# NEURONAL ACTIVITY IN THE SUBTHALAMIC NUCLEUS AND GLOBUS PALLIDUS OF PATIENTS WITH PARKINSON'S DISEASE

by

Ron Levy

A thesis submitted in conformity with the requirements

for the Degree of Doctor of Philosophy

Graduate Department of Physiology

University of Toronto

NEURONAL ACTIVITY IN THE SUBTHALAMIC NUCLEUS AND GLOBUS PALLIDUS OF PATIENTS WITH PARKINSON'S DISEASE, Doctoral Program 2001,

Ron Levy, Department of Physiology, University of Toronto.

## ABSTRACT

Patients with Parkinson's disease (PD) display bradykinesia, rigidity, and tremor and these symptoms are associated with the loss of dopaminergic input to the striatum of the basal ganglia. The current model of the basal ganglia function predicts that the clinical features of PD are related to elevated firing rates of neurons in the subthalamic nucleus (STN) and globus pallidus internus (GPi). However, it is possible that the discharge pattern of neurons in these nuclei also contributes to parkinsonism. The aim of this project was to characterize the pattern of activity and the population behavior of neurons in the STN and GPi and to elucidate the significance of this activity in PD. This thesis describes work carried out in awake patients with PD during stereotaxic brain surgery. Microelectrode recordings of single neurons or pairs of neurons and macroelectrode recordings of local field potentials were performed in the STN, GPi, and globus pallidus externus (GPe). In addition to a reduction in the firing rates of GPi and STN neurons, the dopaminergic medication apomorphine increased neuronal bursting activity, reduced the incidence of cells with tremor-related oscillations, and reduced the receptive fields of neurons to passive movement in these nuclei. Microinjections of inactivating agents in the STN reversed parkinsonian symptoms, especially limb tremor following inactivation of regions with tremor-related cells. In tremulous patients, many STN cells and some GPi cells were observed to synchronously oscillate at the frequency of limb tremor (3-8

Hz) and/or at higher frequencies (15-30 Hz). Both voluntary movement and dopaminergic medication were found to reduce the 15-30 Hz synchronized oscillations in the STN. Interestingly, none of the neuron pairs examined from the STN or GPi showed cross-correlations indicative of synchronization due to direct synaptic connections or direct common input, suggesting that the synchronization of neuronal activity in the basal ganglia is limited to oscillatory activity. These results indicate that neuronal discharge patterns and the population behavior are related to clinical symptoms of PD and may play an important role in the normal and pathological functioning of the basal ganglia.

**ACKNOWLEDGEMENTS**

I am fortunate to have had Dr. Jonathan Dostrovsky as my supervisor. Without his mentoring, support, experience, and patience this work would not have been possible. He always made time to help me and encouraged me to explore to my hearts content. I am also indebted to Andres Lozano, William Hutchison, Peter Ashby, and Anthony Lang for their invaluable assistance, trust, and encouragement.

I would also like to thank the following individuals for their help and encouragement: Helen Belena, Karen Davis, Jennifer Fine, Eileen Halkett , Lisa Johnston, Hon Kwan, Marosh Manduch, Greg Molnar, Peter Pahapill, Jason Parker, John Romas, Jean Saint-Cyr, Steve Sherman, Nagwa Sherman, Eppie Sime, and Yih-ru Wu.

To my love Roksolyana, thanks for taking care of me and being there for me through this long process.

This work is dedicated to my parents, Jack and Rachel.

This research was funded by grants to Dr. Dostrovsky by the Parkinson's Foundation of Canada, the U.S. National Institute of Health, and the Canadian Institute of Health Research and to grants to myself from the Department of Physiology at the University of Toronto and an Ontario Graduate Scholarship.

Permission to reprint figures and tables from the following sources has been granted:

Levy, R., Lang, A.E., Dostrovsky, J.O., Pahapill, P., Romas, J., Saint-Cyr, J., Hutchison, W.D., Lozano, A.M. Lidocaine and muscimol microinjections in subthalamic nucleus reverse parkinsonian symptoms. Brain 124: (in press), 2001.

Levy, R., Dostrovsky, J. O., Lang, A. E., Sime, E., Hutchison, W. D., and Lozano, A. M. Effects of apomorphine on subthalamic nucleus and globus pallidus internus neurons in patients with parkinson's disease. J.Neurophysiol. 86: 249-260, 2001.

Levy, R., Hutchison, W. D., Lozano, A. M., and Dostrovsky, J. O. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. J.Neurosci. 20: 7766-7775, 2000.

TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

**CHAPTER 5 - NEURONAL SYNCHRONIZATION IN THE SUBTHALAMIC NUCLEUS AND GLOBUS PALLIDUS**

## ABBREVIATIONS

| | |
|---|---|
| Accelerometer | Acc |
| Apomorphine | APO |
| Basal ganglia | BG |
| Centromedian and parafascicularis complex | CM/Pf |
| Deep brain stimulation | DBS |
| Electromyography | EMG |
| Globus pallidus | GP |
| Globus pallidus internus | GPi |
| Globus pallidus externus | GPe |
| 6-hydroxydopamine | 6-OHDA |
| Joint peri-stimulus time histogram analysis | JPSTH |
| Magnetic resonance imaging | MRI |
| Magnetoencephalography | MEG |
| 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine | MPTP |
| Nucleus ventro-intermedius | Vim |
| Nucleus ventro-oralis posterior | Vop |
| Nucleus ventro-oralis anterior | Voa |
| Parkinson's disease | PD |
| Pedunculopontine tegmental nucleus | PPN |
| Positron emission tomography | PET |
| Receptive field | RF |
| Subthalamic nucleus | STN |
| Substantia nigra pars compacta | SNc |
| Substantia nigra pars reticulata | SNr |
| Tonically active neurons | TANs |
| Tremor cells | TCs |
| Unified Parkinson's Disease Rating Scale | UPDRS |

# CHAPTER 1 - GENERAL INTRODUCTION

## 1.1 - The clinical features of Parkinson's disease

The neurodegenerative disorder Parkinson's disease (PD) was first described in 1817 by James Parkinson but only became well-known to neurologists in the last century when it was recognized that PD was a unique disorder and not an extreme variant of the normal aging process (Horowski et al. 1995). PD has a prevalence rate of 100 per 100,000 people (Tanner 1992; Mayeux et al. 1995) with approximately one million people in North America affected (Lang and Lozano 1998a). PD significantly shortens life expectancy (Bennett et al. 1996) and with future increases in the size of the elderly population, the mortality rate due to parkinsonism will rise dramatically (Lilienfeld and Perl 1993). The mean age of onset is approximately 60 years old but 10% of cases are diagnosed before the age of forty and are considered to have "young-onset" PD (Hughes et al. 1993; Bennett et al. 1996; Lang and Lozano 1998a).

The cardinal symptoms of PD include akinesia, bradykinesia, rigidity, limb tremor, and the impairment of postural reflexes. The initial diagnosis is made on the basis of the presence of some or all of these symptoms and a good initial response to levodopa (Lang and Lozano 1998a). PD symptoms increase with time (Calne and Langston 1983; Koller and Montgomery 1997; Obeso et al. 2000), with one side of the body initially affected and bilateral involvement as the disease progresses (Poewe and Wenning 1998). It is important to describe the clinical symptoms expressed by parkinsonian patients because they provide valuable clues regarding the normal function and pathophysiology of the brain regions involved in PD.

### *1.1.1 - Akinesia and bradykinesia*

Akinesia is defined as the lack or paucity of spontaneous movement while bradykinesia is defined as a slowness in the speed of movement. Most research is directed towards the latter symptom because it is inherently easier to measure a deficit in movement rather than the absence of movement. It is also thought that bradykinesia is the most fundamental sign of PD (Marsden 1984). It has been proposed that bradykinesia results from an inability of parkinsonian patients to generate the appropriate amount of muscle activity as measured with electromyography (EMG) (Hallett and Khoshbin 1980). This is supported by studies showing that PD patients have slower and less regular force production when performing isometric contractions (Stelmach et al. 1989). It has also been proposed that akinesia might result from an inability to integrate cognitive and motor processes (Brown and Jahanshahi 1996).

Patients with PD initiate and execute rapid simple movements more slowly than healthy people do. These movements are usually accomplished with multiple cycles of EMG bursts rather than with a single triphasic pattern as observed in normal subjects. This indicates that patients require more agonist-antagonist cycles to complete a movement (Hallett and Khoshbin 1980) and that patients are unable to scale the activation of the first agonist burst (Berardelli et al. 1986a). Clinical ratings scales and the majority of movement studies tend to measure movement time rather than reaction time because overall movement time is a better measure of bradykinesia (Teravainen and Calne 1981).

### *1.1.2 - Rigidity*

Rigidity is defined as an increase in resistance to passive movement of the limbs. It is presently unclear what causes rigidity in parkinsonian patients but it is likely that a variety of mechanisms are involved. Lesions of deep brain regions can relieve rigidity thereby indicating that central mechanisms play a role in rigidity (Lang et al. 1999). Rigidity may also be due to increase in reflex excitability (Rack and Ross 1986; Burne 1987; Lee 1989), an increase in muscle activity during movement due to enhancement of stretch reflex activity (Meara and Cody 1992), or changes in soft tissue properties with long-term reduced use (Dietz et al. 1981).

### *1.1.3 - Tremor*

Resting tremor occurs in approximately 75% of patients with PD (Hughes et al. 1993). Unlike bradykinesia, correlations of PD motor deficits with clinical rating scales demonstrate that tremor does not predict the severity or progression of motor deficits in PD (Stebbins et al. 1999). Limb tremor consists of 3-6 Hz rhythmic activation of antagonist muscles, usually in the distal portions of limbs (Shahani and Young 1976). This tremor is termed a "resting tremor" because it is present in the absence of active movements and is dampened in a limb during active movements of that limb (Deuschl et al. 1998). Resting tremor can also be enhanced during periods of mental stress (so called "enhanced" resting tremor). For example, the amplitude of a resting tremor can be increased if a patient is asked to perform mental arithmetic.

The rhythmicity of parkinsonian rest tremor is quite variable in time (Schwab and Cobb 1939; Bishop et al. 1948). Tremor frequency is dissimilar between different sides

of the body and it is generally observed that tremulous limbs in PD oscillate independently whereas muscles within a limb are more likely to be coupled (Raethjen et al. 2000). It has been suggested that differences in the frequency of tremulous limbs might be due the presence of multiple tremor generating circuits (Alberts et al. 1965) and this is supported by studies using spectral techniques to correlate the frequency relations between different tremulous limbs (Hurtado et al. 2000; O'Suilleabhain and Matsumoto 1998). Increases in intra-limb muscle coupling are observed during enhanced resting tremor induced by mental arithmetic (Hurtado et al. 2000). Low amplitude 4-10 Hz postural and action tremors are also expressed in ~60% of parkinsonian patients (Findley et al. 1981; Hadar and Rose 1993; Palmer and Hutton 1995). Postural tremors appear when patients hold a posture while action tremors are expressed during voluntary movement of the affected limb (Lance et al. 1963; Findley et al. 1981).

### *1.1.4 - Impairment in postural stability*

In addition to bradykinesia, rigidity, and limb tremor, postural instability is impaired in PD and can become the most debilitating of these symptoms to a patient's quality of life. Clinically rated balance impairment has been correlated with an abnormal modulation of postural reflexes in the lower extremities (Beckley et al. 1991). Although the timing of associated postural adjustments is normal in PD, the size of postural adjustments may be decreased (Dick et al. 1986) and is related to difficulty in modifying the size of posturally stabilizing long-latency reflexes (Beckley et al. 1993). Postural instability may also be due to an increase in muscle tone and tremor in the lower extremities (Burleigh et al. 1995). It has been suggested that patients are unable to select

functional response patterns when placed in situations of postural instability since they display difficulties sequencing motor programs for postural correction (Bazalgette et al. 1987; Horak et al. 1992; Chong et al. 2000) and 'inflexible' postural reflexes (Bloem et al. 1995).

### *1.1.5 - Difficulties with complex tasks*

Parkinsonian patients show a deficit in sequencing movements wherein the movement time for each step of a movement sequence becomes slower and slower and is termed the "sequence effect" (Agostino et al. 1992). Furthermore, patients characteristically display difficulties in performing simultaneous or complex tasks that involve the superimposition and sequencing of simple motor tasks (Schwab et al. 1954; Berardelli et al. 1986b; Benecke et al. 1986; Stelmach and Worringham 1988; Agostino et al. 1998; Alberts et al. 1998). For example, parkinsonian patients experience difficulty when they are required to walk while attending to a complex visuomotor task involving the upper limbs (Bond and Morris 2000). Difficulties are also observed with serial multiarticulate movements for speech (Connor et al. 1989) that include speech hastening and impaired self-paced sequencing (Ackermann et al. 1997).

The performance of complex rather than simple motor tasks correlates better with clinical bradykinesia (Benecke et al. 1987a). It has been suggested that the amount of bradykinesia in patients with PD may be an underlying factor in determining the degree of disturbance in superimposing separate motor programs (Benecke et al. 1986). Marsden (1982) proposed that patients with PD cannot perform repetitive, sequential or concurrent motor actions because of an inability to execute automatically learned motor

plans. It has also been shown that bimanual simultaneous motor performance is degraded since there is an impaired ability to shift attention between the two tasks (Benecke et al. 1987b; Horstink et al. 1990; Jones et al. 1992). This may occur because the combined demands of performing the two tasks outweigh the available resources (Cools et al. 1984; Flowers and Robertson 1985; Goldenberg 1990; Brown and Marsden 1991; Georgiou et al. 1993).

