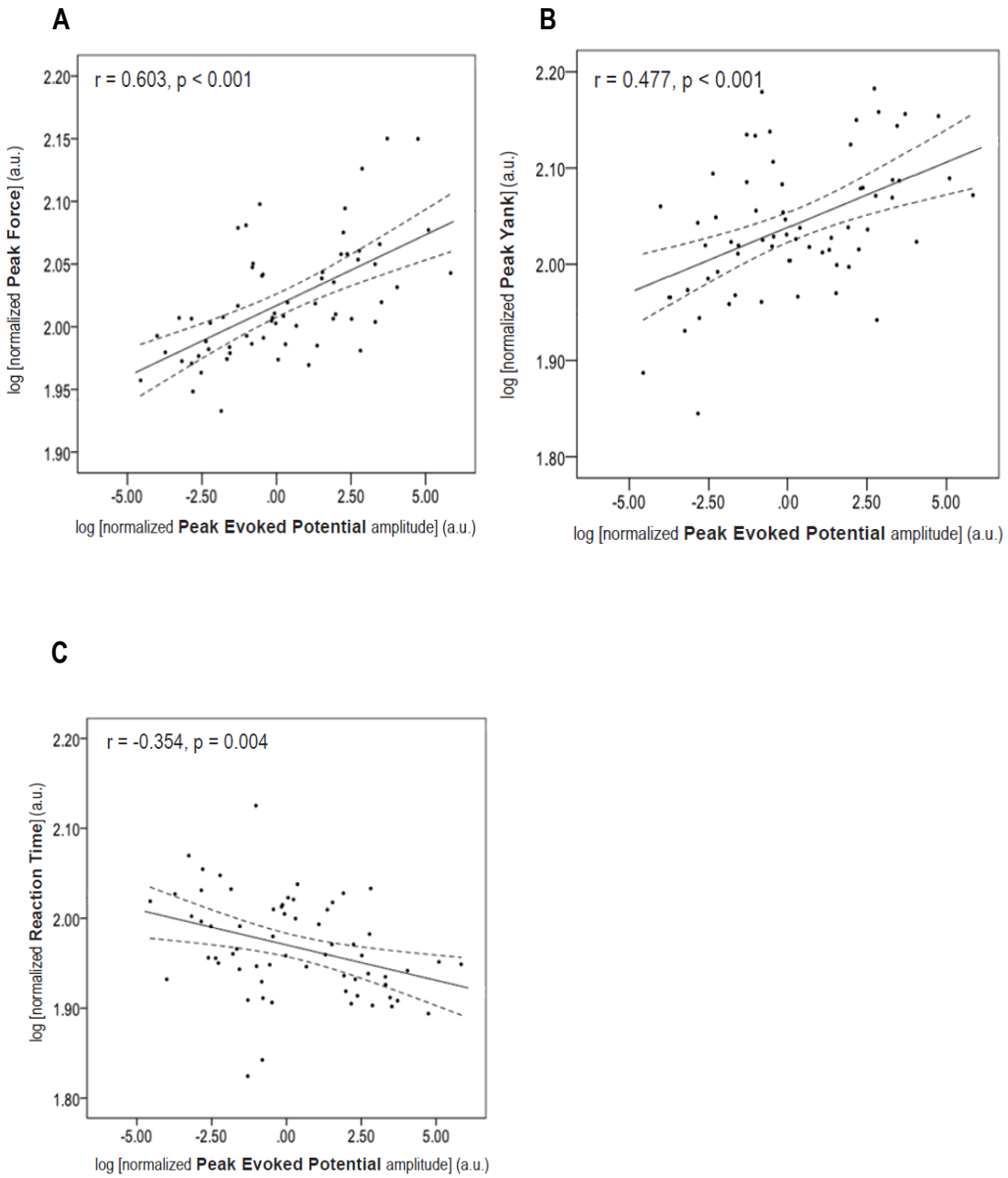


Figure 6.5 Scatter-plots relating increases in average absolute peak evoked potential amplitude to enhancements in (A) peak force (B) peak yank and (C) reaction time, relative to the average of peak responses to the lowest intensity imperative cues. Data are derived from the remaining four sound intensities in the eight subjects. Solid lines represent best-fit lines fitted by simple linear regression. Dashed lines represent 95% CI of the regression line.

6.3.5 Enhancements in force parameters with increasing stimulus intensity are attenuated with STN DBS

Ten patients with PD undergoing chronic high frequency DBS of the STNr were also tested. The facilitating effect of progressively intense stimuli was replicated in these subjects when the DBS stimulator was turned off. However, as evident in **Figure 6.6** when undertaking the paradigm with the DBS stimulator ON, enhancements in PF and PY were attenuated. Such an effect on PF was confirmed through application of a repeated measures ANOVA, with factors DBS (ON vs OFF) and stimulus intensity (82, 88, 94, 100 and 105 dB stimuli), which demonstrated a significant DBS x stimulus intensity interaction ($F_{4,76}$=3.944, *P*=0.012). Post hoc analysis identified a significant difference in the percentage change in the average response to the two lowest intensity stimuli and the two highest intensity stimuli OFF vs ON DBS (22.3% ± 5.2% OFF DBS as compared to 8.0% ± 3.5% ON DBS, *P*=0.043, paired t-test). The ANOVA also revealed a significant effect of DBS ($F_{1,19}$=22.753, *P*<0.001; ON DBS responses significantly greater than OFF DBS responses, *P*<0.001, paired t-test after averaging across all stimulus intensities) and stimulus intensity ($F_{4,76}$=13.179, *P*<0.01; response to 105dB stimuli significantly greater than that to 82 dB stimuli, *P*<<0.0001, paired t-test averaging across ON and OFF DBS recordings). Of note, the absence of an effect of stimulus intensity during DBS of the STNr was not a result of a ceiling effect, as each individual's distributions of PFs - combined across responses to all stimulus intensities - were Gaussian in nature in the ON DBS state (one sample Kolmogorov-Smirnov tests, *P*>0.05).

Whilst the DBS x stimulus intensity effect did not reach significance in a similar repeated measures ANOVA applied to PY data ($F_{4,76}$=1.655, *P*=0.183), a trend towards a diminished effect of stimulus intensity on this parameter with STN DBS was identified in the difference in % change between the average responses to the two lowest intensity stimuli and the two highest intensity stimuli OFF vs ON DBS (35.0% ± 10.9% OFF DBS as compared to 11.7% ± 3.5% ON DBS, *P*=0.051, paired t-test). Significant effects of DBS ($F_{1,19}$=26.857, *P*<0.001; ON DBS responses significantly greater than OFF DBS responses, *P*<<0.0001 paired t-test) and stimulus intensity ($F_{4,76}$=8.812, *P*<0.001; responses to 105dB stimuli significantly greater than those to 82 dB stimuli, *P*<<0.0001, paired t-test) were again evident. The PYs in trials of each individual's grips were normally distributed distributions in the ON DBS state in 18/20 cases. In the two remaining cases, the distributions were skewed towards lower peak yanks and did not demonstrate evidence of a ceiling effect **(Figure 6.7)**.

In contrast, RT decrements were present independent of whether patients were OFF or ON DBS: significant effect of STIMULUS ($F_{4,76}$=4.791, *P*=0.005; responses to 105dB stimuli significantly greater than those to 82 dB stimuli, p=0.011, paired t-test) and no DBS x STIMULUS INTENSITY

interaction ($F_{4,76}$=0.247, P=0.885). An effect on DBS on RT was not observed ($F_{1,19}$=2.644, P=0.120).

