

**The functional significance of oscillatory
local field potential activity in the
parkinsonian subthalamic nucleus**

David Williams

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Sobell Dept. of Neurophysiology

Institute of Neurology

University College London

Queen Square WC1N 3BG



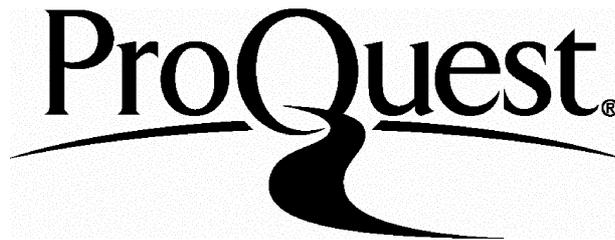
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Abstract

The functional significance of oscillatory local field potential activity in the parkinsonian subthalamic nucleus

David Williams

It has long been evident that oscillations are manifest in the local field potential (LFP) activity recorded in regions of the brain as diverse as olfactory, somatomotor, parietal and occipital cortex within primates. Further investigations have demonstrated similar oscillatory activity within cerebellum and thalamus in primates and sub-primates and in recent years within the LFP activity of the human basal ganglia. However, the capricious nature of much of the frequency content particularly in the beta band, in many of these areas, has resulted in speculation concerning the functional significance of this activity.

The current thesis sought to test the hypothesis that oscillatory activity, particularly in the beta band (ca. 13-30 Hz), evident in the LFP activity of the parkinsonian subthalamic nucleus (STN) has significance in the motor related function of the nucleus. In order to examine this fundamental proposition a series of predictions derived from this hypothesis have been tested. Firstly, that given the known anatomical connectivity of the STN, receiving prominent projections from cortex and in turn sending projections to globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr), activity of functional relevance should display similar patterns of connectivity. Secondly, that suppression of average power in the beta band of LFP activity associated with the presentation of movement-related cues should display response bias for functionally relevant stimuli. Thirdly, that these modulations of power observed in human subjects in response to behaviourally relevant stimuli should correlate not merely in gross terms with behaviour, but in a consistent discernable manner with aspects of behavioural performance.

The present work shows in simultaneous recordings of the electroencephalogram (EEG) and STN LFP that significant coherence exists between regions exhibiting both beta band oscillatory activity and anatomical cortico-striatal connectivity in cortex, and the parkinsonian STN; phase analysis further suggesting a cortical drive. This connectivity appears dopamine dependent with coherent activity in the beta band most evident on withdrawal of l-dopa medication, while coherence in the gamma band (*ca.* 60-80 Hz) is pronounced with l-dopa. Furthermore, beta band activity, previously shown to display suppression with movement is not only shown to exhibit similar modulation after cues allowing movement preparation, but to a greater extent with more informative cues than less informative. Finally, in contrast to prior efforts to display a relationship between beta oscillations and behaviour in the motor system, it is shown that there exists a consistent relationship between beta oscillation *suppression* and motor performance apparent across single trial data. These observations in the context of other work in both cortex and sub-cortex appear consistent with the functional significance of oscillatory activity in the parkinsonian STN and allow the formation of a further hypothesis as to its function and mechanism.

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Abbreviations

AC	anterior commissure	LLD	long latency desynchronization
A-D	analogue to digital	MEG	magnetoencephalography
CL	confidence limit	MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
CT	computerized tomography		
CWT	continuous wavelet transform	MRI	magnetic resonance imaging
DA	dopamine	NMDA	N-methyl-D-aspartate
DBE	deep brain electrode	OFF	off dopaminergic medication
DBS	deep brain stimulation	ON	on dopaminergic medication
DFT	discrete Fourier transform	PD	Parkinson's disease
EEG	electroencephalogram	PC	posterior commissure
EcoG	electrocorticography	PPN	pedunculopontine nucleus
EMG	electromyography	RET	reticular thalamic nucleus
ENK	enkephalin	RT	reaction time
ERD	event-related de-synchronization	SEM	standard error of mean
ERP	event-related potential	SLS	short latency synchronization
ERS	event-related synchronization	SMA	supplementary motor area
FIR	finite impulse response	SNc	substantia nigra pars compacta
GABA	gamma-amino butyric acid	SNr	substantia nigra pars reticulata
GP	globus pallidus		
GPe	globus pallidus externa	STN	subthalamic nucleus
GPI	globus pallidus interna	STNME	STN macroelectrode
GLU	glutamate	SUB P	substance P
LFP	local field potential	THAL	Thalamus
		UPDRS	unified Parkinson's disease rating scale

International system (SI) units are used throughout and are not defined here

CHAPTER I

INTRODUCTION:

Oscillations, LFPs and Parkinson's disease

“What are we to say, now that we are fully informed, when someone talks – as is too often the case – about a “fast rhythm”? How can such a blunder be made by a reasonable person” (Stravinsky, 1942)

Rhythmic activity is a near ubiquitous natural phenomenon, evident from fluctuations in galaxy clusters to neutrino oscillations. It is therefore perhaps unsurprising that oscillatory content was noted in some of the earliest characterizations of electrical activity in the human brain (Berger, 1929,1969; Adrian and Mathews, 1934). From these early and fundamental observations of the human electroencephalogram (EEG), it has become apparent that rhythmic properties are observable at all scales of brain activity; in intracellular neuronal and glial calcium oscillations (Pasti et al, 1997; Flint et al, 1999); subthreshold membrane potential oscillations (Llinas and Yarom, 1986; Alonso and Llinas; 1989; Agrawal et al, 2001); single spike and burst neuronal firing patterns (Steriade et al, 1977; McCormick and Feeseer, 1990; McCormick, 1992); and network neuronal population activity (Miles and Wong, 1983; Fisahn et al, 1998).

The development of techniques allowing the electrophysiological investigation of these phenomena has paralleled this scalar diversity (Makeig, 2002), ranging from patch clamp and intraneuronal microelectrode recordings of single units to scalp EEG recordings of several cm² of cortical surface (Cooper et al, 1965). Local field potential¹ (LFP) recordings via implanted intracortical or subcortical macroelectrodes lie between these two extremes, allowing neuronal population activity to be examined, while limiting the brain volume recorded and muscle noise contamination

¹ While the EEG is essentially a sub-type of LFP activity, LFPs considered in the current text always refer to activity recorded intra-cranially via either macro- or micro-electrodes, as distinct from scalp recorded EEG. The two are considered separately in this introduction as a result of distinctions in the regional accessibility, frequency resolution and types of potential contamination between the two.

inherent in scalp recordings. However, in common with microelectrode techniques access to restricted brain regions is offered at temporal resolutions unrivalled by imaging methods such as computerized tomography (CT) and magnetic resonance imaging (MRI). Furthermore, with the increasing use of deep brain electrode (DBE) implantation and stimulation as treatments for conditions such as epilepsy (Loddenkemper et al, 2001), dystonia (Kupsch et al, 2003), and Parkinson's disease (Limousin-Dowsey et al, 1999), macroelectrode LFP recording techniques have the further benefit of allowing practical access to deep brain structures in alert, active human subjects.

While methods of analyzing oscillatory brain activity are ever increasing, it remains the case that fundamental issues regarding the phenomenon at differing scales, frequencies and locations are still in what Kuhn may have described as, a "pre-paradigm" phase (Kuhn, 1962) – unresolved and characterized by competing explanatory models. What is the origin and mechanism of generation of oscillatory activity? Does this mode of activity have functional significance², and if so what is the nature of this significance? The current thesis deals explicitly with this second question, in the context of the human parkinsonian basal ganglia, at the level of the LFP and in the motor system. The hypothesis that oscillations in the LFP of the parkinsonian basal ganglia, particularly at frequencies between 13 and 30 Hz, have systemic, functional significance is tested by examination of a series of predictions, namely – Does this activity display the distribution and connectivity that may be expected of such a phenomenon? Is this activity modulated in a reproducible fashion by appropriate stimuli? Is there a consistent relationship between any such modulation and behaviour? In order for the informed consideration of these questions, current views concerning the structure and connectivity of the basal ganglia (particularly the STN) as well as the nature, origin and putative role of brain oscillatory activity must first be considered.

² The usage of the phrase "functional significance" in this work denotes a causal linkage between a phenomenon or processes underlying the generation of a phenomenon and behaviour. As such, it does not preclude the pathophysiological significance of any activity so described.

1.1 The functional anatomy of the basal ganglia

Despite their earlier depiction by Versalius (Goetz et al, 2001), the first identification and description of the basal ganglia is typically attributed to Thomas Willis in his “Cerebri Anatome” of 1664 (Swanson, 2000). What Willis described as the “corpora striata” however, represented the mass of subcortical tissue “...connecting the cerebrum to the legs of the medulla oblongata.” (Dewhurst K, 1980a). It is as a result of the further Willis inspired work of anatomists such as Vieussens (1684) that additional subdivision and classification proceeded, eventually resulting in the contemporary conception of the mammalian basal ganglia as a complex of component subcortical nuclei. This complex comprises the dorsal striatopallidal system: dorsal striatum (caudate and putamen), globus pallidus interna (GPi) and externa (GPe)³; and ventral striatopallidal system: nucleus accumbens (ventral striatum) and ventral pallidum - these groups all developmentally derived from the lateral and medial ganglionic eminences of the basal telencephalon (Parent 1997; Smeets et al, 2000, see figure 1). In addition the closely related, and interconnected structures of the substantia nigra (pars compacta SNc, and reticulata SNr) and subthalamic nucleus (STN) are also considered integrated components of this complex of nuclei. While minor variation still persists as to the exact definition of the basal ganglia between authors, in this text the term describes these core components. In addition the term striatum unless further qualified may be considered synonymous with the dorsal striatal components of the caudate nucleus and putamen.

1.1.1 Circuit models of the basal ganglia

Extensive anatomical, pharmacological and physiological investigation of the basal ganglia, over the last three decades has allowed their description, not merely in terms of anatomical connectivity, but as functional circuits of interacting component nuclei. Such basal ganglia circuit models presented by Albin, Young and Penney

³ GPe and GPi in primates are analogous to the globus pallidus and entopeduncular nucleus of non primates respectively

(Albin et al, 1989) and adapted and expanded upon by Alexander, Crutcher and DeLong (Alexander and Crutcher, 1990; DeLong, 1990) derive their significance from their ability to represent putative interactions between nuclei in the healthy state, to represent possible pathophysiological changes in hypokinetic or hyperkinetic disease states, and to predict the consequences of specific interventions (e.g. lesioning) of potential therapeutic significance in these states. Common to these “classical” models (fig 1.1) are a series of assumptions about basal ganglia function:

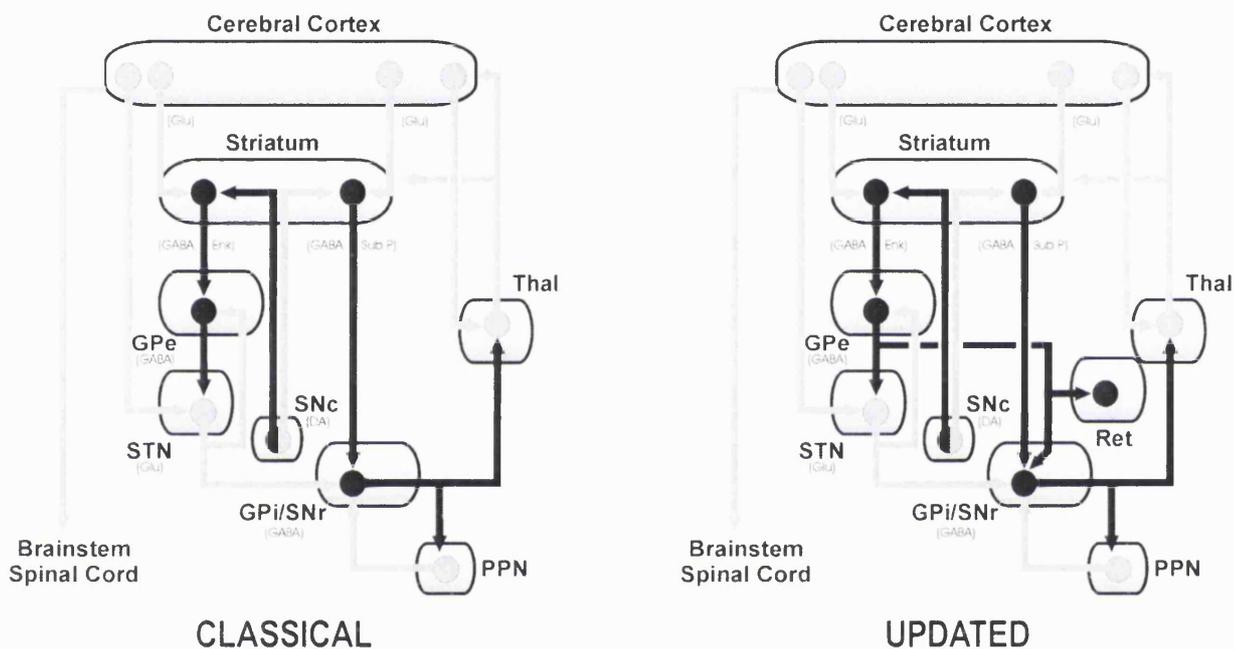


Fig. 1.1 Schematic representation of the basal ganglia functional circuit in the classical conception of the Albin-Alexander-DeLong model, left, and updated with respect to GPe connectivity, right. Neuronal populations with postsynaptic inhibitory effects are filled in black, those with excitatory effects in grey. The primary neurotransmitters mediating these postsynaptic effects are indicated in parentheses. Abbreviations are as per page 11 (Adapted from Alexander and Crutcher, 1990, and Smith et al, 1998).

First, it is implicit that ‘communication’ of nuclei within the basal ganglia is primarily mediated by linear interactions between their constituent neuronal populations. As such all representations of this type are essentially rate models i.e. the consequences of increases or decreases in rate of a given neuronal population may be predicted on the basis of a knowledge of presynaptic/postsynaptic

transmitter/receptor interactions in a deterministic manner. Second, that the principal spiny neuronal population of the striatal nuclei (caudate, putamen, nucleus accumbens) are the primary input component of the system receiving excitatory glutamatergic afferents from widespread regions of cortex in a topographically distinct manner. Third, that GPi and SNr neuronal populations are the primary output stage of the complex with inhibitory GABA efferents to thalamus, superior colliculus, mesopontine tegmentum and reticular formation. Fourth, that basal ganglia effects upon cortex are mediated by output nuclei modulation of excitatory thalamocortical projections. Fifth, that transmission between input and output stages occurs by one of two distinct pathways, direct – via striatal projections to SNr and GPi, and indirect - via striatal projections to GPe and then in turn to GPi and SNr, each mediated by distinct neuronal populations. As such common rate increases to both neuronal pools of the striatum would be predicted to have contradictory effects on neurons of the output nuclei. Sixth and finally, that dopamine modulates the system via projections from the SNc with differential consequences upon striatal neurons of the direct and indirect pathway, expressing D1 and D2 receptor subtypes respectively. In the functional circuit derived from such assumptions the hypokinetic features of Parkinson's disease are envisaged as a consequence of selective degeneration of SNc striatal afferents, resulting in reduced dopaminergic inhibition of 'indirect' striatal projections to GPe and reduced excitation of 'direct' projections to SNr and GPi - the net result being an increase in the tonic activity of output nuclei neuronal populations leading to reduced thalamocortical excitation. Similarly, the hyperkinetic features of Huntington's disease are considered the consequence of reduced inhibition via the 'indirect' striatopallidal projection with consequent excessive inhibition of subthalamic activity – resulting in decreased output nuclei neuronal population activity and excessive thalamocortical excitation (Albin et al, 1989; DeLong, 1990).

While experimental observation supports some of the classical model of basal ganglia functional circuitry (Albin et al, 1989; Alexander and Crutcher, 1990; DeLong, 1990), and important interventions such as STN lesioning in Parkinson's disease have resulted from its use as a conceptual framework for prediction (Bergman et al, 1990; Aziz et al, 1991) more recent investigation suggests a need for significant refinement of some of its assumptions – in terms of components incorporated,

connectivity displayed and the nature of nuclei interactions. With respect to components, it is now apparent from observations in both rat and squirrel monkey that GABA and neuropeptide Y interneurons as well as cholinergic neurons of the striatum receive cortical input (Lapper and Bolam 1992; Lapper et al, 1992; Bennet and Bolam 1994). The interactions and projections of these populations may significantly alter the conception of a two pool striatal input population. In addition with respect to the output populations, the presence of striatal projections and similarities of firing rate, pattern and conduction velocity between SNr neurons and midbrain reticular formation neurons (Rodriguez et al, 2001), as well as the presence of subsequent projections to thalamus (Veazey and Severin, 1980) have suggested that the midbrain reticular formation may represent a further significant output nucleus of the complex. New emphasis concerning connectivity is also being made. It is now apparent that GPe neurons, far from predominantly projecting to STN, send significant afferents to both SNr and GPi in both rat and monkey (Parent and De Bellefeuille, 1983; Bevan et al, 1996; Smith and Bolam, 1990; Kincaid et al, 1991; Smith et al, 1993). Such connectivity significantly alters the perceived role of GPe in the basal ganglia (see fig 1.1 updated) from relay in a single 'indirect' pathway, to a major modulator of output nuclei in a series of 'indirect' pathways. Further anomalies discussed in section 1.6.1 relating the classical model to Parkinson's disease suggest that beyond components involved and their connectivity, patterns of activity, particularly oscillatory patterns, may have a bearing in the normal and abnormal function of the basal ganglia – completely absent from the classical model.

1.1.2 Connectivity of the subthalamic nucleus

Despite evolving ideas of basal ganglia circuitry, the STN appear integral to function. On a theoretical basis this is apparent in their role in circuit models both as a major source of cortical input to the system and as modulators of SNr/GPi nuclei output. The capacity of STN lesions in the healthy state to induce the hyperkinetic disorder, hemiballismus, both in humans and non-human primates (Martin, 1927; Whittier and Mettler, 1949), and to ameliorate motor symptoms in human parkinsonism and the MPTP primate analogue (Alvarez et al, 1999; Bergman et al, 1990; Aziz et al, 1991)

also make the STN of practical significance – potentially giving insight into the function and possibly therapeutic manipulations of the basal ganglia as a whole in both healthy and parkinsonian states. Furthermore, the relatively recent emergence of repetitive electrical stimulation (DBS) of the STN as an effective reversible therapy in Parkinson's disease (Benabid et al, 1994; Limousin et al, 1995) raises questions such as - How does DBS of the STN work? and - What is the role of oscillatory phenomena in the function of the STN and basal ganglia? The degree, manner and pattern in which oscillatory activity evident in cortex relates to that of the STN may either support or refute the notion that frequency content apparent in LFPs of both regions may reflect integrated and therefore more likely functionally significant activity. Such connectivity in the frequency domain is considered in the work of Chapter 3. Any functionally significant pattern of observed frequency connectivity would however be predicted to be limited by anatomical connectivity and regional functional significance, as such the distribution of corticosubthalamic projections is of importance.

Corticosubthalamic anatomical connectivity exists both indirectly, particularly via striatum, or directly via corticosubthalamic projections. Both electrophysiological and tracer studies have demonstrated widespread corticostriatal projections in non-human primates, showing evidence of anatomical connectivity between motor and premotor cortical regions and putamen (Kunzle, 1975, 1977; Flaherty and Graybiel, 1991); associative cortex and caudate and rostral putamen (Goldman and Nauta, 1977; Yeterian and Pandya, 1991); amygdala, hippocampus, limbic cortex and nucleus accumbens (Brog et al, 1993; Kunishio and Haber, 1994; Russchen et al, 1985). In addition there is strong evidence of bilateral projection of cortical regions to striatum (Kunzle, 1975; Fallon et al, 1979; Battaglini et al, 1982). As such a large proportion of cortex may conceivably influence subthalamic neuronal activity via polysynaptic interactions. The capacity of a cortical region to directly influence subthalamic neuronal activity via monosynaptic projections in addition suggests that such cortical regions may be of particular significance to STN function.

In addition to receiving significant direct projections from brainstem nuclei⁴, the centromedian parafascicular nucleus of the thalamus (Sugimoto and Hattori, 1983; Groenewegen and Berendse, 1990) and GPe (Carpenter et al, 1981a; Carpenter et al, 1981b), the STN receives substantial direct projections from cortex. Attempts have been made to characterize the cortical origins of this input both in rat and monkey species. Tracer studies in rats have been consistent in demonstrating a major afferent component of motor cortical origin (Afsharpour, 1985 (only anterograde); Canteras et al, 1990 (anterograde and retrograde), Orioux et al, 2002 (anterograde and retrograde)). Furthermore staining has localized this source predominantly to the layer 5 cortical population (Kitai and Deniau, 1981; Orioux et al, 2002). Contradictions are apparent however with regards the degree of somatosensory input, with some investigators suggesting a substantial component (Afsharpour, 1985; Canteras et al, 1990) but more recent work none at all (Orioux et al, 2002). In addition, these investigators have reported a more extensive input area reporting corticosubthalamic origins in insular, anterior and medial cingulate and anterior frontal lobe cortex. Indeed electrophysiological investigation by Rouzair-Dubois and Scarnati (1985) has demonstrated that stimulation of widespread regions of rat cortex may elicit excitatory responses in the STN neuronal population in a monosynaptic manner. In addition this STN excitation may result from stimulation of either ipsilateral or contralateral cortex. This appears consistent with similar observations of contralateral sensorimotor cortex stimulation responses in STN, abolished by rostral corpus callosum transection (Fujimoto and Kita, 1993), but contrary to tracer studies in both rat and monkey that suggest predominantly ipsilateral connectivity (Monakow et al, 1978; Carpenter et al, 1981b; Canteras et al, 1990). Monkey tracer studies in common with their rat analogues have also shown major projections from motor cortex to STN (Nambu et al, 1996), but in addition have shown evidence of substantial other premotor sources in Brodmann's areas 6, 8 and 9 and cingulate cortex (Monakow et al, 1978; Huerta et al, 1986; Takada et al, 2001), particularly from supplementary motor area (SMA) (Jurgens, 1984; Nambu et al, 1997). Further combinations of tracing and microstimulation have illustrated a dorsolateral representation of motor cortical input, with SMA and pre-SMA regions

⁴ Substantia nigra (Canteras et al, 1990), pedunculopontine nucleus (Carpenter et al, 1981b; Jackson and Crossman, 1983) and dorsal raphe nucleus (Woolf et al, 1986; Canteras et al, 1990)

more medial and ventral respectively (Nambu et al, 1996; Nambu et al, 1997; Inase et al, 1999).

There is therefore considerable evidence to date of direct mammalian corticosubthalamic connectivity from motor cortex, SMA and pre-SMA areas and indirect from most regions of cortex. While the majority of evidence supports the dominance of ipsilateral connectivity in monosynaptic connections, electrophysiological observation suggests the potential for contralateral interactions in both monosynaptic and polysynaptic projections. Though these observations particularly in non-human primates represent the best available basis for predicting the limit of any functional connectivity that might be examined between the two regions, it must be remembered that the potential exists for minor variations in anatomical connectivity between species⁵ (let alone genus or family).

1.2 Origins of local field potential oscillations

Oscillatory activity at the level of the EEG and LFP may be classified by location, amplitude, morphology and behavioural correlate. Early investigations of the human EEG associated these features with specific frequency bands (Berger, 1929,1969), and it is this extended categorization by frequency bands, denoted alpha (*ca.* 8-13 Hz), beta (*ca.* 13-30 Hz), gamma (> 30 Hz), delta (< 4 Hz) and theta (*ca.* 4-7 Hz) which remains the dominant, and expanding⁶, means of classification. This work is consistent with this convention. A minor degree of controversy in such classification exists in the variation in definition of band boundaries. Variability is both inherent in comparisons between subjects (Klimesch, 1999), and comparisons between studies.

⁵ E.g. Evidence has been presented of input from Brodmann's area 8 of the owl monkey and macaque to STN, apparently absent in squirrel monkeys (Huerta et al, 1986).

⁶ Beyond the well-established activities listed here there is increasing interest in ever higher frequency bands such as rho (*ca.* 200 Hz) hippocampal ripple activity and somatosensory evoked sigma burst (*ca.* 600Hz) activity (Curio, 2000). These bands and activity in the lower theta and delta bands (e.g. Steriade et al, 1993a) are peripheral to the investigations detailed here and are therefore treated as such in this introduction.

Steriade, for example suggests that the subdivision of activity > 20 Hz into distinct beta and gamma components is “an analytical effort with terminology, worthy of a better cause” (Steriade, 1997), arguing that activity within the beta range may potentially fluctuate in frequency within a 1 sec epoch up to 40 Hz without behavioural correlate. In this work, the usage of alpha, beta and gamma bands as detailed above, is justified because activities are predominantly considered within the STN and GPi where peaks observed in the respective bands typically differ in frequency by a factor of 3 or more (Brown, 2001). In addition and more importantly, it should be emphasized that though frequency bands common to EEG taxonomy are used in the context of basal ganglia LFPs, the LFPs do not necessarily share the behavioural associations of their EEG counterparts. As such, bands are better considered in terms of their reactivities to stimuli (e.g. increases or decreases in power with movement), which clearly distinguishes beta and gamma activity irrespective of minor variation of frequency band (Brown, 2001, Cassidy 2002).

Brain local field potentials are dynamic entities, displaying spatio-temporal fluctuations in amplitude of frequency content in response to stimulation. As will be discussed with respect to movement specifically (section 1.5) these changes may be reproduced by a specific stimulus or in association with particular behaviour. A thorough interpretation of the meaning of such changes however requires some conception of what field potentials in a given region actually represent. What cell populations are engaged in their generation? To what extent are they the result of local synchrony? How do they relate to known task-related neurons? In addition, how are oscillations generated in field potentials? While the origins of oscillation in field potentials are still somewhat hazy and complicated by the possibility of distinct methods of generating different frequency bands, in different regions, a degree of insight exists regarding cortical field potential generation.

1.2.1 Local field potential generation in cortex and basal ganglia

The origins of transcranial brain LFP activity, the EEG, are now well established with a small contribution from glial cells but by far the majority derived from the activity of

convoluted pyramidal neuronal layers (Bishop 1949, Creutzfeld and Houchin, 1974). Despite the complexity of each neuron, elongated morphology, coupled with the asymmetric representation of synapses on the archetypal cortical pyramidal neuron, has allowed the characterization of each as a dipole source.

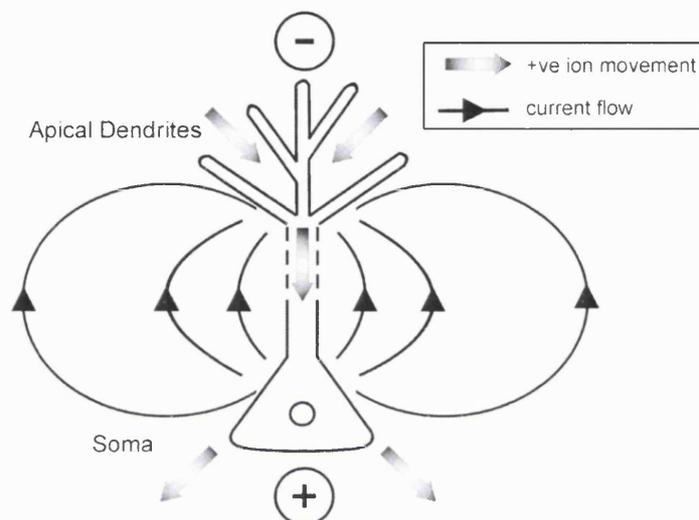


Fig. 1.2 Schematic representation of a pyramidal neuron as a dipole source, illustrating inward dendritic and outward apical +ve ion movement on afferent excitation, resulting in the generation of a local extracellular -ve dendritic current 'sink' and +ve apical current 'source' (Adapted from Gloor, 1985).

In such a model (fig 1.2) the transient membrane permeability consequent upon neurotransmitter release at a dendritic excitatory synapse, results in the passage of positively charged ions down an electrochemical gradient into the cell. This influx and build up of isoelectric charge, itself results in the displacement of ions along the dendrite towards the cell body and a regional extracellular deficit of positive charge at the synapse. As such a 'sink' is said to develop into which flow positive ions from a 'source' that may be considered the efflux of positive charge from basal dendrites or the neuronal soma.

At a larger scale the laminar arrangement of pyramidal neurons in addition to their parallel orientation with apical dendrites at right angles to the cortical surface means that generated potentials may summate relative to a surface recording electrode. Consideration of the functional structure of a sensory cortical column further elucidates this point. Layer 4 spiny stellate or spiny pyramidal neurons receive the

majority of excitatory input to the cortical column (e.g. lateral geniculate nucleus or thalamic relay nuclei afferents to striate cortex, Hubel and Weisel, 1962; McGuire et al, 1984; Guillery and Sherman 2002). These neurons in turn relay excitation to the pyramidal neuronal population of layers 2/3 whose projections are excitatory both laterally to neighbouring columns and vertically to adjoining layers (Feldmeyer and Sakmann, 2000). As such, many neighbouring output pyramidal neurons of layer 5 may receive afferent excitation via their dendrites in layers 2/3, each allowing the formation of an above described dipole. In addition thousands of neuronal synapses may be formed by single cortical afferents (Landry and Deschenes, 1981, Landry et al, 1982) and numerous anatomically independent inputs may fire simultaneously. All of these anatomical realities combine to allow the temporal summation of simultaneous inputs within laminar pyramidal neurons and spatial summation of large numbers of aligned potentials across them. Despite the greater amplitude of pre-synaptic and post-synaptic action potentials, it is excitatory and inhibitory post-synaptic potentials that predominantly contribute to the fields generated by such summations. This results not only because they involve greater degrees of membrane surface area but also because of their slower temporal evolutions – increasing the probability of summation. Rat layer 5 pyramidal neurons for example, display excitatory postsynaptic potential decay time constants of approximately 40ms (Feldmeyer and Sakmann, 2000; Feldmeyer et al, 2002), far in excess of the ms time scales of associated presynaptic or postsynaptic action potential activity. Furthermore, the greater reliability of input, as opposed to output layer neurons, in the production of postsynaptic potentials from given action potentials, may suggest that pyramidal neurons initially recruited by afferent excitation contribute more to resultant fields than their output counterparts (Feldmeyer and Sakmann, 2000).

This simplified approximation of EEG generation has allowed the explanation of why large fibre tracts with approximately synchronous activity fail to produce similarly large field effects in the EEG, and the ubiquitous inverse relationship between spectral power⁷ and frequency (Gloor P, 1985). The former may be considered the failure of ms duration action potentials to summate with comparable temporal

⁷ The term 'spectral power' used here and throughout denotes the proportion of the energy per unit time of a signal within a given frequency window

variability in generation and transmission; the latter, similarly the result of ever smaller oscillatory period durations with higher frequency, decreasing the likelihood of coincidence in two local sources. Additionally, the predicted inverse square relationship between generated field strength and distance from a dipole source has allowed the already mentioned contention that DBE recording of field sources should result in higher amplitude representations of smaller volumes of tissue. A degree of difficulty however arises in consideration of field sources beyond the laminar cortex. As has been described the asymmetric, anisotropic characteristics of cortex may allow the discernment of fields at distance from their origin, with more symmetric, isotropic cellular arrangements however, closed-fields may exist (Lorente de No, 1947), resulting in the apparent obliteration of regional potential shifts at a distance. Such an arrangement is exemplified by the oculomotor nucleus and may result from multipolar neuronal morphology in thalamus (Lopes da Silva and van Rotterdam, 1987).

Cytoarchitectural investigations of monkey and rat STN suggest that despite minor inter-species variations in arborization, the nucleus contains tightly packed principal neurons with elliptic dendritic fields, typically aligned along its primary axis (Rafols and Fox, 1976; Kita et al, 1982; Change et al, 1983; Hammond and Yelnik, 1983). Similar studies in pallidum also demonstrate elliptic field morphology, but with pallidal dendritic fields always parallel to the lateral body of the nucleus (Difiglia et al, 1982; Yelnik et al, 1984). No specific investigation of field generation from these nuclei, *in vivo*, in primates has been performed to date but such morphologies might be predicted to result in some degree of local field generation with synchronous activation, perhaps more so in pallidum than STN. Neither however would be expected to display a clear open field morphology comparable to that generated by cortex. As such authors such as Wennberg and Lozano (2003) contend that potentials recorded from DBEs in STN represent volume conduction from cortical sources. There is direct evidence however of both simultaneous membrane potential state transitions, and the dependence of field potentials recorded in basal ganglia nuclei upon synchronous membrane potential fluctuations, from recordings made in both dorsal and ventral rat striatum that show coincident modulations in both (Stern et al, 1998; Goto and O'Donnell, 2001). Additionally it is important to note that even

with entirely closed field architecture, field potentials resulting from synchronous activation should readily be recorded if a multicontact macroelectrode pierces the isoelectric field line, i.e. if the electrode enters the nucleus. Such a circumstance may exist particularly in a small nucleus such as the STN where only one contact may be expected to be within the nucleus (see Methods section 2.1). Assessments performed with bipole examination (across contiguous contacts) therefore in a closed field nucleus may potentially record activity across the 'nucleus dipole'. Evidence presented both in Chapter 3 of variations in cortico-subthalamic coherence along STN DBEs in differing subjects, and in Chapter 4 of the maximization of event-related changes to the middle DBE bipole, supports the contention that such LFPs represent the activity of a local subcortical source.