### *1.1.6 - Difficulties with internally versus externally generated movements*

Parkinsonian patients display difficulties in normally initiating movements that may be due to the inability of patients to utilize movement cues (Bloxham et al. 1984; Sheridan et al. 1987) or an inability to deal with attentional demands of the task at hand (Brown and Marsden 1988a). For example, reduced reaction time in PD is similar to behavior in reaction time tests of normal individuals performing a concurrent attention demanding secondary task (Bloxham et al. 1987). The freezing of gait that occurs in PD can also be diminished with the use of an inverted walking stick to cue movements (Dietz et al. 1990; Camicioli et al. 1998). Therefore, patients with PD are significantly impaired on tasks where they have to rely upon internal control for the regulation of behavior rather than external cues (Brown and Marsden 1988b; Crawford et al. 1989; Cools et al. 1990; Buytenhuijs et al. 1994). Performance deteriorates when visual guidance is lacking but the provision of external cues improves this deficit (Georgiou et al. 1994; Cunnington et al. 1999).

### *1.1.7 - Other dysfunctions*

Greater than 90% of patients at 4 years after their initial assessment are reported to have at least one psychiatric symptom (depression, apathy, hallucinations, delusions, irritability, and anxiety) (Aarsland et al. 1999). 28% of older patients with PD have dementia in addition to the motor manifestations of PD (Aarsland et al. 1996). The prevalence rates of depression in patients with PD have been reported to be as high as 40% (Cummings and Masterman 1999) which may be due to frontal lobe dysfunction and greater involvement of dopaminergic and noradrenergic systems suggesting that frontal dopaminergic projections are involved in parkinsonian depression (Cummings 1992). Cognitive impairment in PD might also result from the dysfunction of non-dopaminergic neuronal systems (Pillon et al. 1989). Parkinsonian patients that suffer from depression and cognitive impairment can still provide an accurate self-report of their level of disability (Brown et al. 1989). Parkinsonian patients can also display esophageal motor abnormalities (dysphagia, acid regurgitation, pyrosis, and noncardiac chest pain) (Bassotti et al. 1998), visuo-cognitive impairment (Bodis-Wollner et al. 1987; Bodis-Wollner 1990; Antal et al. 1998), and visual hallucinations that may be related to visual deficits of color and contrast discrimination (Diederich et al. 1998).

In this thesis, neuronal activity of brain regions in patients with PD will be correlated with the motor symptoms bradykinesia, rigidity, and tremor only. Although postural instability, inability to perform complex movements, and poor cognition might account for a greater debility in PD, given the limitations of stereotactic surgery, these features cannot easily be assessed during stereotactic neuronal recordings.

## 1.2 - Dopamine therapy in Parkinson's disease

This section describes the effects of dopaminergic drug therapy in parkinsonian patients. The effects of this anti-parkinsonian medication on neuronal activity will be a major focus of this thesis. Carlsson first suggested that dopamine may be a transmitter in the central nervous system involved in the control of motor function and that it may be involved in the Parkinsonian syndrome (Carlsson, 1959). PD is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) that project to the striatum (Ehringer and Hornykiewicz 1960; DeLong et al. 1985; Kish et al. 1988). However, the dopaminergic projection from the ventral tegmental area to the nucleus accumbens (the mesolimbic dopamine system) is not greatly affected. The success of dopamine replacement therapy supports the theory that a lack of dopamine results in parkinsonism (Kish et al. 1988). There is also selected degeneration of neurons in the aminergic brain-stem nuclei (catecholaminergic and serotoninergic), cholinergic nucleus basalis of Meynert, hypothalamus, cortical cingulate neurons, sympathetic ganglia, and parasympathetic neurons in the gut (Lang and Lozano 1998a). In addition to loss of dopaminergic neurons in the SNc in PD, there is a loss of balance between the cholinergic and dopaminergic output of the striatum.

The exact cause of neural degeneration in the SNc is presently unclear and may be due to a combination of factors. Cells degenerate by processes that are suggested to involve mitochondrial dysfunction, oxidative stress, disturbed calcium homeostatis and excitotoxic cell death (Gerlach and Riederer 1999), viral agents (Elizan and Casals 1983), age-related immune system dysfunction, genetic factors, trophic substances, or toxins (Elizan and Casals 1983). It is also likely that toxic environmental factors are

superimposed on a background of slow, sustained neuronal loss due to advancing age (Calne and Langston 1983). A detailed review of the pathology and mechanisms of cell degeneration is given by Lang and Lozano (1998a).

By the time PD is diagnosed, a large population (~90%) of dopaminergic SNc cells have been depleted (Hornykiewicz and Kish 1987). Positron emission tomography (PET) with levodopa analogue 6-fluorodopa has demonstrated that in humans exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, a substance that is selectively toxic to SNc cells), dopaminergic impairment can exist without clinical deficits (Calne et al. 1985). Before clinical deficits become apparent, remaining SNc cells produce more dopamine and striatal cells increase their sensitivity. It has also been demonstrated that glutamatergic inputs to the SNc are involved in compensatory mechanisms during the presymptomatic period when neuronal death in the SNc exceeds 50-60% but clinical symptoms are not yet present (Bezard et al. 1997a, 1997b; Bezard et al. 1999). When enough SNc cells are lost, compensatory mechanisms cannot balance the loss of dopamine and PD symptoms appear (Zigmond et al. 1990; Bezard and Gross 1998).

Diagnosis of PD is dependent on evaluation of patient responses to acute challenges with levodopa or apomorphine (APO) (Bonuccelli et al. 1993; Albanese et al. 2001), each with a different mechanism of action. The dopamine precurser levodopa was discovered in the 1960's and is the main treatment for PD (Cotzias et al. 1967). Levodopa is a pharmacologically inactive dopamine precursor that crosses the blood brain barrier and is converted enzymatically to the neurotransmitter dopamine by striatal terminals of a declining population of neurons in the SNc (Hurtig 1997). Following absorption into brain, levodopa is taken up by residual dopaminergic neurons and

decarboxylated by aromatic amino acid decarboxylase, then synaptically released to stimulate dopamine receptors on post-synaptic cells. However, since levodopa efficacy does not decrease with disease duration, there likely are alternative mechanisms of presynaptic handling of levodopa (Koller 2000). Patients using levodopa are also given an aromatic amino acid decarboxylase inhibitor (such as benserazide or carbidopa) to block the peripheral breakdown of dopamine (Koller 2000). The drug APO, a non-specific $D_1$/ $D_2$ dopamine receptor agonist, binds at post-synaptic receptor sites and has similar clinical effects as levodopa (Corboy et al. 1995; Colosimo et al. 1996). APO is rapidly absorbed following subcutaneous injection, with peak levels achieved within 5-10 minutes in most patients and has an elimination half life of 33 minutes (Gancher 1995). A detailed review of the treatment of PD is given by Lang and Lozano (1998b).

### *1.2.1 - Beneficial effects of dopamine therapy*

Levodopa therapy has revolutionized the treatment of PD despite its major shortcomings after long term use (Hurtig 1997). Levodopa significantly improves bradykinesia and akinesia. PET studies have demonstrated that nigrostriatal deficit in PD correlates more highly with bradykinesia than other functional deficits in patients with PD (Vingerhoets et al. 1997). Levodopa also improves tremor, rigidity, the performance of complex tasks (Benecke et al. 1987a), hypometria (small amplitude movements) (Beckley et al. 1995), and the generation of internally cued movements (Burleigh-Jacobs et al. 1997).

However not all symptoms of PD are similarly responsive to dopaminergic medication. Postural instability might be the result of stooped posture or rigidity (Bloem

et al. 1992; Bloem et al. 1999) since dopamine has been shown to improve tonic background postural muscle tone but not automatic postural responses to external displacements (Horak et al. 1996). The lack of effect of dopaminergic medication on postural stability suggests that nondopaminergic lesions are involved in the pathophysiology of postural abnormalities in PD (Bloem et al. 1996).

### *1.2.2 - Non-beneficial effects of dopamine therapy*

The benefits of levodopa only last for 5-7 years before causing motor complications (Lang and Lozano 1998a) such as dyskinesias and motor fluctuations (Obeso et al. 2000). Fluctuations occur in well over half of PD patients after five years of levodopa therapy (Contin et al. 1997; Reardon et al. 1999; Rascol et al. 1999) and might be related to the pulsatile stimulation of dopaminergic receptors on striatal GABAergic neurons (Chase 1998) or postsynaptic changes in the striatum (Colosimo et al. 1996). Motor fluctuations are also related to the cerebral pharmacokinetic or pharmacodynamic factors of levodopa (Contin et al. 1990).

The effectiveness of anti-parkinsonian drugs gradually diminishes and more than 50% of patients on long-term levodopa treatment develop dyskinesias. Rotation-sensitive movement monitoring of choreic and dystonic dyskinesias demonstrate that these movements have predominant frequency peaks ranging from 0.25-3.25 Hz. High-frequency dyskinesia correlates with choreic type and low-frequency dyskinesia correlates with dystonic type (Burkhard et al. 1999). Peak-dose dyskinesias are present with high concentration of brain levodopa while choreas or dystonias occur at the begining and end of dose (so called "diphasic dyskinesias") (Fahn 2000). The emergence

of dyskinesia in patients with PD is related to the levodopa-induced reduction in bradykinesia, but not rigidity (Caligiuri and Peterson 1993). Other complications of levodopa use are nausea, postural hypotension, postural instability, motor fluctuations, and mental changes (hallucinations, confusion, and delirium) (Bloem 1992; Hurtig 1997; Koller 2000).

Therefore, given the dramatic effects of dopaminergic therapy in patients with PD, it is important to increase our understanding of the effects of these medications in the parkinsonian brain. It is fortunate that those features which are most easily measured during stereotactic surgery, namely bradykinesia, tremor, rigidity, and dyskinesias also respond best to dopaminergic therapy.

### 1.3 - Anatomy and physiology of basal ganglia and associated regions

The basal ganglia (BG) are a group of subcortical nuclei. The major divisions of the BG are the striatum, the globus pallidus (GP), the subthalamic nucleus (STN), and the substantia nigra (SN). The striatum is the main input nucleus and is divided into the caudate, putamen, and nucleus accumbens. The caudate and putamen subdivisions of the striatum are separated by the internal capsule. The GP is divided by the internal medullary lamina into the internal segment (GPi) and external segment (GPe). The SN is divided into SNc and SN pars reticulata (SNr). The GPi and SNr are the major output nuclei of the BG. In rodents, the GPi is called the entopenduncular nucleus and GPe is referred to as the GP.

Disorders related to BG dysfunction involve hypokinetic or hyperkinetic movement abnormalities. These movement disorders can be found in diseases such as

Huntington's disease, dystonia, obsessive-compulsive disorder, depression, addiction/substance abuse, and schizophrenia. Given that all disorders of BG origin involve some amount of movement deficit, it is interesting that the BG receive no direct sensory input and do not send direct motor output to the spinal cord. For example, pallidal receiving areas of the thalamus have relatively weak access to direct motor outputs (Buford et al. 1996).

*The serial organization of the basal ganglia*

The BG are part of larger circuits that also involve the cortex, thalamus, and brainstem areas (Alexander et al. 1986; Alexander et al. 1990; Hoover and Strick 1993; Middleton and Strick 1997). The BG receive major input from all the cerebral cortex (particularly supplementary motor area, premotor cortex, precentral motor, and postcentral sensory areas) and send output back to the same areas of the cortex via the ventrolateral thalamus. Thus the BG are considered part of a re-entrant circuit that emanates from the cortex. The BG also have outputs to the superior colliculus and the pedunculopontine tegmental nucleus (PPN). Therefore, the BG primarily exert their effects through premotor neurons in the thalamus and brainstem. A detailed schematic of the interconnections of the BG, cortical, and brainstem regions is shown in Figure 1.F1.

*The parallel organization of the basal ganglia*

In addition to the serial connections between nuclei, there are many distinct re-entrant circuits which link the BG, thalamus, and vast regions of the cortex. Electrophysiological and anatomical studies provide evidence that the main circuits

passing through the BG remain "segregated" under normal conditions and that the functional architecture of the BG is essentially parallel in nature (DeLong 1983; Alexander et al. 1986; Hoover and Strick 1993; Yoshida et al. 1993). There are five such loops in cortico-striatal-pallidal-thalamic system, each of which sends output to a different part of the frontal lobe (Alexander et al. 1986). The "motor" circuit connects the primary motor cortex, supplementary motor area, and ventral premotor cortex (i.e. the precentral motor fields). The "oculomotor" circuit involves the frontal and supplementary eye fields. There are two "associative" circuits, one projecting to the dorsolateral prefrontal cortex and the other projecting to the lateral orbitofrontal cortex. Lastly, a "limbic" circuit connects to the anterior cingulate and the medial orbitofrontal cortex (Alexander et al. 1990). The segregation between these circuits may be maintained within each subcircuit as well (Alexander and Crutcher 1990). It has been proposed that this organization may allow the BG to concurrently participate in both the motor and complex non-motor functions of the cerebral cortex (DeLong et al. 1984; Alexander et al. 1990; Middleton and Strick 1994).