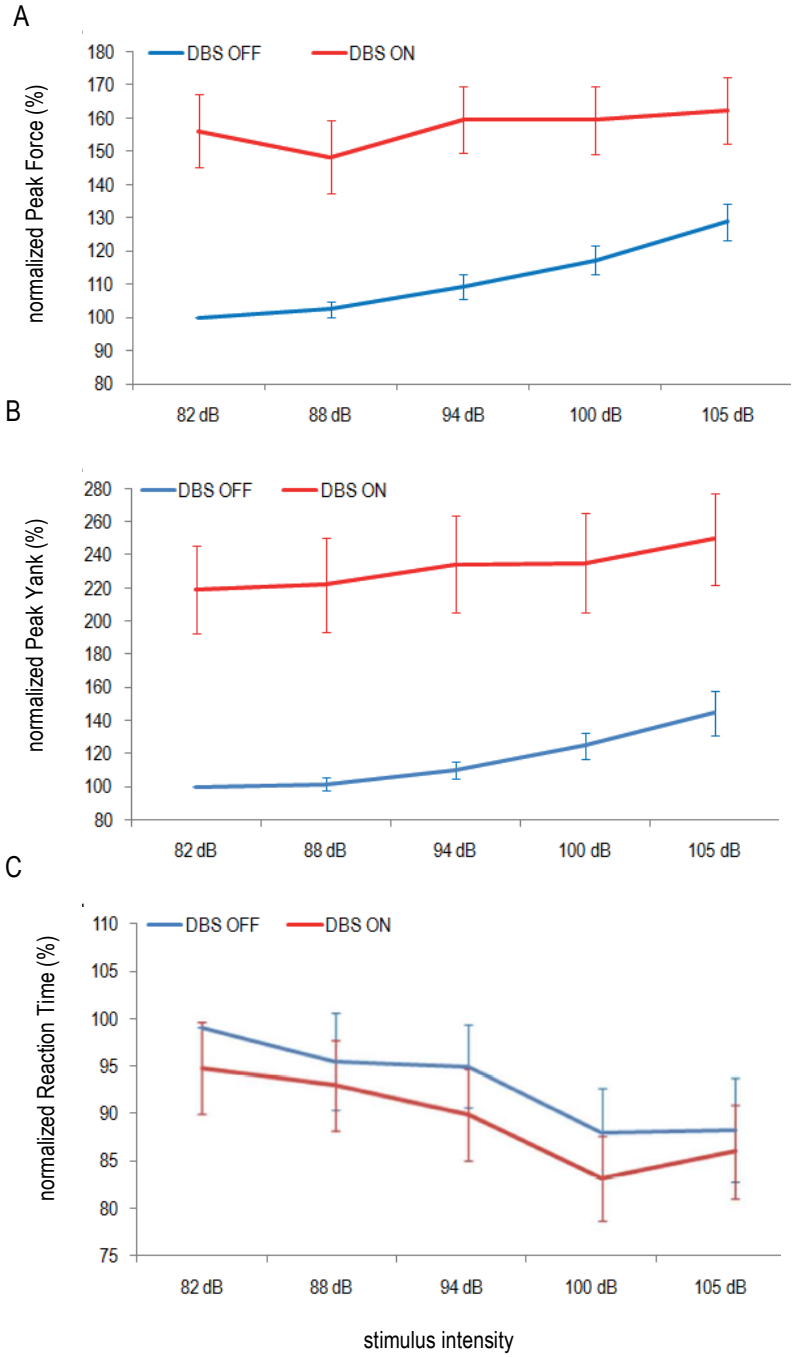


Figure 6.6 Percentage change in peak motor parameters in response to increasing stimulus intensity with DBS ON and OFF. n=20 gripping hands. Each individual's responses have been normalized to the average peak motor parameters achieved in response to the lowest intensity (82 dB) auditory stimulus, when OFF DBS, before averaging across subjects. Error bars represent SEM.

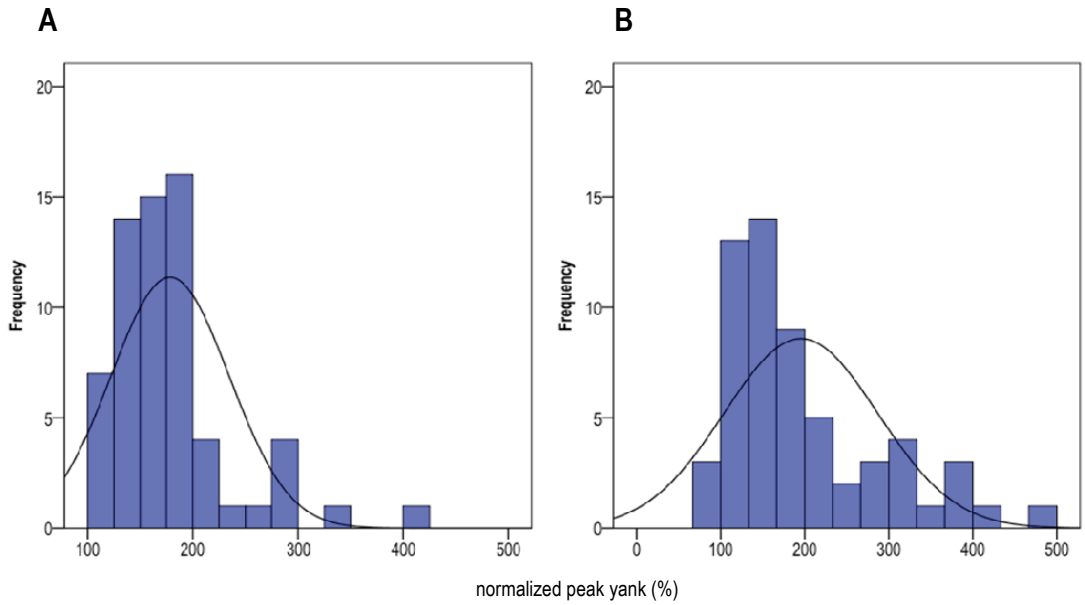


Figure 6.7 A skew towards lower peak yanks is observed in distributions of this parameter in the left-handed grips of two individuals (A) and (B) when ON DBS. Individual peak yanks attained in response to cues of all intensities are presented, normalized as a percentage of the response to the lowest stimulus intensity when OFF DBS. Distributions can be compared to a Gaussian bell-shaped curve (shown in each figure). Peak forces and yanks attained by all other individuals whilst ON DBS were normally distributed.

6.3.6 An evoked potential, with similar latency and morphology to that in the STNr, is locally generated in the PPNr

We also recorded evoked activity in the PPNr during execution of the same gripping paradigm in a further patient with PD in whom DBS electrodes were implanted bilaterally in both the PPNr and STNr. In this subject, the PPNr LFP activity was characterised by two components, the first of which was of very similar onset latency to the initial evoked potential in the patient's STNr (see vertical line in **Figure 6.8**). PPNr evoked potentials scaled with sound intensity, without dependence on dopaminergic state (**Figure 6.9)**. Importantly, the steep gradient in the peak amplitude of the evoked potential between the contact pair in which it was maximal and the remaining contact pairs indicated local generation of the evoked potentials in the PPNr (gradient 50.0 ± 3.2 %) and STNr (gradient 52.3. ± 3.4%). The PPNr contact pair recording the maximal short-latency evoked potential bilaterally was 1-2.The STNr contact pairs with the maximal short-latency evoked potentials were 0-1 on the left and 1-2 on the right.