1.2.2 The generation of oscillations in local field potentials

Ritz and Sejnowski (1997) classify oscillations in neuronal population activity into those that are a consequence of the intrinsic oscillatory characteristics of neurons within the population, and those that emerge from the interconnection of non-intrinsically oscillatory populations. To these should probably also be added the third category of regular rhythmic activity dependent upon the presence of both. However comprehensive the system of classification, at present there are no all-inclusive explanations of the gamut of oscillatory population phenomena seen *in vivo*. This is not only a result of the variety of mechanisms that may exist, but also a consequence of the difficulty inherent in producing experimental models that both maintain the structural complexity of the intact alert brain, and allow controlled manipulation. A piecemeal understanding of specific modes in varying regions is however emerging.

The intrinsic oscillatory properties of thalamocortical neurons appear integral to the occurrence and propagation of sleep spindle activity and involved in the generation of the superficially similar waking alpha cortical rhythm (Steriade et al, 1990). As well as action potential related sodium, potassium and high threshold calcium conductances, these cells possess a low threshold calcium conductance. On

hyperpolarization of the cell membrane this latter conductance may result in a rebound spike and bursts of action potentials (Llinas and Jahnsen, 1982). Additionally these cells further possess a slow transient inactivating A-type potassium conductance (Pape et al, 1994) and non-inactivating sodium conductance (Llinas and Sugimori, 1980). These combined make thalamocortical neurons capable of existing in a hyperpolarization related burst firing or depolarization associated tonic firing mode. GABA releasing reticular thalamic neurons appear even more predisposed to oscillate, having an additional calcium induced rebound excitation conductance (Llinas and Geijo-Barrientos, 1988). In sleep spindle generation spontaneous bursts of reticular thalamic neurons at between 7 and 14 Hz induce hyperpolarization of thalamocortical neurons activating the rebound calcium spike and bursting (Steriade et al, 1993b). These bursts of thalamocortical activity result both in excitation of their projection neurons in cortex and further recurrent activation of the thalamic reticular nucleus neuronal population. Despite similarities of frequency between sleep spindles and alpha activity, the higher levels of coherence seen in alpha activity between neighbouring cortical regions (Lopes da Silva and Storm van Leeuwen, 1977) in comparison to equivalent corticothalamic coherence measurements (Lopes da Silva, 1973) have suggested differing mechanisms of generation. This apparent difference in the significance of intracortical connectivity is further emphasized when it is noted that transection of intracortical connections in the barbiturate anaesthesia model of spindling does not significantly effect cortical coherence (Contreras et al, 1996). In addition to evidence of cortical sources of alpha (section. 1.3.1.2) and the observed abolition of certain thalamic alpha oscillation with cortical inactivation (Fanselow et al, 2001), current conceptions consider cortical alpha a consequence of the interaction of thalamocortical and as yet poorly understood local cortical generators. This possibly in a manner where during waking alpha, cortex is the dominant generator, but during sleep spindling the thalamus is the primary source of rhythmicity (despite cortex being able to initiate, entrain and synchronize thalamic activity (Contreras and Steriade, 1997)).

Gamma frequency population activity has also undergone extensive investigation in computer, hippocampus and neocortical models. The observed capacity of a solely inhibitory reticular thalamic interneuronal population to synchronize in the alpha band

(Wang and Rinzel, 1993) spurred interest in similar networks elsewhere. Both computer modelling and hippocampal slice experimentation has shown that with an appropriate GABA(A) receptor time constant and sufficient excitation such interneuronal networks may potentially oscillate in the gamma frequency range (Whittington et al, 1995, Jefferys et al, 1996). Subsequent investigations further demonstrate that with the introduction of excitatory neurons to the pool and interconnection of several of these intraconnected, mixed neuronal pools, the synchrony induced by local GABAergic populations may induce phase locked excitatory neuronal firing, which in turn if populous enough may result in a second inhibitory population spike (Traub et al, 1996).

Hence inhibitory pools and mixed inhibitory and excitatory pools interconnected have shown the capacity to oscillate with synchrony. The STN-GPe axis of the basal ganglia however comprises primarily distinct excitatory and inhibitory pools with reciprocal connectivity particularly from dorsolateral STN (Parent, 1990; Parent and Hazrati, 1995). Freeman *et al.* have examined similar neuronal population organizations in the olfactory system. They suggest that such interconnected populations may display oscillatory dynamics in which the inhibitory population lags the excitatory by a quarter of a cycle, reasoning a four step process of excitatory neuronal activation, inhibitory neuronal activation, excitatory neuronal inhibition and inhibitory neuronal disfacilitation (Freeman 1975; Eeckman and Freeman, 1990). It is unclear why each step should necessarily have equal duration in the oscillatory cycle but nonetheless recordings throughout the olfactory system have isolated populations that fire in phase and others that fire a quarter of a cycle out of phase with the associated LFP activity. This model however describes essentially a single population with interneuronal inhibitory activity, as distinct from the STN-GPe coupled system where conduction delays between nuclei are an important distinguishing component. It also describes oscillations predominantly in the gamma band. Further work based on the findings of the hippocampal doublet interneuron firing model have gone on to suggest that transitions from gamma to beta oscillation may occur, in circumstances where strong connections exist between excitatory neurons which possess after-hyperpolarization currents (Kopell et al, 2000). This

beta synchrony is observed to occur specifically when there are long delays between excitatory and inhibitory populations.⁸

Coupled excitatory-inhibitory networks with GABA(A) transmission and strong excitatory coupling, may therefore have relevance to STN-GPe coupled basal ganglia oscillation generation of beta and gamma rhythms. As will be discussed in section 1.3.2.2 investigations particularly in rat STN and pallidum (GPe), suggest that significant proportions of their neuronal populations possess oscillatory tendencies with significant potential effects of each population activity on the other (Bevan et al, 2002). Furthermore recurrent connectivity between these nuclei in an *in vitro* culture model of basal ganglia is sufficient to produce significant, though low frequency (0.4 – 1.9 Hz) oscillatory population activity (Plenz and Kitai, 1999). Evidence also implicates cortical influence in these rhythms. In states of slow wave activity associated with anaesthesia a strong tendency of cortical activity to be correlated with, and indeed possibly drive that of STN and GPe is observed (Magill et al, 2000). As such, current evidence in basal ganglia suggests that, similarly to cortical alpha, oscillations at unit and LFP levels may result from the interaction of local subcortical STN-GPe generators with external cortical modulation.

1.3 Oscillations and the brain⁹

1.3.1 Cortical oscillatory activity

1.3.1.1 Electroencephalography and magnetoencephalography

At the level of the EEG, alpha activity was the first (Berger, 1929, 1969) and is the most pronounced oscillatory mode observed, classically described in the conscious

⁸ The recent demonstration of linkage disequilibrium between the frequency of observed cortical beta activity and GABA(A) receptor genes also provides interesting circumstantial evidence of a role of GABA(A) activity in the generation of cortical beta rhythms (Porjesz et al, 2002).

⁹ This section deals predominantly with the contextually relevant frequency bands, alpha (Ca. 8-13Hz), beta (Ca. 13-30Hz) and gamma (> 30Hz).

subject as most evident with their eyes closed and in a mentally inactive state. Early posterior cortical localizations have given way to increasingly detailed source modelling with magnetoencephalography (MEG) (Hari and Salmelin, 1997) suggesting multiple foci dominated by activity in the region of the parieto-occipital and calcarine sulci (Salmelin and Hari, 1994). Beyond this initially identified oscillatory activity, subclasses of alpha activity, mu¹⁰ and tau rhythms have been detected in other cortical regions and associated with differing behavioural contexts. Activity around the central sulci, with origins in the region of the hand representation (Salmelin and Hari, 1994a; Tiihonen et al, 1989) and supplementary motor areas (Pfurtscheller et al, 1997) represents the alpha component of the mu rhythm (ca. 7-13 Hz) (Chatrian et al, 1959), which itself has been joined recently with electrocorticography (EcoG) and MEG analysis by the temporal lobe tau rhythm (ca. 10 Hz) (Niedermeyer, 1990; Tiihonen, 1991). These three sources of alpha are distinguished by their broad modality specificity. Evidence of this was also present in early observations of the human EEG, with the demonstration of posterior alpha oscillation suppression when subjects opened their eyes (Adrian and Mathews, 1934). Mu activity displays similar modulation associated with motor related task requirements (Jasper and Penfield, 1949; Chatrian et al, 1959; Gastaut, 1952; Neuper and Pfurtscheller, 2001) and tau with acoustic stimulation (Tiihonen, 1991). These waking alpha rhythms also display attenuation during the transition from wakefulness to sleeping (Dement and Kleitman, 1957), with the onset of spindle oscillations at a similar frequency. Mounting observations of alpha band oscillatory activity localized to various task specific regions of cortex and displaying appropriate task related modulation of activity (e.g. in language, Crone et al, 1994, 1999) suggest that these oscillations should best be considered a widespread, but context specific, mode of activity rather than a topographically limited, highly frequency and behaviour specific modality.

In addition to the activity evident in the alpha band, movement modulated oscillatory activity in the region of the central sulci, also occurs in the beta band at about 20 Hz and may be present in the region of the SMA (Pfurtscheller et al, 2003). This

¹⁰ Mu activity merely reflects movement modulated, peri-central sulcus, oscillatory activity. It has two dominant peaks. A lower peak in the alpha band and higher in the beta band.

represents what some consider the beta component of the mu rhythm, forming its second prominent peak. While both alpha and beta elements display similar stimulus related modulations, the capacity of each to appear both independently and in combination (Tiihonen et al, 1989) has suggested that they are independent entities. This is further supported by EEG and MEG studies that have localized beta activity to a more anterior precentral source in contrast to the more posterior alpha (Pfurtscheller, 1996; Salmelin and Hari, 1994b). In addition, while post-movement increased oscillatory activity displays a somatotopic distribution with body part moved, alpha rebound maintains a constant distribution irrespective (Salmelin et al, 1995). This has subsequently been supported by similar findings in EcoG recordings (Crone et al, 1998a). Hence beta and alpha activities in the EEG are distinguished by their differing degrees of specificity to motor task performance but share a basic pattern of responsiveness to motor stimuli.

Gamma frequency oscillations were first described as >30 Hz rhythmic activity superimposed upon occipital alpha (Jasper and Andrews, 1938). Moving beyond the beta band however, the human EEG and MEG become increasingly limited tools for the investigation of oscillatory components of cortical electrical activity. This arises not merely because of the inverse relationship typically observable between frequency of oscillatory components and their amplitude, resulting in increasingly poor signal to noise ratios; but also as a result of the spatial averaging properties of the skull and scalp, effectively low pass filtering components of cortical origin (Pfurtscheller and Cooper, 1975). As a result, those observations that have been made in EEG and MEG have largely focused upon the lower boundary of this band, circa 40 Hz. In common with alpha activity, these observations suggest that gamma oscillations have a widespread cortical representation and that regional activity may display modality specificity. Hence, they have been observed to be evident in EEG and MEG of somatosensory cortex in tactile discrimination tasks (Sauvé et al, 1998), and in auditory cortex in equivalent auditory temporal discrimination investigations (Joliot et al, 1994; Tiitinen et al, 1993). Furthermore 40 Hz activity appears evident in MEG of somatomotor cortex during self-paced movement (Salenius et al, 1996), as well as across widely distributed cortex (including visual cortex) in visual perception tasks (Tallon-Baudry et al, 1997; Rodriguez et al, 1999). Detailed EcoG

investigations in auditory (Crone et al, 2001) and somatomotor cortex (Crone et al, 1998b; Pfurtscheller et al, 2003) however suggest that activity in a higher, 'upper gamma band' (ca. 70-100 Hz), may also be a component of cortical electrical oscillations. Indeed activity in this higher band in somatomotor cortex appears to display a better somatotopic relationship to movement than beta activity or even lower gamma activity (Crone et al, 1998b). Common to all the above observations in the gamma band however and in contrast to activity in alpha and beta bands, is the consistent augmentation rather than suppression of activity in response to relevant stimuli.

1.3.1.2 Intracortical local field potentials

EEG and MEG studies have allowed the non-invasive consideration of brain population activity in humans with millisecond temporal resolutions. However the potential conclusions obtainable from such recordings are circumscribed, as alluded to above, both by their limited spatial, and frequency resolutions. As such, until more extensive multi-neuron recording techniques become available, cortical LFP electrode recordings in animals, intra-operatively in humans or post-operatively from patients are the only means of further investigating brain population activity with high temporal, frequency and spatial resolution. Observations using such techniques almost universally, report oscillatory activity as occurring in bursts though with varying morphology – spindle shaped, sudden onset or sudden offset (e.g. Murphy et al, 1996a).

Alpha LFP recordings corroborate their EEG analogues with respect to both visual occipital and motor peri-central activities and further suggest that this may be a fundamental mode of activity. Not only have they been reported in the auditory and visual pathways of both cats (Basar, 1980; 1998) and dogs (Lopes da Silva and Storm van Leeuwen, 1977; Lopes da Silva 1980); but in invertebrate species such as *Aplysia* and *Helix Pomatia* (Bullock and Basar, 1988; Basar 1999). Cortical phase reversals in vertebrate species at layers IV and V further suggest local sources in the pyramidal neuron layer (Lopes da Silva and Storm van Leeuwen, 1977; Lopes da Silva 1980). With respect to mu activity, both cat and rat somatomotor and sensory

cortex display activity displaying similar properties to their human EEG equivalents (Semba, 1980; Bouyer, 1983; Nicoletis, 1995). Interestingly, detailed localization in cat primary somatosensory cortex even shows that the activity is focused in the forepaw and wrist projection area (Bouyer et al, 1983) consistent with the apparent human locus.

Beta LFP activity in intracranial recordings of human motor cortex has long been recognized (Jasper and Penfield, 1949) and over the last two decades in particular has undergone substantial investigations with respect to its role in motor function (considered in section 1.5). Microelectrode recordings in monkey sensorimotor cortex have numerously been demonstrated to display oscillations with frequencies between 20 and 30 Hz (Murthy and Fetz, 1992; Sanes and Donoghue, 1993; Murthy and Fetz, 1996a; Murthy and Fetz, 1996b; Donoghue et al, 1998; Fetz et al, 2000). These characteristically occur in bursts, present for about 4 cycles duration, but may persist for up to 30 cycles (Murthy and Fetz, 1996a). In addition they appear capable of synchronization over distances as great as 14mm (Murthy and Fetz, 1992; Sanes and Donoghue, 1993) and even between cerebral hemispheres (Murthy and Fetz, 1996a). Furthermore, the intracortical as opposed to volume conducted subcortical origin of this activity has been established by relative phase considerations, showing reversal at between 0.5 and 1 mm depth (Murthy and Fetz, 1996a).

Oscillations of LFP activity >30 Hz were evident in the recordings of Adrian published in 1942 from hedgehog olfactory bulb. Subsequent similar studies in duck (Wenzel and Sieck, 1972), rat (Woolley and Timiras, 1965), rabbit (Moulton, 1963), cat (Gault and Leaton, 1963), monkey (Domino and Ueki, 1960) and man (Hughes et al, 1969) have all likewise displayed spontaneous oscillatory activity in the 30 to 80 Hz range. This activity as observed in the beta band is evident in periodic bursts, which are distributed and may be coherent throughout not only the olfactory bulb, but the anterior olfactory nucleus and prepyriform cortex (Boudreau, 1963). In addition, while similar activity has been observed throughout the olfactory system across species, variations of frequency between species within the 30 to 80 Hz band appear tuned to olfactory bulb oscillation frequency (Bressler and Freeman, 1980). In the olfactory system gamma LFP oscillations therefore display characteristics consistent with a

functional role, showing evolutionary conservation across species, and consistent, system distributed activity within species. Observations such as these have supported and fostered hypothetical roles of gamma oscillations at both LFP and unit levels in the integration of dispersed sensory processing (Engel and Singer, 2001), and it is a role in such integration that has largely stimulated the copious research into gamma oscillations that has occurred over the last decade. Consistent with EEG and MEG findings LFP gamma oscillations are also observable in the visual, somatosensory and auditory systems, displaying analogous distributions to that seen in the olfactory system - apparent in the retina (Heynenet al, 1985), superior colliculus and lateral geniculate nucleus (Munemori et al, 1984) as well as visual cortex (Freeman and van Dijk, 1987). In addition though reported to occur spontaneously in these systems, it is again the case that gamma oscillatory LFP are a reactive phenomenon, i.e. a single appropriate stimulus may elicit bursts of oscillations. In this respect a potential but highly important species difference may exist however, since it has been reported that while monkeys display such reactivity in visual cortex, the same is not true in humans (Juergens et al, 1999). This investigation was to a certain extent flawed by the inability to compare LFP recordings from both, relying on a combination of LFP and EEG in monkey in comparison to EEG in man. The discrepancy may therefore merely reflect differences in skull attenuation of high frequency activity between the two species, or slight variations in source orientation. Nonetheless the offhand equivalence of non-human primate investigations with human must be guarded against.

In summary, focal LFP recordings of oscillatory cortical activity across mammalian and non-mammalian species appear broadly consistent with EEG, MEG and EcoG recordings in man and monkeys displaying activities in the alpha, beta and gamma bands, and corroborating derived EEG localizations of activity. While differences may exist in terms of gamma band frequency content all frequencies display similar stereotypical patterns of reactivity in both intra-cranial and extra-cranial recordings.

1.3.1.3 Single unit activity

Despite the fact that field potentials may allow the consideration of activity derived from large neuronal populations, it is at the level of the neuron that insights have largely been made concerning the nature of information coding. The observations concerning EEG, MEG and LFP oscillations in cortex detailed up to this point illustrate this fact. Although modulations of oscillatory LFP activity may be observed in numerous regions, specifically and appropriately related to task performance, the responses that have been described are typically stereotyped – that is they lack the subtle scaling that would be required to distinguish say the tactile sensation of silk from velvet. Fresh investigations in motor cortex using multiple LFP recordings show the capacity of such data to show tuning to movement parameters at least equal to similar single unit recordings (Pesaran et al, 2002; Mehring et al, 2003). This suggests that this delineation between unit activity and field potentials may to a certain extent be a technical issue, the result of there typically being too spatially coarse a level of sampling at the LFP level - resolved perhaps with more numerous, higher impedance, simultaneous electrode sampling. Nonetheless this distinction is at present valid and consideration of oscillations at the neuronal level, and their relationship to LFP activity in specific functional states (sections 1.5.3 & 1.6.1) may relate LFP activity to information processing.

All neuronal spiking activity may essentially be considered rhythmic, if not regularly so. Regular, oscillatory neuronal activity, if present however may be considered in two forms, either ends of a spectrum. The first is the interaction of single units at common frequency displaying discrete single action potentials, the second the capacity of certain neuronal populations under given circumstances to exhibit regular bursts of action potentials. The former is exemplified by observations made in some of the many papers examining visual cortical gamma activity. Here it has been demonstrated in both cats and monkeys that in response to an optimally orientated moving bar stimulus, neurons in areas 17 and 18 display an increased tendency to fire at a rate of ~40 Hz. In addition this 40 Hz tendency is phase locked to peaks of the negative hemicycle of associated 40 Hz LFP oscillations (Gray and Singer, 1989). Similar findings have been documented in monkey sensorimotor cortex where

the activity of a significant proportion of sampled neurons is observed to be phase locked to concurrent beta LFP oscillations (Murthy and Fetz, 1996b). When considered across the entire neuronal population of a given region of cortex, this propensity of a proportion to fire at a given point in a common LFP cycle may help to explain the often noted association of oscillatory states with synchrony. Returning to visual cortex it is apparent that this increased synchrony of firing may display the same types of modulation as have been discussed in LFP oscillations. This is seen in the suppression of alpha LFP locked firing and augmentation of gamma LFP locked firing in the transition from a delay period to presentation of a visual signal (Fries et al, 2001, 2002). A further important factor of this mode of unit activity is also seen, the separation of firing rate from oscillation. While significantly less alpha modulation of spike activity may be observed in the non-attentive as opposed to the attentive state, average firing rates may remain constant. These oscillatory modulations therefore reflect a change in the temporal distribution of action potentials at one scale independent of others. The logical extreme of such a change is the second pattern of neuronal oscillation, burst firing. Again in the visual cortex, *in vivo*, Gray and McCormick (1996) have isolated a group of pyramidal neurons that when depolarized intrinsically fire ~800 Hz bursts of action potentials in the gamma frequency. Subsequent similar observations have been made *in vivo*, in cat motor cortex (Steriade et al, 1998). In addition it may be the case that these modes of firing are dynamic properties of individual neurons, hence a single unit may move from regular firing to burst firing and back again.

While dynamic alterations of firing mode may well be a feature of certain cortical neurons, a propensity to regular rhythmicity also appears to be. *In vitro* rat slice preparations from somatosensory cortex exhibit field potential oscillations in either the 8-12 Hz or 1-5 Hz range. The former, elicited with low Mg^{2+} opening¹¹ of NMDA channels may be traced to the activity of layer 5 neurons. The latter, kainate activated however appears to originate in layers 2/3 (Flint and Connors, 1996). Interpretation of such *in vitro* investigations is difficult as a result of the absence of complex local and distant afferent and efferent connectivity necessitated by the

¹¹ NMDA channel opening via the removal of Mg^{2+} blockade.

preparation. The alpha band activity localization however appears consistent with *in vivo* phase reversal estimated sources (section 1.3.1.2), and at the very least such an observation suggests an intrinsic inclination to oscillatory modes that may be modulated by more complex connectivity and varying input. The spectrum of oscillatory behaviour from regular single spike activity to bursts of action potentials observed in relation to various bands of oscillatory LFP activity may therefore to a large extent be a consequence of the intrinsic properties of local neuronal populations as opposed to an exclusively externally driven pattern of activity.

1.3.2 Extracortical / extracerebral oscillatory activity

1.3.2.1 System distributed local field potentials

Demonstration of the systemic, functional significance of oscillatory modes of LFP activity at the very least requires that they be evident throughout different regions that may reasonably be considered to have cooperative roles in some common function. Furthermore it requires that they show some degree of coupling. Such distributed oscillations throughout a system have already been mentioned regarding gamma band rhythms in the olfactory and visual systems, apparent from sensory organ through subsequent projection nuclei to cortex with associated functional coupling, quantified by coherence measures. They exist elsewhere however. The hippocampal formation *in vivo* shows oscillatory LFP activity in the theta, lower gamma (30 to 100 Hz in this context), and high gamma ranges (*ca.* 200 Hz) (Buzsaki et al, 1985; Buzsaki et al, 1992; Draguhn et al, 2000). This activity shows the same burst patterning observed in similar cortical LFP activity elsewhere, with 5 to 15 cycles of 200 Hz oscillations recorded in area CA1 of awake, mobile rats (Buzsaki et al, 1992). In the 30 to 100 Hz band particularly, and with respect to the memory functions of the hippocampus specifically, systemic distribution has been suggested by dynamic modulations of coupling between hippocampus and rhinal cortex with successful declarative memory task performance (Fell et al, 2001, 2003). Although the criteria of distributed presence and inter-regional coupling are obligatory for functional relevance, it must be remembered that they do not necessarily imply it.

One need only consider the significant degree of coupling present between regions of cortex and thalamic alpha activity (Lopes da Silva et al, 1973). While there may potentially exist common information processing between some regions showing coupling the potential role of thalamus in oscillation generation (section 1.2.2), might also suggest that such a relationship merely reflects the propagation of modulatory activity from one to the other.

With regards to the motor system and co-ordinated volitional action, in addition to the marked beta band LFP oscillations that have been documented in sensorimotor cortex, recordings from cerebellum in awake, immobile monkeys and rats, show evidence of comparable activity focused in the granular cell layer (Pellerin and Lamarre, 1997; Courtemanche et al, 2001). No functional coupling of this activity with its cortical analogue has however yet been published, although direct evidence of functional connectivity between cerebellar nuclei and primary motor cortex at a single unit level is demonstrable (Holdefer et al, 2000). In the basal ganglia, recordings in parkinsonian patients made intraoperatively and postoperatively via micro- and macroelectrodes have shown beta and gamma band (ca. 70 Hz) oscillations of LFP activity in STN and GPi (Levy et al, 2000, 2002; Brown et al, 2001; Cassidy et al, 2002). The modulation of activity evident in both bands with alterations in dopamine status in patients (section 1.6.2), coupled with the lack of beta LFP oscillations in rat STN recordings (Brown et al, 2002), has resulted in speculation as to how much this mode of activity in human basal ganglia is actually representative of a pathological state. Increasing evidence now suggests that to some extent at least beta oscillations are a normal component of the LFP in human basal ganglia. Recordings made from the unaffected putamen of epileptic subjects display beta power oscillations (Sochurkova and Rektor, 2003). Yet more recently recordings in monkey striatum have somewhat ironically confirmed the numerous observations in humans, also showing pronounced beta oscillatory activity (Courtemanche et al, 2003). Chapter 3 of this work considers the degree to which this activity in STN and GPi is coupled to cortical oscillations and is therefore consistent with having a distributed network function.

1.3.2.2 Basal ganglia single unit activity

The cortex is not exclusive in possessing neurons with the intrinsic propensity to fire in an oscillatory fashion. *In vitro* investigations suggest that activity in both beta and gamma bands, evident in the STN and GPi LFPs of dopamine treated Parkinson's disease patients (Brown et al, 2001; Cassidy et al, 2002), and in the beta band in healthy alert rats (Brown et al, 2002) may to some degree result from the properties of local neuronal populations. Several studies have shown that neurons of both STN and GPe may display spontaneous rhythmic firing when either anatomically or chemically isolated from other neuronal inputs (Nakanishi et al, 1985; Bevan and Wilson, 1999; Beurrier et al, 2000). In GPe in particular, both Cooper and Stanford (2000), and Nambu and Llinas (1994) have identified subtypes of the population with either spontaneous oscillatory properties or tendencies to oscillation on stimulation. When type A neurons¹² are isolated in slice preparations, and glutamate is administered, oscillatory activity between 8 and 80 Hz is observed with frequency positively correlated with durations of excitatory stimulation (Stanford, 2003). Oscillations are not only induced in action potential activity, but in subthreshold membrane potentials as well (Nambu and Llinas, 1994, Stanford, 2003). Furthermore, the administration of GABA antagonists does not affect the generation of oscillations. These observations suggest that STN mediated depolarization of GPe neurons may be sufficient without pallidal interneuronal activity to induce both beta and gamma rhythmic modes. The activity produced is not synchronous or coherent between neurons and there is evidence to suggest that local GABA inputs by phase resetting oscillations might act to facilitate coherent, short phase lag relationships (Stanford, 2003). Reciprocal inhibition of STN by GPe neurons also may markedly modulate activity however. GABA(A) mediated inhibition may potentially have effects ranging from the elongation of interspike intervals to the activation of low threshold calcium conductances and rebound burst firing (Bevan et al, 2002). As such as has been mentioned in section 1.2.2, reciprocal connectivity between the two with

¹² Type A neurons of GP are characterized by the presence of anomalous inward rectifier and low threshold calcium conductances. Such neurons represent about 60% of the rat GP neuronal population.

associated activity may be important in the generation of the rhythmic field potentials recorded from these structures.

An emerging body of work now suggests that firing rates of neurons in STN and pallidum may also be modulated at significantly slower temporal scales. Slow oscillations at approximately 1 Hz are evident in the firing rates of both STN and GP neurons of rats under ketamine or urethane anaesthesia (Magill et al, 2000). This rate modulation additionally appears correlated but not coherent with concurrent cortical slow wave activity. Considered in the context of intrinsic pallidal neuronal oscillations these rhythms under general anaesthesia may well reflect slow cyclical fluctuations in levels of excitatory glutamatergic input to pallidum with resultant induction of independent local oscillators. Ultra-slow oscillations with periods of 15 to 30 s in contrast are only evident with local anaesthesia in STN and GPe neurons of rats and abolished by general anaesthesia (Ruskin et al, 1999; Allers et al, 2002). They may however be recorded from STN, GPi and GPe in alert monkeys at rest (Wichmann et al, 2002). The intriguing observation of correlation between this ultra-slow basal ganglia activity and similar frequency modulations of hippocampal theta activity may well also implicate this very slow mode in co-ordinated systemic function between the two regions (Allers et al, 2002).

1.3.3 Neuromuscular oscillatory activity

The physiological basis of human skeletal muscle electromyography (EMG) signals is well established and will not be considered in detail here, however several points are worthy of note. First, both in surface EMG and intramuscular needle EMG recordings the single muscle fibre action potential may be considered the fundamental contributor to the EMG signal, with the motor unit action potential a consequence of the spatial summation of these individual entities (Buchthal et al, 1954a, Buchthal et al, 1954b). Second, despite the observed capacity for multiple motor endplate innervations of selected human brachioradialis muscle fibres (Lateva et al, 2002; Lateva et al, 2003), the classical conception of the motor unit comprising an alpha motoneuron, its axon and the motor fibres it innervates (Sherrington, 1929)

may be considered representative of the motor unit studies detailed here. Third, the composition of the motor unit so described means that intramuscularly recorded motor unit firing reflects the selected activity of the spinal motor neuronal population, which in turn may be influenced by descending neuronal input (Brown, 2000).

Beyond the brain altogether motor units of humans themselves are capable *en masse* of demonstrating multiple oscillatory modes in the delta, beta and gamma bands of humans. Two types of activity have been described in the delta band. For some time it has been apparent that modulation of motor unit firing rates at about 2 Hz may be observed during isometric muscle contractions (Farmer et al, 1993; DeLuca and Erim, 1994). The absence of significant levels of linear correlation between EMG, 2 Hz delta power, and synchrony between motor unit pairs (Semmler et al, 1997), coupled with the persistence of oscillatory activity after strokes expected to abolish cortico-spinal transmission (Farmer et al, 1993), suggests that while this mode of oscillation may have a central origin, this is not cortico-spinal (Brown, 2000). More recently it has also been observed that yet slower modulations of EMG activity at less than 0.3 Hz may occur in neck and proximal upper limb muscles during sleep and possibly also wakefulness (Westgaard et al, 2002). The similarity of this pattern of activity to ultra slow basal ganglia fluctuations is noteworthy and investigation into coupling between basal ganglia nuclei, cortical EEG/LFP and EMG in this band seems an obvious course of action. As yet however its genesis remains unclear.

Coherence investigations have however given a degree of insight into the drives underlying the higher frequency oscillations detectable in human EMG. Synchronized discharge of motor units of the same muscle and task related multi-units in muscle pairs occur in the alpha/beta band during submaximal contractions (Elble and Randall, 1976; Farmer et al, 1993; Kakuda et al, 1999), particularly during the precision maintenance of isometric contractions (Kilner et al, 1999). The link between this activity and motor cortical beta LFP oscillations has been demonstrated by several studies showing significant coherence between the two (Conway et al, 1995; Salenius et al, 1997a, 1997b). A correlate of motor cortical rhythmic LFP activity also exists in the gamma band (ca. 40 Hz), the Piper rhythm (1912). This activity particularly evident (though not exclusively) during maximal contraction, not only shows marked coherence with its motor cortical analogue but with appropriate

somatotopy and movement-related modulation (Brown et al, 1998). Phase analysis in both of these bands has shown phase lags between different cortico-muscular pairs consistent with pyramidal conduction (Salenius et al, 1997a; Brown et al, 1998, 2000; Mima et al, 1998). Absolute phase lags between cortex and EMG appear unexpectedly short however and require further clarification. Despite this fact the majority of reports to date in this field support the notion of EMG lagging behind coherent cortical activity in both bands (Salenius 1997, Brown et al, 1998; Mima et al, 1998). Further work has integrated both cerebellar thalamus and STN in this functional connectivity, illustrating significant coherence between both and EMG activity in beta and gamma bands (Marsden et al, 2000, 2001). In addition predicted task related modulation is evident (Marsden et al, 2001). It is worth noting that the work examining STN-EMG coherence, performed in PD patients, did not show gamma coherence at the higher frequency of activity typically evident in the autospectrum of dopamine treated subjects in the gamma band (section 1.6.2). Both gamma frequencies are evident in cortical LFPs and the reason for this discrepancy has yet to be established.

Considered as a whole the work performed to date appears consistent with the existence of oscillatory EMG activity in multiple bands, and particularly in beta and low gamma bands displaying cortically driven functional connectivity, with motor related cortical and subcortical sites.

1.4 Relating oscillatory activity to stimuli and behaviour

1.4.1 Event-related potentials

Irrespective of the mechanisms underlying the generation of oscillatory activity at varying scales throughout the nervous system, its relation to specific modulating stimuli may essentially be either via the generation of new activity, the alteration of ongoing activity, or a combination of both. Detection of these small amplitude evoked changes in EEG or LFP, event-related potentials (ERP), typically consists of

averaging time-locked data derived from the repeated presentation of a stimulus, whether internally or externally derived. Such averaging increases the magnitude of phase and time-locked response components linearly while non-phase and non-time-locked components increase as the square root of trial numbers (Lewine and Orrison, 1995). While the technique is superficially simple, interpretation may be complicated by difficulty in attributing the derived phase-locked activity to the ongoing or *de novo* sources mentioned above (Karakas et al, 2000; Makeig et al, 2002; Rizzuto et al, 2003). In addition it is inherent in such analysis that non-phase locked components largely represent extraneous, uninformative noise, which may be an inappropriate assumption in the context considered. Indeed significant oscillatory modulation within specific frequency bands may be completely undetected within the ERP.