### *1.3.1 - Striatum*

*Projection neurons of the striatum*

The projection neurons of the striatum are GABAergic "medium spiny neurons" and account for more than 90% of the total neuronal population of the striatum (Bolam et al. 1981). The medium spiny neurons of the striatofugal pathways primarily project to the GPe, GPi, and SNr but also send local axon collaterals to other striatal medium spiny neurons (Gerfen 1988). Anterograde tracing studies demonstrate that the striatopallidal

projection system in primates is highly ordered and displays a high degree of specificity with respect to its target sites in the pallidum (Hazrati and Parent 1992a). Stimulation of the striatum produces a short latency inhibition in both the GPi and GPe and is followed by a longer period of excitation, especially in the GPe (Tremblay and Filion 1989). This excitation is topologically arranged and may serve to spatially focus the striatopallidal inhibitory signal onto a restricted number of pallidal neurons. The medium spiny projection neurons have a low spontaneous discharge rate but can be phasically active and have burst discharges in relation to behavioural events.

In the primate, somatosensory and motor cortical areas project mostly to the putamen, and this structure is more related to pure motor aspects of task execution such as the execution of movements or the processing of proprioceptive information (Crutcher and DeLong 1984a; Crutcher and DeLong 1984b; Kimura 1986; Alexander 1987). Putamen neurons are somatotopically organized throughout the rostrocaudal extent of the nucleus (Alexander and DeLong 1985a). Microstimulation in the putamen results in movements of individual body parts, likely due to the activation of putamen output neurons that are grouped into "striatal microexcitable zones" (Alexander and DeLong 1985b). In cats, single unit activity in the putamen is related to motor activity (Cheruel et al. 1994) while in the rat it has been demonstrated that putamen neurons have multisensory integrative receptive fields that may be used to facilitate motor responses (Chudler et al. 1995).

The caudate nucleus receives substantial input from prefrontal and parietal association areas and therefore serves associative functions such as planning and anticipation of upcoming events (Apicella et al. 1991a). Neurons in the caudate nucleus

of monkeys integrate sensory, motor, and non-motor responses driven by the frontal cortex to produce coordinated behavior (Aldridge et al. 1980a, 1980b; Nishino et al. 1984; Anderson and Horak 1985). In freely moving cats, caudate neurons show changes of activity related to conditioned stimuli and to initiation of movement or to reinforcement (Amalric et al. 1984). Lastly, the nucleus accumbens subdivision of the striatum serves limbic (emotional aspects) functions and receives input from the limbic cortex (Alexander et al. 1986).

*Direct and indirect output pathways of the striatum*

Although all medium spiny neurons are GABAergic, they can further be subdivided based on differences in their projection targets and neurotransmitters used. Medium spiny neurons expressing GABA and substance P and dynorphin (an opioid peptide) monosynaptically project to the SNr and GPi (the output nuclei of the BG) and comprise the "direct pathway" of the BG. The "indirect pathway" arises from medium spiny neurons expressing GABA and enkephalin that project to the GPe (Albin et al. 1989a). This pathway then affects the GPi and SNr via the STN (DeLong 1990). It has been suggested that the activity in the direct pathway exerts a specific inhibitory control of output neurons while activity in the indirect pathway uniformly excites a larger collection of neurons (Hazrati and Parent 1992b; Parent and Hazrati 1993).

However, the separation between these two pathways is not sharp. There is anatomical evidence that indicates that striatal neurons can give rise to axon collaterals that arborize in all the target nuclei of the striatum (Parent et al. 1995; Parent et al. 2000). There is also evidence of a direct GPe to GPi inhibitory connection (Parent and Hazrati

1995a). A third population of medium spiny neurons contains GABA, dynorphin, and substance P and projects to the SNc (Gerfen and Young 1988).

*Interneurons of the striatum*

Axons of non-spiny striatal interneurons terminate on other interneurons or onto the medium spiny projection neurons. Similar to projection neurons, they can be subdivided according to the neuronpeptides and enzymes that they express (Parent 1996). For example, cholinergic interneurons are called "tonically active neurons" (TANs) and are recruited by becoming synchronized in firing or developing pauses after a conditioning stimulus (Aosaki et al. 1995;Raz et al. 1996). During the acquisition of sensorimotor associations in monkeys, TANs that are widely distributed through the striatum become responsive to sensory stimuli that induce conditioned behavior (Aosaki et al. 1994a), are influenced by predictive information (Apicella et al. 1998), and display context- dependent phasic activity in specific behavioral situations (Apicella et al. 1991b). This distributed change in activity is hypothesized to modulate the activity of surrounding projection neurons in the striatum engaged in mediating learned behavior (Aosaki et al. 1994a).

*Input to the striatum*

The striatum is the main input nucleus of the BG and receives afferent input from the cortex, centromedian-parafascicular complex of the thalamus (CM/Pf), and the SNc. Cortical areas send somatotopically organized glutamatergic projections onto the dendritic tips of medium spiny neurons (Kemp and Powell 1970). Cortical input to the

striatum is distributed but there is also massive convergence of cortical-striatal inputs to individual striatal neurons (Flaherty and Graybiel 1991; Flaherty and Graybiel 1993; Flaherty and Graybiel 1994). This convergence of corticostriatal projections might play a role in the integration of cortical information from diverse regions of the cortex (Graybiel et al. 1994). In rats, electrical stimulation of motor cortex and intracellular recordings in the ipsilateral striatal projection field demonstrate long-term potentiation of cortico-striatal synaptic transmission suggesting the activity-dependent plasticity of glutamatergic cortico-striatal synapses (Charpier and Deniau 1997). Since physiological long-term potentiation at corticostriatal synapses can be induced by low frequency synchronization of cortical afferents it has been hypothesized that the striatal output neuron may operate as a coincidence detector of converging cortical information (Kincaid et al. 1998; Charpier et al. 1999).

The striatum receives excitatory input from the CM/Pf (Sadikot et al. 1992a,1992b; Deschenes et al. 1995; Deschenes et al. 1996). It has been proposed that the centromedian inputs are related to sensorimotor, while the parafascicular inputs are related to limbic aspects of BG involvement (Sadikot et al. 1990). Cortical and parafascicular thalamic projections do not converge upon the same medium spiny neurons in the striatum (Dube et al. 1988).

The main source of dopamine in the striatum is the dopaminergic neurons located in the ventral portion of the SNc (Smith et al. 1994a). Dopamine release modulates the activities of striatal neurons since post-synaptic dopamine receptors are located at the base of the dendritic spines, and hence are in a good position to modulate activity from the cortex (Gerfen 1988). Presynaptic dopamine receptors are present on corticostriatal

terminals and other dopaminergic terminals. Striatal aspiny neurons (cholinergic interneurons) are also modulated by dopamine (Aosaki et al. 1998). Long-term depression of synaptic transmission in the corticostriatal pathway is blocked by dopamine receptor antagonists or lesions of the nigrostriatal dopaminergic pathway and can be restored by the application of exogenous dopamine (Calabresi et al. 1992). In monkeys trained with a conditioning task, unilateral dopamine loss substantially reduced the acquired sensory responsiveness of striatal neurons. This effect could be reversed by APO suggesting that the nigrostriatal system modulates expression of neuronal response plasticity in the striatum during sensorimotor learning (Aosaki et al. 1994b).

The $D_1$ and $D_2$ dopamine receptors are the major subtypes expressed in the striatum, and are differentially expressed in medium spiny projection neurons of the direct and indirect pathways. Dopamine via $D_1$ receptors is excitatory to striatal neurons that give rise to the direct pathway (i.e. those neurons expressing GABA/SP/dynorphin). Dopamine via $D_2$ receptors is inhibitory to striatal neurons that give rise to the indirect pathway (i.e. those neurons expressing GABA/enkephalin) (Gerfen et al. 1990). This is supported by the observation that mice lacking the $D_1$ receptor exhibit selective functional alterations in the striatal neurons giving rise to the direct striatal output pathway (Drago et al. 1994). However, it has been suggested that the direct and indirect pathways are not necessarily distinct and that the effects of $D_1$ and $D_2$ receptor activation may not simply be described as pure excitation or inhibition (Nicola et al. 2000).

*Striosome and matrix organization of the striatum*

In addition to the putamen/caudate and direct/indirect pathway organization, there is another way in which the striatum is organized. Staining of the striatum with acetylcholinesterase reveals a patchy distribution of lightly stained regions within regions that are more heavily stained. The former regions are called "striosomes" and the latter is referred to as the "matrix" (Graybiel and Ragsdale, Jr. 1978). The matrix forms the majority of the striatum and receives input from the cerebral cortex and the striosomes receive input from limbic and the prefrontal cortex. This arrangement of cortical inputs to the striatum may serve in context-dependent behavioral planning (Eblen and Graybiel 1995). In addition, while both striatal compartments receive dopaminergic input from the SNc, only striosomes project back to the SNc (Gerfen 1992).

### *1.3.2 - Substantia nigra pars compacta*

The SNc receives GABAergic input from the striosomal neurons of the striatum and sends dopaminergic input back to the striatum (Graybiel 1990; Smith et al. 1994a). Extrastriatal dopaminergic innervation in the GPi and STN may be provided by collaterals of these nigrostriatal axons (Cossette et al. 1999). Dopamine can also directly modulate the activity of SNc cells (Aebischer and Schultz 1984; Carlson et al. 1987).

Dopaminergic neurons subserve an integrative role by modulating the flow of information from the cortex through the BG at the level of the striatum and nucleus accumbens (Bevan et al. 1996). In intact monkeys, SNc dopaminergic neurons respond to rewards and change their activity during procedural learning and in response to conditioned stimuli (DeLong et al. 1983; Schultz 1986a).

Dopaminergic neurons in the SNc are innervated by several other BG nuclei in addition to the striatum. In the rat, SNc neurons receive multiple GABAergic synaptic inputs both from neurons in the ventral pallidum (which receives input from limbic areas via the nucleus accumbens) and from neurons in the GP (which receives input from associative and sensorimotor cortices via the neostriatum) (Smith and Bolam 1990; Celada et al. 1999). Electrical stimulation of GABAergic pathways originating in the striatum, GP or SNr produces inhibition of SNc dopaminergic neurons (Paladini et al. 1999). The STN has also been shown to promote burst discharge in a subpopulation of SNc dopamine neurons (Chergui et al. 1994).

### *1.3.3 - Subthalamic nucleus*

The STN of species such as man, monkey, and cat, contains only one type of neuron and is a closed nucleus (i.e. dendrites do not extend beyond borders) (Afsharpour 1985a). In the STN there are no intra-nuclear interactions as a result of recurrent collaterals (Kita et al. 1983) or interneurons (Rafols and Fox 1976) although the existence of interneurons in the STN remains unclear (Yelnik and Percheron 1979; Van Der Kooy and Hattori 1980; Ryan et al. 1992).

#### *Neuronal activity of the subthalamic nucleus*

The STN in primates can be divided into a dorsolateral "sensorimotor" portion and a ventromedial "associative" portion. In primates, neurons in the dorsolateral portion of the STN respond during movements and to somatosensory stimulation (Georgopoulos et al. 1983; DeLong et al. 1985; Wichmann et al. 1994a). These neurons have mean firing

rates 18-25 Hz with some bursting activity and 55% respond to limb movements (Bergman et al. 1994). The ventromedial portion of the STN appears to be involved in oculomotor and associative aspects of motor behaviour and the neurons are activated during visuo-oculomotor tasks (Matsumura et al. 1992). STN neurons in rats have also been shown to display slow, rhythmic discharge oscillations that are dependent on intrinsic membrane currents (Bevan and Wilson 1999; Beurrier et al. 1999; Allers et al. 2000).

*Inputs to the subthalamic nucleus*

The STN receives inhibitory input from the GPe (Rouzaire-Dubois et al. 1980; Carpenter et al. 1981; Parent and Hazrati 1995a). Injections of bicuculline (a GABA receptor antagonist) into the rat STN increases STN activity and results in a pronounced increase in the activity of the STN target structures (Robledo and Feger 1990) thereby indicating that the GPe provides a tonic inhibition of the STN.

The STN, in addition to being part of the indirect pathway (striatum-GPe-STN-GPi), is part of the cortico-STN-GPi-thalamic pathway (Alexander and Crutcher 1990). It receives topographically organized excitatory glutamatergic projections from diverse regions of the ipsilateral cortex (Kitai and Deniau 1981; Afsharpour 1985b; Rouzaire-Dubois and Scarnati 1985, 1987; Canteras et al. 1988; Nambu et al. 1996; Awad et al. 2000). Cortical input to the STN also arises from the frontal eye field and from the supplementary frontal eye field (Akert and Hartmann-von Monakow 1980). Interactions between cortical and GPe inputs to the STN are also observed. In the rat, the response of the STN to cortical stimulation can be shaped by the GPe (Ryan and Clark 1991;

Mouroux et al. 1995). Electrical stimulation of the cortex results in a short latency excitation of the STN followed by an inhibitory period that is likely mediated by the GPe (Fujimoto and Kita 1993).

The STN also receives cholinergic, GABAergic and glutamatergic projections from the mesopontine tegmentum, an area that includes the PPN, the midbrain extrapyramidal area, and the laterodorsal tegmental nucleus (Hammond et al. 1983; Canteras et al. 1990; Bevan and Bolam 1995). Lastly, the STN receives excitatory input from the CM/Pf complex of the thalamus (a part of the thalamic intralaminar structure) (Canteras et al. 1990; Feger et al. 1994; Mouroux et al. 1995). The glutamatergic terminals of the inputs to the STN from the cortex and the CM/Pf of the thalamus converge with GABA-positive terminals that are thought to originate from the GP (Bevan et al. 1995). Therefore, the STN likely has motor, associative, and cognitive functions since it is a convergent site of pallidal, brainstem, corticomotor and frontal projections (Monakow et al. 1978; Parent and Hazrati 1995a).