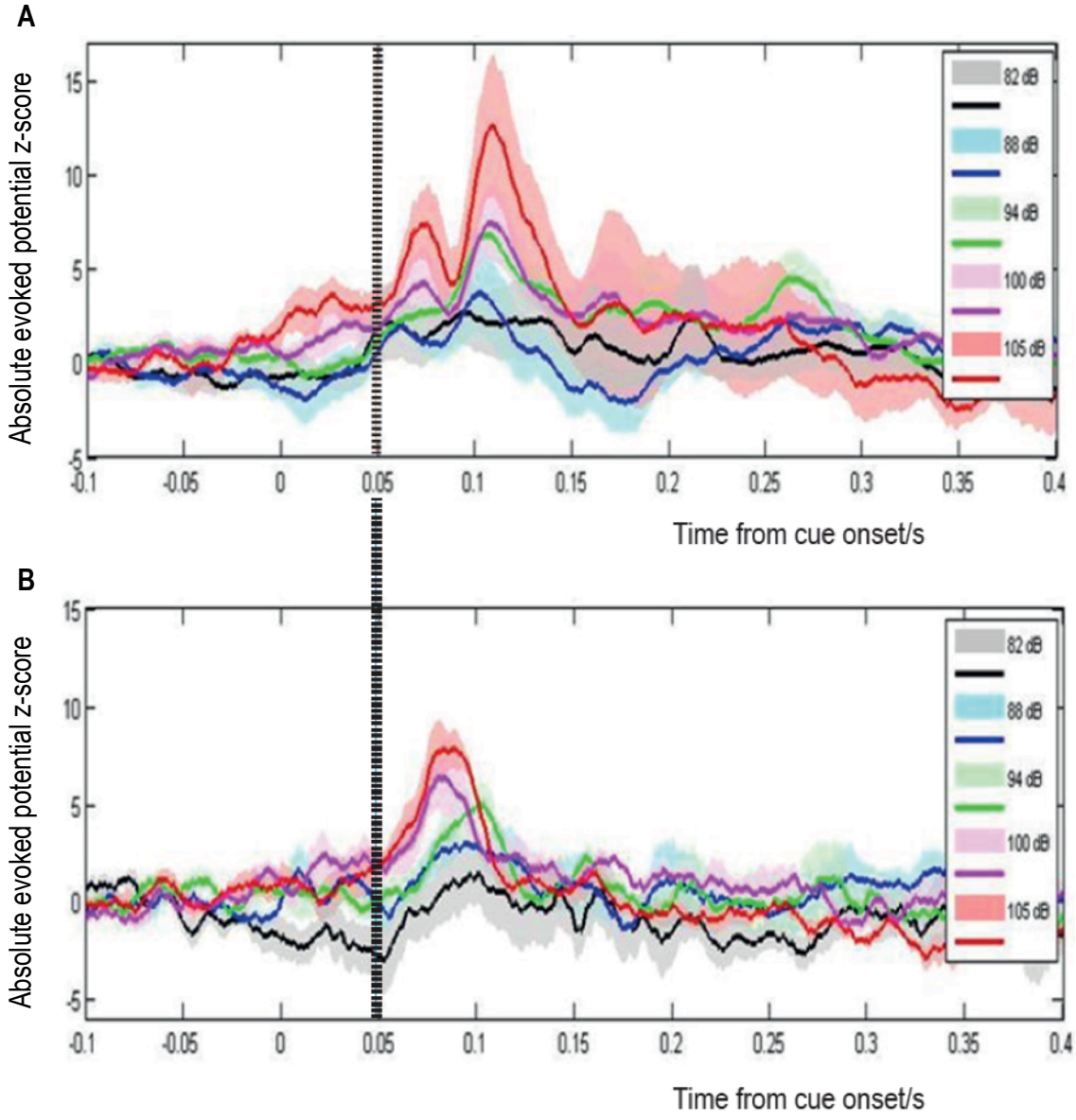


Figure 6.8 Average evoked potentials recorded simultaneously in (A) PPNr and (B) STNr in a single patient. Traces represent the grand averages of recordings from left and right nuclei whilst OFF and ON L-DOPA. Normalisation technique and CI representation is as in Figure 6.3. Dashed vertical line denotes the common onset latency of the first evoked potential in both structures.

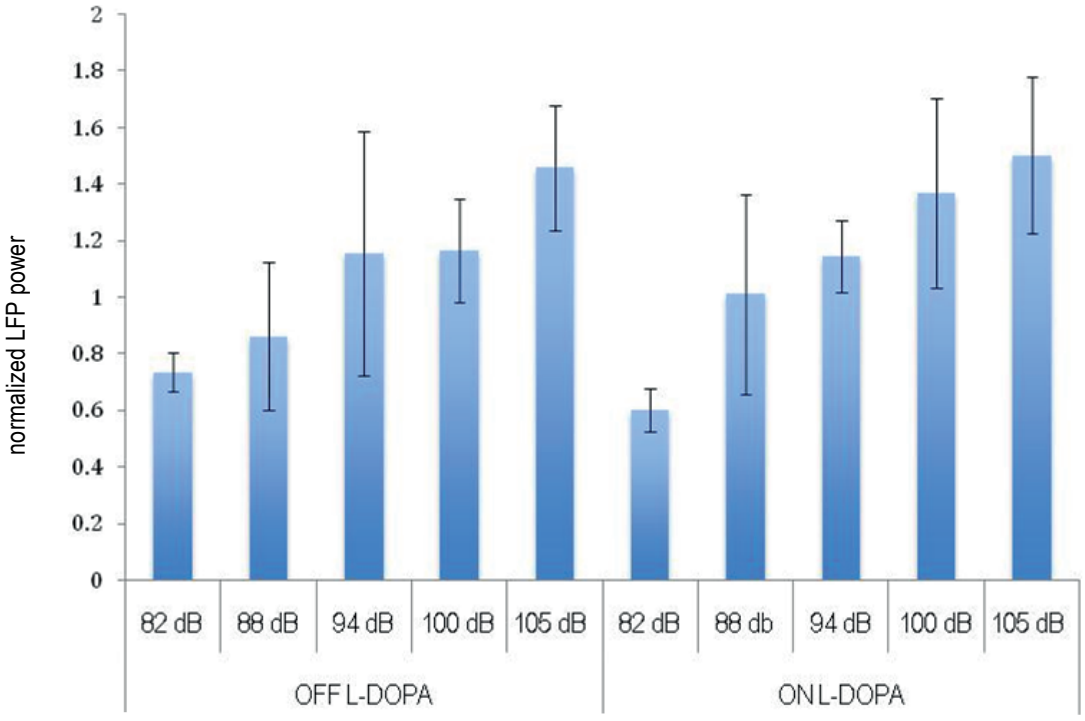


Figure 6.9 Average peak amplitude of the absolute evoked potentials recorded from n=2 PPNr in one individual, in response to five different cue intensities. Average responses under experimental runs when the patient was OFF followed by ON their normal antiparkinsonian medication (L-DOPA) are shown. Error bars represent SEM of recordings averaged across all contact pairs in left and right PPN DBS electrodes. Evoked potential amplitudes were normalized to the greatest amplitude peak across the trials recorded in response to the lowest intensity stimulus, for each PPN, before averaging across sides.