1.4.2 Event-related spectral techniques

A series of alternative techniques have been derived and applied over the last two decades in order to consider the elements in both the time *and* frequency domains, obscured within the ERP. These either examine non phase-coherent modulations of oscillation amplitude or consider phase resetting independent of amplitude altogether. While numerous variations of the former group of analyses exist (e.g. event-related spectral perturbation, Makeig et al, 1993; temporal-spectral evolution, Salmelin et al, 1995; task-related power increase/decrease, Gerloff et al, 1998), common to all is the derivation of dynamic estimates of power (in varying bandwidths), aligned to a given stimulus and independent of phase. This is exemplified in the techniques of Pfurtscheller in which trigger aligned activity in independent trials is filtered within a narrow band, squared and averaged across trials (Pfurtscheller and Aranibar, 1977). Consistent with early conceptions of waking cortical activity, considered to be characterized by desynchronized fast, low amplitude oscillations, reductions of power were considered desynchronization of slow underlying synchronous activity, event-related desynchronization (ERD). In an analogous manner, increases were considered the formation of new synchronous assemblies and termed event-related synchronization (ERS). Numerous

observations of synchronous neuronal activity in the waking state (consider for example the review of Engel et al, 2001, regarding roles in sensory processing) have made the waking 'desynchronized' cortical state, sleeping 'synchronized' state duality untenable. Nevertheless the terms have gained common currency in the context of event-related spectral analysis and as such are used within this text. The terms synchronization and desynchronization therefore, in the context of modulations of field potential activity should be considered synonymous with increases and reductions in power, respectively.

1.4.2 Oscillatory activity and functional connectivity

Friston et al (1993) in the context of neuroimaging studies, define functional connectivity as 'the temporal correlations between spatially remote neurophysiological events'. Implicit in the use of the term, is the idea that by establishing significant degrees of covariation of parameters measured in distinct, anatomically connected and functionally related areas of the nervous system; regional interdependence or integration may be inferred. This simple but circumspect definition however highlights the problems of such inference. While significant degrees of correlation may indeed be evident between spatially segregated neurophysiological events, this does not necessarily imply that such events are integral to inter regional coordination. Common covariation may readily be envisaged where the two neurophysiological events are driven, independently, by a third; or where both events though independent display common intrinsic oscillatory characteristics. Many techniques that have been used for establishing functional connectivity to date at varying scales of brain activity from unit spike firing (Michalski et al, 1983, Steriade et al, 1996) and EEG frequency coupling (Rodriguez et al, 1999), through to functional MRI and positron emission tomography parameter covariance (Cordes et al, 2000; Friston et al, 1993), are open to these theoretical confounding elements. The problems of spurious covariance inherent in these investigations have however been avoided under circumstances where the system examined may be manipulated. The demonstration of altered motor cortical excitability with repetitive transcranial magnetic stimulation specifically of premotor

cortex is an example of such a system (Münchau et al, 2002), showing in a convincing manner a degree of causal linkage between the two regions¹³ (though there may potentially be other criticisms). A similar technique has been used to illustrate subtle changes in motor cortical excitability associated with DBS of the STN (Dauper et al, 2002; Cunic et al, 2002). The work considered here however attempts to examine the degree to which oscillatory activity evident in basal ganglia nuclei is of functional significance, not merely that integration exists between anatomically connected areas. In addition, the difficulty of restricted manipulation of regional oscillatory LFP activity excludes the use of comparable methods of examination in the current context. Coherence techniques described in section 2.3.1.2 have therefore been used to establish functional connectivity as one component of testing the overall hypothesis. Though demonstration of significant corticosubthalamic coherence in appropriate bands of LFP activity, with appropriate distribution, does not categorically *prove* functional significance, the absence of such coherence may be considered, consistent with Popper's falsifiability reasoning, strong evidence for a lack of functional significance (Popper, 1934).

1.5 Local field potential oscillations and movement

Extensive event-related spectral investigations in EEG, MEG and EcoG have characterized modulations of non-phase locked oscillations in relation to passive, self-paced and externally cued movement in humans. These show that self-paced movements are associated with ERD followed by an ERS predominantly in the beta band, in somatomotor cortex and over SMA with onset preceding movement by as much as 2 s - consistent with the temporal characteristics of the "slow negativity readiness" or Bereitschafts-potential (Pfurtscheller and Aranibar, 1979, Nagamine et al, 1996; Ohara et al, 2001). Interestingly, EcoG partial coherence analysis further suggests that ERD in both somatosensory cortex and SMA are associated with pre-movement increases in coherence between the two at frequencies < 30 Hz (Ohara et al, 2001). These changes are accompanied by a somatotopically prescribed

¹³ A similar type of linkage between regional activation and anatomical connectivity may be seen in the mapping of c-fos induction after regional stimulation (Sagar et al, 1988).

augmentation of oscillatory activity in the gamma band (Pfurtscheller et al, 1993; Crone et al, 1998b). While these modulations in their respective bands show localizations and somatotopy already detailed, they fail to show the marked lateralization that might be expected of distal limb movements, with unilateral movements eliciting suppression of alpha and beta activity bilaterally (Chatrian et al, 1959; Nagamine et al, 1996; Crone et al 1998a). Indeed, it should be noted that movement-related potentials (MRPs) display more circumscribed and lateralized changes than associated mu ERD (Babiloni et al, 2002). A degree of asymmetry however does exist in terms of the temporal evolution of the changes, with suppression occurring earlier in contralateral than ipsilateral cortex (Nagamine et al, 1996; Crone et al, 1998a).

Similar modulations are observed not only with externally cued (Kaiser et al, 2001) and sustained movement (Cassim et al, 2000), but also with passive movement (Alegre et al, 2002) (though with passive modulations not preceding movement onset), and indeed with the cessation of ongoing movement (Alegre et al, 2003). A degree of the movement ERD observed is therefore probably related to afferent activity. The mere visualization of movement is indeed capable of inducing somatomotor ERD (Beisteiner et al, 1995; Leocani et al, 1999). The capacity of LFP recordings to both achieve high spatial and temporal resolution, and allow relationships between population activity and single unit activity to be examined has been exploited to further investigate these phenomena.

1.5.1 LFP oscillations beyond motor cortex and movement

The broadly consistent nature of observations made in EEG and MEG relating averaged alpha, beta and gamma band oscillations to motor activity is compatible with comparable observations made in the DBE LFP activity of parietal cortex and cerebellum. Oscillatory LFP activity in macaque parietal cortex displays significantly lower power below 20 Hz during periods of motor activity than in control rest episodes (Mackay and Mendonça, 1995). Above 25 Hz increases in power have not

only been observed preceding and continuing throughout movement, but also during periods of cue preparation, and in a directionally tuned manner (Pesaran et al, 2002). This pattern holds true across species. Alpha cortical oscillations in the rat decrease with chewing and sniffing (Semba et al, 1980). Activity ca. 40 Hz in cat parietal cortex is observed to increase during immobile target fixation prior to motor activity (Bouyer et al, 1983). The pattern is also true beyond the cerebral cortex however. In cerebellum, it has been shown that reductions of the observed oscillatory LFP bursts in the 13-25 Hz frequency band occur both with movement and interestingly with movement preparatory cues. Furthermore, these are associated with increases in firing rates in task modulated Purkinje cells, these self same cells showing beta rate oscillation during periods of increased LFP oscillation (Pellerin and Lamarre, 1997; Courtemanche et al, 2002). Alpha, beta and gamma bands are however not the only oscillatory frequencies that have been implicated in motor control. In hippocampus oscillations in the theta range appear associated with walking and eating in dogs (Yoshi et al, 1966), and in rats both velocity and magnitude of movement have been correlated with frequency, and amplitude of theta oscillations (Vanderwolf, 1969).

Hence, LFP activity in the alpha and beta bands in a series of motor-related areas outside sensorimotor cortex demonstrates marked attenuation in association with movement and cues preparatory of movement, while higher frequency gamma activity shows augmentation and in a task specific manner.

1.5.2 Motor cortical LFP oscillations and movement

This consistent picture relating cortical LFP oscillations to behaviour in averaged activity is in marked contrast however to the confusion in investigations relating individual oscillatory LFP bursts and single unit activity to motor action, which has been particularly studied in the primary somatomotor cortex of monkeys. Much of this results from the failure or inability of investigators to present data specific to individual stereotyped movements rather than complex behaviours, in the context of

similar averaged responses. However further confusion results from the variety of bands considered across these investigations, examining 20-80 Hz (Donoghue et al, 1998), 20-40 Hz (Murthy and Fetz, 1996a; Murthy and Fetz, 1996b), 25-35 Hz (Murthy and Fetz, 1992), 15-50 Hz, (Sanes and Donoghue, 1993) and 10-40 Hz (Fetz et al, 2000) oscillations in small numbers of monkeys. The breadth and diversity of bands examined coupled with the current vogue for gamma frequency oscillations in the context of sensory integration, has resulted in much of the literature considering these studies representative of 'gamma' band activity, with concomitant bias in interpretation and expectation. The absence of averaged event-related modulations allowing for comparisons with equivalent activity derived by alternate techniques makes such a classification arbitrary, based only upon personal band definition.

Despite these caveats, several important observations regarding sensorimotor cortical LFP activity and its relationship with single unit activity have been made in these studies. While no consistent relationship is apparent between LFP oscillations and behaviour (Murthy and Fetz, 1992; Murthy and Fetz, 1996a; Donoghue et al, 1998), activity with a mean frequency of ~ 20-30 Hz occurs preferentially before go cues and is infrequent during movement performance (Sanes and Donoghue, 1993; Donoghue et al, 1998). This activity is associated with widespread synchrony between LFP that reduces with movement onset (Sanes and Donoghue, 1993). Moreover, careful examination of examples demonstrating the infrequent occurrence of oscillations during early movement, show activity at significantly higher frequencies (*ca.* 70-80 Hz) (Donoghue et al, 1998). In cats, the LFP oscillations in somatosensory cortex at ~ 14 Hz that occur while at rest, disappear with movement, replaced by 40 Hz activity when immobile, focusing upon a target (Bouyer et al, 1981; Bouyer et al, 1983). Atypically, the higher frequency oscillations are attenuated by movement however taken together these elements of findings in monkey and cat appear broadly compatible with beta and high gamma activity described in EEG, MEG and EcoG in humans. Several of the studies however report that these oscillations are more prevalent during motor tasks requiring increased attention (e.g. monkey retrieving raisins from hidden locations) (Murthy and Fetz, 1992; Murthy and Fetz, 1996a, Donoghue et al, 1998). The failure to present detailed relationships

between components of the complex motor tasks involved, oscillation frequency and oscillation occurrence make interpretation difficult. The potential source of misinterpretation becomes apparent when studies in precision grip tasks are considered. Here, *increased* levels of beta power in motor cortex coherent with pyramidal tract neuronal activity and relevant EMG are observed during the holding phase of the precision tasks (Baker et al, 1999; Kilner et al, 1999). As such, suppression of oscillations in at least the beta band of motor cortical LFPs appears less related to steady motor state than its alteration, less velocity of movement than acceleration. Complex tasks may therefore involve numerous increases and decreases in alpha/beta oscillatory activity. The variable occurrence throughout tasks and inconsistent relationship of individual oscillations with task that these motor cortical studies as a whole report, does however show that oscillations are not directly necessary for task performance.

1.5.3 Single units, LFP oscillations and movement

Insights have also been made into the inter-relationships of single units, LFP oscillations and movement. These suggest that unit activity and LFP oscillations may be coupled throughout the motor system. Hence, a significant proportion of unit activity in somatomotor cortex associated with oscillations displays oscillatory modulation of its own with synchronization between units occurring over substantial distances (Murthy and Fetz, 1992; Murthy and Fetz, 1996b). Furthermore, oscillations in the 20-30 Hz range are observed to entrain corticospinal projections (Murthy and Fetz, 1992, Baker et al, 1997). This unit activity may also show similar alterations with movement as have been mentioned with the LFP, for example alpha band thalamic unit firing in rats is reduced with movement (Nicoletis et al, 1995).

However, only a proportion of neurons coupled to rhythmic LFP activity at any given moment are task-related. The relationship between this task-specific activity and the LFP appears more complex. It is observed in the motor cortex that while firing may be associated with oscillatory LFP periods, task-related modulation of firing rates

occurs during reductions in 20-30 Hz LFP oscillations (Murthy and Fetz, 1996b; Donoghue et al, 1998). The same holds true as mentioned above with respect to the Purkinje cell activity of the cerebellum (Courtemanche et al, 2002). This is in contrast however to task-related parietal cortex neurons, which show preferential firing and rate tuning at peaks of 25-90 Hz LFP oscillation, during task-relevant periods (Pesaran et al, 2002). None of these studies explicitly attempted to isolate subtypes of neuron involved in these interactions. Preliminary work has however not only shown that inhibitory and excitatory synaptic activity appears intrinsic to oscillatory LFP episodes in motor cortex (Matsumura et al, 1996), but also that intrinsic properties of some neurons may predispose to 25-35 Hz firing (Chen and Fetz, 1991; Chen and Fetz, 1993). Hence, a subpopulation of neurons may well support the rhythmic activity amongst others, task-related or otherwise.

In summary, although further studies are required, it appears that neurons that may reasonably be considered associated with the performance of voluntary motor actions, in motor-related regions of the primate nervous system, may be coupled to 20-30 Hz LFP oscillations in a static rate state¹⁴. Task related modulation of unit activity appears associated with uncoupling from 20-30 Hz oscillations and may be associated with coupling to a higher frequency population activity.

1.5.4 Basal ganglia LFP oscillations and movement

It appears universally accepted that basal ganglia function is at least to some degree motor-related. This association of structure and function is hardly recent. Indeed Thomas Willis' 17th century descriptions, despite largely attributing a sensory integration role to the structures lectured that, "Will is exercised by the circulation of spirits from the corpora striata to the medulla oblongata, and thence through the nerves, to the sensory organs and movements are initiated like rushing out into the embrace of the desired object" (Meyer and Hierons, 1964; Dewhurst K, 1980b). Willis would perhaps be somewhat disappointed that over three hundred years later

¹⁴ i.e. with neurons maintaining a roughly constant rate of firing

a lack of clarity still persists as to the precise role played by these structures in motor function. Nevertheless, the association of the basal ganglia with movement in recent years has largely resulted from the more obvious motor consequences resulting from specific lesions (Bhatia and Marsden, 1994), e.g. the hemiballismus of subthalamus lesioning or dystonia associated with lesions of the putamen; and the symptom profiles of basal ganglia related pathologies, e.g. Parkinson's disease, Huntington's disease. Recordings of neuronal activity over the last 30 yrs have supported the relationship, demonstrating in numerous studies that the activity of a significant proportion of single units in the GPi, GPe, putamen, caudate and STN of primates demonstrate rate changes in relation both to passive and active limb movements whether internally or externally paced (DeLong, 1971; DeLong, 1972; DeLong et al, 1985; Alexander, 1987; Romo et al, 1992; Schultz and Romo, 1992; Gardiner and Nelson, 1992; Wichmann et al, 1994). These studies in addition to more recent intraoperative work in humans particularly implicate dorsal pallidum and dorsolateral STN (Ianssek and Porter, 1980; Wichmann et al, 1994; Rodriguez-Oroz et al, 2001; Abosch et al, 2002). The exact relationship between this neuronal activity and movement performance remains open to question. While there is evidence of specificity and tuning with selective responses on the basis of body part and direction of movement (Georgopoulos et al, 1983), the temporal relationship of much of the documented activity in pallidum and STN appears to coincide with or succeed self-paced movement initiation (Brotchie et al, 1991; Wichmann et al, 1994; Jaeger et al, 1995) but precedes movement after preparatory cues, particularly in striatum (Schultz and Romo, 1992; Romo et al, 1992; Jaeger et al, 1993).

Increasingly evidence suggests that population oscillatory activity may also have a role in basal ganglia motor function. Rhythmic firing of a small proportion of striatal neurons between 10 and 50 Hz has been reported to occur during preparatory holding periods prior to ballistic movements (Lebedev and Nelson, 1999). Specifically in the LFPs of primates, putamen oscillations in the beta frequency are suppressed prior to and during movement performance in humans and monkeys (Sochurkova and Rektor, 2003; Courtemanche et al, 2003). Similar beta power suppression has been observed in the LFP activity of both GPi and STN (Priori et al, 2002, Levy et al, 2002). Indeed the very coupling of oscillatory activity between these

nuclei in this band is observed to decrease, while increasing in the upper gamma band (Cassidy et al, 2002). These changes appear to occur in association with self-paced movement and after external imperative cues, furthermore they appear to precede movement onset significantly in both conditions (Levy et al, 2002; Cassidy et al, 2002). Circumstantial evidence to date therefore implicates alterations of LFP oscillations in the nuclei of the basal ganglia, in some manner, to their associated single unit changes and in addition to performance of motor actions.

1.6 Local field potential oscillations and Parkinson's disease

Parkinsonism is a syndrome characterized by the cardinal symptoms of bradykinesia or akinesia, rigidity and tremor. Of the many potential aetiologies of parkinsonism (Bradley et al, 2000), Parkinson's disease, idiopathic parkinsonism is primary. At the most superficial of levels, Parkinson's disease is a disorder with an oscillatory component – literally visible in the classically described 4-8 Hz rest tremor of the disorder. The very search for the central or peripheral origins of such tremor has spurred much investigation into the periodic pathophysiology of the illness. The failure of interventions such as dorsal root ganglion removal (Pollock and Davis, 1930) and muscle stretch reflex anaesthesia (Walsh, 1992) to significantly alter parkinsonian tremor however, has suggested that oscillatory spinal reflex activity is a far less significant component of tremor generation than central sources (Bergman and Deuschl, 2002). Moreover, while there is evidence that may support the hypothetical role of regions such as thalamus in the central generation of tremor, the fundamental and established pathological abnormalities of the basal ganglia, observable in PD have made them an obvious target in the search for oscillatory generators. The mere fact that repetitive stimulation of basal ganglia (i.e. DBS) nuclei may alleviate parkinsonian symptoms, and in a non-linear fashion, is an intriguing manifestation of the involvement of oscillation in the structures. Why should stimulation be preferentially beneficial above a frequency of ~70 Hz, and why, typically optimal at ~130 Hz? Over recent years, several lines of evidence have implicated synchrony and oscillatory activity within the basal ganglia evident at

neuronal and local field potential levels in not only the generation of tremor, but also the other cardinal features of rigidity and bradykinesia.

1.6.1 Single unit oscillations and PD pathophysiology

The dominant circuit models of the basal ganglia, considered in section 1.1.1 developed and contextualized to movement disorders have proved valuable because of their ability to successfully predict the location of some lesions beneficial in the treatment of parkinsonian pathology. In the context of PD, the model as it still stands remains primarily a rate model in which striatonigral degeneration results in differential alterations of activity in 'direct' and 'indirect' pathways; namely increased striatal inhibition of GPe and decreased striatal inhibition of GPi – both resulting in increased GPi unit activity, and subsequently motor unit suppression via thalamus (DeLong, 1990). However, assumptions about the primacy of direct and indirect pathway balance and simple deterministic neuronal population interactions are drawn into question by several observations. While recordings of STN neuronal activity in vivo, in the rat 6-OH dopamine model, display the increased rates of activity predicted as well as reduced rates on systemic administration of the non-specific dopamine agonist apomorphine, administration of specific D2 receptor agonists fail to significantly alter firing rates (Kreiss et al, 1997). Such an observation is inconsistent with a model of PD in which increased STN activity results from increased D2 mediated indirect pathway GPe inhibition. In addition in the 6-OH dopamine rat model, one group has reported evidence of hyperactivity of pedunclopontine neurons projecting to STN (Orieux et al, 2000), a pathway not typically included in most circuit models. This raises the possibility of excessive pedunclopontine afference as an alternative to the 'indirect' pathway, as a partial mediator of increased STN activity in the PD state. However, this hypothesis should be treated with caution as it seems contradictory not only by the observed ability of pedunclopontine lesions to induce akinesia in normal monkeys (Aziz and Stein 1997, Munro-Davies et al, 1999) but also the marked degeneration of the pedunclopontine nucleus observed in human PD (Hirsch et al, 1987; Jellinger

1988). Patient and animal model studies of PD have also failed to consistently observe the decreases of unit activity in GPe (Levy et al, 1997) and motor cortex (Doudet, 1990; Watts and Mandir, 1992) predicted by the classical model. Moreover, not only have some investigators not observed decreases in GPi unit rates in a hyperkinetic disorder such as dystonia relative to PD (Lenz et al, 1998; Pralong et al, 2003), but the reported capacity of (propofol) anaesthesia to induce GPi rate reductions may draw into question earlier observations (Hutchison et al, 2003). These studies, in addition to the common beneficial effects of deep brain stimulation (DBS) and lesioning of GPi and STN upon both hypokinetic and hyperkinetic disorders, have suggested that abnormal patterns of unit activity not merely rates may be of significance.

This speculation has been supported by recordings made both intra-operatively in PD and dystonia patients and in experimental animal models of PD. While GPi firing rates are observed to be increased as predicted in MPTP primates, the proportion of neurons displaying burst discharges in both GPi and STN is increased (Filion and Trémbay, 1991; Bergman et al, 1994). Furthermore, oscillatory neuronal population activity with a bimodal distribution, peaking within tremor frequency range at ~6 Hz and in the alpha to beta range ~8 to 20 Hz, emerges in both nuclei (Filion et Trémbay, 1991; Bergman et al, 1994; Raz et al, 2000). These self same units that display oscillations in the lesioned state also show significant degrees of correlation, untypical of the healthy state (Raz et al, 2000; Levy et al, 2002); and dopamine treatment capable of alleviating the parkinsonian symptoms of the lesioned state also reverse this increased cross neuronal correlation (Heimer et al, 2002). It may also be noted that an oscillatory character is introduced to the firing patterns of the tonically active neurons (TANs) of monkey stratum with MPTP administration (Raz et al, 1996). The 6-OH dopamine lesioned rat provides further evidence for a role of oscillation in PD pathology. Here, an increased tendency for STN neurons to display the low frequency (*ca.* 1 Hz) burst firing behaviour associated with anaesthesia (section 1.3.2.2), independent of apparent ipsilateral cortical input has been documented (Magill et al, 2001). In addition globus pallidus activity is observed to switch from largely tonic, regular firing to low frequency bursting as well. The primacy of patterns of neuronal activity over rate is further supported by the observed

increase in burst activity in MPTP lesioned primate motor cortex, displaying changes in pattern while rates remain constant (Goldberg et al, 2002); and the described oscillatory synchronization between GPe and GPi in PD patients (Levy et al, 2002). The parkinsonian state therefore appears at a neuronal level to be one in which abnormal degrees of oscillation and synchrony exist within the basal ganglia and its projections.

1.6.2 Local field potential oscillations and PD pathophysiology

Analogous investigations of basal ganglia LFPs, primarily in parkinsonian patients, also appear to show disease related alterations. LFPs recorded via the STN and GPi DBEs of PD patients show marked increases in oscillation power *ca.* 20 Hz on withdrawal of anti-parkinsonian medications and may also display increases in the oscillatory activity *ca.* 70 Hz on reinstatement (Brown et al, 2001; Levy 2002). Activity in both bands further demonstrates significant coherence between nuclei, and is not attributable to a common 'noise' source (Brown et al, 2001, Cassidy et al, 2002). This demonstration of constant phase relationships between oscillators may be interpreted as evidence of either a common drive to both structures, the driving of one nucleus by the other, or the existence of independent but constant common frequency oscillators in each nucleus. The latter of these at least, seems highly unlikely and is unsupported by single unit observations. Irrespective of the relative contributions of the other two, both imply that oscillatory activity is a network phenomenon distributed between nuclei. Following the pattern of similar frequency activity presented above in cortical and extracortical regions, experiments undertaken with both self-paced and externally-cued movements have shown attenuation of beta band oscillations and augmentation of gamma band with movement (Cassidy et al, 2002; Levy et al, 2002). In addition to associated alterations of coherence, with decreases in the beta band and increases in the gamma band (Cassidy et al, 2002; Levy et al, 2002). When considered in the context of DBE recordings from healthy pallidum in epileptic patients, which also show beta ERD associated with movement (Sochurkova and Rektor, 2003) and very recent

evidence of similar modulated activity in normal monkey striatum (Courtemanche et al, 2003), LFP oscillations at least in the beta band of PD patients appear to be an exaggeration of an existing basal ganglia phenomenon.

The data presented here associating synchrony, bursting activity and LFP oscillations with PD at both an LFP and neuronal level is all essentially correlative. No one experiment to date has provided the clear causative relationship between the two, analogous to a simple lesion paradigm of the SNc in supporting the role of nigrostriatal degeneration. Taken as a whole however, current data appear at least consistent with hypotheses that have proposed that synchrony and oscillations, perhaps in tandem underlie the pathophysiological origin of many PD symptoms (Brown and Marsden, 1998; Raz et al, 2001; Levy et al, 2002).

1.7 The functional significance of local field potential oscillations

Despite the copious research that has examined the issue of oscillation and oscillatory synchrony at various levels of the human nervous system, no evidence to date proves any role of this mode of activity in normal human function. Indeed only one experiment to date has directly supported a role of oscillations in any function within animals. This is the work of the Laurent group who have shown that honeybees conditioned to respond to an olfactory stimulus show difficulty in distinguishing this stimulus from a similar one (Stopfer et al, 1997) when local GABA(A) mediated transmission and consequently gamma LFP oscillations are disrupted. These observations at a behavioural level have subsequently been supported by similar work on slugs at a neuronal level showing similar levels of tentacle orientating neuronal activation, with conditioned and similar non-conditioned odour presentation *in vitro* (Teyke and Gelperin, 1999). Both groups however report no difficulty in the capacity of their respective models to distinguish conditioned stimuli from markedly dissimilar ones, as such gamma oscillations do not appear fundamentally necessary for olfaction but as a tuning mechanism in the olfactory system of these organisms. A similar role of gamma oscillatory LFP activity in human

olfaction has yet to be similarly proven, nevertheless numerous roles for oscillations and oscillatory synchrony have been proposed in the human nervous system, some of which are supported by substantial correlative evidence.

The majority of such correlations have been observed with respect to gamma oscillations. This has largely resulted from the interest associated with the hypothesized role of this mode in feature binding, i.e. the coherent grouping of features of an image, processed in a spatially segregated manner within the brain into a single percept. This theory was proposed as a solution to the 'binding problem' of sensory integration, which did not suffer the excessive population requirements inherent in prior, reductionist 'grandmother cell' type theories (Von der Malsburg, 1995). Support for a gamma role in binding initially came in recordings both in anaesthetized cat and awake monkey visual cortex, that showed greater degrees of gamma activity with the presentation of moving bars than less cohesive moving stimuli (Eckhorn et al, 1988; Gray et al, 1989). The same change reported in human EEG (Lutzenberger et al, 1995) may be considered in the light of the caveat added towards the end of section 1.3.1.2. The coupled oscillations in the gamma band seen in other systems in man (discussed earlier in olfactory, but also the auditory system) have however suggested that a more general integrative function of gamma may exist, and some manner of system specific attention mediator role has been proposed (Fell et al, 2003).

The confusion that remains in terms of oscillatory roles is exemplified in the often diametrically opposed theories posited. In broad terms the long appreciated association of ongoing alpha suppression occipitally with eye opening, waking to sleep transitions (Dement and Kleitman, 1957) and rolandic mu-alpha desynchronization with movement resulted in the consideration of alpha as an idling rhythm, representative of inactive cortex. More recent observations of phase-locked alpha *increases*, such as in response to cues with oddball auditory protocols as opposed to passive listening (Kolev et al, 2001) have however led to suggestions of an active role in attention processes. Even with the same suggested role different relationships may be reported. In contrast to observed increases in phase-locked alpha, *reductions* of mixed non-phase locked and phase locked alpha have been

considered indicative of increased attention in visual oddball protocols (Klimesch et al, 1998). Investigations by Nicoletis and Fanselow (2002) of alpha rhythmic activity in the primary somatosensory cortex and thalamus of rats, in association with similar frequency whisker twitching, have suggested that such activity may be a potential model of human mu activity. Despite reporting that responsiveness of neurons in both regions to whisker stimulation is least likely during episodes of this alpha oscillation (Fanselow and Nicoletis, 1999), further more subtle observations of increased responsiveness prior to alpha associated burst firing have led this group to suggest that alpha oscillation and whisker twitching are states of peculiar sensory sensitivity (Fanselow et al, 2001). Finally it has also been proposed in humans, that rather than existing in idle cortex, alpha oscillations are indicative of a process of active inhibition. This has been supported by the recently reported increases in appropriate alpha EEG activity during tasks requiring internally directed attention and processing loads (Cooper et al, 2003). Theories of alpha function therefore span the gamut, from the facilitation of sensory processing, through idling, to the active inhibition of processing. This range of roles, from facilitatory to inhibitory, has similarly been ascribed to the beta band oscillations of the sensorimotor system though no consistent correlation of such oscillations and behaviour has yet been demonstrated (MacKay, 1997).

1.7.1 Aim of this Thesis

The investigations that follow in Chapters 3, 4 and 5 test the idea that oscillations, particularly in the beta band, observed in STN and GPi reflect system relevant modes of activity by considering (a) whether there is appropriate functional connectivity, (b) whether responses to stimuli are behaviourally biased, and (c) whether consistent relationships exist with behaviour. In addition in Chapters 4 and 5 some degree of insight into the manner of any functional role that might exist is sought by consideration of the nature of behavioural responses observed.

CHAPTER II

MATERIALS AND METHODS

In this chapter the details of techniques and principles common to the investigations described in chapters 3-5 are outlined, additional elements such as experimental protocols specific to each study are considered in their respective chapters.

2.1 Subjects and surgery

All subjects involved in the experiments were parkinsonian patients who had undergone surgical implantation of DBEs for therapeutic stimulation. The clinical details of subjects investigated are presented in chapters 3 and 4. The subject population of chapter 5 was the same as that of chapter 4. All subjects had at least one DBE implanted into a STN; the majority of subjects had bilateral implantation and several subjects had GPi electrodes implanted, from which recordings were also made. All patients participated with informed consent and the permission of the local ethics committee.

Subjects were operated on and recorded at four institutions, (1) the Department of Neurosurgery, Academic Medical Centre, Amsterdam, (2) the Operative Unit of Functional and Stereotactic Neurosurgery CTO Hospital, Rome, (3) the Departments of Neurology and Neurosurgery, Charité Campus Virchow, Berlin, and (4) the Departments of Neurology and Neurosurgery, King's College Hospital, London. Variation in operative centre between patients was not an issue here, since the studies considered in this work do not consider the procedures themselves. Macroelectrodes in GPi and STN were integral components of Medtronic model 3387 and 3389 leads (Medtronic Neurological Division, Minneapolis, USA) with four platinum-iridium cylindrical surfaces (1.27 mm diameter and 1.5 mm length) and centre to centre separations of 3 mm and 2 mm respectively. Hence with a target size of ca. 6 x 4 x 5 mm (anteroposterior, mediolateral, dorsoventral) (Richter et al, 2004), only one bipole of a contiguous bipole pair could be expected to lie within the

STN. Contact 0 is the most caudal and contact 3 the most rostral. Macroelectrodes were inserted after STN or GPi had been identified by ventriculography and preoperative MRI. The intended coordinates at the tip of contact 0 were 19-24 mm from the midline of the patient, 2 mm in front of the midcommissural point and 6 mm below the anterior commissure (AC) – posterior commissure (PC) line for GPi and 12 mm from the midline, 0-2 mm behind the midcommissural point and 4-5 mm below the AC-PC line for STN. Where available (detailed in individual chapters) post-operative imaging was examined to determine if artefacts were consistent with appropriate electrode placement. Incorrect electrode placement on post-operative imaging was a criterion for subject exclusion. No subjects were however excluded on this basis. Functional localization of electrodes in each case was further sought by consideration of optimal recordings from individual bipoles of the three bipole pairs on each electrode (see chapters 3 & 4) and post-operative improvements in the motor united Parkinson's disease rating scale (UPDRS) with bipolar stimulation (see chapter 4).

2.2 Data collection

Recordings were made during the post-operative period prior to implantation of the stimulator while leads from the DBEs were still external. Since internalization of leads and stimulator implantation typically occurred on day 3 or 4 post-operatively a degree of pseudo-subthalamotomy due to persistent local inflammation might have been present in some cases at time of recording. This did not however have consequences for post-operative assessments of stimulation efficacy, which were performed post internalization. Consistent with Medtronic guidelines post-operative DBE impedances were between 50 and 2000 ohms (Fraix and Pollak, 2001). LFPs from DBEs were recorded simultaneously with EEG with the following techniques.

2.2.1 Electroencephalography

EEG was recorded via 9 mm diameter Ag-AgCl electrodes attached with collodion (SLE diagnostics, Surrey, UK), with placement according to the international 10-20 system (Jasper, 1958) using a bipolar derivation. Where there were practical considerations with regards patient care, such as the positioning of post-operative dressings, or with portable equipment, such as limited numbers of recording channels, recording was limited to a single Cz-Fz bipole, numbers in each study are indicated in chapters 3 and 4.