*Output of the subthalamic nucleus*

The STN plays a central role in BG circuitry (Alexander and Crutcher 1990) since it receives input from and projects to many diverse nuclei. The STN is the only nucleus of the BG that exerts an excitatory glutamatergic drive to its target nuclei (Smith and Parent 1988; Albin et al. 1989b). The STN projects massively to the GPi and to the SNr (Carpenter et al. 1981; Parent and Hazrati 1993; Smith et al. 1994b; Parent and Hazrati 1995a; Smith et al. 1998). The excitatory drive of the STN to the GPi is supported by

studies in intact monkeys in which a reduction in the firing rates of GPi neurons is observed following lesion making in the STN (Hamada and DeLong 1992a).

The STN sends excitatory output to GPe and also receives GABAergic input from the GPe, and thus the GPe provides feedback inhibition to the STN (Rouzaire-Dubois et al. 1980; Parent and Hazrati 1995a). These reciprocal connections make up the "STN-GPe network" (Shink et al. 1996) which has been shown to have oscillatory properties (Plenz and Kital 1999) that may be driven by the cortex (Magill et al. 2000). The inhibitory drive of the GPe on the STN is supported by studies in monkeys showing that muscimol (a GABA receptor agonist) injected into the STN decreases the activity of STN neurons while bicuculline (a GABA receptor antagonist) injections slightly increase the activity of STN neurons (Wichmann et al. 1994b). Similar to the GPi, reduced firing rates of GPe neurons are observed following STN lesions in the monkey (Hamada and DeLong 1992a).

The STN also has connections to the striatum, cerebral cortex, substantia inominata, PPN, and mesencephalic and pontine reticular formation (Smith et al. 1990; Parent and Hazrati 1993; Smith et al. 1994b; Parent and Hazrati 1995a). For example, in the rat STN, the dorsilateral sensorimotor portion projects to the GP and the putamen while the ventromedial "associative" zone projects to the caudate nucleus and the SNr (Parent 1990).

*Inactivation studies of the subthalamic nucleus*

Bilateral STN lesions in intact rats have multiple, dissociable effects on attentional performance such as discriminative deficits, impulsivity and perseverative

behaviour (Baunez and Robbins 1997). Bilateral microinfusions of NMDA receptor antagonist or muscimol into the STN of rats reproduce the effects of lesions (Baunez and Robbins 1999). In intact monkeys, blocking excitatory amino acid tramission results in choreiform and ballistic dyskinesias (Robertson et al. 1989). Subthalamic lesions in normal humans and monkeys induce hemiballism or dyskinesias ipsilateral to the lesion (Carpenter et al. 1950; Hamada and DeLong 1992b; Guridi et al. 1996; Absher et al. 2000).

*Dopaminergic modulation of the subthalamic nucleus*

Anatomical data in monkeys suggest that the STN receives dopaminergic input (Francois et al. 2000). In the rat, dopamine can directly affect the STN by acting on dopaminergic binding sites within the STN (Meibach and Katzman 1979; Campbell et al. 1985; Bouthenet et al. 1987; Kreiss et al. 1996, 1997; Hassani et al. 1997; Hassani and Feger 1999; Cossette et al. 1999; Murer et al. 1999). STN neurons receive afferent input from the SNc and are modulated by microiontophoresis of dopaminergic substances (Campbell et al. 1985). Administration of APO in anesthetized intact rats increases STN firing rates primarily through the excitatory effects of $D_1$ receptor stimulation directly on the STN (Kreiss et al. 1996). The localization of dopaminergic markers in the human STN from postmortem tissue sections reveals no $D_1$ or $D_2$ receptor mRNA-expressing cells and only weak $D_1$-like binding suggesting that the effects of dopaminergic agents on the activity of STN neurons may be indirect and mediated via interaction with dopamine $D_1$-like receptors (Augood et al. 2000). STN afferents arising from cortical areas are also innervated by midbrain dopamine neurons (Descarries et al. 1987). The activation of

presynaptic $D_1$ sites distributed on excitatory terminals of these inputs is also excitatory to STN activity (Kitai and Deniau 1981; Fujimoto and Kita 1993; Augood et al. 2000).

### *1.3.4 - Globus pallidus*

Movement-related activity of neurons in the GP occurs primarily after the onset of muscle contraction indicating that the BG are not involved in the preparation for movement or the initiation of movement (DeLong 1971; Anderson and Horak 1985; Mink and Thach 1987). GP units can discharge in relation to visually-cued step-tracking (Georgopoulos et al. 1983), ballistic movements (Mink and Thach 1987), specific limb and direction of movement (Mitchell et al. 1987), passive joint rotation and movement parameters such as force, acceleration, initiation, and termination (DeLong 1971; DeLong et al. 1985), internal movement during the preparatory movement phase (Brotchie et al. 1991a), visually directed-open loop or ballistic movements (Mink and Thach 1991a, 1991b), and pre-cued reaching (Jaeger et al. 1993). In most of these studies the direction of movement is encoded by the cells. It has been suggested that during voluntary movement in monkeys, GP activity is correlated with motor outputs, sensory inputs, and perceptual abstractions of these sensory-motor events (Aldridge et al. 1980a, 1980b). However, it has also been suggested that GP neurons do not consistently code for particular movement parameters (Mink and Thach 1991a, 1991b). Simultaneous microelectrode recordings in the GP of intact monkeys demonstrate that pallidal neurons are not synchronized and "act independently" (Nini et al. 1995).

It is interesting that some of the neuronal activity of the GPi is modulated by movements and tasks that are performed poorly in PD (see section 1.1). Studies of

conscious monkeys performing sequential wrist movements indicate that pallidal neurons code for an internal cue for predictable events and may signal the end of a movement sequence (Brotchie et al. 1991a). This suggests that BG function is related to the performance of automatic movements, rather than voluntary (Brotchie et al. 1991b). It has been shown that remembered sequences are encoded by pallidal neurons and suggested that the pallidum may be involved in the process of learning a sequence of actions (Mushiake and Strick 1995).

*1.3.4.a - External segment of the globus pallidus*

Neurons of the GPe are GABAergic and form a homogenous population. The GPe is considered to be an intrinsic nucleus of the BG because it receives all of its input from and sends output to other BG nuclei (Mink 1996). GPe neurons respond to somotatosensory input and are involved in the control of movement parameters (DeLong 1971, 1985; Georgopoulos et al. 1983; Dormont et al. 1997). Injection of bicuculline into the GPe of intact monkeys causes increased GPe activity and elicits dyskinesias (Crossman et al. 1988; Matsumura et al. 1995). Electrophysiological studies demonstrate that the majority of GPe neurons fire in high frequency discharges that are followed by pauses and have 35-45 Hz mean firing rates (DeLong et al. 1985). APO also modulates slow frequency discharge oscillations of GP neurons in rodent studies (Ruskin et al. 1999).

*Input to the external segment of the globus pallidus*

As described above, the GPe receives an inhibitory projection from the striatum and an excitatory projection from the STN. Striatal input incorporates the $D_2$ receptor and is part of the indirect pathway. The administration of APO in intact rats causes an increase in the firing rates of GPe neurons (Bergstrom et al. 1982). The GP in rats (which is equivalent to the GPe in primates) also receives excitatory input from the parafascicular nucleus of the thalamus (Mouroux et al. 1997).

*Output of the external segment of the globus pallidus*

The GPe sends inhibitory output to the STN (Rouzaire-Dubois et al. 1980; Carpenter et al. 1981; Parent and Hazrati 1995a) and can exert significant control over the firing patterns in the STN. For example, it has been shown that the GPe influences the firing rate and discharge pattern as well as the degree of correlated firing of adjacent STN neurons in the rat (Ryan et al. 1992). The GPe sends GABAergic input to the GPi and the SNr (Bolam and Smith 1992), projects to the striatum, and to the reticular nucleus of the thalamus (Parent and Hazrati 1995a). Therefore, the GPe can strongly inhibit the neurons of the output structures of the BG through it's connections with the STN and directly to GPi (Alexander and Crutcher 1990).

*1.3.4.b - Internal segment of the globus pallidus*

Similar to GPe, neurons of the GPi are GABAergic and form a homogenous population. Anatomical evidence shows that the dendritic trees of the GP cells can cover up to 30 % of the cross sectional area of the nucleus which is indicative of the

opportunity for the convergence of information from the striatum (Parent and Hazrati 1995b). In intact monkeys, GPi neurons have a mean firing rate of 60-80 Hz and respond to somotatosensory input (Georgopoulos et al. 1983; DeLong et al. 1985; Hamada et al. 1990). This high rate of activity is believed to exert a tonic inhibitory effect on the target nuclei of the GPi (Chevalier et al. 1985).

*Afferent input to the internal segment of the globus pallidus*

The GPi receives inhibitory striatal input and is part of the direct pathway of the BG. The GPi also receives substantial excitatory input from the STN as part of the indirect pathway (Parent and Hazrati 1995a). STN efferent fibers establish numerous synaptic contacts on GPi neurons. This is in contrast to the much higher specificity of striatopallidal projection (Parent and Hazrati 1993). The GPi also receives GABAergic input from the GPe (Bolam and Smith 1992; Bevan et al. 1997)

Anatomical tracing techniques demonstrate that subthalamic and neostriatal axonal terminals make convergent synaptic contact with GPi output neurons that project to the thalamus (Bevan et al. 1994a) and may modulate direct striatopallidal input (Bolam and Smith 1992; Hazrati and Parent 1992b; Smith et al. 1998). It is suggested that the STN uniformly excites a large number of GPi neurons, whereas the striatum exerts a more specific inhibitory control upon selected subsets of subthalamically driven pallidal neurons thereby providing a more focalized effect (Parent and Hazrati 1993). GPi firing rates are also reduced following the administration of APO in intact monkeys (Boraud et al. 2001), likely due to the influence of APO on both the direct and indirect pathways.

*Output of the internal segment of the globus pallidus*

The GPi is the major output nucleus of the BG and sends inhibitory projections to nucleus ventro-oralis posterior (Vop) and nucleus ventro-oralis anterior (Voa) of the thalamus and the brainstem (Carpenter et al. 1981; Ilinsky et al. 1993; Parent and Hazrati 1995b; Inase and Tanji 1995). Three-dimensional tracings of pallido-thalamic axons in the monkey demonstrate that GPi information might be distributed throughout the pallidal territory of the thalamus by means of numerous axonal branches and dense terminal arborizations (Arecchi-Bouchhioua et al. 1996, 1997). The outflow of the GPi on the thalamus has an impact on the supplementary and presupplementary motor cortices (Alexander et al. 1986; Hoover and Strick 1999).

*Inactivation studies of the internal segment of the globus pallidus*

In intact monkeys, bicuculline injected into the GPi induces dose-dependent hypokinesia with dystonic attitudes in contralateral limbs whereas muscimol injections elicit choreiform movements (Burbaud et al. 1998). Neurotoxic blockade or lesions of the GPi in normal monkeys lead to poor braking of movement (Horak and Anderson 1984; Mink and Thach 1991c) and inaccuracy of control of the final adjustment of the limb to the target (Kato and Kimura 1992).

### *1.3.5 - Substantia nigra pars reticulata*

The SNr is the other major output pathway of the BG. The motor portion of the SNr has similar morphological and physiological properties as the motor portion of the GPi (Grofova et al. 1982; DeLong et al. 1983; Francois et al. 1987; Yelnik et al. 1987).

In monkeys, SNr neurons show phasic responses in motor tasks or with somatosensory examination (Mora et al. 1977; DeLong et al. 1983; Schultz 1986b; Lestienne and Caillier 1986). The SNr is also involved in occulomotor functions (Hikosaka and Wurtz 1983a). It has been shown that injections of muscimol in the SNr disrupts guided and reflex eye movements in the cat (Boussaoud and Joseph 1985).

*Afferent input of the substantia nigra pars reticulata*

The SNr receives input from the motor territory of the striatum (Szabo 1967; Hedreen and DeLong 1991; Lynd-Balta and Haber 1994), GABAergic inputs from GPe (Bevan et al. 1996), and excitatory drive from the STN (Parent and Hazrati 1993). Afferent inputs from the striatum, the GP, and the STN converge onto single SNr neurons (Chang et al. 1984; Bolam and Smith 1992; Bolam et al. 1993; Bevan et al. 1994b). It has also been demonstrated that cortico-STN input can modulate the inhibitory influence of the direct striato-nigral pathway on SNr neurons (Maurice et al. 1999).

*Output pathways of the substantia nigra pars reticulata*

Similar to the GPi, the SNr sends efferents to the thalamus (Carpenter et al. 1976; Ilinsky et al. 1993; Percheron et al. 1996) which then projects to pre-motor cortical areas. Transitory blocks of SNr firing (induced by either intranigral application of GABA or by stimulating the inhibitory striato-nigral pathway), demonstrates that the striatum causes excitation of thalamocortical cells by a disinhibion process mediated via the striato-nigrothalamic pathway (Deniau and Chevalier 1985). The SNr also projects to the superior colliculus (Hikosaka and Wurtz 1983b; Parent et al. 1983; Nishimura et al.

1997). SNr projections to the superior colliculus and thalamus are mainly derived from different neurons, with some neurons projecting axon collaterals to both the superior colliculus and thalamus (Bentivoglio et al. 1979).