6.4 Discussion

The findings of our study are four-fold. First we demonstrate progressive enhancements in peak motor performance, over and above maximal effort of will, with delivery of increasingly intense imperative stimuli. Such a graded effect has thus far only been demonstrated in submaximal movement parameters (Angel, 1973; Jaskowski et al, 1995). Second, we identify a short latency (peaking at 50-100 ms) evoked potential, locally generated in the STNr, which scales with increasing stimulus intensity and correlates with enhancements in peak force and peak yank as well as reductions in reaction time. Third, we show that interference with this evoked potential, by high frequency DBS of the STN, diminishes stimulus-intensity dependent enhancements in peak force. Finally, we provide evidence of an evoked potential with a striking similarity to that in the STNr, but with focal origin in the PPNr – a key component of the reticular activating system (RAS).

What might be the basis for the locally generated STNr potential evoked by loud sounds? A role in the modulation of movement rather than in specific auditory processing seems likely given the pre-eminent role of the STN in motor control (Turner & Desmurget, 2010). It has been posited that a cue not only instigates specific processing related to stimulus analysis, but also 'automatic alertness' or 'phasic arousal' (Sanders et al, 1983; Posner et al, 1976). Here the latter term is used to describe an evoked increment in vigilance - of short duration - that is dependent upon stimulus attributes like novelty and intensity, and which impacts on motor behaviour. It has previously been suggested that such a mechanism speeds early processes of movement preparation and action selection (Hackley, 2009a; Hackley, 2009b; Hackley & Valle-Inclan, 1999), as well as increasing activity in primary motor areas (Jepma et al, 2008). Accordingly we posit that the short-latency sub-cortical potentials identified in the present study may represent the electrophysiological correlates of intense auditory stimulus induced phasic arousal, and that their existence in the STNr and PPNr relates to the interaction between such arousal and motoric related processing.

Of note, the demonstration of a linear relationship between enhancements in motor performance and the amplitude of the STNr short-latency evoked potential, but not with changes in any induced frequency-specific activities in the STNr, provides support for a functional dissociation between these two LFP components. In line with such a proposal, we have previously shown that induced STN activity over a broad gamma range constitutes a substantial factor in optimizing an individual's peak motor response at maximal effort of will, but much less so in performance increments over and above this, when the imperative visual cue was accompanied by a loud auditory tone on random trials (Anzak et al, 2012). Indeed, whilst induced frequency-specific

components in the STN have previously been ascribed pro-kinetic functions (Foffani et al, 2003; Özkurt et al, 2011; Brücke et al, 2012; Thobois et al, 2007; Turner et al, 2003), induced activity is widely believed to reflect top-down modulatory influences via backward connections (Chen et al, 2012). In contrast, evoked responses have been purported to represent bottom-up driving processes, mediated by forward connections, and largely initiated by linear mechanisms (Chen et al, 2012).

The recording of an evoked potential in the PPNr, with a similar latency and reactivity to that of the short-latency STNr evoked potential, implicates the ponto-mesencephalic limb of the ascending arousal system (Moruzzi & Magoun, 1949; Jones, 2008) as the likely source of bottom-up processes related to phasic arousal. Indeed, on the basis of the strong reciprocal connections known to exist between the STN and PPN (Aravamuthan et al, 2007; Mena-Segovia et al, 2004; Hammond et al, 1983; Bevan et al, 1995), a potential role for the STN as one *bridge* between arousal and motor circuitry is plausible. The PPN-STN pathway may thus constitute an additional movement gain (Turner & Desmurget, 2010) system, enabling the regulation of the speed and size of motor parameters in response to intense or arousing stimuli, and acting in parallel to those afferent systems related to emotional (Schmidt et al, 2009) or incentive motivation (Pessiglione et al, 2007) processing which have previously been described to influence movement.

In such a framework, the dopamine independent (see Results) short-latency STNr evoked potential likely embodies the propagation of arousal to a motor structure from which an energizing or 'activating' influence on motor cortico-subcortical loops can be exerted. The term 'activating' is used here to describe the task related mobilization of resources induced by arousal (Pribram and McGuinness, 1975; Barry et al, 2005, VaezMousavi et al, 2007). Support for a physiological basis for such a mechanism, rather than one related exclusively to parkinsonian pathology in our study-subjects, is provided by the homology of our sub-cortical evoked potential with a well described *cortical* marker of arousal, reported in both animal studies and healthy human subjects, termed the P50. It too has been posited to originate from the PPN (Garcia-Rill et al, 2011; Baruth et al, 2010; Reese et al, 1995; Skinner et al, 1995; Miyazato et al, 1999; Erwin and Buchwald, 1986). However, on the basis of the current work, we must be cautious in drawing parallels between the two markers, as the intensity of the auditory stimuli used in the present study was sufficient to induce eye blinks which precluded EEG recordings of a concurrent cortical response.

To summarize, irrespective of whether it is propagated from the PPN, our results suggest a substantial contribution of activity in the STNr to enhancements in force over and above maximal effort of will. Thus a strong correlation between the amplitude of the short-latency evoked

potentials in the STNr and facilitation of peak force was observed. Accordingly, the behavioural effect of intense cueing on this parameter was significantly diminished during STN DBS. High frequency DBS of the STN likely 'over-rides' both pathological and physiological processes in the vicinity of the electrode (Eusebio et al, 2012), and in line with this, has been suggested to reduce variability in spiking (McIntyre & Hahn, 2009). Weaker, albeit still significant, correlations between the evoked potential and peak yank increments and reaction time decrements were also observed. This suggests less marked contributions of STNr evoked activity to performance enhancements in peak yank and reaction time, and consistent with this, the effects of DBS were less conspicuous on cue related enhancement of these parameters. It remains to be seen what other processes contribute to improvements in peak yank and reaction time with stimulus intensity. As mentioned above, however, circumspection is warranted when interpreting the potential physiological associations and functions of the evoked potentials recorded here, given that they were necessarily recorded in patients with PD.

By what mechanism might the STNr evoked potential lead to paradoxical enhancements in peak motor parameters? It has previously been suggested that movements may essentially be 'selected' from an underlying range of physiological capabilities, so as to optimize the use of neuromuscular energy (Mazzoni et al, 2007) or maximise reward when this is temporally discounted (Haith et al, 2012). Indeed, recent work has now provided experimental evidence to support the everyday observation that individuals appear to 'select' a certain natural speed for routine movements (Mazzoni et al, 2012). It is thus plausible that even under instruction to execute maximal handgrips, our patients continued to 'select' grips from an underlying distribution of physiological capabilities, which included submaximal responses. In such a framework, arousing or intense stimuli have previously been ascribed an 'energizing' effect (Ballanger et al, 2006), leading to an increased probability of selection of stronger and faster grips (Chapters 3 & 4), over and above any considerations of force - or speed - energetic cost trade-offs, or temporal discounting.

To conclude, our results identify an evoked potential locally generated in the STNr, the amplitude of which scales with both auditory cue intensity and enhancements in motor performance achieved at maximal effort of will. Interference with this evoked potential, with simultaneous high frequency stimulation of the STN, leads to an attenuation of the behavioural effect with respect to peak force. We further provide evidence of an evoked potential with similar latency and reactivity to cue intensity but with focal origin in the PPNr, a key component of the RAS. In sum, the findings suggest that the subcortical short-latency evoked potential demonstrated is a correlate of arousal related 'activating' influences on motor processing. Manipulation of this system may

provide a novel approach for the non-dopaminergic enhancement of motor performance in patients with hypokinetic disorders such as PD.