2.2.2 Basal ganglia nuclei local field potentials

STN and GPi LFP were recorded from the adjacent 4 contacts of each macroelectrode via alligator clipped leads attached to the exposed DBE lead contacts. These leads were in turn connected to the amplifier equipment. This allowed the bipolar assessment of 3 contiguous regions (0-1, 1-2, 2-3). By convention specific DBE bipoles in the text are referred to on the basis of this DBE contact numbering, e.g. R STN 23 refers to the 2-3 bipole of the DBE in the right STN. While stimulator electrodes allow the recording of LFPs, they do not possess the high impedance of microelectrodes used in intra-operative subcortical target localization (Hutchison et al, 1998; Benazzouz et al, 2002). As such, the isolation of associated single and multiple unit activity was not possible in the current investigations.

2.2.3 Amplification and filtering

Recorded EEG and LFP activity was filtered at 1-250 Hz in the chapter 3 study and 1-300 Hz in the chapter 4 and 5 studies. All data were amplified (x100-500,000). Signals were sampled and monitored online at 1 KHz except where indicated in individual chapter methods, in order to constrain record sizes. Reductions of sampling frequency where undertaken were never to less than twice the Nyquist

frequency associated with the filtering parameters. Amplification, filtering and recording were performed using the Schwartz 34 amplifier system (Schwartz GmbH, Medical Diagnostic Equipment, D-81245 Munich, Germany) and Brainlab software (OSG bvba, B 2840 Rumst, Belgium) at the Academic Medical Centre, Amsterdam. Signals were amplified and filtered using a custom made 9V battery operated portable amplifier and recorded through an A-D card (PCM-DAS16S, ComputerBoards, Middleboro, MA 02346, U.S.A.) into Spike2 v4.0 software (Cambridge Electronic Design, Cambridge, UK) on a portable computer using a custom written program at the Rome, Berlin and London centres. Amsterdam recorded data underwent conversion from a proprietary format to formats that could be used in Spike2 and Matlab v6.0 (The Mathworks Inc, Natick, MA, USA) with Analysisisto software (D. Buckwell, MRC, HMBU).

2.3 Data Analysis

Converted data was analyzed offline in Spike2 and sections containing artefact whether it was due to eye-movements, muscle contractions or lead movements were removed across all channels. Mains noise was not a significant issue in the current analysis since frequencies of interest were significantly below 50 Hz artefact. Power, coherence, phase and cumulant density analysis in chapter 3 used software written by D. Halliday (Division of Neuroscience and Biomedical Sciences, Glasgow). Digital band-pass filter design and implementation in chapter 4 was performed with the visual design interface tool of Spike2. Wavelet power derivations in chapter 5 were performed in Matlab. The details of subsequent analysis are considered individually in consequent chapters.

Both EEG, denoted $a(t)$ and LFP, denoted $b(t)$, were considered realizations of zero mean time series (Brillinger, 1978) sampled at frequency, k . For the purpose of power, coherence and phase estimation in chapter 3 the further assumption of stationarity was made. That is to say that derived components were considered time independent during the period considered. This allowed the use of the discrete Fourier transform (DFT) for the derivation of spectral parameters, in both time and

frequency domains (Halliday et al, 1995). Despite the well-established non-stationarity of the human EEG (Blanco et al, 1995), this was justified because the experimental protocol consisted of simple, stable, physiological states. Event-related spectral analysis and wavelet transform techniques were specifically used in the analysis of chapters 4 and 5 respectively to allow power estimation without the assumption of stationarity. All time series were considered to consist of real values with samples equally spaced at intervals of k^{-1} and it was further assumed in the Fourier analysis that samples with wide intervals between them were independent. The latter was legitimate in the chapter 3 analysis as the protocol applied did not introduce external stimuli rhythmic or otherwise. In the chapter 4 study the addition of randomization within the protocol prevented the introduction of excessive regularity in the data that could potentially have given rise to erroneous rhythmic derivatives.

All analysis undertaken was fundamentally dependent upon spectral estimation. The primary tools used in these studies for this estimation were Fourier analysis and the continuous wavelet transform. The method relevant details and principals underlying these techniques are now considered.

2.3.1 Fourier Spectral analysis

Fourier analysis was performed by means of the method of disjoint sections (Rosenberg, 1989; Halliday et al, 1995; Halliday and Rosenberg, 1999) in which each time series of length R , was divided into L non-overlapping sections, each of length T , such that $R=LT$. Hence estimation was limited to frequencies within the range T^{-1} to $k/2$, with a resolution of k/T within each section. The discrete Fourier transform of the l^{th} segment of each LFP or EEG time series, $x(t)$ at frequency λ was then derived, defined as:

$$d_x^T(\lambda, l) = \int_{(l-1)T}^{lT} x(t) e^{-i\lambda t} dt \approx \sum_{t=(l-1)T}^{lT-1} e^{-i\lambda t} x_t \quad \text{Eqn 2.1}$$

, where $i = \sqrt{-1}$ and $e^{it} = \cos(t) + i\sin(t)$. Spectral estimates were then obtained from the averaged algebraic combination of all segments. Segment sizes and the associated frequency resolution as well as the numbers of segments averaged are detailed where relevant in specific investigations. While larger segment sizes result in better frequency resolution of estimates, the variance of each estimate does not tend to zero – as such ‘overfitting’ of the data may result. In addition there is the increased potential of violating the stationarity assumption. Segment sizes were therefore chosen to best satisfy these competing demands.

All estimates of the auto-spectrum (power spectrum), cross-spectrum, phase, coherence and cumulant density were based upon the basic transformation of Eqn 2.1. The significance of any of these derived components could be tested by initially obtaining the variance of the estimate of the given parameter, \hat{w} , $\text{var}(\hat{w})$. Confidence limits could then be calculated on the assumption of the normal distribution of these estimated parameters, hence at a 95% level:

$$\hat{w} \pm 1.96\sqrt{\text{var}\{\hat{w}\}} \quad \text{Eqn 2.2}$$

2.3.1.1 Cross-spectrum and auto-spectrum

The estimate of the cross-spectrum of EEG, $a(t)$ and LFP $b(t)$ time series at frequency λ , denoted f_{ab} was defined as:

$$\hat{f}_{ab}(\lambda) = \frac{1}{2\pi LT} \sum_{l=1}^L d_a^T(\lambda, l) \overline{d_b^T(\lambda, l)} \quad \text{Eqn 2.3}$$

, where $\overline{\quad}$ indicates the complex conjugate. The products of DFT and complex conjugated DFT were therefore averaged across the L sections, smoothing the variability that would be associated with equivalent analysis of the non-segmented time series (Halliday and Rosenberg, 1999). The auto-spectra of EEG and LFP,

denoted, f_{aa} and f_{bb} respectively were similarly derived with substitution of the appropriate DFT into Eqn 2.3.

The variance of the cross-spectrum was approximated by $\text{var}\{f_{ab}(\lambda)\}$ which itself was approximated by $L^{-1}(f_{ab}(\lambda))^2$, (Bloomfield, 1976). Stabilization of the variance by base 10 logarithmic transformation resulted in an estimate independent of the value of the original. Auto-spectral variance was similarly derived by use of the auto-spectral estimate, and consequentially where represented in Chapter 3 power spectra are plotted on \log_{10} scales. The resultant cross-spectral variance was therefore:

$$\text{var}\left\{\log_{10}\left(\hat{f}_{ab}(\lambda)\right)\right\} = (\log_{10}(e))^2 L^{-1} \quad \text{Eqn 2.4}$$

from which 95% confidence limits were defined as:

$$\log_{10}\left(\hat{f}_{ab}(\lambda)\right) \pm 0.851 L^{-\frac{1}{2}} \quad \text{Eqn 2.5}$$

Auto-spectral confidence limits were derived in an analogous manner.

2.3.1.2 Coherence

The linear relationship between EEG and LFP time series in the frequency domain was assessed by means of the coherence function, which is a normalized measure having values from 0 to 1, where 0 represents the independence of the two frequency components and 1 an entirely linear relationship between them (Brillinger, 1981; Rosenberg et al, 1989; Halliday et al, 1995). Coherence estimates, $|R_{ab}(\lambda)|^2$ were defined as:

$$\left|\hat{R}_{ab}(\lambda)\right|^2 = \frac{\left|\hat{f}_{ab}(\lambda)\right|^2}{\hat{f}_{aa}(\lambda)\hat{f}_{bb}(\lambda)} \quad \text{Eqn 2.6}$$

Hence coherence of the two time series at a given frequency was essentially a correlation coefficient relating the covariance of the two sets of parameters with their independent autovariances and could be calculated using the outputs from Eqn 2.3.

Confidence limits of coherence based upon variance estimates are inaccurate with low coherence levels; as such an alternate derivation based upon numbers of segments was used (Halliday et al, 1995). This defined the upper 95% confidence limit as:

$$1 - (0.05)^{1/(L-1)} \quad \text{Eqn 2.7}$$

Hence confidence limits of coherence estimates were entirely independent of frequency and are depicted as horizontal lines in all coherence plots¹⁵. Values greater than this level were considered significant.

2.3.1.3 Phase

Although coherence where significant established a consistent linear relationship over the course of the two time series at a given frequency, it gave no information about the temporal nature of this relationship, which in turn might give insight into the dependence of one time series with another, and allow inference of causality. This question concerning temporal relationships of linear dependence was addressed by consideration of the phase spectrum, $\Phi_{ab}(\lambda)$, where each estimate at frequency, λ represented the phase lag of frequency components between time series $a(t)$ and $b(t)$. Phase estimates were defined as:

$$\hat{\Phi}_{ab}(\lambda) = \arg\{\hat{f}_{ab}(\lambda)\} \quad \text{Eqn 2.8}$$

¹⁵ Alternate techniques of determining coherence significance including probability of detection and exact confidence limit methods have been applied to STN DBE data and are considered in Wang et al, 2004

Phase estimates were therefore dependent upon cross-spectral estimates and could be calculated with the outputs of Eqn 2.3. The arctangent of the cross-spectral estimate derived the argument, consideration of the signs of real and imaginary parts further allowed the assessment of phase over the range $-\pi$ to $+\pi$. The isolation of relationships where at a given frequency one time series mirrored another at a lag of greater than 1 cycle was not possible with this technique. Further potential ambiguity exists where two oscillators at a common frequency in independent time series drive one another, though such a relationship may be manifest in non-stationary dynamics anyway. In addition, as is true of all such correlative relationships the common drive of both by a third factor remains a potential confounding factor. Phase relationships as such are interpreted in a circumspect fashion.

Where significant coherence existed between two time series over a restricted frequency range, two patterns of phase spectra allowed interpretation of the temporal relationship of this coherence. The first was where the phase spectrum was horizontal within the significant frequency range. The second where a non-horizontal straight line was present. The former was interpretable as the existence of phase locking across the frequency range, the phase difference between the two time series evident in the phase level on the spectral plot. The latter however showed that a constant temporal delay as opposed to fixed phase was significant across frequency range. This temporal delay could be estimated since the phase curve of such a relationship is a straight line passing through the point 0 rads phase lag, 0 Hz frequency (Halliday and Rosenberg, 1999) where a positive gradient may indicate that time series $a(t)$ leads $b(t)$, and negative $b(t)$ leads $a(t)$. The temporal lag could therefore be estimated by fitting a line to the derived phase spectrum. Such linear regression of the phase spectrum was performed only over regions where significant coherence had been established (Chapter 3). Estimates were further only derived where at least 5 contiguous 'significant' phase estimates existed and were only considered significant if the linear regression accounted for $\geq 71\%$ of the variance.

Confidence limits for the phase spectrum were derived from variance estimation, the variance of the phase estimate being defined as (Brillinger, 1991, Rosenberg, 1989):

$$\text{var}\{\hat{\Phi}_{ab}(\lambda)\} = \frac{1}{2L} \left(\frac{1}{|\hat{R}_{ab}(\lambda)|^2} - 1 \right) \quad \text{Eqn 2.9}$$

, which assuming normal distribution resulted in 95% confidence limits of:

$$\hat{\Phi}_{ab}(\lambda) \pm 1.96 \left[\frac{1}{2L} \left(\frac{1}{|\hat{R}_{ab}(\lambda)|^2} - 1 \right) \right]^{1/2} \quad \text{Eqn 2.10}$$

The confidence of phase estimates was therefore inversely proportional to the strength of coherence at the frequency considered.

2.3.1.4 Cumulant density

While the coherence function was used to assess linear time series relationships in the frequency domain, time domain relationships were investigated with cumulant density analysis. In a manner analogous to coherence, strong linear relationships between two time series are represented by high values of the cumulant function and more independent relationships by low values. In contrast however the cumulant density is both a vector, measure with positive values demonstrating positive correlations and negative showing negative correlations; and a non-normalized measure with maxima extending towards + and – infinity. Peaks of the cumulant at time 0, represent correlations of activity between the two aligned time series with zero lag, peaks at times deviating from time 0 however may be considered correlations in the time series shifted along one upon another, i.e. with varying time lag. As such cumulant density analysis was able to give the same information as phase analysis in terms of the temporal relationship of linear correlation, demonstrating appropriately timed peaks with constant phase lagged or time lagged data. In addition however, the breadth of the peaks gave an indication of the period over which significant correlation occurred. In Chapter 3, the capacity of the cumulant to demonstrate simultaneously the dominant oscillatory character and

phase/temporal relationship between time series was primarily used to readily observe reversals of coupling between cortex and subcortex about a given EEG bipole.

Cumulant density estimates $q_{ab}(u)$, were defined by the inverse Fourier transform of the cross-spectrum (Halliday et al, 1995) as:

$$\hat{q}_{ab}(u) = \frac{2\pi}{T} \sum_{|j| \leq T/2w} \hat{f}_{ab}(\lambda_j) e^{i\lambda_j u} \quad \text{Eqn 2.11}$$

, where u represented the time lag considered, $j = 1, 2, 3, \dots, T/2w$, and $\lambda_j = 2\pi j/T$ were the frequencies considered up to the Nyquist limit in bin widths of w . The cumulant density therefore considers relationships across the entire frequency spectrum, where however correlations are dominated by a common oscillatory character between the two time series, this is manifest in the derived cumulant density.

The determination of cumulant density via the frequency domain allowed the calculation of associated confidence limits (Halliday et al, 1995). These were again calculated based on estimates of function variance, which were estimated as:

$$\text{var}\{\hat{q}_{ab}(u)\} \approx \left(\frac{2\pi}{R}\right) \left(\frac{2\pi}{T}\right) \sum_{j=1}^{T/2-1} 2\hat{f}_{aa}(\lambda_j) \hat{f}_{bb}(\lambda_j) \quad \text{Eqn 2.12}$$

Confidence at a 95% level about zero correlation were therefore defined as:

$$0 \pm 1.96 \left[\left(\frac{2\pi}{R}\right) \left(\frac{2\pi}{T}\right) \sum_{j=1}^{T/2-1} 2\hat{f}_{aa}(\lambda_j) \hat{f}_{bb}(\lambda_j) \right]^{1/2} \quad \text{Eqn 2.13}$$

These limits appear in all plots of cumulant analysis represented, points beyond these limits were considered time lags at which significant linear correlation occurred between time series.

2.3.2 Finite impulse response filtering

In contrast to the study detailed in Chapter 3, the investigations of both Chapter 4 and 5 required the consideration of dynamic spectral estimates particularly in the alpha and beta bands. In both chapters this was primarily in order to measure change in event-related oscillatory power, whether phase or non-phase locked. The non-stationary nature of such analysis was incompatible with power estimation by means of the techniques detailed above. As a result the further techniques of band power and continuous wavelet transform (CWT) power estimation were used. The first of these was based upon the dynamic analytical techniques of Pfurtscheller et al (Pfurtscheller and Lopes da Silva, 1999). Time series were first band-pass filtered to select oscillatory activity within the frequency range of interest. This filtered activity was then squared giving a dynamic power estimate. Squaring activity allowed assessment of power in averages, independent of phase. This data was then averaged, aligned to cue presentation in the paradigm considered (methods, Chapter 4).

Linear-phase, non-recursive (FIR) filters with $M+1$ coefficients were designed consistent with the generalized frequency response $H(\omega)$, defined as:

$$H(\omega) = A(\omega) e^{j(\beta - \omega\alpha)} \quad \text{Eqn 2.14}$$

, where $A(\omega)$ represents the filter coefficients at frequencies ω , and $j = \sqrt{-1}$, $\alpha = M/2$, $\beta = 0$ or $\pi/2$. As such the frequency response was essentially the DFT (Eqn 2.1) of the filter kernel. Since the intention was the selection of oscillatory activity in a restricted frequency band, the idealized amplitude characteristics of the filter at frequencies between 0 and π (Nyquist) could be defined as:

$$A_d(\omega) = \left\{ \begin{array}{ll} 0 & \omega \in [0, \omega_{s1}] \\ 1 & \omega \in [\omega_{p1}, \omega_{p2}] \\ 0 & \omega \in [\omega_{s2}, \pi] \end{array} \right\} \quad \text{Eqn 2.15}$$

, where ω_{s1} and ω_{s2} are the lower and upper stop frequencies respectively, while ω_{p1} and ω_{p2} are the upper and lower pass frequencies. This idealized filter gives the desired frequency response, $D(\omega)$. Actual filter coefficients were optimized by minimization of the error function, $E(\omega)$ between actual frequency responses and the desired frequency response:

$$E(\omega) = W(\omega)[H(\omega) - D(\omega)] \quad \text{Eqn 2.16}$$

, where $W(\omega)$ was a weighting function. The optimization method used was the McClellan-Parks-Rabiner technique, an efficient means of implementing the Remez algorithm (McClellan et al, 1973). Equiripple filters that were thus defined produce the best possible performance with the minimum number of filter coefficients, as such efficient and optimized filtering of time series was performed.

Selection of the pass band frequencies was individual to each subject though all time series from a given subject underwent the same filtering. The choice of band was on the basis of peaks in the power spectrum, and are detailed with the relevant analysis in Chapter 4. Stop frequencies were adjusted to produce the smallest possible transition gap without the introduction of excessive pass-band ripple.

2.3.3 Wavelet spectral analysis

Band-pass filtering estimation was able to measure power dynamically in relation to a given cue but required *a priori* selection of bands of interest. While heuristic selection of such bands was undertaken in Chapter 4, the potential existed for the shifting of oscillatory frequency from within the examined band to a neighbouring unexamined band. As such, further data investigations in Chapter 5 were performed

in a manner that did not require assumptions of band significance to be made. The CWT coefficients, $C_{x,y}$, of LFP time series data, $b(t)$ were derived via a constant interpolation estimation of the non-discrete transform:

$$C_{x,y} = \int_{-\infty}^{+\infty} b(t) \frac{1}{\sqrt{x}} \overline{\psi\left\{\frac{t-y}{x}\right\}} dt \quad \text{Eqn 2.17}$$

, where x was the scaling factor of the mother wavelet, ψ , y the wavelet time translation and $\overline{}$ the complex conjugate. Hence the CWT coefficients represented the summated product of scaled and shifted versions of the mother wavelet basis function with the time series, and could be considered a regression of the signal with the wavelet function, where large positive values represented strong correlation between the two at a given scale. Coefficients could therefore be squared to give a measure of power at a given wavelet scale. The relationship between wavelet scale and equivalent Fourier period (or pseudo-frequency), F_x in a time series sampled at frequency k , was derived using:

$$F_x = \frac{F_c}{xk} \quad \text{Eqn 2.18}$$

, where F_c was the mother wavelet centre frequency. This allowed the representation of power at varying frequencies (Torrence and Compo, 1998). Non-linear scaling was initially performed to allow assessment of activity in a frequency range from 6 to 50 Hz. Frequencies of interest were defined as a result of this initial investigation and subsequent analysis was limited to linear frequency scaling over the range, 8 to 30 Hz at 0.5 Hz resolution.

No clear means of optimal wavelet function choice exists to date. The Meyer wavelet was however used as the *basis* function because it broadly matches the oscillatory characteristics of recorded basal ganglia LFP activity, is orthogonal allowing efficient localization of scale and temporal properties, and has been demonstrated capable of isolating frequency components of EEG event related potentials (Samar et al, 1999).

CHAPTER III

LOCAL FIELD POTENTIAL OSCILLATIONS AND FUNCTIONAL CONNECTIVITY

As has been discussed in Chapter I, both the GPi and subthalamic nuclei of the human, parkinsonian basal ganglia, display oscillations of the LFP broadly in both the beta and high gamma bands (sections 1.3.2.1 & 1.6.2). While beta oscillatory activity is most evident in parkinsonian patients withdrawn from levodopa and dopaminergic agonists, higher gamma activity is apparent in subjects on anti-parkinsonian medication (Brown et al, 2001). It has been proposed that these oscillations may in some manner reflect or facilitate the transmission of information not only within the basal ganglia but between basal ganglia and cortex (Brown and Marsden, 1998). For such activity to have any functional *systemic* significance however requires the coupling of functionally related areas in these bands. Such coupling may distinguish between independent oscillatory activity in separate brain regions and an integrated property of a dispersed network. The former might merely reflect an epiphenomenon of local activity, while the latter is clearly required if the oscillations are integral in some manner to function throughout the system. The question of whether or not oscillatory activity in either band within the basal ganglia shows coupling with similar activity in other anatomically connected and functionally related regions is therefore pertinent. Previous investigations have demonstrated significant constant phase relationships within basal ganglia, between oscillations in STN and GPi (Brown et al, 2001), and to regions outside the basal ganglia, between oscillations in STN and both Cz-FCz and C3/4-FC3/4 (Marsden et al, 2001).

The work detailed in this chapter extends such observations to test the hypothesis not only that significant coupling, as demonstrated by coherence, exists between oscillations in STN, GPi and cortex, but also that the distribution and strength of such coupling between cortex and sub-cortex is consistent with a role in basal ganglia motor-related function.

3.1 Methods

3.1.1 Subjects

The clinical details of the 8 subjects that participated in the study are presented in Table 3.1. Single stage implantation of bilateral STN DBEs was performed in 5 cases and of ipsilateral STN and GPi DBEs in 2 cases. In the latter, surgery was performed in the context of a comparative clinical study of the efficacy of stimulation at different sites at the Operative Unit of Functional and Stereotactic Neurosurgery CTO "A. Alesini" Hospital, Rome. Post-operative imaging using computerized tomography (CT) or MRI (n=2) was consistent with macroelectrode placement in the intended targets in cases 5-8. The macroelectrode position determined by post-operative CT was superimposed on pre-operative MRI using image fusion systems in 2 cases. No post-operative imaging was performed in cases 1-4, who were operated on at the Department of Neurosurgery, Academic Medical Centre, Amsterdam. Cases 1-4 were recorded on their usual antiparkinsonian medication. Cases 5-8 were recorded after overnight withdrawal of antiparkinsonian medication and again after administration of levodopa 200mg.

3.1.2 Protocol

Subjects were supine and recorded at rest and/or while they tonically extended the wrist contralateral to the DBE from which activity was recorded. Simultaneous EEG was recorded consistent with the method of section 2.2.1. The hypothesis required the demonstration of coherence (with or without spectral power) and phase between cortex and basal ganglia in given frequency bands. Tonic contraction data durations were relatively short compared to rest (less than a quarter of total trial duration). Since fast Fourier analysis was the basic technique for estimation of spectral power, coherence and phase, optimization of estimates was achieved by combination of rest and tonic activity.

Case ¹	1 ²	2 ²	3 ²	4 ²	5	6	7	8
Age (yr) & Sex	62M	53M	51M	67F	67M	69F	49F	37M
Disease duration (yr)	16	9	11	28	13	15	17	10
Predominant symptom	Bradykinesia, rigidity	Tremor, dyskinesias	Response fluctuations	Response fluctuations Dyskinesias	Response fluctuations Dyskinesias	Bradykinesia Dyskinesias	Bradykinesia Dyskinesias	Bradykinesia Dyskinesias
DBE Locations	Bilateral STN	Bilateral STN	Bilateral STN	Bilateral STN	RSTN	Bilateral STN	LGPi & LSTN	RGPi & RSTN
Motor UPDRS on/off	37/50	21/31	14/48	27/53	10/69	10/69	12/80	7/65
Medication (daily dose)	Levodopa 600 mg Pergolide 4 mg Amantadine 300 mg	Levodopa 400mg Benzhexol 2 mg	Levodopa 500 mg Selegiline 5 mg Roperinole 20 mg Entacapone 1000 mg	Levodopa 300mg Roperinole 5 mg	Levodopa 250mg	Levodopa 1050mg Pramipexole 3mg	Levodopa 1500mg	Levodopa 150mg Ropinirole 4mg
Coherence ³								
2-10 Hz	+ ⁴	+	-	+	+	+	+	+
10-20 Hz	+	+	+	+	-	+	+	+
20-30 Hz	+	+	+	+	+	+	+	+
70-85 Hz	-	+	-	-	+	+	+	+

Table 3.1: Clinical details and summary of coherence between STN DBEs and EEG.

¹Cases 2 and 4 were left-handed.

²Simultaneous EEG recordings from several scalp sites possible.

³Coherence between at least 1 STN DBEs contact and at least 1 bipolar EEG lead greater than 95% CL in ≥ 2 contiguous bins.

⁴+ represents the presence, and – represents the absence of coherence in the given frequency band

This was justified since acceptance of the hypothesis depended upon the demonstration of relative, significant levels of coherent activity in given bands not absolute levels and similarly the examination of the relationship of phases between bands more than absolute phase determination. Furthermore, patterns of cortico-subcortical coherence similar to the distribution of cortical motor-related oscillatory activity (section 1.5), in either or both of the combined states would be consistent with acceptance of the hypothesis.

3.1.3 Analysis

When determining the cortical topography of coherence between EEG and STN DBEs, data was down-sampled to 200 Hz and segment lengths of 256 points used, giving a frequency resolution of 0.78 Hz (except in Fig. 1 in which segment length was 128 points and resolution 1.56 Hz). A mean of 280 segments (range 122-410) was averaged. Phase was only analyzed over those frequencies showing significant coherence between STN/GPi and cortex. A segment length of 512 points (resolution 1.95 Hz with a sampling rate of 1 kHz) gave the best compromise between frequency resolution and variance in the phase estimate. For phase estimates a mean of 976 segments (range 451-2044) was averaged. The constant time lag between 2 signals was calculated from the slope of the phase estimate after a line had been fitted by linear regression. The time lag was only calculated from the gradient if the number of contiguous data points included in the segment ≥ 5 and a linear relationship accounted for (r^2) $\geq 71\%$ of the variance ($p < 0.05$). Phase between STN DBE LFP and CzFz EEG did not meet criteria in 6 patients in whom only CzFz was available and these are therefore not included here.

To compare coherences by ANOVA, the variance of the modulus of the coherency (given by the square root of the coherence) was normalized using a Fisher transform. The variance of spectral power estimates was stabilized by logarithmic transformation. No corrections for non-sphericity were required in the ANOVAs (i.e. variance of the differences between conditions were roughly equal).

3.2 Results

Patients were divided into two groups. In the first (cases 1-4) EEG was sampled with multiple electrodes, but recordings were only made during treatment with routine antiparkinsonian medication. In the second group only CzFz was available (cases 5-8), and recordings were performed after overnight withdrawal of medication and again after levodopa in each case. The first group permitted an analysis of the topography of those cortical areas coupled to STN DBE activity, while the second group allowed temporal differences between cortex and STN DBEs and, in cases 7 and 8, GPi DBEs to be compared at different frequencies in the same subjects.

3.2.1 Cortico-subthalamic connectivity

Coherence between EEG and STN DBE LFP activity was apparent in three major frequency bands; 2-10 Hz, 10-30 Hz and 70-85 Hz. The presence or absence of coherence in these frequency bands is summarized for each patient in Table 3.1, and Fig. 3.1 shows a representative example of the cortical topography of STN DBE-EEG coherence in case 1.

Coherence at 2-10 Hz was fairly evenly distributed over the midline and lateral cortical areas compared to that in the 10-30 Hz band. Coherence at these low frequencies between activity in the human globus pallidus and tremor has been reported previously (Hartado *et al*, 1999), while the presence of tremor-related neuronal discharge in the human STN is well recognised (Hutchinson *et al*, 1998; Bejjani *et al*, 2000). The coherence at frequencies above 10 Hz was greater over midline cortical areas than ipsilaterally and much greater than contralaterally in all four patients (Fig. 3.1). Topographic differences between transformed coherences in the 2-10 Hz and 10-30 Hz bands across all four patients were confirmed by a two-way ANOVA with area (midline, ipsilateral and contralateral to the ME) and frequency (2-10 Hz and 10-30 Hz) as factors. There was no main effect for frequency, but there was a significant main effect for area ($F = 8.757$, $p =$

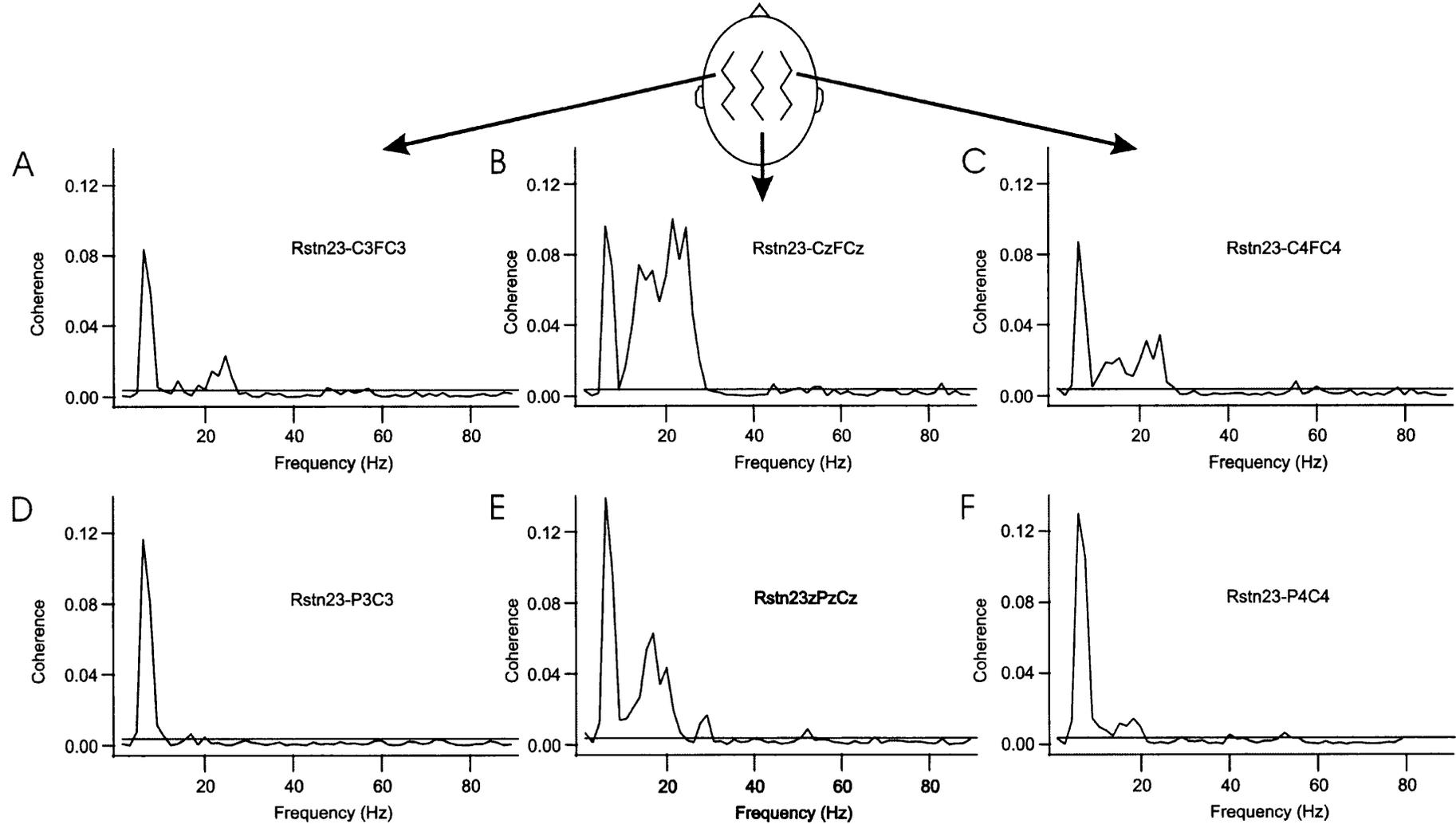


Fig. 3.1 Coherence spectra between R STN 23 and EEG in case 1 on their usual antiparkinsonian medication. Note coherence is strongest over the midline (287 blocks have been averaged). The horizontal lines in the coherence spectra are the 95% CL. The apparent topographic difference in 2-10 and 20-30 Hz coherence was confirmed by two-way ANOVA, (maximum mean coherences in 2-10 and 10-30 Hz bands respectively: 0.053, 0.045, 0.013, 0.020; 0.056, 0.066, 0.067, 0.04 for the four subjects).

0.017) and an interaction between area and frequency ($F = 7.944$, $p = 0.021$). Post-hoc paired t -tests confirmed that the transformed coherence in the 10-30 Hz band was greater in the midline than contralaterally ($p = 0.030$) or ipsilaterally ($p = 0.026$) and that transformed coherence ipsilateral to the DBE in the 2-10 Hz band was greater than contralaterally ($p = 0.039$). There were no significant differences between transformed coherences over the different cortical areas in the 2-10 Hz band otherwise.