### *1.3.6 - Thalamus*

Thalamocortical projection neurons in the ventral anterior, ventrolateral thalamus and CM/Pf complex receive input from the GPi and SNr (Kultas-Ilinsky et al. 1983; Ilinsky et al. 1993; Inase and Tanji 1995). Thalamocortical neurons exert a strongly excitatory glutamatergic effect on the cortex. Pallidal and cerebellar receiving areas of the ventrolateral nuclear complex of the thalamus are the two main areas of interest with regards to PD. According to the Hassler terminology, pallidal receiving areas (Voa and Vop) are located anterior to cerebellar receiving areas (nucleus ventro-intermedius, Vim). Although pallidal and cerebellar afferents do not converge in the ventrolateral thalamus, their thalamic-receiving regions send overlapping input to the motor and premotor cortex (Rouiller et al. 1994). This suggests that pallidal activity can interact at the cortical level with cerebello-thalamocortical loop.

In the Voa and Vop thalamus of intact monkeys, 50% of cells respond to sensory stimuli, 30% of cells respond to voluntary movements, and 20% of cells have no response to movement or sensory stimuli. Neuronal responses in the ventral motor thalamus are somatotopically arranged with distinct subregions representing each limb (Vitek et al. 1994) and focal lesions of this region in humans result in prominant movement disorders especially those involving dyskinesias or dystonias (Lee and Marsden 1994).

### *1.3.7 - Pedunculopontine nucleus*

The PPN contains both cholinergic and non-cholinergic neurons and is located in the mesopontine tegmentum. The PPN is involved in posture and locomotion (Garcia-Rill 1986; Albin et al. 1989a) and the ongoing control of motor performance and reinforcement processes (Dormont et al. 1998; Conde et al. 1998). PPN neurons receive descending GABAergic projections from the GPi and SNr but afferents also arise from other sources (Carpenter et al. 1981; Edley and Graybiel 1983; Inglis and Winn 1995; Steininger et al. 1997). A major projection of the PPN is to the SNc (Carpenter et al. 1981) where dopaminergic nigrostriatal neurons receive excitatory input from the PPN (Kojima et al. 1997). It has been suggested that lesions of the PPN in intact macaque monkeys result in parkinsonism (Kojima et al. 1997) due to a decrease in nigrostriatal neuron activity. Thalamostriatal neurons are also contacted by axons emerging from the PPN and indicates the possible existence of tegmento-thalamic feedback circuits in the rat (Erro et al. 1999).

### *1.3.8 - Cortex*

Cortical ablation experiments in monkeys demonstrate that the cerebral cortex strongly influences the spontaneous discharge properties in the BG (Aldridge et al. 1990). For example, ablations of areas 4 and 6 in the precentral cortex demonstrate that neuronal discharge bursting in the putamen is under cortical control (Aldridge and Gilman 1991). All regions of the cortex project to the striatum but BG output pathways lead most strongly to the frontal cortex (motor cortex, premotor cortex, and prefrontal cortex)

suggesting that the BG can affect such cortical functions as planning, memory, and intention (Hoover and Strick 1993).

## 1.4 - Models of the function of the basal ganglia in Parkinson's disease

### *1.4.1 - The box model of the basal ganglia*

The current model of BG function has considerably advanced our understanding of the pathophysiological mechanisms of movement disorders (Albin et al. 1989a; DeLong 1990; Wichmann and DeLong 1996). It provides a coherent explanation of opposing movement disorders, those involving hypokinesia and hyperkinesia (DeLong 1990), and can be used to predict the effects of dopamine or lesions in the BG (Lang and Lozano 1998b). For lack of a better name, this model will be referred to as the "box" model which reflects the serial order of its nuclei. A schematic diagram of the box model of BG function is shown in Figure 1.F2.

In the model shown in Figure 1.F2A, corticostriatal activity can influence the activity of the rest of the BG through two main pathways (Alexander and Crutcher 1990). Cortical activity which activates the direct pathway causes decreased activity in GPi and facilitation of intended movements through a process of disinhibition of thalamocortical relay neurons (Chevalier et al. 1985; Chevalier and Deniau 1990). In contrast, activation of the indirect pathway disinhibits the STN and causes increased activity in GPi, therefore leading to suppression of unintended movements. The model proposes that there is a balance between the direct and indirect pathways at the level of the output nuclei of the BG whereby the inhibitory effect of the direct striatal output counteracts the

excitatory effect of the STN in the indirect pathway. Some of the limitations of the box model are that it does not include (1) the direct connections from the GPe to the GPi (Parent and Hazrati 1993), (2) the reciprocal relation between the STN and the GPe, (3) the role of the cortico-STN projection or the CM/Pf-striatal projection., (4) the role of extrastriatal dopamine, and (5) the role of the PPN.

*The box model of the basal ganglia and Parkinson's disease*

The loss of striatal dopamine affects the activities of the direct and indirect pathways in an opposite manner. Since dopamine is excitatory to striatal neurons that give rise to the direct pathway (i.e. those neurons expressing GABA/SP/dynorphin), the lack of dopamine will disinhibit the GPi via the direct path. The resultant changes in the box model are shown in Figure 1.F2B. Since dopamine acting on $D_2$ receptors is inhibitory to striatal neurons that give rise to the indirect path, dopamine depletion will cause an inhibition of the GPe in the indirect path and subsequent increased activity in the STN. In turn, the STN further drives the GPi via excitatory glutamatergic connections. Therefore, the box model predicts that the activity of the GPi is elevated in PD. The increase in GPi activity provides an increased inhibition of the ventroalateral thalamus and brainstem areas and hence a reduction cortical activity (Albin et al. 1989a; Mitchell et al. 1989; DeLong 1990; Filion and Tremblay 1991). Diminished cortical activity, secondary to a hyperactive GPi output, therefore underlies bradykinesia and akinesia. The abnormal increase in GPi activity might also manifest itself as near saturation discharge, noisy output, and hyper-responsiveness to sensory input that would then lead to an impaired modulation of neuronal activity in the BG-thalamo-cortical loop

(Miller and DeLong 1987; Filion et al. 1988; Filion and Tremblay 1991; Bergman et al. 1994; Hutchison et al. 1994a; Tresilian et al. 1997).

In addition, increased inhibitory drive by the GPi is predicted to lead to a hyperpolarization of thalamic target neurons and an increased tendency for these neurons to discharge in 3-6 Hz oscillatory bursts which would result in limb tremor (Jahnsen and Llinas 1984; Paré et al. 1990; Llinás and Paré 1995). The systemic administration of dopaminergic medication would be predicted by the box model to decrease GPi and STN activity and increase GPe activity. Lesions of the GPi or STN, which are expected to produce a reduction in the outputs of these nuclei should also lead to a disinhibition of the thalamus and an improvement in parkinsonism. This model is discussed in further detail elsewhere (Albin et al. 1989a; DeLong 1990; Wichmann and DeLong 1996).

### *1.4.2 - Parallel subcircuits model of the basal ganglia*

As mentioned above, the functional architecture of the BG can be viewed as being composed of a collection of segregated pathways (DeLong 1983; Alexander et al. 1986; Hoover and Strick 1993) and this organization may allow the BG to concurrently participate in both the motor and complex non-motor functions of the cerebral cortex (DeLong et al. 1984; Alexander et al. 1990; Middleton and Strick 1994). However, other studies also suggest that there is a high degree of convergence of these functionally distinct circuits. Corticostriatal, corticosubthalamic, subthalamopallidal, and striatopallidal pathways all have the potential to "funnel" information within the BG (Percheron et al. 1984; Tremblay and Filion 1989; Flaherty and Graybiel 1991; Flaherty and Graybiel 1993; Parent and Hazrati 1993; Flaherty and Graybiel 1994; Parent and

Hazrati 1995a). This indicates that cross talk between parallel subcircuits is possible and may play a role in the integration of cortical and striatal information through the BG (Percheron and Filion 1991; Hazrati and Parent 1992b; Graybiel et al. 1994).

*Parallel subcircuits model of the basal ganglia in Parkinson's disease*

It has been hypothesized that the segregation between parallel subcircuits in the BG breaks down due to dopamine depletion in the striatum and this may account for many of the features of PD (Filion et al. 1994; Raz et al. 1996; Bergman et al. 1998a). This hypothesis predicts that a loss of striatal dopamine leads to an increase in synchronized neuronal activity in the BG which may play a role in genesis of limb tremor (Bergman et al. 1998a) or dyskinesias (Vitek and Giroux 2000) and that oscillations of the whole BG may underlie the clinical features of PD (Raz et al. 2001). It predicts that a loss of dopamine leads to a reduction in the specificity of somatosensory responses in the target nuclei of the striatum that is reversed with APO administration (Tremblay et al. 1989). It also predicts that lesions would have a desynchronizing effect on the abnormally synchronized activity in the BG-thalamo-cortical network and may explain why certain lesions of the BG, such as pallidotomies, can relieve both akinesia and hyperactive movements (i.e. limb tremor or dyskinesias) (Bergman et al. 1998a, Vitek and Giroux 2000).

### *1.4.3 - Tremor models*

There are two hypotheses concerning the generation of parkinsonian limb tremor, the peripheral and central mechanisms, that should also be discussed. The peripheral

mechanism hypothesis states that parkinsonian tremor results from unstable long-loop transcortical reflex arc (Oguztoreli and Stein 1976). Sinusoidal mechanical driving can entrain PD rest tremor with an EMG discharge that is indistinguishable from a reflex response (Rack 1987; Rack and Ross 1986) suggesting that peripheral reflexes are important in parkinsonian tremor. It has been suggested that 4-Hz resting tremor of PD can be attributed to a flip-flop oscillation involving the mutually inhibitory connections between the spinal stretch reflexes of antagonist muscles, the supraspinal contribution to the tremor limited to an "aperiodic" descending facilitation of spinal reflex pathways (Burne 1987).

The central oscillator hypothesis proposes that tremor is caused by oscillations in central structures in the absence of sensory input. In PD patients with tremor, PET analysis demonstrates increased metabolic activity in a network comprising the thalamus, pons, and premotor cortical regions, indicating increases in the functional activity of thalamo-motor cortical projections (Antonini et al. 1998). This hypothesis is supported by a variety of studies (Lee and Stein 1981; Britton et al. 1992; Britton et al. 1993a; Volkmann et al. 1996). Consistent with the central oscillator hypothesis, it has been demonstrated that magnetic brain stimulation over the motor cortex can modulate limb tremor in patients with PD (Britton et al. 1993b).

It is also possible that the origin of tremor oscillations might involve both peripheral and central mechanisms (Stiles and Pozos 1976; Oguztoreli and Stein 1979; Elble 1996; Rothwell 1998). Peripheral input might resonate with central structures and affect strength of phase of oscillation (Lee and Stein 1981; Rack and Ross 1986; Lenz et al. 1993; Zirh et al. 1998).

### *1.4.4 - Other models of basal ganglia function*

As demonstrated above in section 1.3, there is an anatomical basis for both motor and non-motor functions of the BG. The general aspects of motor control of the BG include execution, planning, learning, and memory. The non-motor functions of the BG include motivation (reward, conditioning), memory and cognition (action oriented, internally directed). There are various hypotheses that incorporate many of these features and some of the more interesting of these are listed below.

The BG are involved in context-dependent behavioral planning (Eblen and Graybiel 1995). The cortico-BG-thalamocortical circuit is a neural optimal control system (Baev 1995). The BG support a basic attentional mechanism in the executive forebrain to bind voluntary effort, sensory input, and the calling up and operation of a sequence of motor programmes or thoughts. (Brown and Marsden 1998). The BG permit the routine automatic execution of sequences of movements generated in cortical motor areas (Marsden and Obeso 1994). The BG are involved in the internal cueing of sequences of movements (Brotchie et al. 1991a, 1991b). The BG play a role in scaling the magnitude of muscle activity (Anderson and Horak 1985; Berardelli et al. 1996a). The BG use focused selection and inhibition to turn off "automatic" postural activity (or other competing motor programs) so that voluntary movement can occur (Mink 1996).

## 1.5 - The neurophysiology of Parkinson's disease

The animal models that have been used to investigate PD include rats, monkeys, marmosets, guinea pig, dogs, cats, sheep, mice, and goldfish. However, all of these

animal models do not necessarily display the wide spectrum of clinical and pathological features observed in humans with PD. By far, the most widely used animals are rats and monkeys and the following review of the neurophysiology of PD will concentrate on these animals in addition to findings in parkinsonian patients. The rat model of PD is produced by making 6-hydroxydopamine (6-OHDA) lesions in the nigrostriatal tract. In rats with unilateral lesions of the nigrostriatal tract, the administration of APO produces a circling response towards the lesioned side.

Research of central brain structures in humans using invasive methods like electrophysiological recordings is only possible during brain surgery for movement disorders. The neurosurgical treatment of PD in humans started in the late 1930's (Meyers 1940) and led to the work of Cooper (Cooper 1954, 1956, 1960), Narabayashi (Narabayashi 1954), Leksell (Svennilson et al. 1960). Cooper initially showed that chemical lesions of the pallidum in patients with PD could effectively treat parkinsonian symptoms (Cooper 1954, 1955). Surgery was then reduced after the introduction of levodopa in 1968. With the advancements in imaging such as magnetic resonance imaging (MRI) and microelectrode techniques, there was a resurgence of pallidotomy in the early 1990s and a refinement in the lesion location (Laitinen et al. 1992a; Lozano et al. 1995). Greater understanding of parkinsonian pathophysiology led to surgery of the STN (Pollak et al. 1993; Benabid et al. 1994; Barlas et al. 2001; Alvarez et al. 2001). Our knowledge of neurophysiology of PD in humans also comes from the use of non-invasive techniques, such as PET, MRI, EEG, magnetoencephalography (MEG), and transcranial magnetic stimulation.