Chapter 7

Discussion

7.1 Insights into the neural basis of paradoxical kinesia: where do we stand?

Whilst obvious ethical constraints in inducing frightening or life-threatening situations have, to-date, made paradoxical kinesis a difficult phenomenon to study systematically, in the work presented in this thesis intense auditory stimuli have successfully been used to reproduce enhancements in peak motor performance in a controlled experimental environment. The parallels that can be drawn between this effect and that of classical reports of paradoxical kinesia have afforded novel insights into the neural underpinnings of this phenomenon at the mechanistic, electrophysiological, and pharmacological level.

First, the demonstration of enhancements in peak motor performance in response to intense auditory stimuli, both in patients with PD (Chapter 4) and in healthy subjects (Chapters 3 & 4), implicates a physiological mechanism for this phenomenon, rather than one related exclusively to Parkinsonian pathophysiology. This is further corroborated by the absence of an effect of dopaminergic medication on the magnitude of motor enhancements observed in patients with PD (Chapter 4), the aetiology of which is known to include a marked decline in dopamine producing neurons.

A second mechanistic observation relates to the process by which overall average improvements in motor performance are achieved. Analysis of the distributions of peak motor parameters revealed a skew, but no shift, in the parameters attained by subjects in response to a loud auditory stimulus accompanying the imperative visual cue (Chapters 3 & 4). Such a skew may be interpreted as an augmented motor energy or 'vigor' in response to loud auditory-stimuli, manifest as an increased likelihood of selection of stronger motor parameters from an underlying range of physiological capabilities. Such optimization of behaviour is in-line with previous proposals of a role of intense or arousing stimuli in improving activation of motor areas (Baumgartner et al, 2007; Jepma et al, 2007), and amplifying the effect of the specific processing stream (Miller et al, 1999; Stahl & Rammsayer, 2005).

The discovery of an evoked potential in the STN, scaling with both stimulus intensity and enhancements in peak motor performance, and bearing a striking resemblance to a well-described surface EEG marker of arousal (the P50; Garcia-Rill et al, 2011), provides support for the latter process as the underlying mechanism driving intense auditory stimulus induced motor

enhancement (Chapter 6). An evoked potential of similar latency, morphology and reactivity to stimulus intensity, was further observed in recordings taken from electrodes implanted in the PPN – a key component of the RAS (Chapter 6). The locally generated STN short latency evoked potential is thus proposed as a correlate of phasic arousal, propagated from the RAS via the extensive anatomical connections known to exist between the STN and PPN (Bevan et al, 1995), to have an 'activating' influence on motor circuitry.

In such a network, the STN may act as the 'bridge' between arousal and motor circuitry, thus enabling the formation of a supplementary arousal-driven movement 'gain' (Turner & Desmurget, 2010) system, distinct from that mediated by those induced frequency-specific oscillatory activities found to encode grip parameters at maximal effort (Chapter 5). Moreover, the attenuated effect of stimulus intensity on motor performance when patients were 'ON' STN DBS (Chapter 6), provides further support for the latter nucleus as a key node in the propagation of the evoked potential identified, as chronic high frequency stimulation has been posited to interfere with electrophysiological task-related processing in the vicinity of the electrode (whether pathological or physiological; Eusebio et al, 2012).

Finally, the consistent demonstration of an absence of an effect of levodopa on behavioural enhancements (Chapters 4 - 6) implicates a likely independence of dopaminergic systems from this phenomenon. Consistent with this finding is the largely cholinergic basis of the PPN, from which our correlate of arousal is believed to originate.

7.2 Phasic arousal, the P50-100 and the PPN

As discussed in previous chapters, parallels may be drawn between the motor enhancements elicited by the behavioural paradigms utilized in the current work, and those observed in other studies describing the StartReact phenomenon (Valls-Sole et al, 1999; Carlsen et al, 2004, 2009), intersensory facilitation (Woodworth 1938; Dufft & Ulrich, 1999; Miller et al, 1999) or intensity effects (Angel,1973; Jaśkowski et al, 1995). However, support for a single common mechanism, underpinning each of these phenomena, can be derived from a number of sources. First, as described in Chapter 3, the demonstration of similar enhancements in motor performance with or without the observation of an overt startle response (as traditionally indexed by a short burst of sternocleidomastoid activity), argues against the necessity of the former in intense stimulus-induced movement facilitation. Second, against intersensory facilitation as the sole mechanism driving the motor augmentations described in Chapters 3-5, is the demonstration of progressive enhancements in peak motor parameters when the visual cue was at all times accompanied with a loud auditory tone, of successively greater intensities (Chapter 6). Stimulus intensity is thus

implicated as the single most important factor in driving motor enhancements in the paradigms presented in this thesis. At the central processing level, it has previously been posited that a cue not only instigates specific processing related to analysis of the stimulus and execution of the response, but also 'immediate arousal' (Sanders, 1983) or 'automatic alertness' (Posner et al, 1976; Posner 2008). Thus, it is likely that it is such 'phasic arousal' or alertness that underpins both intersensory facilitation and intensity effects. Indeed, the latter has previously been proposed as the basis for force increases in a number of 'redundant-signal' tasks (Dufft & Ulrich, 1999; Giray & Ulrich, 1993; Mordkoff et al, 1986).

Further support for the hypothesized role of phasic arousal in driving motor enhancement is derived from the similarity in morphology and latency of the subcortical electrophysiological marker of this effect, reported in Chapter 6, to a well described *cortical* evoked potential related to arousal - termed the P50. This potential, measured at the scalp vertex, has a latency variously described to lie between 40-100 ms in humans (Garcia-Rill et al, 2011; Baruth et al, 2010), and has been reported in aroused states such as waking and REM, but not slow wave, sleep (Erwin and Buchwald, 1986). In addition, the amplitude of the cortical P50 has also been reported as increased in disorders broadly characterized by up-regulation of RAS output (Garcia-Rill et al, 2011), including schizophrenia (Reese et al, 1995) and post-traumatic stress disorder (Skinner et al, 1995). An arousal-related equivalent of the P50, termed the P13, has also been described in rodent models (albeit falling at shorter latency; Garcia Rill & Skinner, 2001; Miyazato et al, 1999). In these studies, interventions that modulate arousal, such as anaesthesia, head injury and ethanol, have been shown to decrease the amplitude of the evoked potential. Of note, the P13 has been shown to remain intact after decerebration and after ablation of the primary auditory cortex bilaterally (Reese et al, 1965). That the cortical P50 is indeed a correlate of arousal itself, and not simply an auditory evoked electrical potential, is further supported by studies in humans where it has been demonstrated that the click stimulus evoked P50 response, but none of the earlier latency primary auditory evoked potentials, diminishes and disappears during deep stages of sleep (Kevanishvilli & von Specht, 1979).

A considerable amount of correlative evidence has suggested that the PPN is at least a part generator of the cortical P50 in humans (Garcia Rill et al, 2011). Indeed, it has been shown that injections of various neuroactive agents known to inhibit the PPN lead to a decreased P13 potential, but no alteration in the primary auditory P7 potential in rats (Miyazato et al, 1995). In Chapter 6 of this thesis, however, the first evidence of a comparable potential (peaking between 50-100 ms; subsequently termed the P50-100) in *direct* recordings from the PPNr - of *human* subjects - is presented. As alluded to in the Introduction, a role of the PPN in arousal has been

implicated since Moruzzi and Magoun's classical experiments (1949), which demonstrated generalized EEG desynchronisation and behavioural arousal following stimulation of a superior cerebellar peduncle target, with which PPN as well as laterodorsal tegmental nucleus fibres are known to intermingle (Siegel, 2002). It must be stressed however, that on the basis of the current work, the relationship between the subcortical P50-100 and the cortical P50 remains speculative, as it was not possible to isolate a clear potential of cortical origin from EEG recordings in our patients. This is because the sound intensities used in Chapter 6 were more intense than those in previous studies, and led to concurrent blinks that masked any underlying cortical response.