The activity at 10-30 Hz could be sub-divided into two further bands (15-22 Hz and 23–30 Hz). That at lower frequency was proportionately greater in the posterior midline bipolar lead than in the anterior midline (Compare Fig. 3.1B, 3.2A, 3.3B and 3.4A with Fig. 3.1E, 3.2D, 3.3E and 3.4D, respectively), although differences were not confirmed by an ANOVA with area (anterior midline and posterior midline) and frequency (15-22 Hz and 23–30 Hz) as factors, perhaps because of the small number of subjects. Coherence at 10-30 Hz was evident in all 4 cases. Coherence between 70 and 85 Hz was only present in one case with multiple EEG recording sites (case 2). In this patient it was only seen following treatment with levodopa and was only recorded between STN DBE LFP activity and CzFz. This was perhaps because these 4 patients were studied on their usual medication rather than at the time of peak anti-parkinsonian effects of levodopa 200mg given after overnight drug withdrawal (as in cases 5-8).

In summary, EEG-STN DBE coherence was greatest over midline cortical areas in the 10-30 Hz band. However, coherence analysis may suffer two drawbacks when determining the topography of cortical areas coupled to STN activity. These are the problems of volume conduction and, most importantly, non-linear data contamination (see for example, Florian et al, 1998). The biggest source of non-linearly coupled activity over the frequencies of interest is EMG artefact (Daly and Pedley, 1990). As coherence is a normalized measure, greater contamination of EEG signals by EMG over lateral compared to the midline channels might lead to spuriously low estimates of coupling with STN over lateral cortical areas.

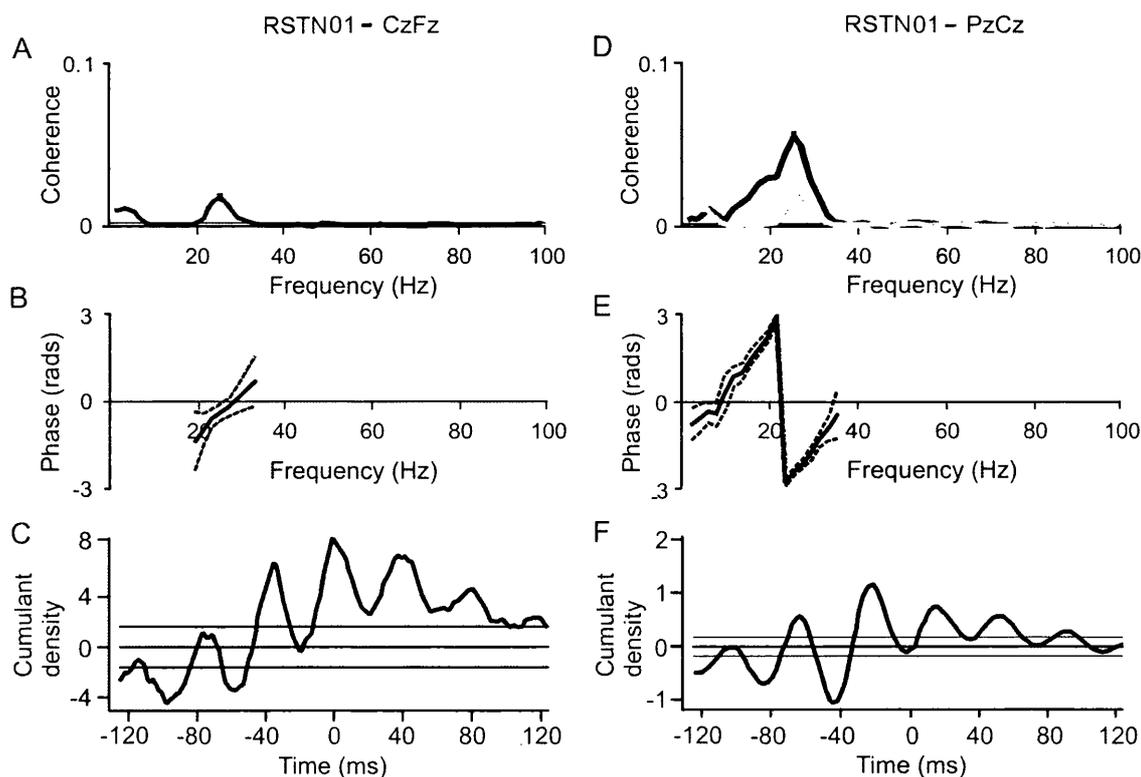


Fig. 3.2 Coherence and phase spectra and cumulant density estimates between the R STN DBE 01 and midline EEG activity in case 4 on their usual antiparkinsonian medication. A-C results for STN DBE 01 LFP v CzFz. D-F results for STN DBE 01 LFP v PzCz. Note that coherence at 20-30 Hz is seen with both scalp electrodes, but that over 10-20 Hz is only seen with the posterior midline channel. The coherence from A has been superimposed in grey in D for comparison of frequencies. EEG led STN DBE LFP by 20-30 ms. The cumulant density estimates suggest polarity reversal about Cz for the activity with a period of about 40 ms, implying that the cortical activity coupled with the STN DBE LFPs at 25 Hz arises in the area of Cz. In this and ensuing figures the horizontal lines in the coherence spectra and the thin dashed lines in the phase spectra are the 95% CL. (1499 blocks have been averaged).

The absolute magnitude of EEG power linearly correlated with the STN DBE signal can be estimated by multiplying the autospectra by the coherence spectra (see for example Mima et al, 2000). The log-transformed EEG power at each bipolar electrode linearly correlated with the STN DBE signal was therefore calculated. Fig. 3.3 shows the distribution in case 1, and it is noteworthy that the distribution was little different to that seen in Fig 3.1. In particular, coupling at 10-30 Hz remained strongest over the midline. The importance of the midline electrodes was further supported by the identification of one instance of clear polarity reversal at Cz in cumulant density estimates (Fig. 3.2). Polarity reversal involved activity with a period of 40 ms, consistent with a frequency of 25 Hz.

It was noteworthy that the EEG-STN DBE coherence at 10-30 Hz and that at 2-10 Hz was greatest in different STN DBE leads in 3 out of the 4 patients, as illustrated in Fig. 3.5. In addition, within the 10-30 Hz frequency band, coherence between CzFz and STN and between PzCz and STN was greatest at different STN DBE leads in 2 patients, as shown in Fig. 3.4. The pattern of the log-transformed LFP power at each bipolar STN electrode linearly correlated with EEG (not shown) was little different to that seen in Figs. 3.4 and 3.5, so that variations in coherence were unlikely to be due to different degrees of non-linear contamination. It should also be noted that maximal 10-30 Hz coherence could occur in differing directions along DBE in different subjects, increasing from rostral to caudal in Figs 3.4 A, B, C and caudal to rostral in Figs 3.5 C, B, A. Such an observation is consistent with differing depths of the macroelectrode relative to the potential source and entirely incompatible with volume conduction from a cortical source. Together these observations suggest that different oscillatory activities could have slightly different origins within STN and the surrounding fields. Nevertheless, no convincing examples of polarity reversal at different STN DBE contacts for any of the different oscillatory activities were observed, perhaps because of the small size of STN relative to the distance between electrode contacts (Hutchinson et al, 1998; Ashby et al, 1999).

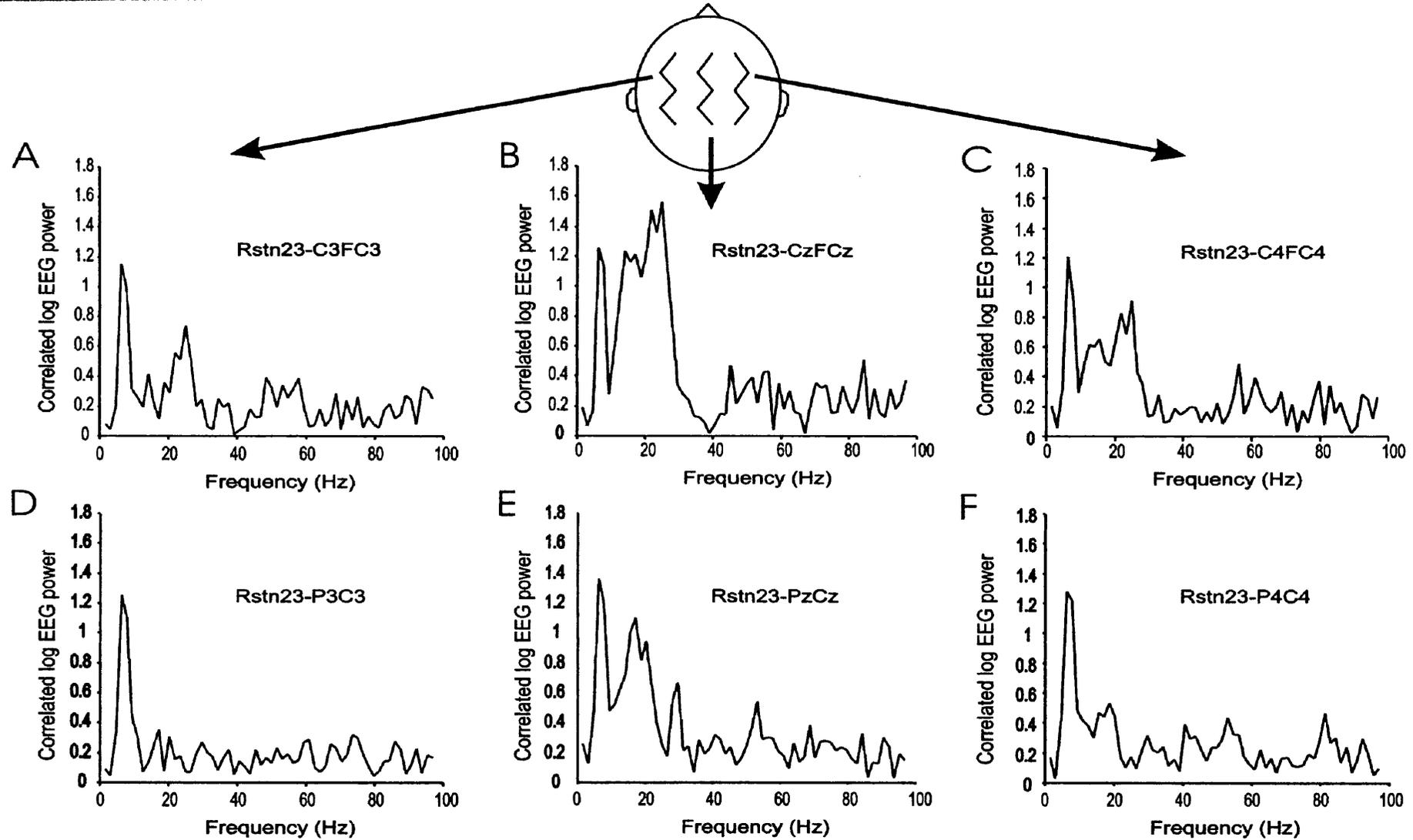


Fig. 3.3 The log-transformed EEG power at each bipolar electrode linearly correlated with the signal from R STN DBE 23 in case 1 on their usual antiparkinsonian medication. Coupling is strongest over the midline. The same data have been analysed as in Fig 3.1.

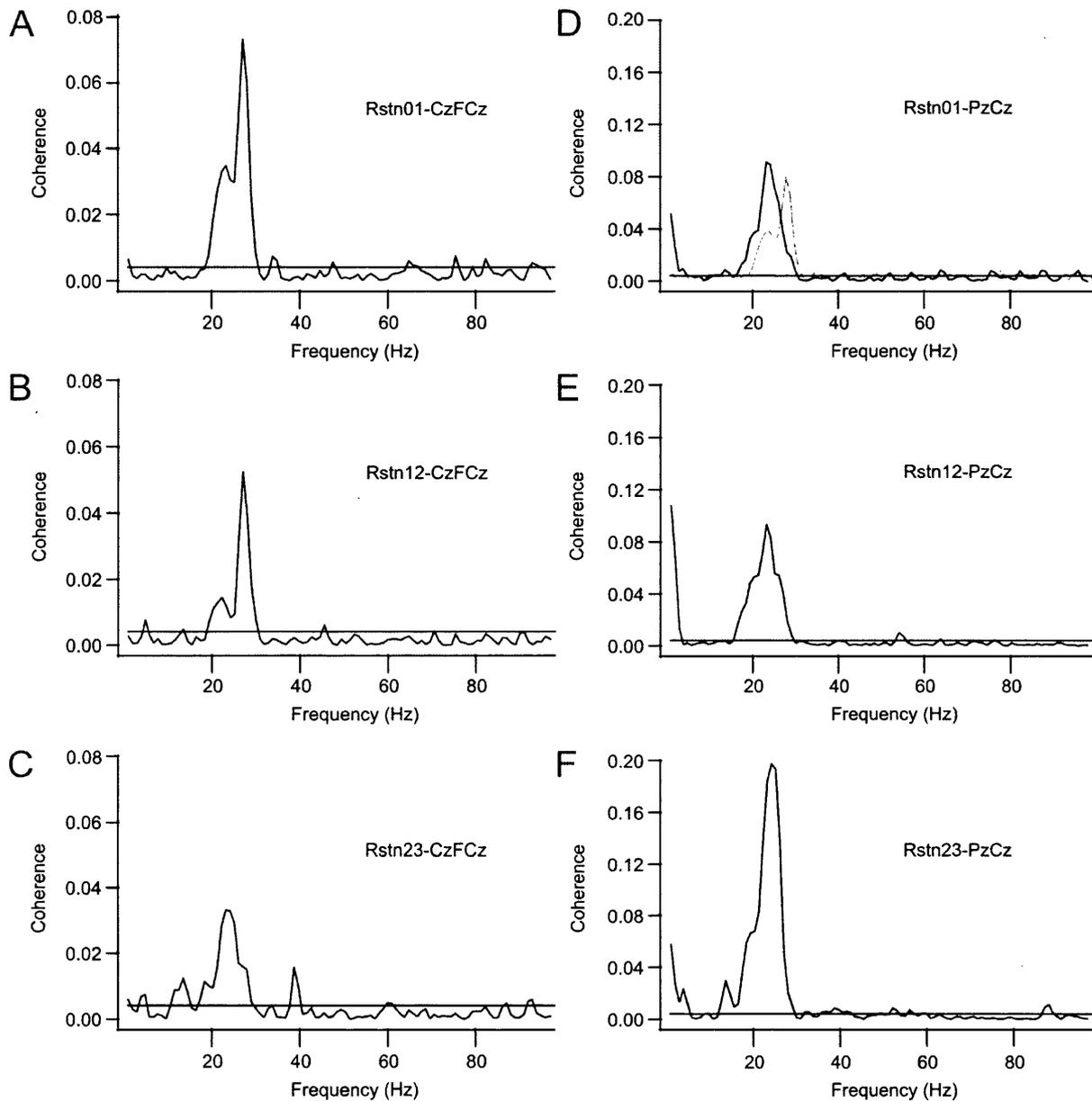


Fig. 3.4 Coherence spectra between right STN DBE and CzFCz (A-C) and PzCz (D-F) in case 4 on their usual antiparkinsonian medication. Note that peak coherence between STN DBE and PzCz had a slightly lower frequency (spectrum from A has been superimposed in grey in D for comparison of frequencies) and a different distribution around STN. (287 blocks have been averaged).

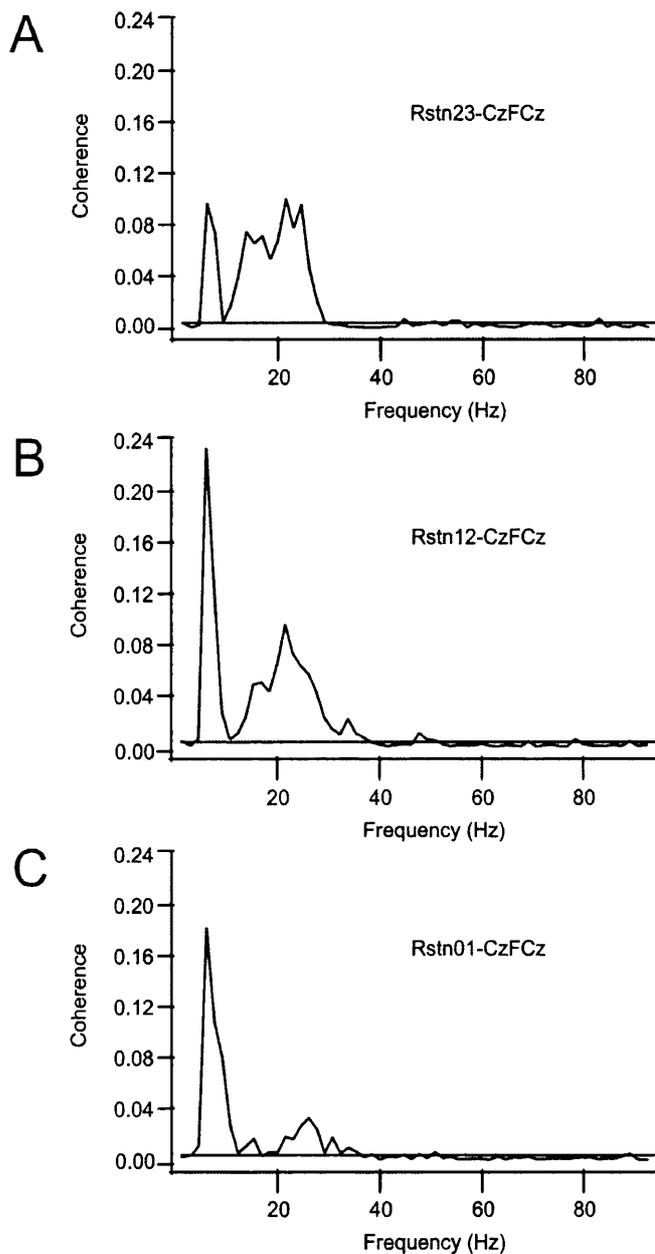


Fig. 3.5 Coherence spectra between R STN DBE contacts and CzFz in case 1 on their usual antiparkinsonian medication. Note that tremor related coherence at frequencies below 10 Hz was greatest at bipoles 01 and 12, while that at 10 to 30 Hz was greatest at bipoles 12 and 23 (300 blocks have been averaged).

3.2.2 Phase relationships of connectivity and dopamine dependence

Phase relationships were determined in the 4 patients in group 2. A representative example of the autospectra, coherence and phase spectra from data recorded on and off levodopa in a patient with only a single STN DBE (case 5) is illustrated in Fig. 3.6. Strong coherence between STN DBE and CzFz is evident at 70-85 Hz, but only after treatment with levodopa.

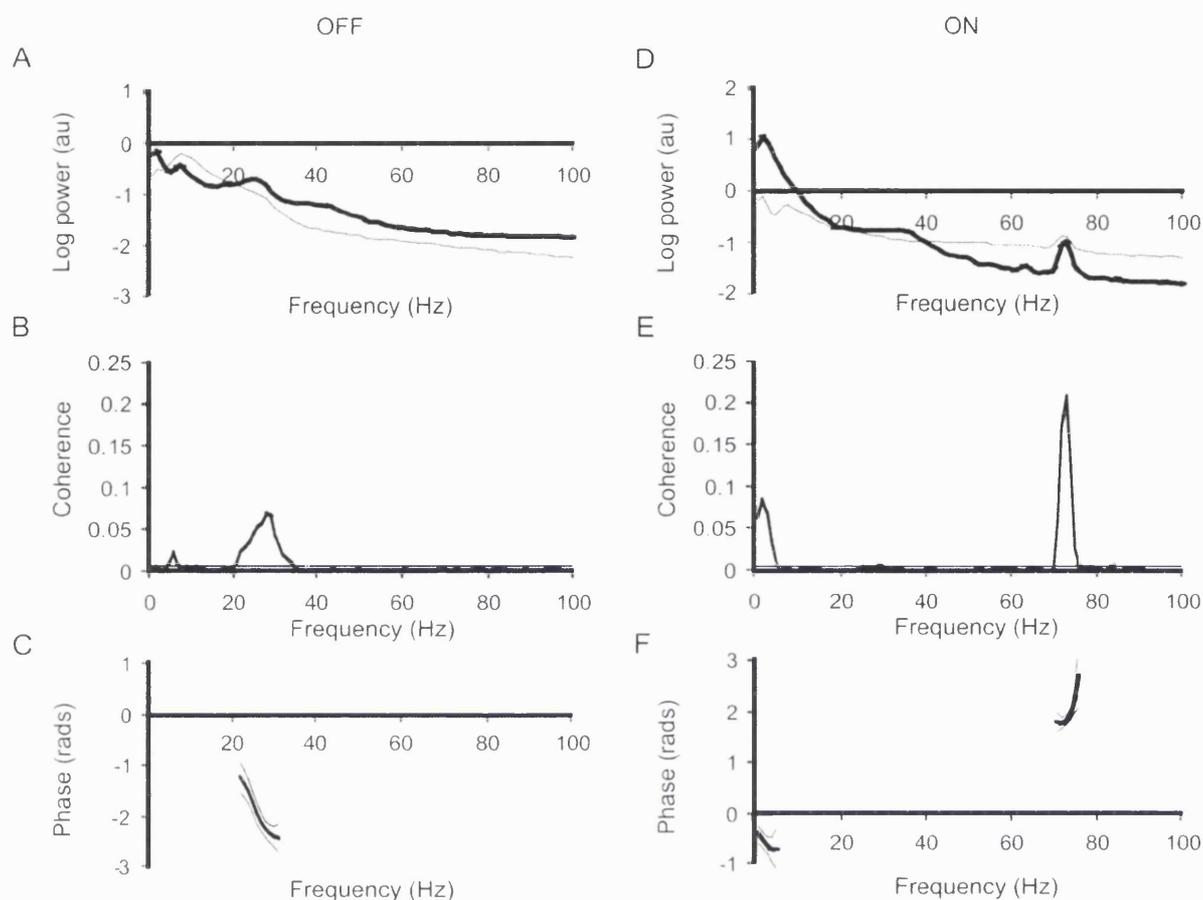


Fig. 3.6 Power, coherence and phase spectra for CzFz and left STN DBE 23 in case 5. A-C and D-F are the results after withdrawal and reinstition of treatment with levodopa, respectively. The bold and thin lines in the power spectra are the STN DBE LFP and CzFz EEG, respectively. Note the shift in coherence to higher frequencies and the reversal of the phase slope after treatment with levodopa. (918 blocks have been averaged off and on treatment).

Coherence at 70-85 Hz was limited to the treated 'on' state in all 4 patients and was only evident at a maximum of two bipolar pairs of contiguous contacts. The time differences between STN and EEG activity calculated from phase spectra are summarized for all subjects in Fig. 3.7. Both on and off dopaminergic therapy, activity at CzFz lead that recorded by the STN DBE by $26.1 \pm (\text{SEM}) 5.4$ ms at frequencies under 30 Hz. In contrast, activity at the STN DBE led that at CzFz by 17.3 ± 4.3 ms over the 70-85 Hz band. Two patients in this group also had a

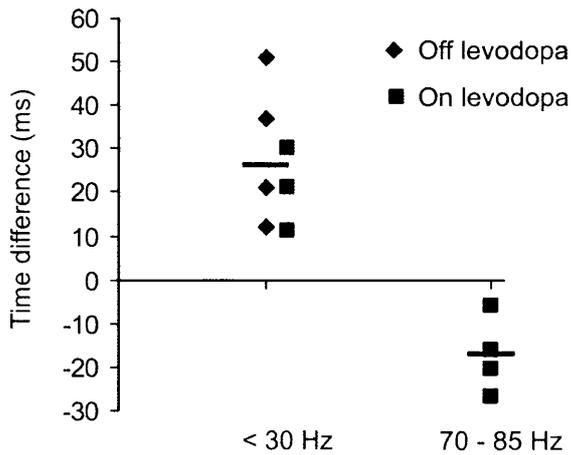


Fig. 3.7 Time differences between STN DBE LFPs and CzFz. Positive latencies indicate that the EEG phase led the STN DBE LFP. For frequencies < 30 Hz EEG led STN DBE LFP by a mean (indicated by horizontal bar) of 26.1 ms (95%, confidence limits 12.9 to 39.3 ms), but over the 70-85 Hz band STN DBE LFP led EEG by a mean of -17.3 (6.3 ms, confidence limits -3.5 to -30.9ms).

unilateral GPi DBE implanted simultaneously with the STN DBE. The phase relationship between EEG and GPi DBE LFP was similar to that found with the STN DBE. Activity at CzFz led the GPi DBE LFP by 21 ms (case 7) and 15 ms (case 8) at frequencies under 40 Hz. However, in the one patient in whom phase could be determined over the 70-85 Hz band, activity at the GPi DBE led CzFz EEG by 4 ms. Fig. 3.8 compares the phase and coherence spectra on and off treatment between CzFz EEG and STN DBE LP and CzFz EEG and GPi DBE LP in case 8. The spectra are derived from simultaneous recordings from the two sites and their general pattern is similar.

In summary, autospectra, coherence and phase spectra were similar in cases 5-8, with relatively little difference between STN and GPi. The biggest differences were seen within the same subject, according to treatment state. Coherence between STN and EEG and GPi and EEG at high frequency (70-85 Hz) was only seen after treatment with levodopa. In contrast, coherence below 30 Hz was seen in both states.

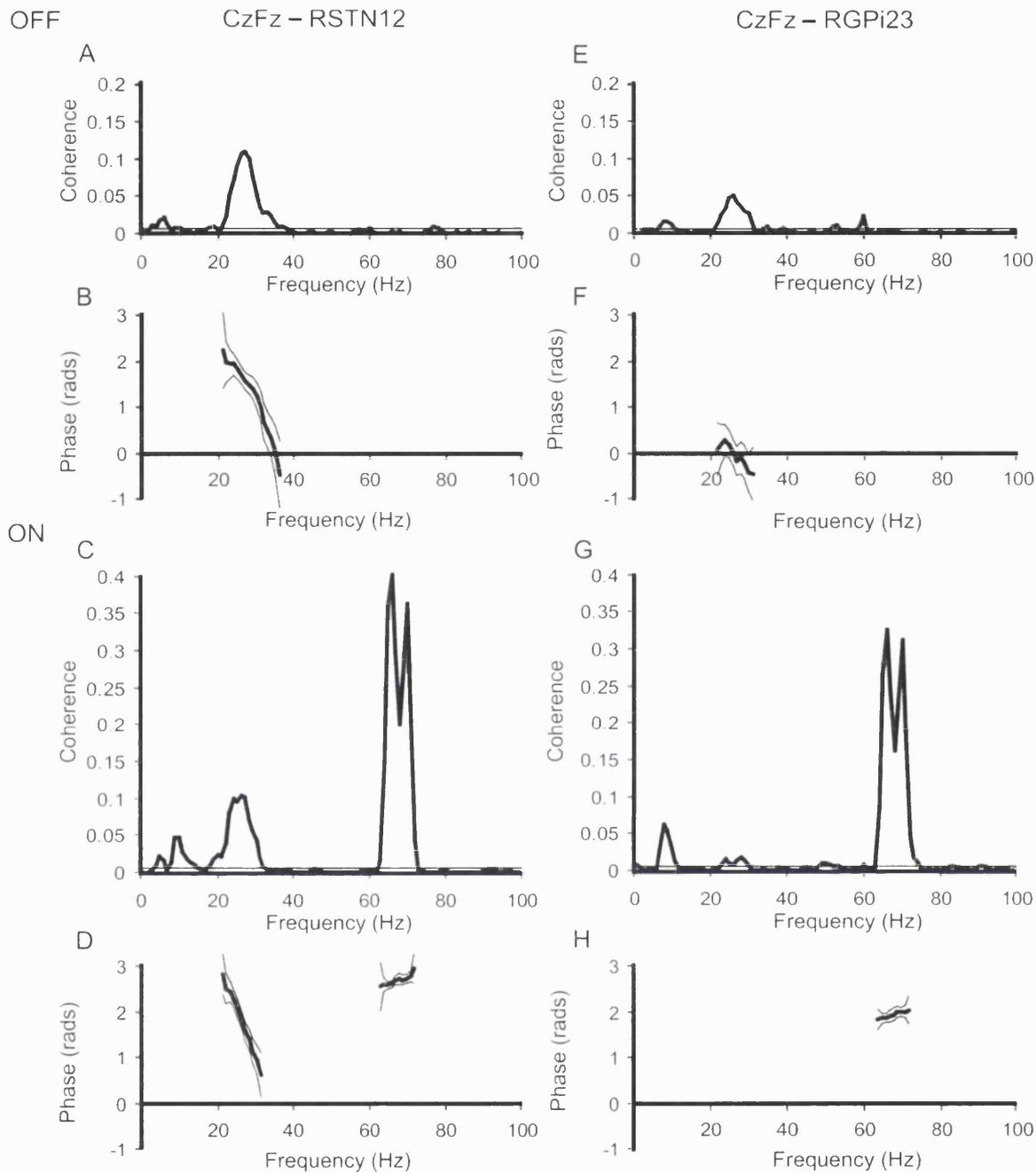


Fig. 3.8 Coherence and phase spectra between CzFz and R STN DBE (A-D) or R GPi DBE (E-H) in case 8. A, B, E and F and C, D, G and H are the results after withdrawal and reinstition of treatment with levodopa, respectively. Note the change in coherence to higher frequencies and the reversal of the phase slope after treatment with levodopa. The pattern is similar for STN and GPi. (451 blocks have been averaged off and on treatment).

3.3 Discussion

The investigations described in this chapter sought to test the hypothesis that oscillatory activity may have a systemic role in the motor-related function of the basal ganglia. The acceptance or at least the failure to reject such a hypothesis requires firstly that there be significant coherent oscillatory connectivity between cortex and basal ganglia nuclei, and secondly that the character, i.e. the distribution, frequency and strength of such connectivity be consistent with the distribution of motor-related oscillatory activity in cortex.

3.3.1 Cortico-subthalamic connectivity

The data presented here, consistent with previous findings, demonstrate significant cortico-subthalamic and cortico-pallidal connectivity (Marsden et al, 2001). This connectivity is dominated by activity in two frequency bands, alpha-beta activity in the 10-30 Hz range and high gamma oscillations from 70-85 Hz, both as discussed in sections 1.3.1.2, 1.5.1 and 1.5.2 are prominent components of motor-related cortical LFP activity and high gamma in particular has been observed to display a highly somatotopically specific representation in association with motor action (Crone et al, 1998b). In addition, lower frequency 2-10 Hz connectivity that has been associated with tremor (Volkman et al, 1996; Hurtado et al, 1999) is observed in the patient population detailed. As such not only do nuclei of the basal ganglia in PD patients display oscillations of their LFP at similar frequencies to those observed in motor-related cortical regions (section 1.5.1, 1.5.2) but they do so in an inter-related fashion.

It is further observed that distinct frequencies display differing inter-regional relationships, with cortical alpha/beta activity appearing to lead its subcortical analogue, while the reverse appears true of the high gamma activity. However, the temporal differences with which cortical activity leads or lags that in STN appears similar, around 20 ms, regardless of the overall direction of information flow and frequency band. Where STN drives cortex the likely path based on anatomical

considerations (Parent and Hazrati, 1995) is via GPi/SNr and thalamus, and a delay of 20 ms or so seems reasonable. Where cortex drives STN, this could be achieved either directly through the large cortico-subthalamic projection or indirectly via the putamen/GPe (Parent and Hazrati, 1995). A delay of around 20 ms would seem to favour the latter and it is of note that similar delays were seen between cortex and GPi, where pathways are, of necessity, indirect. In contrast, stimuli applied within the motor cortex of the monkey facilitate STN neurones with a mean latency of 5.8 ms (Nambu et al, 2000) and frontal cortical potentials may be elicited with a latency of 5-8 ms after probable antidromic activation of the direct cortico-subthalamic pathways in humans (Ashby et al, 2001).

A further dimension to this regional connectivity in the frequency domain is the dopamine dependence of the relationships. Broadly consistent with prior observations that have noted prominent beta spectral power in patients off dopaminergic medication, reduced with medication, and opposite patterns in the gamma band (Brown et al, 2001), the current results display similar relationships with variations in dopamine state. It is of note that the recurrent reciprocal association of alpha/beta oscillations and gamma activity is yet again evident here.

3.3.2 The central role of midline cortical motor areas

Despite the enforced post-operative limitations, analysis was possible of scalp EEG from up to nine sites. Coherence appears greatest over midline cortical areas and one instance of polarity reversal around Cz was observed. These results suggest that functional connections are particularly strong between STN and the midline cortical areas, particularly supplementary motor area (SMA) underlying Cz. The consistent nature of coherence results after compensation for potential EMG contamination further excludes such a confounding factor as a potential explanation of the results. These findings would be consistent with other data indicating a central role for SMA in motor loops involving the basal ganglia and cortex. Activity in SMA is a major contributor to the Bereitschaftspotential that precedes self-generated

movements (Kornhuber and Deecke, 1965; Shibasaki et al, 1980; Deecke, 1987), and this potential is reduced in Parkinson's disease (Deecke et al, 1977; Shibasaki et al, 1978; Dick et al, 1987, 1989; Jahanshahi et al, 1995; Cunnington et al, 1995). Imaging studies confirm impaired activation of SMA during some movements in untreated Parkinson's disease (Playford et al, 1992; Rascol et al, 1992, 1994; Jahanshahi et al, 1995; Limousin et al, 1997), reversible with the dopaminergic agonist, apomorphine (Jenkins et al, 1992; Rascol et al, 1992). These results suggest a net transmission of 'information' from midline cortical motor areas to STN at frequencies under 30 Hz and transmission from STN back to these midline areas in the 70-85 Hz band.