*Current primate model of Parkinson's disease*

The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated non-human primate model of PD is the most reliable model of PD discovered (Burns et al. 1983; Langston et al. 1984a, 1984b; Kopin and Markey 1988; DeLong 1990; Bloem et al. 1990). This neurotoxin produces similar biochemical, anatomical, and physiological changes both in humans and non-human primates that closely resemble the degeneration found in patients with PD (Chiueh et al. 1985; Doudet et al. 1985; Kitt et al. 1986; Forno et al. 1986; Elsworth et al. 1987a, 1987b, 1989; Schultz et al. 1989). Administration of MPTP leads to the selective loss of dopaminergic neurons in the SNc since MPTP is metabolized by monoamine oxidase B to the toxin MPP+ which is then taken up by dopaminergic neurons in SNc. MPTP can be infused into the internal carotid artery of monkeys to produce toxin-induced injury to the ipsilateral nigrostriatal pathway with sparing of other dopaminergic neurons on the infused side and with negligible or little injury to the opposite, untreated side (Benazzouz et al. 1992). Similar to humans, a decrease of greater than 95% of striatal dopamine in monkeys with SNc neurodegeneration is required to produce parkinsonian motor abnormalities (Elsworth et al. 2000). These parkinsonian monkeys display contralateral limb dystonic postures, rigidity, and bradykinesia. Untreated animals circle towards the injured side, whereas treatment with levodopa or APO stimulates circling towards the intact side (Bankiewicz et al. 1986). The MPTP model can also replicate levodopa-induced dyskinesia and response fluctuations that are commonly observed in the later stages of PD (Clarke et al. 1987; Clarke et al. 1989).

*Drawbacks of the current primate model of Parkinson's disease*

A drawback of the MPTP-treated non-human primate model of PD is that not all primate species develop similar parkinsonian symptoms. Although the MPTP model produces symptoms that closely resemble those found in patients with PD, species differences exist especially with regard to the presentation of rest tremor (Bergman et al. 1998b). Vervet (African green) monkeys develop 3-6 Hz rest tremor that can be aggravated by stress (Bergman et al. 1990; Raz et al. 2000) thereby closely resembling that found in patients with PD. Rhesus monkeys develop akinesia/bradykinesia and rigidity but do not develop low frequency resting tremor but instead they develop 10-16 Hz action/postural tremor (Burns et al. 1983). It has also been demonstrated that the schedule of MPTP administration might induce different mechanisms of neuronal death in the SNc in monkeys (Bezard et al. 1997c; Bezard et al. 1998). The occurrence of various dyskinesias also depends on the time span of dopaminergic treatment (Boyce et al. 1990).

### *1.5.1 - Striatum*

*Dopaminergic activity in the striatum*

In patients with PD, the loss of dopamine in the striatum is not uniform, such that there is a greater loss of dopaminergic input to the putamen than the caudate (Bernheimer et al. 1973). PET in parkinsonian patients also indicates long-term down regulation of striatal dopamine $D_2$ receptor binding. These receptor changes may be induced by chronic dopaminergic therapy or occur independently of treatment, as a result of structural adaptation of the postsynaptic dopaminergic system to the progressive decline

of nigrostriatal neurons (Antonini et al. 1997). Pharmacological manipulation of both $D_1$ and $D_2$ receptors is however required for an optimal therapeutic response (Barone et al. 1987). It has also been shown that the striatum responds to repeated stimulation by dopamine agonists with an increase in sensitivity (Deshaies et al. 1984) and with repeated administration of dopaminergic medication leading to dyskinesias (Henry et al. 1998).

*Neuronal activity in the striatum*

Unilateral dopamine depletion in MPTP-treated monkeys substantially reduces the acquired sensory responsiveness of striatal interneurons. This deficit is reversed by APO administration (Aosaki et al. 1994b). Following the development of parkinsonian symptoms in MPTP-treated monkeys, there is also the emergence of 15-25 Hz oscillatory activity in the TANs that is correlated with neuronal activity in the GPi and STN (Raz et al. 2001). However, the strength of coupling between TANs in the dopamine depleted state is not changed (Raz et al. 1996). In rats treated with unilateral nigral injection of 6-OHDA, there is an absence of corticostriatal long-term potentiation (Centonze et al. 1999).

### *1.5.2 - Globus pallidus*

*Firing rates of the globus pallidus*

In rhesus monkeys treated with MPTP, the subsequent loss of striatal dopamine has been shown to lead to an increase in the spontaneous activity of neurons in the GPi (Miller and DeLong 1987; Filion and Tremblay 1991;Bergman et al. 1994;Boraud et al. 1996). Conversely, the mean firing rates of neurons in the GPe are reduced below the

firing rates exhibited in the GPi (DeLong et al. 1985). Although no data are available from normal humans, consistent with these observations, the mean firing rates of the GPi are greater than those in GPe in patients with PD (Vitek et al. 1993; Hutchison et al. 1994a; Beric et al. 1996). The two subdivisions of the GPi in parkinsonian patients, a posteroventral portion (GPii) and an anterodorsal portion (GPie), display different mean firing rates with activity in the GPii being even more elevated than in the GPie (Hutchison et al. 1994a). These observations support the box model which predicts an increase in GPi firing rates and a decrease in GPe firing rates in PD.

*Firing patterns of the globus pallidus*

In addition to an increase in mean firing rates of the GPi following MPTP-treatment in monkeys, an increase in bursting activity is observed (Boraud et al. 1998; Bergman et al. 1994; Wichmann et al. 1999) and is correlated with the degree of parkinsonism (Filion and Tremblay 1991). In the GPe, neurons that display "low frequency discharge bursting" behavior have more frequent and longer bursts in the parkinsonian monkey (DeLong et al. 1985; Filion and Tremblay 1991).

Tremor cells (TCs) are defined as cells with periodic bursting or "oscillatory" activity that is time-locked to limb tremor. They are present in the GPi of patients with PD (Hutchison et al. 1997; Lemstra et al. 1999; Hurtado et al. 1999). Using simultaneous microelectrode recording techniques, it has been demonstrated that GPi neurons with tremor-related oscillatory activity are synchronized in parkinsonian patients (Hurtado et al. 1999) and in tremulous MPTP-treated vervet monkeys (Bergman et al. 1998a, 1998b; Raz et al. 2000) and tremulous MPTP-treated rhesus monkeys (Nini et al. 1995). It is

interesting to note that in addition to tremor-related oscillatory activity (3-8 Hz), synchronized neuronal oscillations at 15-25 Hz are observed in the GPi and GPe of tremulous MPTP-treated monkeys (Raz et al. 2000).

*Movement related responses of the globus pallidus*

In monkeys treated with MPTP, there is an increased proportion of GPi neurons that are responsive to somatosensory stimulation with an increase in the duration and magnitude of neuronal activity to limb movement (Bergman et al. 1994; Boraud et al. 2000a). GPi neurons in parkinsonian monkeys also have exaggerated responses and multi-limb receptive fields such as bilateral responses (Filion et al. 1988). In patients with PD, 20-35% of GPi neurons respond to somatosensory input (Hutchison et al. 1994a; Sterio et al. 1994) with many of these neurons responding to both contralateral and ipsilateral limb movements (Ohye et al. 1996). Similar responses are observed in the GPe (Hutchison et al. 1994a). It is interesting to note that lesions of the STN in parkinsonian monkeys decrease the magnitude of responses in the GPi to somatatosensory stimulation (Wichmann et al. 1994b).

*Inactivation effects of the globus pallidus*

In both MPTP-treated monkeys and parkinsonian patients, inactivation of motor territories of GPi with muscimol, a $GABA_A$ agonist, alleviates parkinsonian motor signs (Wichmann et al. 1994c; Penn et al. 1998). These results suggest that part of the increase in GPi activity is accounted for by a decrease in the activity of the GABAergic direct striatopallidal projections as predicted by the box model. It has been shown that

administration of the anti-glutamatergic drug riluzole normalizes GPi firing rates in MPTP-treated monkey (Boraud et al. 2000b) supporting the notion that the increased activity of the glutamatergic STN drives the GPi. The direct injection of the excitatory amino acid antagonist, kynurenic acid, into the GPi also reverses parkinsonism (Graham et al. 1990; Brotchie et al. 1991c).

Pallidotomy significantly improves all cardinal parkinsonian motor signs (tremor, rigidity, akinesia/bradykinesia) and reduces drug-induced motor fluctuations and dyskinesias (Laitinen et al. 1992a, 1992b; Sutton et al. 1995; Lozano et al. 1995, 1998; Dogali et al. 1995; Baron et al. 1996; de Bie et al. 1999) with benefits lasting at least 4-5 years following surgery (Baron et al. 2000). A review of the effects of pallidotomy performed by different centers is given by Vitek and Bakay (Vitek and Bakay 1997). The amelioration of parkinsonian symptoms following lesions of the GPi indicates that this nucleus is hyperactive and/or has aberrant neuronal patterns in patients with PD (Lozano et al. 1995; Vitek and Giroux 2000). Direct evidence is provided by a PET study showing that glucose hypermetabolism in the lenticular area of PD patients is reduced following pallidotomy (Dogali et al. 1994). The prediction of the box model that pallidotomy results in an improvement in motor function in patients with PD due to a release of motor cortical areas is supported by functional imaging and PET studies (Ceballos-Baumann et al. 1994; Grafton et al. 1995; Eidelberg et al. 1996; Samuel et al. 1997).

However, there are two major points of interest concerning the effects of pallidotomy. First, dramatically reducing pallidal outflow would be predicted by the box model of BG function to produce hyperactive movements (i.e. dyskinesias) and not

abolish them. It has been suggested that the reduction of dyskinesias and tremor by GPi lesions might be due to the desynchronizing effect of the lesion (Vitek and Giroux 2000; Deuschl et al. 2000), which would be consistent with the predictions of the parallel model of BG function in PD. This is supported by studies demonstrating that better tremor control is shown in those patients in whom tremor-synchronous cells have been included in a lesion of the GPi (Taha et al. 1997) or of the thalamus (Lenz et al. 1995). Second, it is interesting that movement deficits are not produced following pallidotomies given that the BG are extensively involved in motor control. The effectiveness of pallidotomy is a paradox because eliminating most of the pallidal motor output might worsen voluntary movements (Marsden and Obeso 1994). Limited data suggest that while pallidotomy is effective in reducing bradykinesia of upper limb movements, it has "costs" to movement patterns, particularly for reach to grasp movements to objects of differing sizes (Bennett et al. 1998). Another drawback of pallidotomy is that it may adversely affect cognitive performance if performed bilaterally but it has been reported that staged bilateral pallidotomies do not produce this deficit (Counihan et al. 2001).

Furthermore, the box model of BG function does not predict that inactivation of motor territories of GPe in MPTP-treated monkeys would have no effect on parkinsonian motor signs (Wichmann et al. 1994c). GPe inactivation would be predicted to disinhibit the STN and worsen parkinsonism. Similarly, GPe inactivation has been shown to worsen drug-induced dyskinesias (Blanchet et al. 1994) but the opposite would be predicted by the box model.

*Deep brain stimulation of the globus pallidus*

Deep brain stimulation (DBS) is a reversible neurosurgical procedure in which chronic electrodes are placed in the brain. It is possible to alter the electrical stimulation parameters in order to obtain maximal improvement in symptoms with minimal adverse side effects. In patients with PD, chronic bilateral GPi DBS improves parkinsonian symptoms such as akinesia and tremor and drug-induced dyskinesias (Krack et al. 1998a). High-frequency stimulation of the GPi reduces the neuronal activity of the GPi activity in MPTP-treated rhesus monkeys (Boraud et al. 1996) and it has been proposed that a possible mechanism mediating the effects of DBS in the GPi is via activation of GABAergic afferents within the GPi (Boraud et al. 1996; Dostrovsky et al. 2000). Similar to pallidotomy, imaging studies have revealed that GPi DBS causes increases in regional cerebral blood flow in motor cortical areas (Davis et al. 1997; Limousin et al. 1997). One advantage of DBS over pallidotomy is that bilateral stimulation of the GPi does not produce cognitive impairment (Ardouin et al. 1999). However, given the position of pallidal DBS electrodes relative to the internal capsule, a possible unwanted side effect is that GPi DBS may inadvertently activate the corticospinal tract (Ashby et al. 1998).

*Effects of dopaminergic drugs on the globus pallidus*

Consistent with the predictions of the box model, in monkeys made parkinsonian with midbrain electrolytic lesions of the nigrostriatal dopaminergic pathway, APO reduces the activity of GPi neurons and reverses parkinsonian symptoms (Filion 1979). Similar effects are observed in monkeys rendered parkinsonian with MPTP following the

administration of levodopa or APO (Filion et al. 1991; Boraud et al. 1998; Boraud et al. 2001). During episodes of dopaminergic drug-induced dyskinesias in parkinsonian monkeys, firing rates of GPi neurons are reduced or even nearly silenced (Papa et al. 1999;Boraud et al. 2000b;Boraud et al. 2001). Metabolic studies in monkeys with APO or levodopa induced dyskinesias show increased activity in the GPi that is interpreted as an increase in the GABAergic input from the striatum (Mitchell et al. 1992). Also consistent with the predictions of the box model, an increase in GPe activity following APO administration has been reported in MPTP-treated monkeys (Filion et al. 1991; Boraud et al. 2000a).