7.3 The STN as a bridge between motor and arousal circuitry

The recording of a similar locally generated potential in the STNr to that in the PPNr, in Chapter 6, prompts speculation that the P50-100 is an electrophysiological substrate of arousal, propagated from arousal related circuitry in the RAS (Moruzzi & Magoun, 1949) to exert its 'activating' influence on motor cortico-subcortical loops. In such a framework, and on the basis of the strong reciprocal connections known to exist between the STN and PPN, a potential role for the STN as one *bridge* between 'arousal' and motor 'activation' pathways is plausible. Note, the term '*activating'* is used here to describe the task related mobilization of resources induced by arousal (Pribram and McGuinness, 1975; Barry et al, 2005, VaezMousavi et al, 2007). In support of this proposal, evidence for bilateral PPN projections to the STN have been widely demonstrated in the primate (Carpenter et al, 1981; Lavoie and Parent, 1994b), cat (Edley and Graybiel, 1983; Graybiel, 1977; McBride and Larsen, 1980; Nomura et al, 1980) and rat (Bevan et al, 1995; Woolf and Butcher, 1986; Saper and Loewy, 1982; Hammond et al., 1983; Jackson and Crossman, 1983; Rye et al., 1987; Lee et al., 1988). The nature of these pathways has been shown to be both cholinergic (Woolf and Butcher, 1986) and non-cholinergic (Lee et al, 1988) and excitatory (Hammond et al, 1983). Most recently, a DTI study has confirmed reciprocal STN-PPN connectivity in the human (Aravamuthan et al, 2007). Recordings from multiple basal ganglia structures and subsequent coherence analyses, as well as stimulation studies, would however be required to confirm whether the STN is indeed the primary port of access of arousal systems to motor circuitry, as PPN connections with other nuclei within this network have also been described (Jenkinson et al, 2009).

7.4 The basal ganglia 50-100 ms evoked potential as an 'energizer' of movement

It has previously been suggested that movement parameters are essentially 'selected' from an underlying range of physiological capabilities, so as to optimize the use of neuromuscular energy (Mazzoni et al, 2007). In the paradigms used in this thesis, it is plausible that even under instruction to execute maximal handgrips, individuals (both healthy and with PD) continued to select grips from such a distribution. In line with these proposals is recent work suggesting healthy individuals prefer certain 'natural' or habitual movement speeds (Mazzoni, 2012), and in the case of PD, although patients experience 'decrements' in force, they are not essentially weakened by the disease (Fahn 2003), and so can apply more force when asked to do so (Schwab et al 1959).

It has further been posited that an arousing or temporally pressing situation acts by forcing the system to adopt a more 'expensive' trade-off (Ballanger et al, 2006). Accordingly, in Chapters 3 & 4, analysis of the distributions of the peak forces and peak yanks generated in response to V and AV trials, both in patients with PD and healthy subjects, revealed an increase in the proportion of stronger grips selected from a similar range of movement capabilities present in both conditions. Thus in our paradigms the arousing or alerting nature of the loud auditory stimulus might have acted by 'energizing' movement, over and above any considerations of force or speed–energetic cost trade-offs, thus bringing about a more consistent 'best' performance. The STN P50-100, the amplitude of which correlates with both stimulus intensity and motor enhancements - over and above maximal effort of will - may thus represent the electrophysiological correlate of this energising process, exerting its influence through the selection of stronger and faster corticomuscular, or perhaps even reticulospinal, drives. The *physiological* basis of this process, rather than one related to parkinsonian pathology, is supported by the similar magnitudes of motor enhancement in both patients with PD and healthy subjects in response to loud auditory stimuli (Chapter 4), independent of the existence of any baseline shifts in motor 'energy' that may occur in the diseased state (Hallet & Khoshbin, 1980).

7.5 Energizing movement – a novel therapeutic approach

The potential for manipulation of motor arousal systems in order to facilitate movement has recently been highlighted by dorsal column stimulation (DCS) work (Fuentes et al, 2009). Here a shift in activity in the primary motor cortex and dorsolateral striatum into a state 'permissive of movement' - from lower (Hammond et al, 2007) to higher frequency LFP activity - has been suggested to be elicited through DCS mediated activation of brainstem arousal systems (alongside specific somatosensory pathways).

In particular, the discovery of an evoked increase in power in the STN, which scales with the magnitude of motor enhancements, is most exciting in the context of the current wave of interest in developing 'demand-driven' deep brain stimulation devices for PD (Little & Brown, 2012). As mentioned in the Introduction, high frequency DBS is posited to exert its influence through a suppression of abnormal oscillatory activity in the basal ganglia (Eusebio et al, 2012). However, whilst high frequency DBS delivered chronically at pre-set stimulation parameters is the current treatment of choice for patients with PD refractory to drug-treatment (Weaver et al, 2009), a number of side-effects are believed to arise from the indiscriminate suppression of physiological - alongside pathological - functioning in basal ganglia-thalamocortical circuits (Eusebio et al, 2012). The rationale behind proposed closed-loop designs is thus to deliver stimulation only when necessary, on the basis of the presence of surrogate neuronal activity. In this way, physiological functioning may be allowed during non-stimulation periods, thus reducing side-effects, stimulator habituation, and preserving battery life. Such a device has recently been successfully designed and trialled by Rosin and colleagues (2011) where the activity of cortical neurons was used as a marker to deliver short trains of high frequency stimulation to the GPi. A novel approach, however, may be offered by reproduction of the evoked potential correlate of activation (identified in Chapter 6) in the vicinity of the STN, in response to LFP markers known to precede movement initiation (Kempf et al, 2007). In this way, motor performance may be enhanced through a facilitating or 'energizing' influence on physiological processing rather than a suppression of pathological rhythms. The artificial reproduction of single evoked potentials may conceivably be more achievable than inducing the complex pattern of cell-to-cell signalling likely required to give rise to those frequency-specific oscillations ascribed pro-kinetic functions in the STN (see Chapter 5).

7.6 DBS as an investigative tool: methodological limitations

Whilst implantation of DBS electrodes has afforded a unique opportunity to directly record from and stimulate the STN in human subjects (Chapters 5 & 6), the technique introduces a number of confounding factors that must be considered:

First, as our participants in Chapters 5 & 6 were necessarily patients with PD, it is unclear whether the neural activity recorded, and the associations drawn with behavioural performance, represent normal physiological functioning, compensation, or pathological activity related to PD. The possibility of a micro-lesional effect in these patients, post- DBS electrode implantation, is additionally possible.

With what confidence can we localise the electrophysiological activity recorded to local

processing within the vicinity of the electrode? The bipolar recordings made across adjacent contacts of the DBS electrodes in our studies, representing differential activity across contact pairs, meant that the signals analysed were most likely the product of locally generated activity in the STN rather than reflecting volume conduction from synchronous cortical areas. Further evidence for a focal origin of the signals comes from the clear gradient of LFP power across the contact pairs, demonstrated in both STN (Chapters 5 & 6) and PPN (Chapter 6) recordings, since in volume conduction one would expect LFP power to be equally distributed between adjacent contact pairs of the electrode, or present a decrement at contacts more distant from the cortical source (Williams et al, 2003). Finally, as alluded to in the Introduction, a number of intraoperative microelectrode recording studies have now demonstrated the locking of neuronal spike activity to the STN LFP (Kühn et al, 2005, Trottenberg et al, 2006), thus providing strong support for its local generation.