In contrast, though significant coherence is present there appears relatively little coherence at frequencies above 10 Hz over lateral electrodes covering the sensorimotor and premotor cortices, suggesting that oscillatory coupling between STN and these cortical areas is not as important as that with midline areas such as SMA.

3.3.3 Independent oscillating loops?

It has been proposed that multiple, functionally heterogeneous oscillatory activities may be engaged in linking human basal ganglia and cerebral cortex (Brown and Marsden, 1998). This is in line with current views of multiple anatomically segregated circuits linking basal ganglia and cortex (Alexander et al, 1990), although this is not to say that specific oscillatory activities can be associated with specific anatomical pathways. The notion that the human basal ganglia may consist of multiple independent oscillating circuits was first suggested by Hurtado et al (1999) based on the dynamics of tremor-related oscillations in the globus pallidus. Some aspects of the findings presented here support this model. It is observed that activities connecting cortex and basal ganglia at different frequencies exist with different drives. Furthermore there is the suggestion from the current results that differing distributions exist in these separate oscillatory modes not only at the cortical stage but also at the subthalamic level. Two significant caveats must be considered

however. Firstly, the inability in the current investigation to know categorically *pre mortem* where electrodes are precisely located makes over interpretation of nuclei LFP localizations a possibility. Secondly, of necessity the subject population in the study is parkinsonian as such the pathological nature of specific modes of activity must be questioned. Irrespective of whether subcortico-cortical synchronization is primarily physiological or a pathological consequence of Parkinson's disease, it is likely to be important in functional terms. Synchronization increases post-synaptic efficacy at subsequent projection targets, while non-linearities in the frequency-current relationship of basal ganglia neurones may increase the saliency of inputs in particular frequency bands (Bevan and Wilson, 1999).

3.4 Outstanding issues

Despite the observations detailed here, and insights derived, there are of course many questions that remain unanswered, of interest not merely because they may allow a better theoretical understanding of corticosubthalamic connectivity but of potential significance in the understanding of PD pathophysiology.

- 1) What is the distribution of cortico-subcortical connectivity at high spatial resolution both in motor cortex and in the region of basal ganglia nuclei?

Although the current study detailed functional connectivity across the cortex, the spatial resolution presented was limited both as a consequence of the constraints imposed by the patient population involved and as a result of the limitations of EEG as a technique. Furthermore, while the DBE represents a serendipitous point of access to examine the STN LFP in the alert human, it is not ideal for the examination of LFPs at high spatial resolution, as a consequence of its dimensions, and limited number of contacts. However, a higher resolution representation of human corticosubthalamic functional connectivity in the frequency domain across cortex may potentially allow the detailed representation of regional integration of oscillatory activity. In frequency bands modulated by dopamine in the parkinsonian state particularly (e.g. beta activity), such a representation might allow cortical areas of

significance either in the alleviation of PD symptoms or the exacerbation of them to be better identified. As an extension of the present work for example it may answer the question, - Is SMA in particular the significant link as suggested, or possible pre-SMA/cingulate cortex, and if so which sub-regions? In addition, despite the significant degree of direct anatomical connectivity apparent between cortex and STN (section 1.1.2), motor cortical regions appeared less significant in terms of functional connectivity in the frequency domain than midline sources, - Is this difference solely the result of relatively low degrees of integration of oscillatory LFP in the two regions or perhaps due to very focal representation as distinct to diffuse representation. Examination of coupling at the motor homunculus resolution may answer such a question. Investigating these questions in human subjects is not without difficulty. Assuming the use of a DBE as the source of STN LFP activity, obtaining more detailed cortical representations is theoretically possible using greater EEG regional sampling (i.e. having more scalp electrodes) or by using the higher resolution technique of MEG. It has been estimated that 200 electrodes are required to capture all the spatial information of the human EEG to allow for a reasonable solution of the inverse problem (Gevins, 1984), attempting such investigation would obviously not be practical in post-operative patients. The coordination of surgical centres with MEG facilities and practicality of MEG in post-operative patients appears similarly problematic. A compromise may be conceived however with the use of relatively high levels of electrode scalp coverage in conventional EEG, in addition to post sampling analysis. Independent component analysis (ICA) has been successfully used in the examination of cortical distributions of oscillatory components (Makeig et al, 2002), and even dynamically so – Such a technique may well prove useful. This method would not however aid in the more detailed localization of STN sources. No ready solution of this problem is available in mobile, alert humans. The 6-OH dopamine rat model or more ideally, the MPTP primate might however allow further investigation. The simultaneous stereotactic implantation of several parallel multicontact electrodes may potentially allow the sampling of tissues rostral, caudal, ventral, dorsal, medial and lateral to the STN with far higher spatial resolution than available via DBE, using a bipole source analysis similar to that used in this work. In addition, with an appropriately high electrode impedance and use of variable sampling frequency, the possibility may exist for

detection of both multi-units (or even single units) and LFP. If STN DBS remains an important therapeutic option in the treatment of PD patients this manner of experimentation seems of great importance as it will simultaneously allow several questions to be answered, - Beta oscillatory activity of the STN LFP appears a potential pathological marker, but what is the exact regional representation of this activity? Does it localize to dorsolateral STN (as might be predicted)? Is the localization of oscillatory activity focal enough to be of use in the accurate implantation of macroelectodes? This might allow LFP to be used intraoperatively to guide placement rather than more difficult single unit sampling technique. With further modification of the experiment the question of whether beta LFP oscillations co-localize with the optimal target for deep brain stimulation might be resolved.

- 2) Are there dynamic changes in the spatio-temporal pattern of coherence between basal ganglia and cortex associated with movement, and if so what are they?

The dynamic nature of the STN LFP is considered in chapters 4 and 5, however neither concerns the dynamic nature of corticosubthalamic functional connectivity. If oscillatory activity in restricted bands (particularly beta and gamma), has functional significance one may well expect to see fluctuations of the strength of functional connectivity in task relevant regions with differing behaviour. The observation of appropriate regional changes in oscillatory functional connectivity throughout the course of a task, may not only support the notion of LFP oscillations as functionally significant entities, but may also allow variations in the integrated function of STN with differing regions of cortex throughout tasks to be assessed. Furthermore, with respect to Parkinson's disease, variations of any dynamic regional pattern of functional connectivity throughout the course of tasks may well be of significance to the pathophysiology of the disease and may well correlate with the spectrum of task disability observed in PD. Any work in this area would preferably have high levels of spatial resolution as discussed above. The dynamic nature of the analysis required may however mean that Fourier techniques of spectral estimation may be less than ideal (particularly if the tasks considered evolve over second or millisecond time

scales). Wavelet analysis (as used in chapter 5 and discussed in section 2.3.3) may allow decomposition of spectral components efficiently in non-stationary data; it is now also possible to calculate wavelet coherence (reviewed in the context of neurological signals – Lachaux et al, 2002). An experimental protocol may therefore readily be envisaged, involving a similar patient population to that considered here in which rather than actively seeking long blocks of stationary data, motor tasks as used in chapter 4, 5 could be used and functional connectivity in the frequency (and time) domains examined not only in the course of motor responses but also in their appropriate selection.

3.5 Summary

Findings in this study do not support the rejection of the investigated hypothesis:

- Functional connectivity as evidenced by significant coherence exists between cortex and both STN and GPi in both beta and gamma bands
- The degree of this connectivity appears dopamine dependent
- The cortical distribution of this linkage in the beta band is consistent with the motor cortical representation of similar activity, particularly to SMA.

CHAPTER IV

LOCAL FIELD POTENTIALS AND RELEVANT BEHAVIOURAL STIMULI

Rhythmic LFP activity in nuclei of the parkinsonian basal ganglia is a non-stationary phenomenon, evident in the alterations of oscillatory power phase and non-phase locked to events such as voluntary movement and imperative cues for such movement (section 1.5.4). Furthermore, this non-stationarity is not merely a manifestation of parkinsonian pathology since it has been demonstrated in healthy human putamen (Sochurkova and Rektor, 2003). If the modes of oscillatory activity evident in the beta and gamma bands of STN and GPi LFP activity have functional relevance one may expect that fluctuations of such activity may modulate this function. Indeed if such changes have behavioural relevance one might expect a bias towards the occurrence of power modulation in the context of behaviourally (and functionally) relevant stimuli as opposed to non-relevant stimuli.

Changes in similar activity in the motor cortex, cerebellum and thalamus of humans and other primates have dissociated these event-related changes from movement itself, i.e. they have shown an absence of causal linkage (in either direction) between the performance of a motor act and fluctuations in rhythmic LFP activity. Examples of such dissociation in man come from the capacity for somatomotor cortical mu EEG oscillation suppression with the conscious imagination of movement alone (Beisteiner et al, 1995; Leocani et al, 1999), and in non-human primates in the suppression of beta oscillatory cerebellar LFP oscillations with cues warning of movement, despite significant delays prior to any movement initiation (Pellerin and Lamarre, 1997; Courtemanche et al, 2002).

The work detailed in this chapter sought both to examine whether alterations in beta power LFP oscillations within STN are related specifically to movement or more generally to movement preparation and whether any such modulation of activity displays a bias towards cues for motor behaviour.

4.1 Methods

4.1.1 Subjects

The clinical details of the 9 patients involved in this study are summarized in table 4.1. MRI confirmed that at least one macroelectrode contact was within the STN, except in those 3 patients from Amsterdam who were not imaged post-operatively. A representative example of post-operative imaging of electrode position is illustrated in Fig 4.1. Only patients that derived > 20% reduction in OFF treatment motor UPDRS scores in the contralateral upper limb with bipolar stimulation using adjacent contacts were studied.

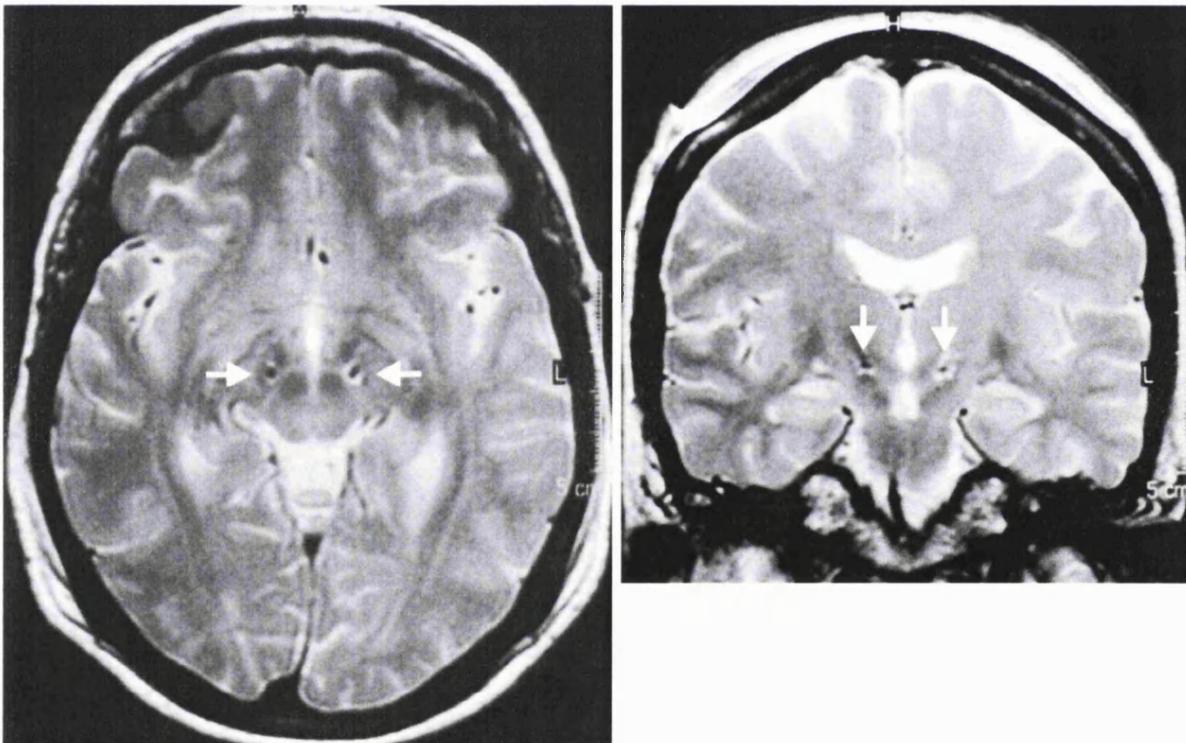


Fig. 4.1. Localization of macro-electrodes at the level of contact pair 12 in the post-operative T2 weighted MRI of case 8. Both are symmetrically placed within STN. Arrows point to the macroelectrode artefacts.

4.1.2 Protocol

Subjects were supine or seated and recorded while performing a visual choice reaction task. This consisted of watching a fixation cross at the centre of a portable PC screen while holding a push button in each hand. A warning signal, a pair of arrows, appeared either side of this central cross for 500ms (Fig 2), indicating the laterality of a subsequent imperative signal.

Case	Age (yr) & Sex	Disease duration (yr)	Diagnosis and predominant symptoms	Surgical centre	Motor UPDRS On/off	Medication (daily dose)	Power ¹ spectral peaks (Hz)
1.	57M	8	PD, bradykinesia, rigidity	Amsterdam	22/64	1200mg L-Dopa 1.25mg Pergolide	α 6-10 $\beta(1)$ 11-20 $\beta(2)$ 21-30
2.	58M	10	PD, bradykinesia	Berlin	36/63	900mg L-Dopa 10mg Pergolide 10mg Domperidone	α 6-12 $\beta(1)$ 14-30 $\gamma(1)$ 33-45 $\gamma(2)$ 75-85
3.	65F	25	PD, bradykinesia	Amsterdam	24/36	300mg Amantadine 1.8mg Lisuride 200mg L-Dopa 5mg Selegeline 1mg Lorazepam	α 6-12 β 15-25
4.	62M	25	PD, hyperkinesias	Berlin	14/52	500mg L-Dopa 62.5mg Clozapine	α 6-12 $\beta(1)$ 13-25 $\beta(2)$ 26-34
5.	67F	13	PD, bradykinesia	Berlin	20/42	400mg L-Dopa	α 6-12 β 13-21 γ 32-47
6.	62F	9	PD, dyskinesias	Berlin	16/48	675mg L-Dopa 1400mg Entacapone 4mg Cabergoline	α 6-13 $\beta(1)$ 14-20 $\beta(2)$ 21-30
7.	65M	17	PD, dyskinesia, bradykinesia	London	32/57	750mg L-Dopa	α 6-12 $\beta(1)$ 13-20 $\beta(2)$ 21-30
8.	50F	6	PD, tremor	Berlin	26/42	950mg L-Dopa 2.8mg Pramipexole 50mg Clozapine	α 5-10 $\beta(1)$ 11-20 $\beta(2)$ 21-30
9.	54M	15	PD, bradykinesia, tremor	Amsterdam	34/56	600mg L-Dopa 8mg Pergolide	α 6-12 β 14-30

Table 4.1: Summary of patient details. All had bilateral STN implantation.

¹ Numbers in brackets denote (1) lower and (2) higher frequency peaks in the beta band. For the analysis activity in β or $\beta(1)$ was used. Spectral peaks assessed OFF l-dopa. All cases were right handed.

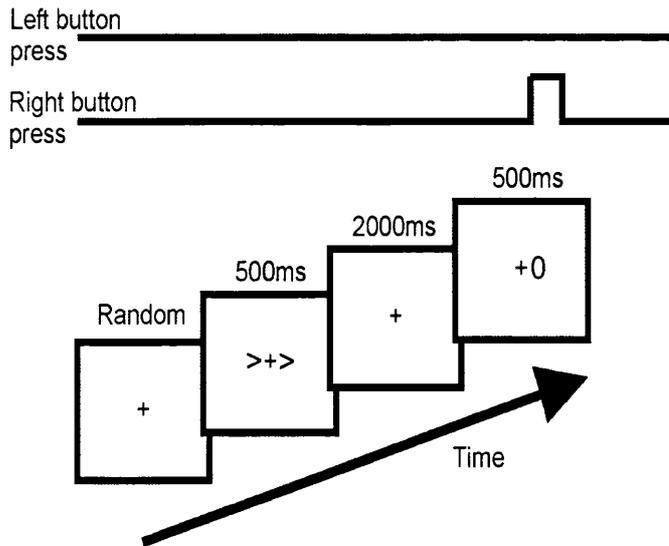


Fig. 4.2. Schema of the experimental paradigm, illustrating successive events observed on screen by subjects and expected subject response. Warning cues and imperative 'go' signals could point right or left and cue-go congruity was kept either 100% or 50% in each block.

The warning arrows and fixation cross subtended a visual angle of 2 degrees. After 2s from the disappearance of the warning cue a 500 ms duration imperative 'go' signal (a circle) appeared either to the right or left of the fixation cross, with similar eccentricity. Subjects were instructed to press the button ipsilateral to the imperative signal as quickly as possible. Inter-trial durations were pseudorandomized between 6 and 7s limiting prediction of the timing of warning cues. Each block consisted of 100 such runs, with a few minutes rest between blocks, except for case 3 who was unable to complete a full block. Blocks were performed in which the warning cue was either 100% or 50% informative of the subsequent imperative location. The cue in 50% blocks was therefore of no value in predicting the side of the eventual motor response, although, because of the fixed cue-go interval, it still provided information on the temporal expectancy of the imperative stimulus. The order of presentation of 100% and 50% blocks was randomized after a short practice run of 10 trials. Subjects were informed about the probability of cue-go signal congruency prior to each block. In pilot recordings on four healthy subjects, the appearance of the warning cue and go signals did not elicit a saccadic eye-movement, as detected by extra-oculography (using methods described in Brown and Day, 1997).

In all patients the blocks of trials were performed after the patient had been off medication overnight (OFF). Blocks were also performed about one hour after the patient had taken levodopa 200 mg, given in combination with a decarboxylase inhibitor (ON). In six patients OFF and ON recordings were performed on the same day.

4.1.3 Analysis

Recorded activity was digitally pass band filtered in Spike2 (section 2.3.2). The resultant activity was then squared giving a dynamic measure of frequency band power. Activity in the spectral peak in the lower beta band (at around 15-20 Hz) was selected for filtering¹⁶, as this was the peak that invariably had maximum amplitude above 12 Hz and was present in all subjects. The choice of this band was further justified because this activity displays significant coherence with widespread cortical areas and GPi (chapter 3, Brown et al, 2001) and LFP activity in this range has been demonstrated representative of synchronous single unit activity in STN (Levy et al., 2002). Table 4.1 gives the exact bands present in each patient, as determined by peaks in fast Fourier transform derived spectra of LFP activity.

Squared filtered activity was averaged across trials of the same warning cue laterality, aligned to the warning cue onset. Data segments were averaged from a period 3 s prior to warning cue onset to 2 s post. Trials in which the patient failed to respond to the go signal, responded with a lag of greater than 1.5 s, or responded incorrectly or prematurely were excluded and underwent no further analysis. Similarly trials corrupted by movement artefact or mains spikes were withdrawn. The timing of any deviation in averaged beta band power was determined by change-point analysis, using commercial software (Change-Point Analyser 2.0 shareware program, Taylor Enterprises Inc., Illinois, USA, <http://www.variation.com>) and techniques described previously (Cassidy et al., 2002). Significance of changes was

¹⁶ This was done on a case by case basis the exact bands chosen are detailed in Table 4.1, power spectral peaks, beta(1) bands

determined by control charting. Control charts consisted of plots of averaged beta band power smoothed with a moving 250ms width window centered at the given sample point. Control limits were determined to give the maximum range over which values were expected to vary (with 95% probability), assuming no change had occurred. The control period was from 3 s to 0 s prior to warning cue presentation. Change-point analysis iteratively uses a combination of time varying cumulative sum charts (cusums) and bootstrapping to detect changes and is more sensitive to change than control charting (Taylor, 2000). For this analysis cusums were determined by plotting the sequentially summed deviation of each spectrum from the average determined for the whole record segment (total of 5s). 10,000 bootstraps were performed in each test and only changes with probabilities of >95% were considered. Band power was averaged with a 50ms window prior to analysis¹⁷. Upward gradients in cusums denote an increase in power (synchronization) whereas downward gradients denote a decrease in power (desynchronization). In the cusums illustrated in Figs 4 and 5 power changes are given relative to the pre-cue mean rather than the power averaged for the whole record.

First it was confirmed that deviations in mean power detected by change point analysis were more likely to occur following the warning cue than in the pre-cue control period. Thereafter the character of cue-related responses was determined. However, as evident from Fig 4.3, change point analysis was a very sensitive detector of change, and to limit the detection of spurious (i.e. non-cue related) changes more stringent criteria, based on control charts alone were used. Short latency synchronizations (SLS, i.e. power increases, see results) were defined from control charts as periods of deviation from the control period mean during which activity equaled or exceeded the upper 95% confidence limit for 50ms, with maximum deviation during the period 0 to 200ms post cue. Long latency desynchronizations (LLD, i.e. power decreases, see results) were defined as deviations during which activity equaled or was lower than the lower 95% confidence limit for 50ms, with maximum deviation within the first 1000ms post cue.

¹⁷ n.b. Smoothing was not performed twice on the data, control charting and change point analysis were performed independently upon averaged beta band power data.

The frequencies of SLS and LLD were compared under different conditions by contingency (chi-square) tables. The amplitude of SLS and LLD were quantified by calculating the mean activity over the duration of the SLS or LLD response as a percentage of mean activity in the period one second prior to warning cue presentation. Where SLS or LLD components were present in a given block of trials paired comparisons were made with equivalent responses or activity during the same period with cues of opposing laterality or contrasting cue-go congruence in the same STN e.g. responses to left cue compared with right cue, responses to 100% cue-go congruence compared with 50% cue-go congruence. Note all comparisons (e.g. between informative and uninformative cues, between on and off drugs and between ipsilateral and contralateral cues) were fixed to the same contact pair of a given macroelectrode within a subject so that variance in positioning between macroelectrodes should have had limited effects on the results. However, the latter was the reason why comparisons between macroelectrodes ipsilateral and contralateral to the active hand were avoided.

Comparisons were performed using two-tailed *t*-tests. Thus the core comparisons were [1] ON vs OFF combining 100% and 50% cue-go congruence and ipsilateral and contralateral conditions in all patients, [2] 100% vs 50% cue-go congruence combining ON and OFF drug conditions and ipsilateral and contralateral pointing warning cues in all patients and [3] ipsilateral vs contralateral pointing warning cue combining ON and OFF and 100% and 50% cue-go congruence conditions in all patients. Frequent absent values (where no SLS or LLD responses occurred within paired data) precluded the use of a general linear model. Chi-square and *t*-tests were corrected for multiple comparisons by the Bonferroni technique. Behavioral results were analyzed by a repeated measures general linear model (GLM). No compensation for non-sphericity was necessary.

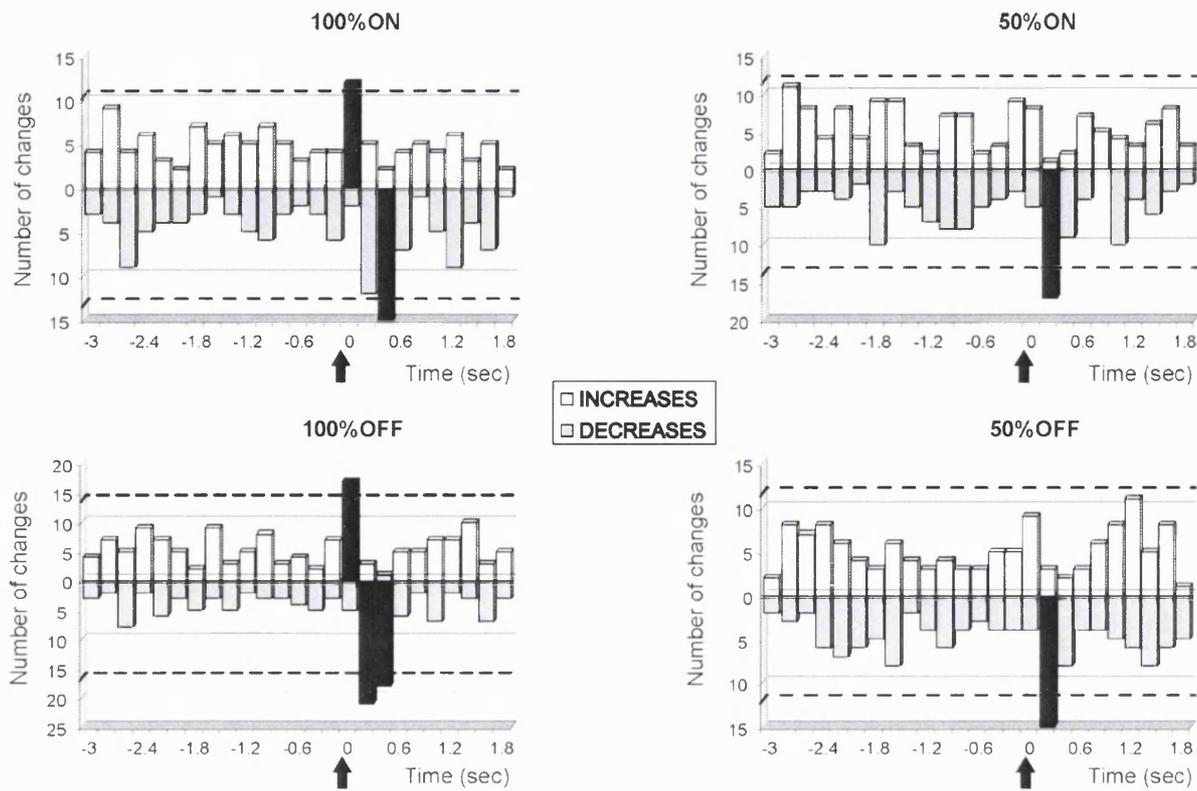


Fig. 4.3. Increases and decreases in average activity in successive 200 ms epochs determined by change point analysis of LFP power in the low beta band summated across all subjects in ON/OFF conditions and with 100%/50% predictive cues. Changes are presented for the period 3 seconds prior to warning cue presentation (arrow) until 2 seconds post. Epochs containing significantly high numbers of changes (greater than 99% confidence limits from mean) are coloured black, 99% confidence limits are indicated by perforated lines. An increased probability of higher beta power is observed within 200 ms of presenting highly predictive warning cues in contrast to poorly predictive cues. An increased probability of decreased power occurs in subsequent epochs irrespective of cue-go congruency, although this lasts longer following predictive cues.

4.2 Results

4.2.1 Behavioral measurements

All 9 cases performed both 100% and 50% visual cue-go compatibility trials. All but 2 of the subjects (cases 1 and 6) showed increased reaction times in 50% trials to both right and left cues. Across the group reaction times were significantly increased in 50% trials relative to 100% (GLM with main effects drug state [on/off medication], hand [left/right] and compatibility [100%/50%]: $F[1,9] = 11.973$, $p < 0.01$) consistent with findings in previous studies (Stelmach et al, 1986; Jahanshahi et al, 1992; Brown et al, 1993; Gueye et al, 1998). The reaction time data are summarized in table 4.2. No significant effect of medication status or hand of response was apparent. In addition reaction times did not significantly differ between validly and non-validly cued 50% responses in the ON state (valid: 572 +/- 39, non-valid 560 +/- 46 $p > 0.05$). Fewer than 5% of trials involved premature responses, response failures (no response to the go signal or one with a lag of greater than 1.5 s) or incorrect responses, in keeping with other observations (Jahanshahi et al, 1992). As the incidence of errors was low and error trials were excluded from calculations, the reaction time (and LFP) findings were not confounded by differential error patterns in the different conditions.

	100% ON	50% ON	100% OFF	50% OFF
<i>Left response</i>	537 +/- 69 ms	598 +/- 56 ms	491 +/- 48 ms	581 +/- 51 ms
<i>Right response</i>	507 +/- 66 ms	578 +/- 61 ms	482 +/- 57 ms	560 +/- 53 ms

Table 4.2: Mean reaction time (+/- SEM) across the 9 patients.

4.1.2 Qualitative characteristics of STN warning cue related responses in the beta band

In blocks with 100% cue-go congruence the probability of increased beta band activity (synchronization) was elevated in the period 0 ms to 200 ms post cue across the 9 subjects, while the likelihood of decreases in beta activity (desynchronization) was greater in the period 200ms to 600ms post cue (Fig 4.3). In contrast, with 50% cue-go congruence there was no increased probability of increases in beta power at short latency although there was still an increased probability of power reduction at longer latency, albeit over a shorter period (Fig 4.3). Medication status appeared to have no effect over these features.

A distinction between short and long latency responses was supported not only by differences in sign (synchronization vs desynchronization) but also by differences in duration. SLS components were much briefer (Table 4.3). In individual records SLS and LLD components could occur in combination (Fig 4.4A) or alone (fig 4.4B and C). Responses were focal phenomena, maximal at the bipolar contact likely to be in STN, based on post-operative imaging and the clinical efficacy of deep brain stimulation. Fig 4.5A shows the SLS recorded at the different contact pairs in case 8. The response was greatest at contact 12, which post-operative MRI suggested covered the STN (Fig 4.1). Fig 4.5B is the LLD recorded at the different contact pairs in case 3. The LLD tended to be deeper and more prolonged at contact 12.

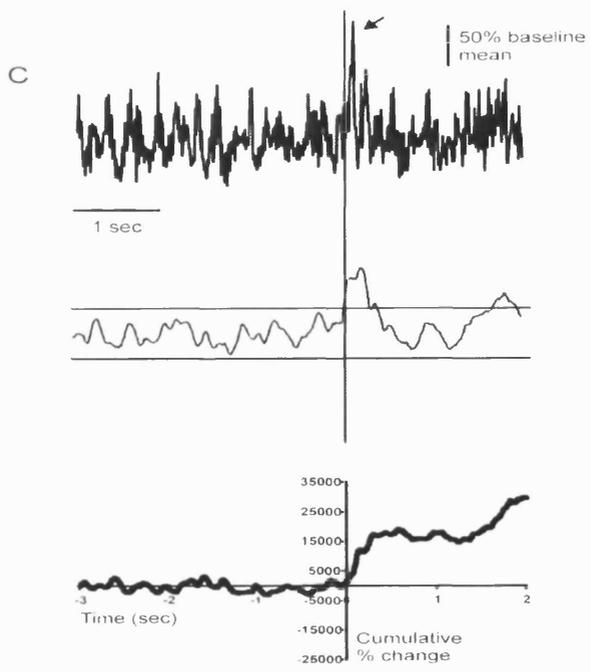
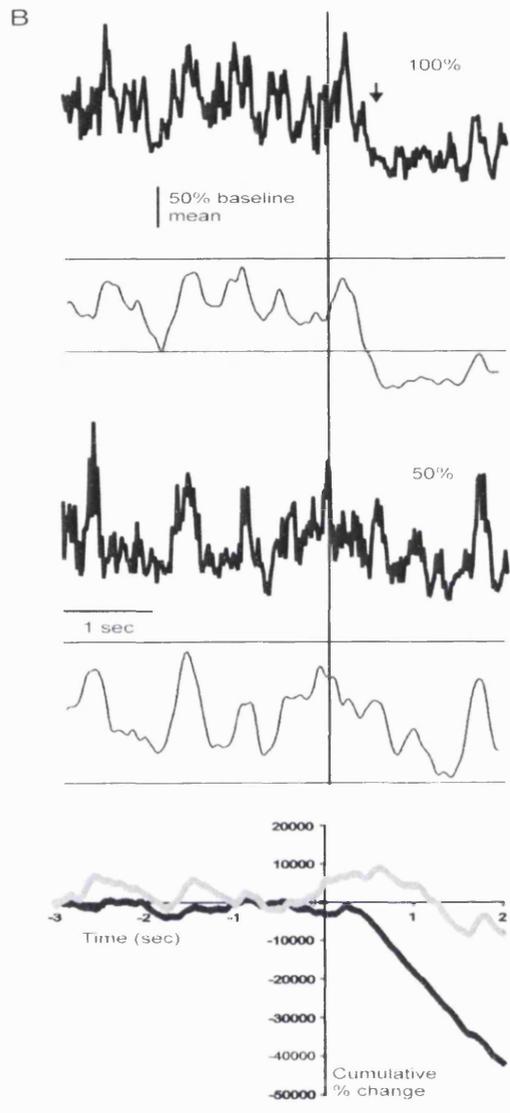
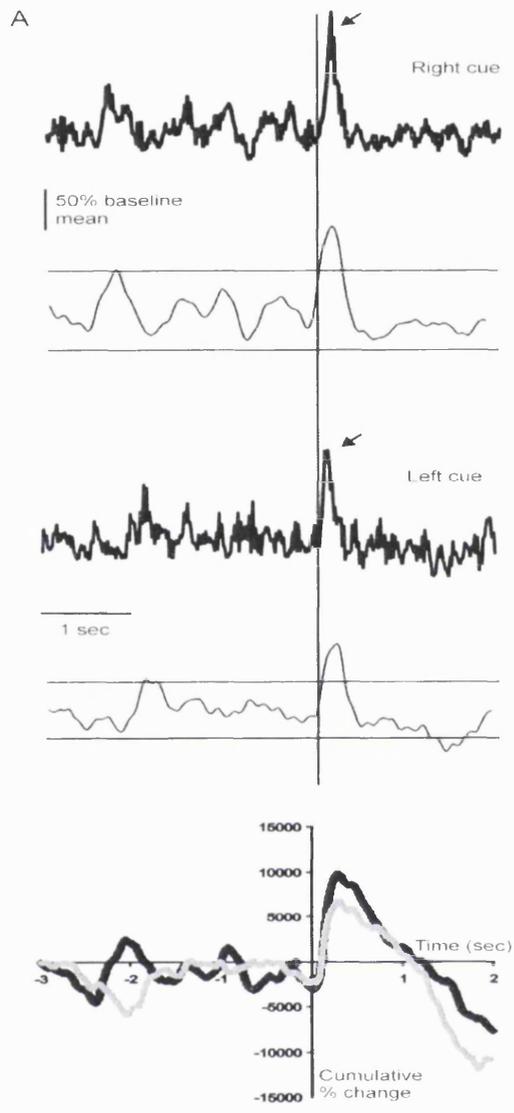


Fig. 4.4. Examples of the characteristic response components to warning cue presentation in the beta band activity of the LFP. Each trace is the average squared filtered activity from 3 s prior to 2 s post warning cue presentation. A) SLS (arrowed) in case 8, left STN, contralateral and ipsilateral cues, 100% trials, OFF levodopa. B) LLD (arrowed) in case 7, right STN, contralateral cues, both 100% and 50% trials, ON levodopa. C) SLS (arrowed) in case 9, right STN, ipsilateral cues, 100 % trials, ON levodopa. In each part the squared filtered data are shown on top, vertical lines indicate warning cue onset. Below these are the derived control charts smoothed using a 250ms moving window centred at the given sample point and at the bottom are the normalised cusums in percentage difference from the mean showing the cumulative deviations of activity from the baseline mean taken from -3 to 0 s. Horizontal lines represent 95% confidence limits on the control charts. Change point analysis was used to determine timings of change and control charts their significance. Upward gradients in cusums denote an increase in power (synchronization) whereas downward gradients denote a decrease in power (desynchronization) relative to baseline. The grey lines in A and B are the ipsilateral and 50% responses, respectively. A shows that there is little difference in the SLS response to warning cues that point contralateral (right) or ipsilateral (left) to the recorded STN. Note how the cusum in A shows that the SLS (upward gradient) is followed by a more prolonged reduction in power (downward gradient) not readily apparent in the control chart. In the 100% cue-go compatibility condition illustrated in B the desynchronization is greater than in A (steeper downward gradient of the black line in the cusum) and can be seen in the respective control chart. There is no significant power change within 1s of the cue in the 50% condition (note more-or-less flat grey line in cusum in B).