### *1.5.3 - Subthalamic nucleus*

*Firing rates of the subthalamic nucleus*

In patients with PD, the mean firing rates of neurons in the STN are 25-45 Hz (Hutchison et al. 1998a). In contrast to firing rate increases in the GPi of monkeys following MPTP-treatment, increases in the firing rates of STN neurons are not as dramatic (Miller and DeLong 1987; Bergman et al. 1994) suggesting that firing patterns may play a role in parkinsonian pathophysiology.

*Firing patterns and somatosensory responses of the subthalamic nucleus*

An increase in bursting activity is observed in the STN following MPTP-treatment in monkeys (Bergman et al. 1994). There is also the appearance of tremor-related oscillatory activity in the parkinsonian monkey. Neurons with 3-6 Hz oscillatory activity that is time-locked to limb tremor are found in the STN of tremulous MPTP-

treated vervet monkeys (Bergman et al. 1994) and similar TC activity has been detected in patients with PD (Hutchison et al. 1998a; Rodriguez et al. 1998; Krack et al. 1998b). In addition to oscillations in the tremor frequency range, STN neurons with 15-25 Hz oscillations have been reported in monkeys treated with MPTP (Bergman et al. 1994). Similar to the GPi, there is an increased proportion of neurons responsive to somatosensory stimulation and an increase in movement related excitability (duration and magnitude) of STN neurons after MPTP-treatment in monkeys (Bergman et al. 1994).

*Inactivation effects of the subthalamic nucleus*

Intentional lesion making in the STN of patients with PD was usually avoided because of the possible risk of causing severe dyskinesias or ballism as was observed in normal individuals with lesions of the STN. However, local inactivation of neuronal activity by injecting fiber sparing neurotoxins into the STN (Bergman et al. 1990; Wichmann et al. 1994b, 1994c; Guridi et al. 1994, 1996) or thermocoagulative lesions (Aziz et al. 1991; Aziz et al. 1992) of the STN in MPTP-treated monkeys was shown to ameliorate parkinsonian symptoms and recent reports have demonstrated good therapeutic effects of subthalamotomy in patients with PD without adverse motor effects (Gill and Heywood 1997; Obeso et al. 1997a; Barlas et al. 2001; Alvarez et al. 2001). This anti-parkinsonian effect of STN lesions is consistent with the notion of STN hyperactivity in parkinsonism (Miller and DeLong 1987; Bergman et al. 1994). In parkinsonian monkeys, 2-deoxyglucose metabolic mapping studies indicate that STN hyperactivity is responsible for the excessive GPi activity (Mitchell et al. 1989). In

addition, lesions in the STN in parkinsonian rats and monkeys lead to the reduction of GPi activity (Wichmann et al. 1994b; Guridi et al. 1996; Blandini et al. 1997).

*Deep brain stimulation of the subthalamic nucleus*

In monkeys rendered hemiparkinsonian by unilateral infusion of MPTP, STN DBS ameliorates parkinsonian motor signs (Benazzouz et al. 1993; Benazzouz et al. 1996). In patients with PD, STN DBS is highly effective in treating parkinsonian symptoms (Pollak et al. 1993; Benabid et al. 1994; Limousin et al. 1995a, 1995b; Pollak et al. 1996; Kumar et al. 1998a; Krack et al. 1998a; Dromey et al. 2000). STN DBS is a particularly effective treatment for parkinsonian tremor (Krack et al. 1997, 1998b; Kumar et al. 1998b) and is comparable to the response obtained by thalamic stimulation for tremor (Krack et al. 1997; Kumar et al. 1999). In patients with PD, intra-operative microstimulation in regions of the STN displaying tremor-related activity reduces resting tremor with a very short latency (Rodriguez et al. 1998).

Similar to GPi DBS and pallidotomy, PET imaging studies have shown that STN DBS causes increases in regional cerebral blood flow in the ipsilateral supplementary motor area and premotor cortex (Limousin et al. 1997; Ceballos-Baumann et al. 1999). It has also been shown that there are comparable improvements in upper limb akinesia by STN DBS and GPi DBS (Brown et al. 1999). These observations support the prediction of the box model regarding the effects of GPi or STN inactivation and the release of cortical areas in PD.

Unlike GPi DBS, STN DBS can also improve the ON medication state (Kumar et al. 1998b). Since STN allows the reduction of anti-parkinsonian medication, it is

therefore preferable to bilateral GPi DBS and can indirectly improve drug-induced dyskinesias by allowing the reduction of levodopa dosage in the long term (Krack et al. 1998a). In addition, reduction of dopaminergic medication might partially reverse receptor sensitization phenomena resulting from long-term intermittent levodopa (Bejjani et al. 2000). Intrastriatal microdialysis in normal and partially dopamine denervated rats also demonstrates that high frequency stimulation of the STN induces a significant increase of extracellular dopamine in the striatum (Bruet et al. 2001).

*Dyskinesias and the subthalamic nucleus*

It has been observed that muscimol injections (Wichmann et al. 1994b) as well as excitotoxic cell-specific lesions of the STN (Bergman et al. 1990; Guridi et al. 1994) both result in the emergence of transient dyskinesias in MPTP-treated monkeys. In patients with PD, stimulation of the STN at higher currents can also induce dyskinesias (Benabid et al. 2000).

*Glutamatergic activity and the subthalamic nucleus*

It is interesting to note that in parkinsonian monkeys, STN activity is increased after local injection of bicuculline and decreased after local injection of muscimol (a $GABA_A$ receptor agonist) (Bergman et al. 1994) suggesting that GABAergic input from the GPe plays a role in STN hyperactivity. However, it has been demonstrated that the increase in the firing rates of STN neurons in 6-OHDA treated rats is not solely dependent on GPe (Hassani et al. 1996) suggesting that excitatory inputs to the STN, such as the corticosubthalamic pathway, play a role in the pathology of the parkinsonian

STN. It has been shown that glutamatergic transmission plays a role in parkinsonism (Klockgether and Turski 1993) and antagonism of glutamatergic mechanisms may have anti-parkinsonian effects (Olney et al. 1987; Klockgether and Turski 1990; Klockgether et al. 1991; Greenamyre 1993, 1996). In situ hybridization for the first subunit of cytochrome oxidase messenger RNA in rats demonstrates that hyperactivity of the STN might also be due to an increase of excitatory input arising from the PPN and parafascicular nuclei (Orieux et al. 2000).

*Effects of dopamine on the subthalamic nucleus*

Consistent with predictions of the box model, the administration of APO decreases the firing rates of STN neurons of rats with 6-OHDA lesions of the nigrostriatal pathway (Kreiss et al. 1997). However, inconsistent with the model is that the hyperactivity of STN in parkinsonian rats is reduced by $D_1$ receptor agonist but not by $D_2$ dopamine agonists (Hassani and Feger 1999). Recall that APO in the STN of intact rats produces a prominent increase in firing rates which is attributed to activation of intrinsic $D_1$ receptors in the STN (Kreiss et al. 1996). It should be noted that there is a substantial loss of the direct dopaminergic innervation of the STN in MPTP-treated monkeys and in PD patients (Francois et al. 2000).

Rats with 6-OHDA lesions also display slow oscillations (<0.5 Hz) in firing rate of STN neurons and the systemic administration of APO increases the frequency of these oscillation (Allers et al. 2000). In monkeys, metabolic studies with APO or levodopa induced dyskinesias show increased activity in the STN that is interpreted as an increase in the inhibition of the GPe, presumably due to the inhibitory effect of dopaminergic

stimulation on the striatal efferents to the GPe (Mitchell et al. 1992). The effects of APO on the neuronal activity of the STN in parkinsonian primates or humans is presently unknown (see Chapter 3 section 3).

### *1.5.4 - Substantia nigra pars reticulata*

Following MPTP-treatment in monkeys, an increase in firing rates and bursting patterns of SNr neurons is observed (Wichmann et al. 1999). Although, SNr neurons in patients with PD fire at rates comparable to GPi firing rates (i.e. 60-90 Hz) the pattern of SNr discharges in PD patients is remarkably regular and no oscillatory activity is observed (Hutchison et al. 1998a). These discrepancies may be due to differences in parkinsonism between humans and monkey or in the location of the sampled neurons. Injections of muscimol into SNr of MPTP-treated monkeys has anti-parkinsonian effects (Wichmann et al. 2001) and indicates that this nucleus is involved in parkinsonism. Rats with unilateral 6-OHDA lesions of the nigrostriatal tract show ipsilateral increases in succinate dehydrogenase and cytochrome oxidase in the SNr (two markers of neuronal activity) which is reversed with STN lesions (Blandini et al. 1997). STN lesions also decrease the occurrence of bursting patterns in the SNr in these animals (Burbaud et al. 1995). Similar to observations in the GPi of parkinsonian monkeys, intrastriatal injections of $D_1$ and $D_2$ dopaminergic-agonists in 6-OHDA lesioned rats decrease the firing rate and regularize the neuronal discharge pattern of SNr neurons (Akkal et al. 1996).

### *1.5.5 - Thalamus*

According predictions of the box model, the characteristic loss of dopaminergic innervation of the striatum is associated with an excessive tonic inhibition of thalamic motor and brainstem nuclei by the GPi (Miller and DeLong 1987; DeLong 1990; Filion and Tremblay 1991; Sterio et al. 1994; Boraud et al. 1998). This is supported by evidence from MPTP-treated monkeys, where a marked increase in the uptake of 2-deoxyglucose in the ventral anterior and ventral lateral thalamic nuclei is observed in comparison to non-parkinsonian monkeys (Crossman et al. 1985). In parkinsonian patients, metabolic studies using PET find a correlation between increased GPi firing rates and ipsilateral ventral thalamic glucose metabolism (Eidelberg et al. 1997). However, it has also been suggested that because pallidotomy (which would be expected to disinhibit the thalamus) doesn't improve the ON motor features, a mechanism other than excessive tonic inhibition of the motor thalamus might be responsible for bradykinesia, possibly where pallidotomy reduces the noise from the abnormally functioning BG (Pfann et al. 1998).

*Firing patterns and somatosensory responses of the thalamus*

The characteristics of neurons in the ventrolateral thalamus of patients with PD are described in detail elsewhere (Raeva 1990; Raeva et al. 1998; Magnin et al. 2000). Tremor-related oscillatory neuronal activity has been identified in the Vop (pallidal receiving) and Vim (cerebellar receiving) nuclei of the thalamus in the patients with PD (Lenz et al. 1985; Zirh et al. 1998). In a study using simultaneous microelectrode recordings, it was demonstrated that TCs in these areas are synchronized during

parkinsonian limb tremor (Levy et al. 1999). These tremor-related neurons can also respond to sensory stimulation and voluntary movement (Lenz et al. 1988a; Lenz et al. 1990; Lenz et al. 1994).

It is curious that parkinsonian tremor can effectively be reduced with lesions restricted to the Vim given that this nucleus receives cerebellar but not pallidal input (Diederich et al. 1992; Koller et al. 1997). Even microinjections of lidocaine (Parrent et al. 1993; Dostrovsky et al. 1993) or muscimol (Pahapill et al. 1999) or small lesions (Lenz et al. 1995) in areas with TCs in the Vim dramatically reduce parkinsonian tremor. Rigidity but not akinesia, bradykinesia or gait can also be improved by Vim thalamotomy (Lang and Lozano 1998b).

*Deep brain stimulation of thalamus*

Parkinsonian tremor can be reduced with chronic Vim DBS (Benabid et al. 1991; Blond et al. 1992; Benabid et al. 1996). It has been proposed that the effects of Vim DBS are mainly associated with a decrease in the activity of the cerebellum (Deiber et al. 1993). Levodopa-induced dyskinesias are also reduced by Vim DBS (Kawashima et al. 1991; Caparros-Lefebvre et al. 1993, 1994), an effect that is possibly due to stimulation of the CM/Pf of the thalamus which itself receives input from the GPi (Caparros-Lefebvre et al. 1999). Similar to lesions, Vim DBS while improving tremor does not improve gait, akinesia, or the activities of daily living (Defebvre et al. 1996a; Koller et al. 1997).

### *1.5.6 - Pedunculopontine nucleus*

In rats with 6-OHDA lesions of the SNc, metabolic activity within the PPN ipsilateral to the lesion is significantly increased relative to intact animals (Carlson et al. 1999; Orieux et al. 2000). A detailed review of the PPN in PD is given by Pahapill and Lozano (2000).

### *1.5.7 - Cortex*

In MPTP-monkeys, two main disturbances of cortical activity are observed. First, there is a loss of the reciprocal pattern of response of movement-related cortical cells, and second, the motor cortex is unable to modify its activity in response to peripheral input (Doudet et al. 1990). EEG studies demonstrate that the Bereitschafts or "readiness" potential recorded over the supplementary motor area in patients with PD is decreased (Dick et al. 1989) and this decrease is correlated with the degree of motor impairment (Ebmeier et al. 1992). The delay in the movement related desynchronization of alpha band EEG (~10 Hz) recorded over the contralateral primary sensorimotor area preceding a voluntary movement is also related to parkinsonian akinesia (Defebvre et al. 1996b) and may be partially corrected by levodopa therapy (Defebvre et al. 1998). The administration of levodopa in patients with PD reestablishes the attenuation of the cortical "idling rhythms" during voluntary tasks providing support for the hypothesis that the BG control the release of cortical elements from low-frequency rhythmic idling activity (Brown and Marsden 1999). Inadequate output from the BG may also lead to a disappearance of the cortical beta and Piper rhythm drive to muscle (Brown 2000).