It should also be pointed out that as histological confirmation of electrode placement cannot be carried out, the placement of the macroelectrodes within their targets remains presumptive. Nonetheless, post-operative imaging was carried out at all sites to assess electrode placement (Hariz et al, 2003). Some element of tissue compression has, however, been reported in thin slice MRI, which could potentially lead to overestimation of the proximity of the electrode to the target structure (Silberstein et al, 2003; Silberstein et al, 2005). In addition, artifact from the recording electrode further limits exact determination of electrode placement.

Intraoperative microelectrode recordings also go some way in confirming correct electrode positioning. These were carried out at two of the four surgical centres from which patients were recruited in Chapters 5 & 6. Intraoperative microelectrode recordings enable characteristic firing patterns of the subthalamic nucleus to be determined (Starr 2002; Starr et al, 2002), thus affording a clear delineation of nuclear boundaries from surrounding white matter tracts prior to fixation of the DBS macroelectrode.

Finally, as alluded to in the Introduction, whilst STN DBS is posited to 'interfere' with activity in this nucleus (Eusebio et al, 2012), the mechanism by which it exerts its effect remains a topic of debate. It has previously been suggested that some of the effects of DBS may relate to the driving of axons and neurons near the point of stimulation (Garcia et al, 2005; Hammond et al, 2008; Montgomery and Gale, 2008), at stimulation frequency (Meissner et al, 2006), with this activity then being propagated to other sites (Hashimoto et al, 2003). Indeed, whilst a suppression of oscillatory activity in the vicinity of the electrode has been widely suggested, it is possible DBS also influences other functionally connected elements of the cortex-BG network (Hashimoto et al,

2003; Dorval et al, 2008; Hammond et al, 2008; Kühn et al, 2008; Montgomery & Gale, 2008). Thus, whether the attenuation of stimulus intensity-induced motor enhancement, when patients with PD were on DBS, is related to interference with the evoked potential correlate of arousal (identified in Chapter 6) at the level of the STN, or elsewhere in basal-ganglia thalamo-cortical circuits, remains to be clarified.

7.7 The neural basis of paradoxical kinesia: reconciling the views in the literature

In this section, the successes and shortcomings of the present experimental work (Chapters 3 - 6) in reproducing paradoxical kinesia, are first examined. Previous evidence for an extra-basal ganglia network, which may provide an additional motor gain pathway - recruited only in urgent situations - is next outlined. This is followed by a summary of the candidate neuroanatomical networks proposed by studies modelling aspects of the phenomenon other than *arousal*-related motor enhancement, namely emotional and motivational processing. The distinction between classical descriptions of paradoxical kinesia mediated by these entities, and motor facilitation resulting from straightforward visual-cueing, is subsequently alluded to. Finally, an attempt is made to explain the apparent inconsistency manifest in the predicament of freezing-of-gait (FOG) or akinesia, which has also been reported to occur in patients with PD in response to 'stressful' situations.

Whilst highly alerting stimuli like an earthquake or fire are nigh on impossible to mimic in the lab, and certainly cannot be made reproducible, the delivery of loud sounds has provided a compromise whereby paradoxical responses can be elicited in a reproducible fashion in a controlled experimental environment. Indeed, in the current work, enhancements in peak motor performance were successfully elicited through delivery of a loud auditory stimulus accompanying the imperative visual cue on random trials (Chapters 3 - 5). In particular, the use of single 96 dB auditory tones likely enabled arousal-related motor enhancement to be disambiguated from potential effects related to emotional or motivational processing. This is because whilst the auditory stimuli were loud, their brevity was unlikely to ascribe emotional content to them. Moreover, the fixed duration of these stimuli meant that no reward (in the form of cessation of the loud auditory tone) would be gained by correct task execution. Thus the movement 'energizing' circuitry alluded to in Chapter 6 may reliably be proposed as the neural basis of arousal related motor facilitation in instances of paradoxical kinesia. Note the term 'arousal' is used throughout to refer to enhanced cortical activation, and must be distinguished from potential contributions of a peripheral sympathetic arousal response ('fight-or–flight'), which would be an interesting avenue for further research. Certainly, it has previously been suggested that noradrenergic

activation of the release and utilization of muscle glucose, through hormonal rather than neuronal pathways, may generate an improved basal metabolic state to overcome starting problems in patients with PD (Verhagen-Komerbeck et al, 1993).

However, it should be pointed out that in contrast to the unexpected nature of the arousing events reported in the literature, each experimental run in the paradigms used in the current work necessarily required delivery of multiple intense stimulus (AV cue) trials in order for conclusions to be reliably drawn. In addition, after initial presentation of the AV cue, subjects were no longer naïve to the stimulus characteristics. A potential stimulus habituation effect, however, cannot be differentiated from effects of fatigue on AV cue induced enhancements in motor performance as the experiment progressed (see Chapter 3). Of note, whilst the intense stimuli delivered were markedly more brief than those in anecdotal case reports, marked enhancements in peak motor performance were still observed (up to ~2s into the grip; Chapter 3). Whether longer duration unexpected stimuli may lead to more pronounced effects, remains to be investigated further.

As discussed in Section 7.3, the findings outlined in Chapter 6 point towards the existence of a RAS-basal ganglia motor 'gain' network, continuously updating the motor system on levels of arousal, as indexed by the positive correlations observed between stimulus intensity and activity in this pathway. In contrast, an extra basal-ganglia pathway, *only* recruited in urgent situations, has previously been described (Ballanger et al, 2008). In this study, patients with PD were asked to press a button to stop a ball from rolling off a ramp. Neither the ramp nor the ball was visible, nor was the sound of the rolling ball audible. Only the time of release of the ball on the ramp was indicated to the subjects, who were simply asked to try and stop as many balls as possible (the ramp tilt was adjusted for each subject during a training session so as to ensure a failure rate roughly equal to 50%). Using PET H(2)(15)O, the authors identified specific activation in the contralateral cerebellum in this externally cued urgent situation, which was present neither in simple self initiated nor externally cued button presses. Moreover, the activation correlated with the movement speed observed at the behavioural level, but not with UPDRS motor scores, suggesting an involvement of specific cerebellar pathways in the scaling of movement in urgent situations irrespective of disease. This in-of-itself, however, does not preclude involvement of the PPN, given the latter's connectivity with the cerebellum (Aravamuthan et al, 2007), and the inherent difficulties in resolving the PPN in PET studies.