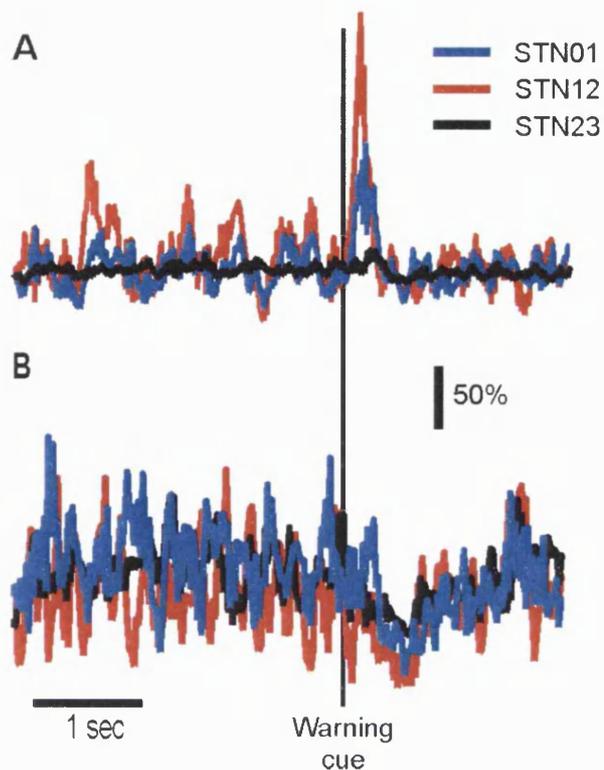


Fig. 4.5. Example of the focal nature of responses. Each trace is the average squared filtered activity. A) SLS in case 8 (left STN, 100% trials, ipsilateral cue, OFF levodopa). B) LLD in case 3 (right STN, 100% trials, ipsilateral cue, OFF levodopa). Recordings derived from the adjacent 3 bipoles of the respective electrode have been overlaid (01,12,23). Note that the SLS and LLD are biggest at contact pair 12 (which in case 8 is the level imaged in fig 1).

4.2.3 Quantitative characteristics of STN warning cue related responses in the beta band

SLS responses were more common in 100% cue blocks¹⁸ (n=21) than 50% (n=12), but neither this difference nor that in frequency between OFF and ON states (OFF=17, ON=16) or between ipsilateral and contralateral pointing warning cues (ipsi=14, contra=19) were significant after correction for multiple comparisons. Across subjects the magnitude of SLS responses was greater in 100% blocks than 50% blocks (137.8 ± 6.15 % background vs 116.5 ± 6.8 % background, $p=0.027$). No magnitude differences were noted with respect to comparisons of ipsilateral vs contralateral warning cues or OFF vs ON medication.

¹⁸ Each condition 100%, 50%, ON, OFF, ipsi, and contra, numbered a total of 72 blocks, all bracketed *n* numbers may therefore be considered of a total of 72 blocks.

LLD were observed in all cases except case 8, and were present both ON and OFF in all the remaining cases except case 4. Responses were more common in 100% cue blocks (n=37) than 50% (n=21, p=0.033), but no difference in response frequency was found between ON and OFF (OFF= 33, ON=25) or between ipsilateral and contralateral pointing warning cues (ipsi=24, contra=34). Across patients LLD response magnitude was also greater in 100% cue blocks than 50% (70.9 ± 3.3 % background vs 82.3 ± 3.8 % background, p=0.02), as illustrated in Fig 4.4b. No magnitude differences were noted with respect to a comparison of ipsilateral vs contralateral warning cues or OFF vs ON medication.

The results are summarized in Table 4.3. Cues predictive of a subsequent behaviourally relevant stimulus resulted in not only bigger SLS and LLD responses but more frequent LLD responses than with cues that did not predict the laterality of the imperative stimulus.

	<i>Mean onset latency (\pm SEM)</i>	<i>Mean duration (\pm SEM)</i>	<i>Magnitude of response</i>	<i>Frequency of response</i>	<i>Effect of cue direction</i>	<i>Effect of levodopa</i>
<i>SLS (n=33)</i>	101 \pm 12 ms	246 \pm 35 ms	100%>50%	100%=50%	None	None
<i>LLD (n=58)</i>	340 \pm 19 ms	884 \pm 62 ms	100%>50%	100%>50%	None	None

Table 4.3: Summary of the character of responses to warning cues in the 9 patients

4.3 Discussion

On the basis of the results presented here several properties of STN LFP oscillations are apparent. Firstly, they are not specifically linked to movement performance, with beta oscillation modulation occurring after cues potentially informative of subsequent requests for movement, seconds before any movement performance. Secondly, though warning cue responses appear most frequently to be manifest as suppressions of beta band oscillations at latencies of several hundred milliseconds, a much shorter latency and duration increase of oscillation may also occur. These two components appear capable of occurring together or independently. Thirdly, irrespective of the type of response, the magnitude of responses to warning cues appears dependent to some degree upon their saliency - more informative cues resulting in greater average oscillation suppression.

None of these factors was affected by dopamine status in the present investigation, though it should be noted that dopamine also effected no change in reaction times. The experimental protocol used does not however exclude the effect of dopaminergic activity upon cue related changes in the STN region under any circumstances. A long cue-go interval was used, whereas the prolongation of cued reaction times tends to be only seen with shorter cue-go intervals in parkinsonian patients (Jahanshahi et al, 1992; Yamaguchi and Kobayashi, 1998). Several other factors may also have obscured a dopaminergic effect. These include microlesional effects of electrode implantation (including the effects of local oedema), the use of a standard 200 mg dose of levodopa, variable responses to medication (see Table 1) and confounding fatigue related effects, given that six patients were recorded off then on medication on the same day. Issues of dopamine responsiveness to one side, what is the significance of the beta modulations described, and how might they be generated?

4.3.1 The significance of changes in beta power activity following cues

The same probability that influenced power changes in the beta band, influenced reaction time. The changes in the beta band may therefore implicate the region of the STN in the exploitation of the information provided by predictive cues in humans. This is supported by the observed impairment of response time in a variant of the present paradigm performed in rats with STN lesions (Baunez et al, 2001). It is of further interest to note that the induced deficit appears specific to cues allowing selection since no impairment is observed in simple reaction tasks where no selective element is involved (Phillips and Brown, 2000; Baunez et al, 2001).

Although LLD have been observed during simple cued reaction time tasks (Cassidy et al, 2002), the observed dependence of the SLS and LLD cue related changes on cue-go compatibility in the present paradigm implies that changes were not merely nonspecific alerting responses to visual input, but required pattern recognition linked to relevance. The use of predictive information as evidenced by cue saliency dependent changes in beta power could have lead to behavioural advantage in two ways. First, LFP power changes in STN may have been related to overt or covert shifts in visuospatial attention, that may have improved the detection of the subsequent imperative stimuli and lead to the shortening of reaction time with reliable cues (Posner et al, 1980). Such shifts in visuospatial attention would have been more likely following laterality cues that were relevant to the task, as in the 100% cue-go compatibility trials. Overt visuospatial shifts involving saccadic eye movements may reasonably be excluded as explanations of cue responses both due to the small visual angle subtended by the fixation point and imperative cue, and secondly because of the lack of eye movements in pilot investigations. Nevertheless, the absence of differences in reaction time between validly and non-validly cued 50% responses means that covert shifts in visuospatial attention remain a possibility in the present paradigm, particularly as impairment in covert visuospatial attention has been reported in PD patients, implicating both the basal ganglia and the dopaminergic system in this function (Yamaguchi and Kobayashi, 1998). Alternatively, or in addition, cue-related power changes with salient cues may have been related to some degree of preparation for movement, prior to the imperative stimulus (Stelmach et al, 1986; Jahanshahi et al, 1992). Studies in rats suggest that

the process whereby the early preparation of movement is dependent on the behavioural relevance of cues is relatively unaffected by dopaminergic stimulation (Brown and Robbins, 1991), as here. Note that in this study patients were given explicit information about the nature of cue-go compatibility. Other studies suggest that the dopaminergic system is intimately involved where reward driven learning is required (Waelti et al, 2001).

Several factors point to the fact that the SLS and LLD components may have different functions related to the behavioural exploitation of relevant cues. They differed in latency, spectral effect and could appear in isolation in different recordings. Further investigation is necessary to determine the function of the SLS and LLD components.

4.3.2 Mechanisms of changes in beta power activity

The premise that LFP changes reflected synchronous activity in neurons within the basal ganglia is supported by the similarity between the cue related responses identified here and those demonstrated in a study of single unit discharge in substantia nigra pars reticulata. In a preselection period equivalent to the cue-go interval, Basso and Wurtz (2002) demonstrated a pause in single unit activity in rhesus monkeys that was greatest when the warning cue was most informative about the imperative target stimulus, though this was not investigated further in the context of synchronous activity. Furthermore, over the same period pauses were bilaterally symmetrical, similar to the lack of lateralization of the LLD cue related feature in the patients, though subsequent selection and movement related responses were lateralizing. Their single cue preselection stimulus, equivalent to the warning cue, may also have elicited a brief increase in firing rate just prior to the pause, paralleling the SLS (see their figure 4, for example).

How are single unit changes such as those reported by Basso and Wurtz (2002) translated into the synchronous activity that determines LFP changes? Mammalian STN possesses intranuclear axon collaterals that may be extensive (Kita et al, 1983, Iwahori et al, 1978). Computer modelling of STN dynamics assuming similar high

levels of intranuclear connectivity predict that the STN may display bistable behaviour with recruitment of large populations of STN neurons (Gillies and Willshaw, 1998). How may this behaviour be locked to the warning cue in this paradigm? Stimulation of both somatomotor and prefrontal cortex produce a characteristic response pattern in STN units, consisting of excitatory peaks, separated by a period of inhibition, followed by prolonged inhibition (Maurice et al, 1998; Nambu et al, 2000; Nambu et al, 2002). The late inhibition lasts several hundred milliseconds, in line with the LLD. The possibility therefore exists that the prolonged desynchronizations of the oscillatory activity in the beta band are the result of input from the cerebral cortex, in keeping with the phase analyses in Chapter 3 that demonstrate that STN activity in this band is locked to, but generally follows, cortical activity. Similarly, it is noteworthy that the cortical lateralized readiness potential, which first becomes significant around 200 ms post warning cues (Wascher et al, 1997), precedes the LLD in STN.

On the other hand a synchronized response comparable to the early excitatory activity following corticosubthalamalamic inputs seems an inadequate explanation for the SLS. Thus the SLS precedes the appearance of the cortical attention shift-related negativity and the cortical lateralized readiness potential, which do not become significant until 200 ms or more post warning cues, with extra delays likely in parkinsonian patients (Wascher et al, 1997; Yamaguchi and Kobayashi, 1998). The temporal characteristics of the SLS component argue that it may be a feature of the subcortical processing of cue related activity.

4.4 Outstanding issues

The electrical responses to behavioural cues recorded via STN DBEs and represented here are exclusively observed at the level of the LFP. The physiology at a cellular level of these responses is however fundamental to a comprehensive understanding of their significance. Several questions are apparent:

- 1) How are basal ganglia LFP oscillations generated at a neuronal level?
- 2) What is the neuronal origin of SLS and LLD components, and how are they related?
- 3) How is the response bias in the magnitude of average power modulations represented at a neuronal level?

The answers to these questions are of importance because they at once clarify the anatomical origin of LFP activity recorded via the STN DBE and may allow their creation to be modelled in a manner analogous to that of the human EEG. Beyond this they may also give insight into the potentially complex relationships that may exist between single unit activity, LFP and behaviour. In section 1.5.3 work was cited that suggested the capacity of motor neuronal subpopulations to display oscillatory firing characteristics in tandem with LFP beta oscillations, and to entrain spinal neurons that they project to. Work has already been reported in monkey striatum suggesting a similar capacity of the neuronal population there (Courtemanche et al, 2003), is this also true of activity in the STN? Furthermore, is it the case that LFP oscillations, however generated, are associated with the entrainment of local neuronal subpopulations? Simultaneous recording of field potential activity and single unit activity in healthy and PD model STN of rat or monkey would clarify this matter by allowing the presentation of LFP phase locked unit firing histograms. Such histograms may demonstrate a) if there is an increased tendency of some neurons in STN to fire at a particular phase of LFP oscillation and b) whether a proportion of the neuronal population fire a short duration after peaks (or troughs) in the LFP oscillatory cycle. The observation of synchronous firing, or membrane potential transitions, with peaks or troughs in the LFP would be consistent with a role of single units in LFP generation. In contrast, the occurrence of such activity with a consistent short lag may be indicative of entrainment from an afferent source. The presence of both might suggest that a local oscillatory 'generator' was entraining other local neurons. The ability of local neuronal populations in the nuclei of the basal ganglia to become entrained to LFP oscillatory activity, particularly in the beta band may be of great importance, in light of the noticeable tendency of task-relevant modulations in

activity to occur in the absence of such oscillatory periods (section 1.5.3). PD, which appears to be a state in which beta LFP oscillations in STN and GPi (and possibly elsewhere in the basal ganglia) are particularly prevalent (section 1.6.2), may well represent the locking of task related neurons into inappropriate oscillatory behaviour. The neuronal basis of the LLD and SLS responses and their magnitude then also appear important since these behavioural modulations of beta LFP activity may well represent changes necessary for appropriate neuronal responses in STN.

- 4) Where dopamine is associated with improvements in reaction times are there concomitant changes in the cue related oscillatory responses?

Although the SLS and LLD responses described displayed evidence of relevant cue bias to their responses, dopamine medication state was not a significant modifier. This may well have been because dopamine medication did not result in any improvement in task performance. It would however be of interest to observe whether an alteration in the character, frequency, relative frequency or magnitude of these response components occurs under circumstances where patient medication with dopamine is associated with a strong behavioural advantage in the protocols used here. In combination with greater insight into the means of generation of these responses such information would again give insight into the mechanisms underlying parkinsonian pathophysiology and allow the consideration of potential mechanisms of intervening in the treatment of the disorder.

4.5 Summary

- Modulations of beta oscillations in the parkinsonian STN are not linked exclusively to the performance of movement.
- Cue-related beta power modulation is influenced by the significance of the cue.
- Cue-related beta responses may display maximal response magnitude to central bipoles of STN DBE
- The behavioural bias in beta power responses to the choice reaction task, in the context of lesion animal experimental work, suggests that the STN may to some extent be involved in the exploitation of predictive cues.

CHAPTER V

CORRELATION BETWEEN LOCAL FIELD POTENTIAL OSCILLATIONS AND BEHAVIOURAL RESPONSE

The suppression of activity in both alpha and beta bands of primate sensorimotor cortex, parietal cortex, thalamus and cerebellum in association with movement has been detailed in section 1.5. That suppression precedes movement, involves motor task related structures and may be induced by cues informative of subsequent movement suggests that it may reflect neuronal population changes associated with movement preparation or execution. Speculation as to the exact role played by oscillatory activity in such preparation or execution however is broadly divided into two seemingly incompatible camps. Those suggesting a facilitatory role, either in the perception of relevant afferent stimuli (Nicolelis and Fanselow, 2002; Semba et al, 1980; Ahissar, 1998), the optimization of efferent output (Baker et al, 1999) or as a general attentional correlate (Murthy and Fetz, 1996); and those implying a passive inhibitory role, and promoting an 'idling' population inactivity (Pfurtscheller, 1992). Indeed, the variable relationship observed between oscillatory activities, motor behaviour and task related single unit activity (section 1.5.2) has resulted in speculation concerning not only its role, but whether it has functional significance at all in the motor system (Fetz et al, 2000).

In Chapter 3, it has been demonstrated that similar oscillations in STN activity display functional connectivity with their cortical analogues. Furthermore, in addition to the established suppression of this activity with self paced and externally triggered movement illustrated in section 1.5.4, Chapter 4 has shown that such suppression may occur merely with cues informative of subsequent movement. As such this pattern of modulation cannot be viewed as exclusively related to a given movement. Indeed prior attempts in cortex to establish behavioural associations of beta band oscillation with movement have failed to show any consistent relationship (section 1.5.2). The characteristic pattern of suppression of oscillation throughout task relevant cortical and subcortical regions suggests however that oscillation

suppression may have far greater significance than oscillation occurrence, reflecting neuronal population changes necessary for appropriate task related information processing and transmission

Here the hypothesis that oscillatory activity between 8 and 30 Hz reflects a state in STN that limits information transmission has been tested by considering three fundamental predictions expected in a motor reaction task. Firstly, that high power during the usual period of oscillation suppression should be associated with slower reactions. Secondly, that a consistent relationship should exist between the onset of oscillation suppression and reaction times (RT); and thirdly, that with increased processing requirements, durations of suppression should be increased. A relationship between oscillatory activity in this band and behaviour is observed in single-trial data of STN LFPs in parkinsonian subjects that is neither consistent with simple facilitation nor idling, but with the active inhibition of information transmission.

5.1 Methods

5.1.1 Subjects

This study was performed using data derived from the same patient population used in Chapter 4. As such clinical details, peri-operative imaging and STN targeting are detailed there.

5.1.2 Protocol

Data used involved the same experimental paradigm as described in section 4.1.2. Behavioural advantage was derived from the informative warning cue in 21/36 block pairs (mean RT, 100%: - 485 +/- 37 ms; 50%: - 623 +/- 40 ms).

5.1.3 Analysis

5.1.3.1 Time-frequency power distributions

Continuous wavelet transformation was the primary tool used to derive time-frequency distributions of the LFPs. The localization of power modulations in the region of the STN has been previously demonstrated in Chapter 4, and here those contacts showing the greatest power modulation in this former study were considered 'optimal bipoles' and used for analysis. Recorded LFP activity from the optimal bipole of each STN was segmented into single trials, time locked to the presentation of go cues and time of button press. Trials ran from 6 sec prior to 4 sec post go cue presentation or button press such that there was no overlapping of trial data. For the purpose of this analysis, no separation of ipsilateral and contralateral responses to the given STN was made and only trials in which subjects successfully responded to the imperative cue were considered. Trial data were downsampled to 180 Hz and wavelet coefficients were then derived as described in section 2.3.3.

5.1.3.2 Single trial oscillation suppression onset latency

Single trial oscillation suppression onset latency was defined as a reduction of oscillation power of at least 30% of mean control period activity for a period of at least 250 ms, the control period being defined as activity during the 3 seconds prior to warning-cue presentation. Trials were categorized as pre-cue suppression, post-cue suppression or no suppression, based on the timing of the last episode of suppression prior to the button press and relative to the go-cue. Hence, no suppression trials included trials with little or no oscillation power throughout and those in which suppression may have occurred after the reaction time.

5.1.3.3 Correlation of oscillation suppression onset and power with reaction time

Correlation coefficients were calculated between single trial oscillation suppression onset times and reaction times in each block of trials, for both STN in all subjects. Resultant r values were tested for significance with an $n-2$, t -test, where n was the number of trials at a significance level of 0.05 and $n \geq 10$,

$$t = r \sqrt{\frac{(n-2)}{1-r^2}} \quad \text{Eqn 5.1}$$

Similarly, correlation coefficients were calculated between averaged wavelet power in moving windows of 200ms at each sample point and reaction time at each sample point and scaling to derive frequency correlation maps. All correlations underwent Fisher's z -transformation to approximate Normal distribution and were two-tailed z -tested for significance against the correlation distribution derived for their given scaling at a 0.005 significance level. Significant event related frequency correlation was considered that occurring within the band examined within 1.5 second of go cue presentation. All correlations detected that resulted from post-movement oscillatory activity on examination of single trial data were excluded. For the purpose of group analysis, frequency-time correlation distributions were averaged across all nine subjects prior to significance testing. Significant differences between means were tested via a general linear model (GLM) for multivariate analysis or paired two-tailed t -test for paired comparisons. All means are presented +/- standard error of the mean (sem).

5.2 Results

LFPs were recorded post-operatively from both macroelectrodes in the interval between their implantation and subsequent connection to the subcutaneous stimulator, with patients both on and off their usual dopaminergic medication. Dynamic estimates of single trial power were derived from the squared wavelet

decomposition coefficients in the 8-30 Hz range. Spectral content at the frequency of peak power modulation in each trial was then aligned to imperative stimulus presentation and rastered according to trial order. Oscillatory activity was characterized by episodic bursts that were suppressed after presentation of the go cue (Fig. 5.1A); it is this suppression of oscillatory bursts in individual trials that appears responsible for modulations of power post stimulus and prior to movement, previously reported in power using averaging techniques. Trials were then sorted on the basis of reaction time to button press response. These sorted trials consistently revealed that though the occurrence of oscillation bursts was variable in the post imperative stimulus period, the latency to onset of power suppression after the cue increased as reaction time increased, so that power suppression gave the appearance of a sloping edge preceding reaction time (Fig. 5.1B).

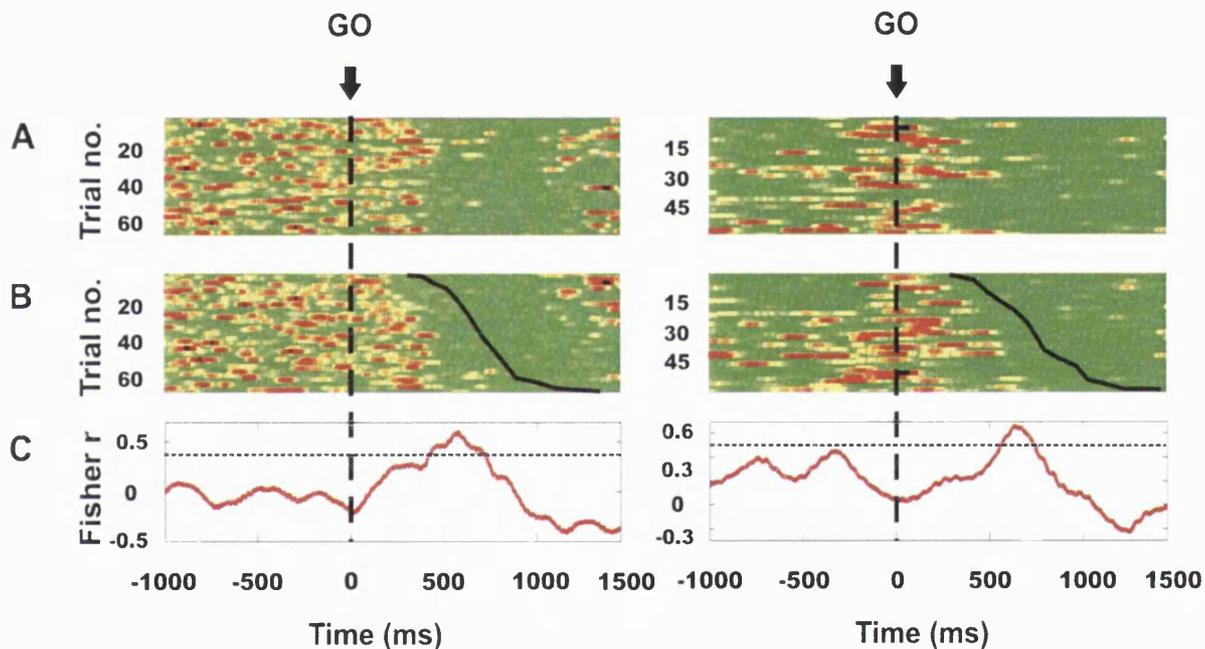


Fig. 5.1. Examples of the relationship between STN LFP power and reaction time across single trials, taken from two parkinsonian patients. (A) Single trials of power at frequency of maximal modulation in the order performed, power ranges from zero – green, to high - red. (B) The same data sorted by reaction time (fastest - top, slowest - bottom) with sorted reaction times superimposed in black. Left column - case 1, 100% OFF RSTN (18 Hz.), Right column - case 3, 50% ON RSTN (9 Hz). (C) Associated Fisher's transformed linear correlation of 200ms windowed power and reaction time (horizontal dashed line indicates the significance level $p < 0.005$. Left column peak $r = 0.59$, right column peak $r = 0.65$. Activity is characterized by episodic power fluctuations that are suppressed after go cue presentation (dashed vertical line). Suppression of higher power fluctuations is observed to occur earlier in faster trials.

5.2.1 Correlations between oscillation power and reaction time

Initially, whether oscillatory activity during the usual suppression period after go-cue presentation was associated with slower reaction times was examined. Correlations between reaction time and power in the frequency range 8-30 Hz were calculated in moving windows of 200ms across trials and tested for significance in each STN separately for experimental blocks with 100% and 50% predictive warning cues (Fig. 5.2), repeated ON and OFF dopaminergic medication (58 +/- 4 trials per condition, range 21-136). Significant positive correlations were observed after go cue presentation in 30 of 72 blocks, -in at least one condition per subject except case 9 (8 of 18 - 100% OFF, 7 of 18 -100% ON, 5 of 18 - 50% OFF, 10 of 18 50% ON). Contrary to expectations if oscillatory activity was associated with the facilitation of the motor response, only four of the remaining blocks demonstrated negative correlations and the remainder no significant correlation. Average peak positive correlation frequency was 14.5 +/- 1.2 Hz and individual correlation frequencies were consistent with the dominant frequency of power suppression. Mean onset of significant positive correlations was 380 +/- 30 ms post presentation with mean peak correlation 521 +/- 28 ms. The majority of significant correlation onsets preceded mean reaction times (26 of 30) and a significant difference was observed between the two (paired t-test, $p < 0.0001$; $df = 29$). Corroboration of the significance of single patient findings was sought by examination of averaged frequency-time correlation distributions across the whole subject population. Group results were averaged across both right and left STN. All imperative cue aligned conditions displayed significant positive correlations (Fig. 5.3). Similarly, significant correlations were also present when left and right STN were examined independently. Contrary to expectations if oscillatory activity in the STN was associated with improved stimulus detection, no significant negative correlations were noted at the time of cue presentation.

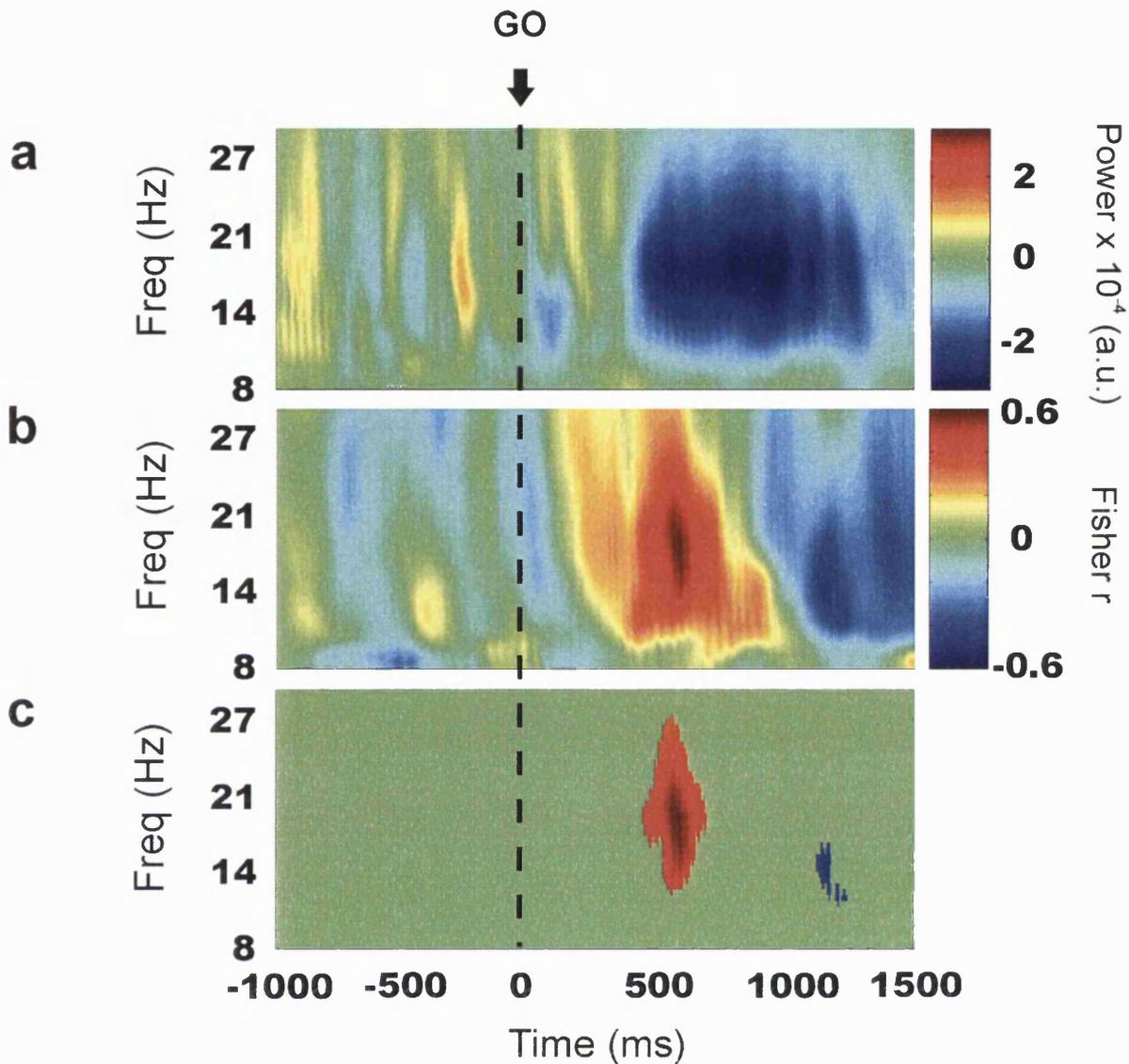


Fig. 5.2. Correlation analysis of LFP activity recorded from the right STN of case 1 (100% predictive warning cue, OFF medication, n=66). (a) Average power change after go cue presentation (dashed vertical line), demonstrates a cue related reduction of activity in the beta band. (b) Correlation of wavelet derived power and reaction time shows positive (red) correlation in the same frequency band during the modulation period (peak = 18 Hz), which is significant (c) after thresholding at $p < 0.005$.