The sight of a fire, sound of a car accident, and sensation of an earthquake are amongst the highly arousing situations in which instances of paradoxical kinesia, in patients with PD, have traditionally been described. In addition to the likely contribution of *arousal* pathways in mediating

this phenomenon, activation of *emotional* processing (in response to the aversive stimulus) and recruitment of *motivationa*l circuitry (in order to remove oneself from harms way) is equally plausible. Indeed, a number of previous studies have successfully demonstrated a role of the latter-two components in 'boosting' motor output:

Electromyography studies by Coombes et al (2007) provided evidence to suggest that exposure to unpleasant images accelerates central processing times. Further studies by Baumgartner and colleagues (2007) revealed enhanced motor-evoked potentials, irrespective of valence, during the simultaneous presentation of emotional music and picture stimuli compared with independent presentation of the two modalities. Further support for a role of emotional processing in motor facilitation has come from evidence of a form of *verbal* paradoxical kinesia in patients with PD. Crucian et al (2001) showed that parkinsonian patients demonstrated a relative increase in the number of words spoken and in discourse duration when talking about emotional experiences, again independent of the valence of the subject matter. Finally, imaging studies by Schmidt et al (2009) have shown that emotional arousal, regardless of valence, can boost force production. In particular, a dissociation between emotional arousal and incentive motivation was highlighted, as no significant interaction between the effect of emotional pictures and that of monetary incentives was found. Indeed, earlier work by the same group (Pessiglione et al, 2007) has also shown that individuals adapt their force according to subliminal incentive levels for monetary rewards. These two studies have implicated activation in the ventrolateral prefrontal cortex and ventral pallidum, related to emotional and reward processing, respectively.

Taken together, the evidence points towards separate arousal, emotion and motivation related pathways, which complement each other in 'energizing' movement. Certainly, all three factors could plausibly come into play to enhance motor performance in the intense, aversive and life-threatening situations described in classical accounts of paradoxical kinesia. Whether the activity in each of these pathways summates in a linear fashion to enhance motor performance, so that the cues with the highest reward and which are most arousing and emotional produce the largest augmentations of movement, would be an interesting area for further research. Furthermore, whether the STN represents the 'door' to motor circuitry, for all of these influences, remains to be clarified.

A distinction between motor enhancements elicited by the above outlined stimuli and visual cueing effects, must however be made. Indeed, marked improvements in gait have long been demonstrated in patients with PD when stepping across lines placed transversely to their walking direction (Hanakawa et al, 1999) and with the use of an L-shaped walking aid (Dunne et al,

1987). A number of studies have now attributed this effect to the cerebellum. 99mTc-hexamethylpropyleneamine SPECT studies showed that both patients with PD and healthy controls showed increased activity in cerebellar hemispheres and posterior parietal cortex whilst walking on a treadmill guided by transverse rather than parallel visual cues (Hanakawa et al, 1999). The importance of a dynamic element to these cues was highlighted by the absence of a facilitating effect when stroboscopic lighting was used to mask the movement of the floor markers during gait (Azulay et al, 1999). A requirement of a perceived downwards movement of these markers in an individual's field of vision, in order for movement to be facilitated, was subsequently suggested. This has led to the hypothesis that visual floor cues generate optical flow that activates a cerebellar visual-motor pathway, as opposed to the cortical-motor pathway. Indeed, it has previously been posited that the receptive fields of neurons relaying visual signals to the cerebellum (mossy fibers via the pontine nuclei) are tuned to horizontal gratings in the lower visual field (Glickstein & Stein, 1991).

The visual cueing strategies mentioned above are often used to alleviate freezing-of-gait (FOG) in patients with PD. The predicament of FOG in response to stressful situations, that limit time or space (as alluded to in the Introduction), appears at first glance at odds to the phenomenon of paradoxical kinesia. However, it has recently been suggested that the effect is sensitive to cognitive load. Studies by Camicioli et al (1998) showed that asking patients with PD and FOG to perform a verbal fluency task, whilst simultaneously walking, increased the number of steps taken to walk 30 feet. According to the Lewis & Barker model of FOG (2009), complementary motor, cognitive and limbic networks all play a part in the completion of normal gait. Increased activation in any of these networks may lead to a transient overload of basal ganglia output nuclei in the diseased state, leading to excessive inhibition of the PPN locomotor region, resulting in FOG. Thus, it is plausible, that distinct from those situations eliciting paradoxical kinesia, situations that elicit FOG may be those that detract a patient's attention from the motor task. In such a framework, it has been proposed that presentation of a visual cue for movement may act to alleviate the freezing episode by suspending performance of additional cognitive and limbic processes (Lewis & Barker, 2009). Indeed, the above outlined hypothesis becomes particularly salient in the context of previous proposals that the loss of dopamine in PD is predominantly in the posterior putamen, a region of the basal ganglia associated with the control of habitual behaviour, resulting in patients being forced into a progressive reliance on a goal-directed mode of action control mediated by comparatively preserved processing in the rostromedial striatum (Redgrave et al, 2010). Thus parallels may be drawn between FOG and the problems of multi-tasking and 'motor set' long recognised in PD (Giladi & Hausdorf, 2006), rather than a response

to stimulus intensity.

7.8 Towards further insights

7.8.1 Acetylcholine as the pharmacological substrate for paradoxical kinesis?

In Chapter 6, the PPN is proposed as the generator of the arousal related P50-100 potential. The PPN is known to be a largely cholinergic structure (Bevan et al, 1995), with 80 to 90% and 25 to 75% of neurons staining CHAT positive in the PPN pars compacta and pars dissipatus, respectively (Mesulam et al, 1989). Might paradoxical kinesis thus be mediated by cholinergic influences on motor processing? Indeed, cholinergic ponto-mesencephalic neurons are known to constitute a key limb of the ascending arousal system (Jones, 2008). In addition, the successful blockade of the *cortical* P50 marker of arousal by the cholinergic antagonist scopolamine (Buchwald, 1991) provides further support for this proposal. At the most basic level, this hypothesis may be investigated by blockade of the cholinergic system in human subjects with the muscarinic antagonist scopolamine. Alternatively, the administration of one of the centrally acting cholinesterase inhibitors, whilst subjects undertake the previously established paradoxical kinesia paradigm, would elucidate any such role.

However, a role in the phenomenon of neurotransmitters other than acetylcholine and dopamine, should also be considered. Indeed, whilst the majority of cells in the PPN express acetylcholine, other cells have been shown to express the excitatory neurotransmitter glutamate (Clements et al, 1990; Lavoie et al, 1994) and the inhibitory amino acid GABA (Ford et al, 1995). It has also been noted that subpopulations of cholinergic neurons are found to express other neurochemical markers as well as those for acetylcholine, including glutamate (Bevan et al, 1995), GABA (Charara et al, 1996), signaling molecules such as nitric oxide (Vincent et al, 1986) and neuropeptides such as Substance P (Vincent et al, 1983).

7.8.2 A search for the interface by which arousal exerts its influence on motor processing

Increased synchrony in induced frequency-specific activities in the STN have been ascribed pro-kinetic (gamma; Alegre et al, 2005) or anti-kinetic (beta; Kühn et al, 2004) functions. However, changes in reactivity in these frequency bands were not found to make a significant contribution to enhancements in motor performance over and above maximal effort of will (Chapter 5). Moreover, in Chapter 6, no interaction between the evoked potential correlate of arousal and induced frequency specific activities was discerned. Thus, the site and mechanism by which the electrophysiological marker of arousal exerts its influence, likely indexed by a recruitment of increased numbers of neurons and amplification of firing rates - resulting in enhanced motor

output - remains enigmatic. An electrophysiological study enabling the mapping of larger neural networks, whilst maintaining the temporal resolution required to analyse short-latency neural and behavioural events, may help some way in resolving this issue. In human subjects, such an approach may be offered by magnetoencephalography (MEG) whilst healthy individuals, or patients with PD with externalized DBS electrodes, undertake the paradoxical kinesia paradigm. Difficulties in resolving subcortical structures with MEG, however, do exist. Thus motor arousal–eliciting studies in animals, coupled with micro- or macro-electrode recordings from multiple cortical and sub-cortical structures, may better elucidate the entire neural network involved in motor enhancement, and subsequently indicate the best potential targets for therapeutic manipulation of this system.

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