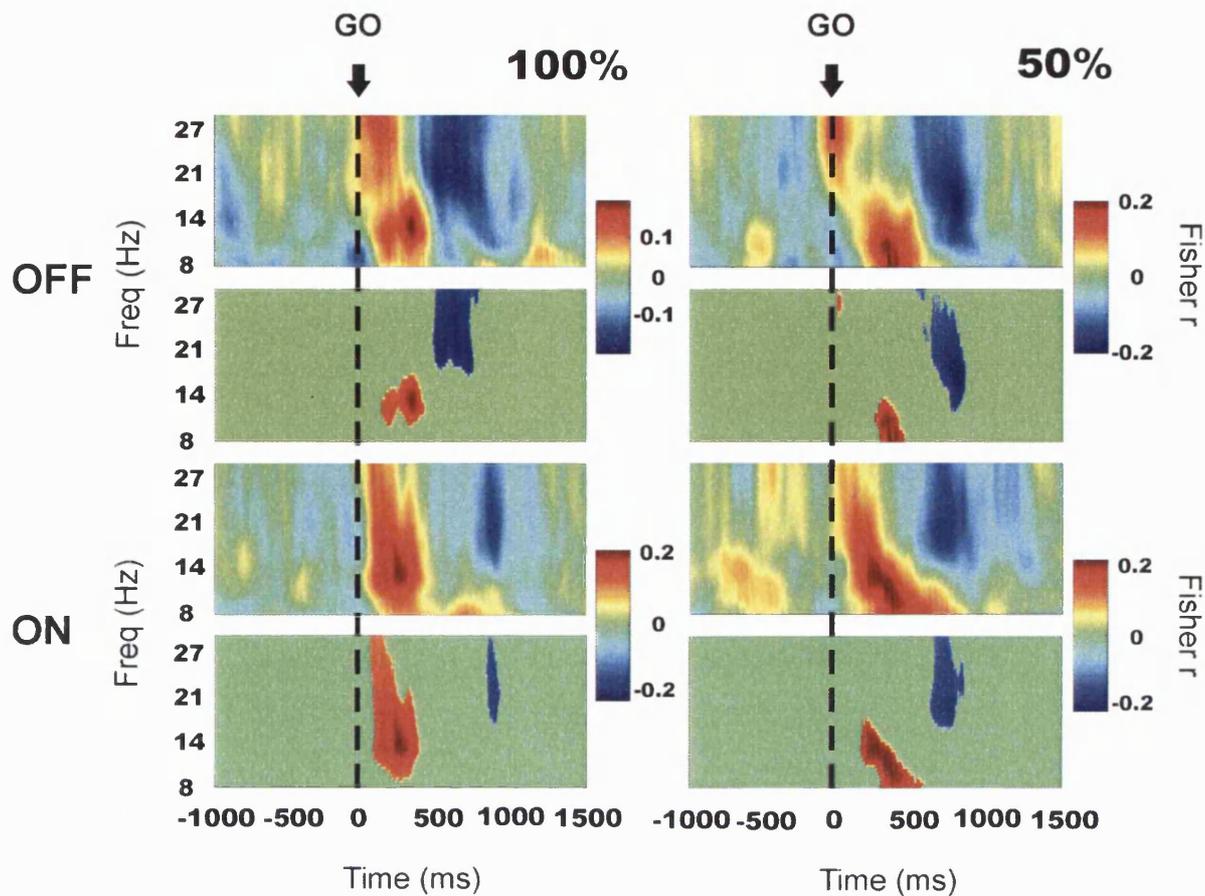


Fig. 5.3. Population averages of oscillation power correlations with reaction time (all 9 cases), in 100% and 50% conditions, with and without l-dopa medication. Positive correlations (red) are observed in all conditions after go cue presentation (dashed line). Late negative correlations resulted from an earlier recovery of oscillatory activity in faster trials. Average correlations threshold at $p < 0.005$ are shown beneath each figure.

5.2.2 Oscillation suppression and reaction time

Next, whether a consistent relationship existed between the onset of go-cue related¹⁹ oscillation suppression and reaction time was examined. Individual trials in each block were categorized as having either pre-go cue oscillation suppression, (mean 26 +/- 2 trials per block), post go-cue oscillation suppression, (mean 14 +/- 1 trials per block) or no oscillation suppression, (mean 17 +/- 1 trials per block) (i.e. no *change* in oscillation power though there may have been very low power) throughout trial. Correlation was investigated between pre-cue and post-cue suppression onset times and reaction times. In trials in which post go-cue suppression occurred, significant positive correlation was present in 30 of 72 blocks (demonstrated in Fig. 5.4 A, B) – again in at least one condition per subject except case 9 (9 of 18 - 100% OFF, 7 of 18 -100% ON, 7 of 18 - 50% OFF, 7 of 18 50% ON, $p < 0.05$). Mean post-cue suppression correlation strength was 0.68 +/- 0.03, and there was no significant difference between correlation strength in 100% v 50% blocks ($p = 0.89$; $df = 23$) or in ON v OFF ($p = 0.19$; $df = 27$). Of the remaining blocks, only one showed significant negative correlation, the remainder no correlation. In contrast, in trials where suppression preceded the go-cue, significant correlation was only present in 1 of 72 blocks and this was negative.

5.2.3 Oscillation suppression durations and processing demand

In Chapter 4 it was demonstrated in this subject population that greater average power suppression occurs after predictive *warning* cues (100%) than non-predictive (50%) and that 100% predictive cues are associated with faster reaction times, suggesting that suppression may be related to the derived behavioural benefit and therefore may be associated with information processing. If oscillation suppression is associated with a state in which information processing occurs one might also expect to see in individual trials, longer pre-reaction suppression after go cues where subjects were not able to pre-select the side of response (50%) compared to those in which they were (100%).

¹⁹ It should not be inferred from the use of the term 'go-cue related' that responses occurred with a fixed latency after go-cue presentation

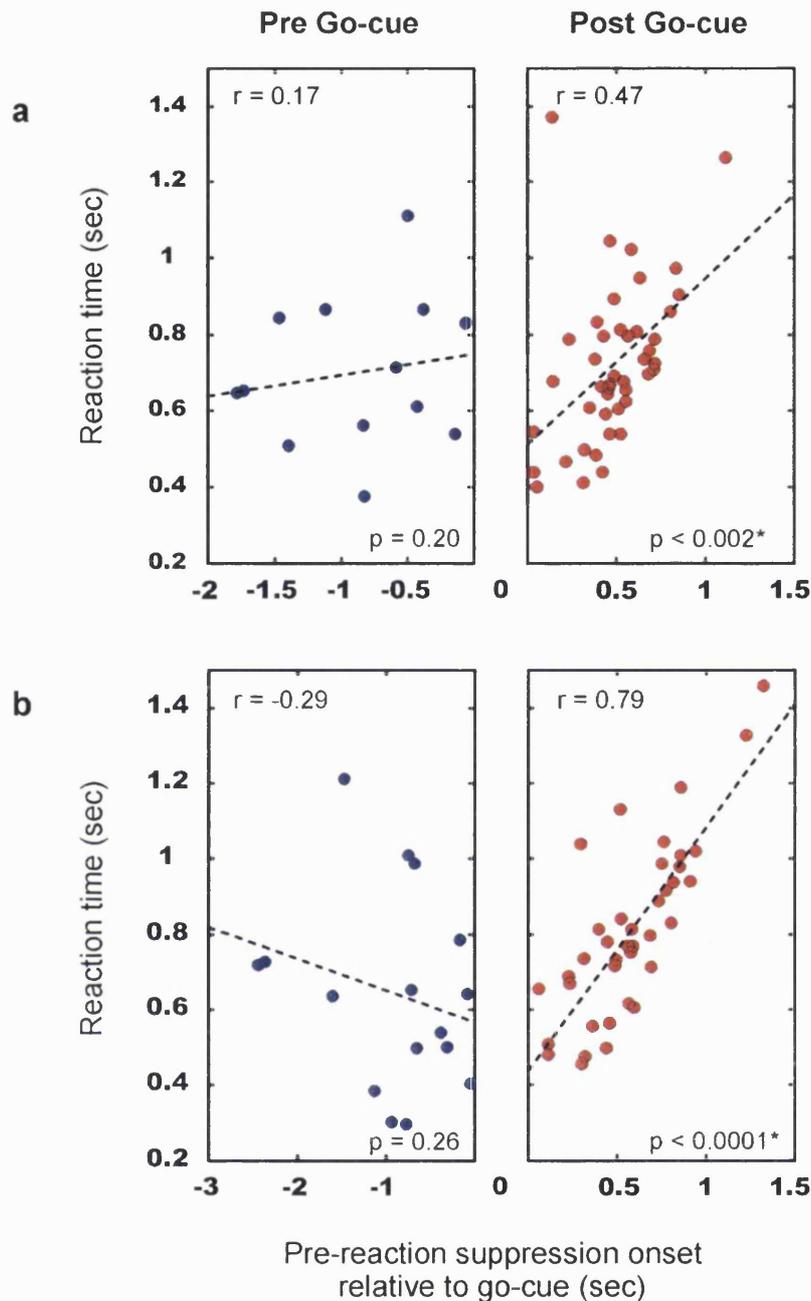


Fig. 5.4. Correlation analysis between onset of oscillation suppression time and reaction time. A significant relationship is observed across trials in which suppression succeeds go-cue presentation (red) as opposed to those in which suppression precedes go-cue presentation (blue). (a) Analysis in the same subjects and blocks as shown in Fig. 5.1 left column (pre: $n = 13$; post: $n = 44$), and (b) right column (pre: $n = 16$; post: $n = 39$) – dashed line represents the associated regression line, asterix denote significant correlations.

Average durations of oscillation suppression in post go-cue suppression trials, prior to button press response were compared in 100% (mean 15 +/- 2 trials per block) and 50% blocks (mean 17 +/- 2 trials per block) where subjects were faster with the 100% predictive warning cue, and therefore presumed to have gained advantage. Mean suppression durations were significantly longer where subjects were forced to select motor response post go cue (50% predictive trials), as opposed to allowing prior selection to occur (100% predictive trials) (Fig. 5.5). In contrast, across blocks where no behavioural advantage was derived from the warning cue, there was no significant difference between suppression durations (Fig. 5.5A). Similarly, in this cohort no improvement in RT was found following l-dopa treatment (Chapter 4), and no difference between suppression durations in the ON and OFF drug status.

5.3 Discussion

The stereotypical suppression of power < 30 Hz with a variety of behaviourally relevant stimuli, e.g. go cues, warning cues, self-paced movement and even nogo cues suggests a crude relationship with information transmission, as opposed to the subtle population coding (vector or otherwise) of movement parameters, where augmentation of synchrony and hence local LFP power might have been expected (Fries et al, 2001). Previous cortical investigations have failed to detect any consistent relationship between oscillatory activity in similar bands and motor behaviour. Here one may note a lack of advantage in the speed of motor responses to afferent stimuli with oscillatory activity, independent of dopaminergic state in the STN. Indeed the very opposite is seen with slower responses in the presence of continued oscillation. These observations seem inconsistent with the hypothesis that such oscillatory activity is either necessary or directly facilitatory for action in the motor system. On the other hand, it is observed that a consistent cue-related attenuation of oscillations occurs in this band prior to motor reactions. This appears more consistent with the oscillatory state in this band being actively inhibitory to motor preparation or execution than representative of an inactive idle state.

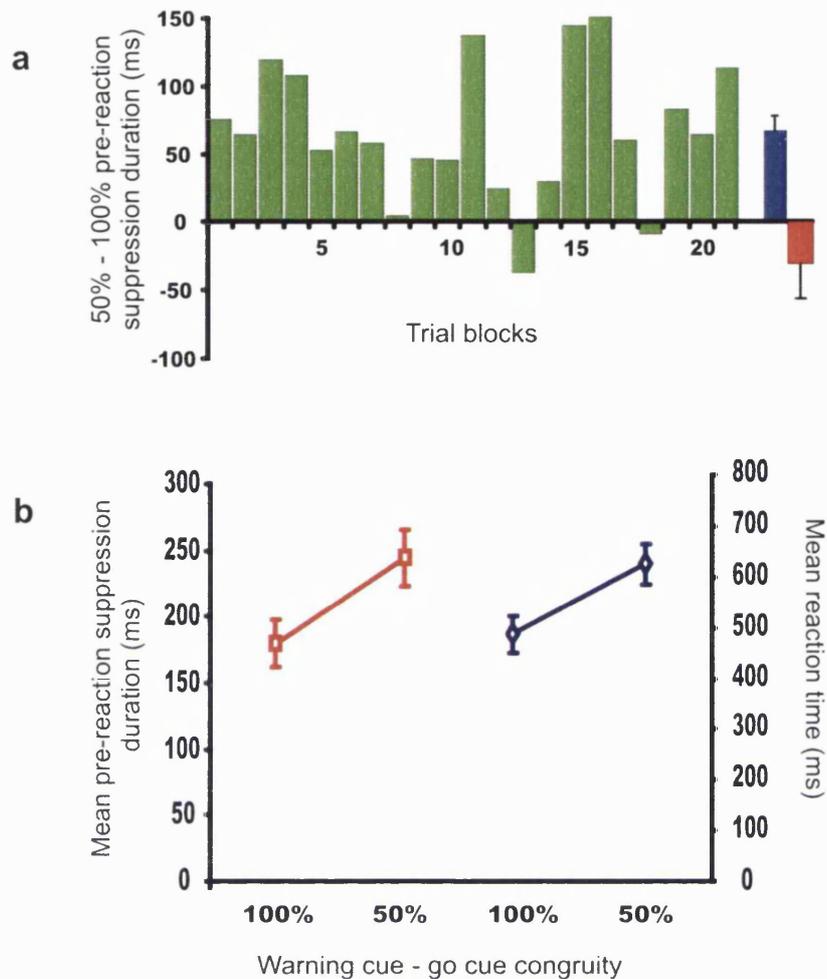


Fig. 5.5. Post go-cue, pre-reaction oscillation suppression durations vary with processing requirements. (a) Differences between post go-cue, pre-reaction oscillation suppression durations (green) in 50% and 100% conditions showed greater suppression durations in all but 2 blocks where behavioural advantage was derived. Blue block is mean difference in oscillation suppression duration between 50% and 100% blocks when behavioural advantage was derived. In contrast, where no advantage was derived there was no significant difference. Red block is mean difference in oscillation suppression duration between 50% and 100% blocks under these circumstances (mean suppression duration, 100%, 287 +/- 19 ms; 50% 255 +/- 17 ms; paired t-test, $p = 0.27$; $df = 12$). (b) Red: mean pre-reaction suppression durations were significantly longer with post-cue selection required (50% trials) as opposed to pre-cue (100% trials) (paired t-test, $p < 0.00005$; $df = 20$). Blue: mean cue related behavioural advantage in reaction time between 100% and 50% blocks (paired t-test, $p < 0.0003$; $df = 20$).

The observed increase of suppression duration with increased processing demand, i.e. the need to appropriately select the motor response, further links periods of suppressed oscillation to information processing. Together these observations may explain the 'complex dynamics during movement preparation and execution' previously commented upon (Pesaran et al, 2002) and described (section 1.5.2) in sub-gamma band cortical LFP oscillations.

5.3.1 LFP oscillations and information transmission

As discussed in section 1.2.1 the bursts of oscillatory 8-30 Hz activity reported here are likely to be a consequence of local synchronous neuronal population activity and suppression of oscillations therefore reductions in network synchrony²⁰ or network size. The consequences of weakly correlated or synchronous afferent activity on cortical neurons has been investigated over recent years in both theoretical models and single unit studies (Vreeswijk and Somplinsky, 1996; Stevens and Zador, 1998; Svirskis and Rinzel, 2000; Salinas and Sejnowski, 2000; Mazurak and Shadlen, 2002). These suggest that, under certain conditions, both synchrony and balanced excitatory and inhibitory neuronal input may significantly limit the capacity of neurons to transmit either rate or temporal codes. Support for this hypothesis in the motor system has come from recordings in motor and parietal cortex demonstrating that neurons with similar directional tuning and higher levels of synchrony have higher noise correlations (Lee et al, 1998) and more directly in the observed 'clamping' of motor cortical single unit firing rates during periods of 20-40 Hz oscillatory synchrony (Murthy and Fetz, 1996).

²⁰ Reductions in synchrony associated with oscillatory power decreases in a given frequency band might be expected to occur in the same frequency band. The possibility therefore exists that synchrony could increase in an alternate frequency with no net change. In the current work non-linear scaling of wavelet power analysis did not show any evidence of such a shift between 6 and 50 Hz. It would however be consistent with other observations to see high gamma increases (Ca. 70Hz). Nonetheless, it is oscillatory synchrony particularly in the alpha/beta band that in motor cortical regions and spinal cord appears associated with reduced task related modulation (section 1.5.3)

These cortical observations may have significance for basal ganglia activity. As in cortex, STN neurons display a great discrepancy between interspike interval variability, neuronal 'noisiness', when recorded in vivo as opposed to in vitro (Bevan and Wilson, 1999; Kreiss et al, 1997). It is significant levels of population synchrony and neuronal balance²¹ that have been proposed to explain this discrepancy (Vreeswijk and Somplinsky, 1996; Stevens and Zador, 1998; Svirskis and Rinzel, 2000; Salinas and Sejnowski, 2000). Thus the distributed synchrony associated with 8-30 Hz oscillatory activities in STN, may bias against processing through rate or temporal codes and thereby against novel information transmission. This appears consistent with the observed increase in oscillatory activity within the band considered here during sustained precision grip tasks (Baker et al, 1999), where the blockade of aberrant motor output may be actively required to accurately maintain the posture. Reductions of 8-30 Hz synchrony may consequently be necessary to facilitate the dynamic performance of task specific neuronal populations. As oscillations decrease in motor cortical LFP, firing rate modulation is observed (Donoghue et al, 1998). These task-modulated neurons may represent neurons uncoupled from the population of neurons synchronized in the 8-30 Hz band and therefore able to rate code effectively. At the population level, uncoupling may translate into the reductions in power in cortical and subcortical oscillatory LFPs at 8-30 Hz (Brown et al, 2001; Cassidy et al, 2002) and increases at >30 Hz (Cassidy et al, 2002; Pesaran et al, 2002) observed not just prior to movement, but also following environmental changes that promote anticipatory pre-programming of movement. As such the alpha and beta LFP activity is not an 'idling activity' holding the local neuronal population inactive (Pfurtscheller et al, 1996), but one that promotes the existing state, which need not be rest. Conversely, a drop in beta activity permits the new information processing necessary for renewed voluntary movement.

²¹ Neuronal balance is a term that has been introduced by authors to describe the relative strength of inhibitory and excitatory input to a neuron (see Salinas and Sejnowski, 2001, pg 543; Salinas and Sejnowski, 2000, Litvak and Sompolinsky, 2003). Under circumstances where neuronal excitatory and inhibitory inputs are evenly matched computer modelling and some single unit observations suggest that rate or temporal code transmission may be significantly impaired.

5.4 Outstanding issues

The findings presented here in addition to those in chapter 4, suggest that the loss or reduction of oscillatory field potential activity in the 8-30 Hz band is a consistent feature of responses both to movement preparatory cues and to imperative cues themselves. Oscillation reduction has been dissociated from movement itself by the observed capacity for reduction when not immediately followed by a motor response (i.e. post warning cue, chapter 4). Similar suppressions of beta LFP activity with preparatory cues alone have been reported in monkey parietal, cortex and cerebellum (see section 1.5.1). Neither the study in this chapter nor that of chapter 4 explicitly tested whether cue presentation unrelated to movement in a naïve subject was capable of eliciting a suppression response. As such it is not possible to state that field potential oscillation modulations in STN are 'general' phenomena as opposed to movement-related 'phenomena', merely that they are not exclusively movement performance phenomena. Irrespective of this fact the findings of this chapter further emphasize the need to understand the neuronal basis for oscillations in the alpha/beta band and their modulation.

- 1) Do cue modulated neurons display rate changes during alpha/beta oscillatory bursts?

The temporal relationship between bursts of LFP oscillations and any cue related single unit rate modulations in STN may be of great interest as this observation may either support or refute the notion that the state associated with 8-30 Hz LFP oscillations is incompatible with appropriate rate coding. While single unit recordings may potentially be made intraoperatively in humans, these would inevitably be from subjects with either parkinsonism or dystonia. Ideally this question could be answered via extracellular microelectrode recordings of single unit or multiunit activity in the STN of monkeys trained to produce a simple motor action in response to a cue, and to wait for the imperative cue after a preparatory cue. Despite the relatively recent observation of oscillatory LFP beta power oscillations in normal monkey striatum (Courtemanche et al, 2003), beta oscillatory activity has not yet been investigated in normal monkey STN, observations made both in the healthy

state and the MPTP lesioned state would therefore further clarify the extent to which beta LFP oscillations were a normal component of the primate STN.

It is also of note that across the literature (excluding the SLS response of chapter 4) stimulus LFP responses in the alpha/beta band are almost exclusively characterized by reductions of power. If it is the case that alpha/beta oscillations to some degree actively block transmission/processing, and do so under normal physiological circumstances, one might predict that highly directing but misleading cues may result in increases to suppress motor action. Is this the case?

5.5 Summary

- Alpha/beta oscillations in the LFP activity of the Parkinsonian basal ganglia are negatively correlated with speed of reaction after external cues independent of dopaminergic state.
- Contrary to difficulties found in correlating alpha/beta cortical oscillations in monkeys to motor behaviour, a very consistent relationship is apparent between the suppression of these oscillations and subsequent movement with later suppression associated with slower movement onset.
- The link observed between durations of oscillation suppression prior to motor responses and the degree of processing required, suggests that processing may occur preferentially during periods absent of oscillation occurrence.

CHAPTER VI

THE ROLE OF LOCAL FIELD POTENTIAL OSCILLATIONS IN THE SUBTHALAMIC NUCLEUS

Churchland and Sejnowski (1992), concerning the causal role of single neurons in a given function, suggest two minimum criteria for the demonstration of causality. Firstly, 'that the cell in question projects to the part of the brain that produces the relevant behaviour', and secondly 'that under the appropriate physiological conditions the output from the specialized cell does in fact drive the motor response'. Using broadly similar criteria this work has sought to test the idea that oscillatory activity, particularly in the beta band, evident in the LFP activity recorded from the STN has systemic functional relevance. The findings may be summarized as follows:

Chapter 3: Findings on corticosubthalamic connectivity in the frequency domain

Functional connectivity as evidenced by significant coherence exists between cortex and both STN and GPi in both beta and gamma bands

The degree of this connectivity appears dopamine dependent

The cortical distribution of this linkage in the beta band is consistent with the motor cortical representation of similar activity, particularly to SMA.

Chapter 4: Findings on beta STN LFP oscillation modulation by behavioural cues

Modulations of beta oscillations in the parkinsonian STN are not linked exclusively to the performance of movement.

Cue-related beta power modulation is influenced by the significance of the cue.

Cue-related beta responses may display maximal response magnitude to central bipoles of STN DBE

Chapter 5: Findings on correlations between beta STN LFP oscillation modulations and behavioural cues

Alpha/beta oscillations in the LFP activity of the Parkinsonian basal ganglia are negatively correlated with speed of reaction after external cues independent of dopaminergic state.

A very consistent relationship is apparent between the suppression of these oscillations and subsequent movement with later suppression associated with slower movement onset.

The link observed between durations of oscillation suppression prior to motor responses and the degree of processing required, suggests that processing may occur preferentially during periods absent of oscillation occurrence.

Though insights are being made, the precise function or functions of the STN still require clarification. Nevertheless, the findings presented here in the context of investigations of similar phenomena examined in the basal ganglia and elsewhere allow questions relevant to determining the significance of LFP oscillations to be considered.

6.1 Are oscillatory basal ganglia LFP phenomena 'real'?

At least one group of investigators has raised valid concerns regarding inferences made from recordings made via DBEs in patient populations. Wennberg et al (2002) argue that such recordings may result merely in the demonstration of volume conducted cortical activity. They have gone on to present evidence of just such an occurrence (Wennberg et al, 2003) showing that interictal discharges, k-complexes and sleep spindles may all be recorded with polarity reversal from the contacts of thalamic DBEs implanted in epileptic patients. The authors assert that 'bipolar recordings showing localization by phase reversal' should be required to assert the subcortical nature of a source. Their own study while using bipolar EEG sources

used monopolar DBE sources, as such their findings are perhaps less than startling. Nevertheless, is it true to assert that LFP activity of nuclei in the basal ganglia exhibit oscillatory activity? Even if one excludes supporting single unit observations, the weight of evidence undoubtedly supports this conclusion. In the beta band oscillations have been observed in the LFP of healthy striatum in epileptic subjects, recorded via DBEs (Sochurkova et al, 2003), substantiated by subsequent multi-electrode monkey recordings (Courtemanche et al, 2003). In the GPi and STN beta band oscillations have been observed and reported post-operatively from DBE recordings in PD patients by at least 3 separate groups (Brown et al, 2001; Cassidy et al, 2002; Levy et al, 2002; Priori et al, 2002). Furthermore these have been observed both on and off l-dopa medication as well as in the 6-OH dopamine lesioned rat (Sharott et al, unpublished observation). Rhythmic activity in the gamma band has also been reported via DBEs post-operatively in the STN and GPi of PD patients on l-dopa medication (Brown et al, 2001; Cassidy et al, 2002), as well as in the healthy rat STN (Brown et al, 2002). In the work reported here activity in both bands is represented. All recordings involve bipolar activity, and not only is it the case that maximization of cue related changes may be observed to a single DBE bipole in Chapter 4, but differences between the distributions of coherence evident along bipoles in separate cases in Chapter 3 are indicative of differing relationships to a local subcortical source and incompatible with cortical generation.

Questions still remain concerning the degree to which activity in given bands in individual nuclei actually represent normal activity. The observations in striatum clearly suggest that beta band oscillations in this nucleus are a normal component of primate striatal LFP activity. This is less clear in STN and GPi, although beta band LFP oscillations are evident in PD patients in the medicated state not only do they show less power (Brown et al, 2001), but as illustrated in Chapter 3, they show less cortical connectivity. This may be interpreted as evidence of the completely pathological nature of beta band oscillations in these nuclei, but if one considers the striatal observations and indeed the widespread cortical observations in undoubtedly healthy tissue, a more consistent interpretation at present would be that this mode of activity is abnormally exaggerated in the parkinsonian state. Differences discerned

between beta activity in PD patients and dystonics further supports such a conclusion (Silberstein et al, 2003).

6.2 Is there consistent functional connectivity in the beta band?

As discussed in section 1.1.2, direct primate cortico-subthalamic connections are characterized by major projections from motor cortex, terminating with somatotopic representation in dorsolateral STN (Monakow et al, 1978; Carpenter et al, 1981b) and premotor cortex terminating more medially and ventrally STN (Jurgens, 1984; Kunzle, 1978; Huerta et al, 1986). Although some investigators suggest far more extensive cortical projections may exist (Rouzaire-Dubois and Scarnati, 1985), it is these two that are the most prominent afferents and indeed from regions that have evidence of movement modulated beta LFP oscillation (section 1.5). In addition indirect projections may reach STN from widespread regions of cortex (section 1.1.2) via cortico-striatal connectivity. Failure to observe significant coherence between cortex and STN in the beta band would be completely incompatible with a system wide functional role and would require rejection of any such hypothesized role. In Chapter 3 it is demonstrated that there not only exists significant coherence in the beta band (to some extent both ON and OFF), and medicated in the high gamma band in PD subjects, but the distribution is consistent both with known cortical representations of beta band activity, but also with the above mentioned corticosubthalamic projection origins.

6.3 Do beta band oscillations display functionally appropriate modulation?

Despite the lack of motor consequences observed on microstimulation of STN neurons (Parent and Hazrati, 1995), a somatotopic neuronal responsiveness to sensory stimulation and movement are known to occur in dorsolateral STN (Georgopoulos et al, 1983; DeLong et al, 1985; Wichmann et al, 1989; Wichmann and DeLong, 1993). In addition both functional disconnection of prefrontal cortex

from STN and bilateral STN lesions may result in impaired selection in choice reaction tasks, slowed reaction times and perseveration (Baunez et al, 2001; Christakou et al, 2001; Chudasama et al, 2003). While it might readily be expected to see movement related changes in a task relevant neurophysiological property, one might also therefore expect to see such changes associated with components of a choice reaction task. The movement-related modulations of beta power have been discussed. In Chapter 4 however it was also demonstrated that beta oscillations show modulation with preparatory cues, long before movement or go-cues and do so with bias towards those that are actually relevant.

6.4 What kind of role of beta oscillations in STN is consistent with observations to date?

The findings of the present study do not allow the rejection of the hypothesis that LFP oscillations have systemic behavioural relevance in the beta band. Lacking however is any demonstration of causality that must be considered a fundamental of proving a role. The results do however allow the critical consideration of various hypothesized roles for motor system beta oscillation function. Go-cues, relevant warning cues, and movement all produce essentially stereotyped responses²², marked suppression of oscillatory burst episodes, as observed in Chapters 4 and 5. Indeed if go-cue related power modulation is compared with no-go change (Kühn et al, 2003) the same magnitude and temporal onset of modulation may be observed, distinguished only by their durations. It must be remembered that the activity sampled in these experiments was via single macroelectrode. Attempting to gain detailed information about coding using such a technique may be considered equivalent to trying to derive many different components of an image from a single visual cortical neuron. Until LFP analysis with decent spatial resolution has been performed with multiple electrodes it may not be possible to state categorically that patterns of suppression are truly stereotyped. Even if spatiotemporal variation is present, as may be predicted from striatal observation (Courtemanche et al, 2003), it

²² Excepting the short duration short latency SLS

remains the case that suppression of oscillations in a given region for a given duration is the fundamental pattern of modulation. The importance of duration of suppression noted in the no-go protocol is also evident in the examination of Chapter 5, showing correlation with the degree of processing required. One may also consider the fact that beta oscillations appear in a capricious fashion, unpredictably related to motor behaviour in a trial-by-trial manner appearing unnecessary for task performance. These facts do not seem consistent with beta oscillations in STN promoting or enhancing movement in any direct or indirect fashion. Their absence during movement and presence during static states, rest or constant force application in cortex, further suggests that they are unrelated to change but more to stasis – though the occurrence during sustained force has yet to also be demonstrated in any basal ganglia nucleus. Suppression of oscillations in the beta band is remarkably consistent from trial to trial as may be observed in Fig 5.1, and as was also observed the onset of this suppression is tightly linked to behaviour. The conjunction of all these factors suggests that task related processing in STN occurs during periods of suppressed oscillation and by inference that the beta band LFP oscillation state may be antagonistic to such processing. The apparent pathological exaggeration of beta band oscillations in the STN and GPi of PD patients viewed in such a light may well therefore have pathological significance in any information transmission related to the function of these nuclei. It is worthy of note however that even in PD patients OFF, cue and short ballistic movement related suppressions appear well preserved – if they move, they suppress. This may reflect how integral such changes are to allowing function.

6.5 Towards further insights

Based on current evidence further investigation of the role of oscillatory LFP phenomena in both the normal function of the motor system and the motor pathologies of the basal ganglia seems valid. Indeed evidence suggesting abnormal degrees or patterns of oscillatory synchronization in disorders as diverse as PD, dystonia (Farmer et al, 1998; Silberstein et al, 2003), schizophrenia (Merrin et al,

1989; Haig et al, 2000; Spencer et al, 2003), epilepsy (Prince and Connors, 1984; Jeffreys JG, 1994; McCormick and Contreras, 2001) and Alzheimer's (Wada et al, 1998; Stam et al, 2002), may suggest the existence of a class of neurological disorders which share a common pathological disruption of normal oscillatory function.

Specifically in Parkinson's disease there appear to be three key areas requiring detailed investigation. Firstly, further evidence, direct or indirect, of a causal role of the processes underlying beta LFP oscillations in basal ganglia nuclei in disease pathology. It is clear in evidence presented here and elsewhere that altered degrees of power and coherence exist in both beta and high gamma bands, but there has been little demonstration so far of a close relationship between specific episodes of activity and symptoms. Levy and colleagues (2000) have presented some evidence of an association between beta band oscillatory activity in STN and tremor but if this mode is in some manner causative of symptoms, and given its observed pattern of spontaneous activity, episodes of bradykinesia and dyskinesia should display characteristic patterns themselves. The second major question concerns the manner in which the activity observed in LFP oscillations is reflective of a pathological state. If oscillatory synchrony in the beta band is detrimental, why so? The first step may be to establish how oscillatory LFP episodes are related to single unit activity, in a manner analogous to the work of Murthy and Fetz in motor cortex. If beta LFP cycle-triggered averages of single unit activity in STN or GPi are constructed one may predict that a significant proportion would display an increased tendency to fire at one phase of the LFP cycle. This in turn may suggest that at this point of the cycle the neuronal population is somewhat more depolarized (or perhaps hyperpolarized with low threshold calcium activation) than at others. If this pattern does exist, does the LFP precede or follow the unit activity peak? – allowing some inference of a causal relationship to be established. Given the current hypothesis one may predict that the LFP will lead, indicative of post-synaptic potentials increasing the likelihood of neurons to fire. If this is the case, why do these alterations of the timing or pattern of neuronal firing result in symptoms? The last major issue concerns questions of how the oscillatory system may be manipulated. How does dopamine alter patterns in striatum? Are there means by which local membrane potential stabilization might

be performed? How does repetitive stimulation alter this system? Is there a role for more sophisticated stimulation algorithms in PD, where stimulation is specifically locked to a given phase of preceding bursts, possibly disrupting the generation of afferent post-synaptic potentials? Is there a non-synaptic role for field effects in treatment?

A more thorough understanding of the 'normal' neurophysiology and neuropharmacology of oscillation generation in the nuclei of the basal ganglia seems paramount to allowing logical manipulation of the system. Such insight may help to explain current anomalies such as why gamma oscillations in STN and GPi are so random a finding in the patient population. At present one cannot successfully predict if a given patient will or will not have evidence of oscillatory activity in the high gamma band. This may result from precise locations of the macroelectrode or levels of dopaminergic 'stimulation', it may however be related to the fundamental mechanisms of oscillation generation. Hippocampal work now suggests that gamma and beta powers may be highly linked (Whittington et al., 1997; Haenschel et al., 2000). If a similar situation exists within normal basal ganglia the gamma anomaly may reflect a pathological disruption of normal physiology.

The field of oscillatory phenomena of the basal ganglia is only in its infancy, but the rate of progress to date, potential for cross-fertilization with analogous phenomena throughout the brain, and possible implications for the treatment of PD and dystonic patients suggests that it should be viewed with cautious optimism.

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