PET studies suggest that more cortical areas (premotor cortex, parietal cortex, anterior supplementary motor area, and cingulate) are recruited to perform sequential finger movements in PD relative to normal subjects (Catalan et al. 1999). It has been proposed that the functional deafferentation of the supplementary motor area during the performance of a sequential task (Playford et al. 1992) is more pronounced during internally-determined than externally determined movements (Cunnington et al. 1995). The decreased activation of supplementary motor area, anterior cingulate, and dorsolateral prefrontal areas in parkinsonian patients can be reversed with APO (Jenkins et al. 1992), DBS of the STN (Limousin et al. 1997) or the GPi (Davis et al. 1997), and is consistent with the predictions of the box model.

Studies with transcranial magnetic stimulation demonstrate an impairment of motor cortex activation and deactivation in PD that may be a physiological correlate of bradykinesia (Ellaway et al. 1995; Chen et al. 2001). Paired transcranial magnetic stimulation demonstrates a prolonged activity in intracortical inhibitory circuits when compared to normal individuals, an effect that is also partly reversed with levodopa therapy (Berardelli et al. 1996b). It has been hypothesized that an instability of motor planning/preparation processes occurs in PD since these processes are more susceptible to disruption by magnetic stimulation in parkinsonian subjects than controls (Cunnington et al. 1996). Motor cortex tremor-related activity in patients with PD has been detected using cortical EEG, PET, and MEG, and shares similar cortical areas with voluntary motor activity, and involves rhythmic activation at the diencephalic level (Alberts et al. 1965; Alberts et al. 1969; Volkmann et al. 1996; Duffau et al. 1996).

## 1.6 - Aim of the present studies

The aim of this project was to characterize the pattern of neuronal activity in the STN and GP of parkinsonian patients and its role in the pathogenesis of PD. Neuronal activity was recorded with microelectrode and macroelectrode techniques during stereotactic surgery for movement disorders (Chapter 2). Three methods were used to gain insight into the function of the BG in PD and test some of the predictions of the box model and parallel model. First, the dopaminergic drug APO was administered to patients during surgery. This was used to correlate the APO-induced changes in single-unit firing rate and pattern and somatosensory responses with the clinical features of PD (Chapter 3). A major hypothesis of the box model of BG function that was tested is that the administration of APO would result in a decrease in the firing rates of the GPi and STN and an increase in the firing rates of the GPe. Second, microinjections of substances to inactivate the STN were performed to elucidate the role of the STN in the clincial features of PD, especially tremor and dyskinesias (Chapter 4). It was hypothesized that pharmacological blockade of neuronal activity in the STN would lead to an improvement in parkinsonism. Third, the simultaneous recordings of neuronal activity were used to examine the population behavior of neurons and the extent and variety of neuronal synchronization in the GPi and STN (Chapter 5). A major hypothesis of the parallel model of BG function that pairs of neurons in the STN and GPi would display synchronized activity was tested.

**Figure 1.F1**

Schematic diagram of the principal interconnections of the basal ganglia, cortical, and brainstem regions. GPe = globus pallidus externus; STN = subthalamic nucleus; GPi = globus pallidus internus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; PPN = pedunculopontine nucleus; SC = superior colliculus; VL = ventrolateral thalamus; CM/Pf = centromedian/parafascicular complex of the thalamus; D1 = $D_1$ dopamine receptor; D2 = $D_2$ dopamine receptor.

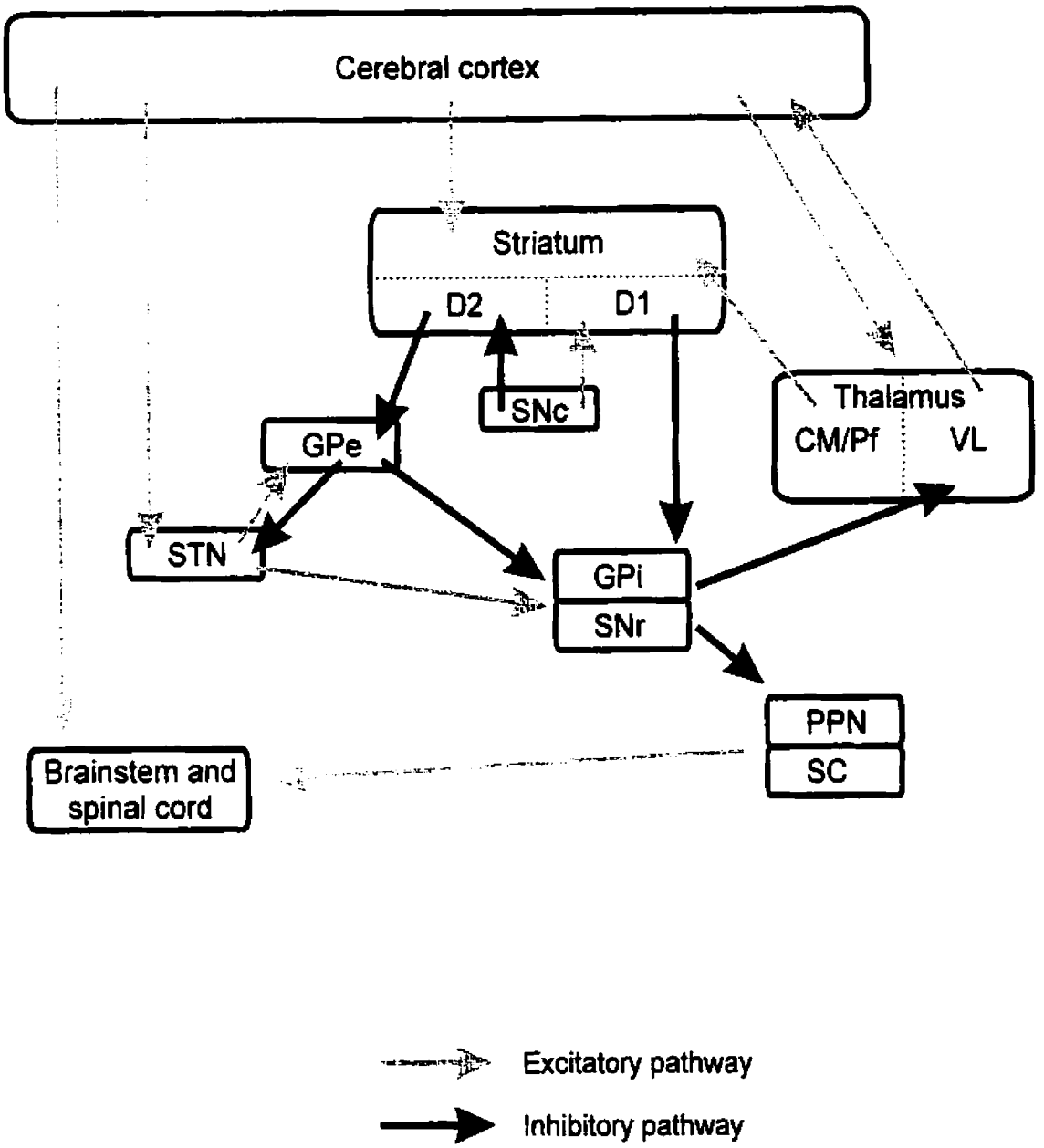

Cerebral cortex
Striatum
D2
D1
SNc
GPe
STN
GPi
SNr
Thalamus
CM/Pf
VL
PPN
SC
Brainstem and spinal cord
Excitatory pathway
Inhibitory pathway

Figure 1.F1

**Figure 1.F2**

The serial or "box" model of BG function in the normal (A) and parkinsonian state (B). Loss of dopaminergic SNc neurons in Parkinson's disease leads to an increase in STN and GPi activity. GPe = globus pallidus externus; STN = subthalamic nucleus; GPi = globus pallidus internus; Thal = thalamus.

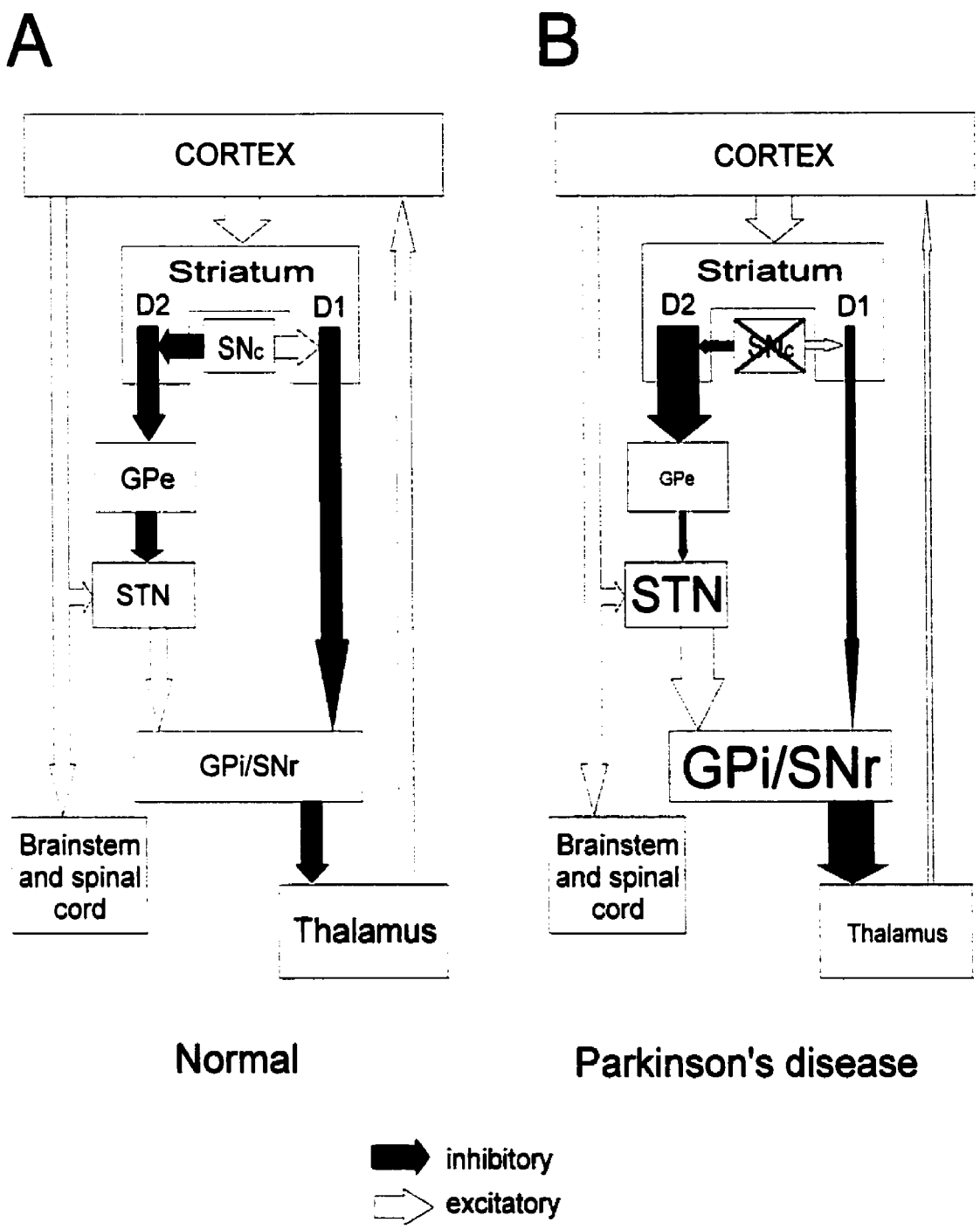

A
B
CORTEX
Striatum
D2
D1
SNc
GPe
STN
GPi/SNr
Brainstem and spinal cord
Thalamus
CORTEX
Striatum
D2
D1
SNc
GPe
STN
GPi/SNr
Brainstem and spinal cord
Thalamus
Normal
Parkinson's disease
inhibitory
excitatory

Figure 1.F2

# CHAPTER 2 - GENERAL METHODS

## 2.1 - Neuronal Recordings

### *2.1.1 - Operative procedures*

A list of all of the patients studied in each section of the Results is shown in Table 2.T1. All patients underwent functional stereotaxic neurosurgery following an overnight drug holiday (i.e. OFF medication). Detailed descriptions of operative procedures are given elsewhere (Lenz et al. 1988b; Lozano et al. 1996; Hutchison et al. 1998b). Briefly, a Leskell stereotactic frame was installed under local anesthesia and MRI or computed tomography imaging was used to locate the frame coordinates for the anterior and posterior commissures. For each patient, a digitized stereotactic atlas plate of a sagittal map (Schaltenbrand and Wahren 1977) at the appropriate laterality for the target that was adjusted to match the patients intercommissural distance was then printed. This computer map allowed the determination of the initial targets in the STN or the GPi. A twist drill hole (~6.4 mm) in the case of lesion making or a burr hole (25 mm) in the case of DBS was then made under local anesthesia. Physiological mapping of neuronal activity using microelectrode recordings was then performed through this opening. Microelectrode recording was started 15 mm or 10 mm above the intended target according to imaging, the microelectrode being lowered by a manual microdrive. All patients were awake during the microelectrode recordings. Microstimulation was performed to elicit sensory or motor effects and was achieved (usually through the same electrode) with an isolated stimulator (World Precision Instruments or Axon system GS3000) which delivered trains of square wave pulses (pulse width 150 μs or 200 μs) at

300 Hz and up to a maximum of 100 μA. Stimulation mapping allowed the identification of physiological landmarks.

*2.1.1.a - Globus pallidus internus*

The recording procedures for the patients undergoing pallidotomy have been previously described (Lozano et al. 1996; Hutchison 1998b). Briefly, functional stereotaxic surgery was undertaken to implant chronic DBS electrodes or to perform radio-frequency lesions in the posteroventral GPi. Parasagittal trajectories were oriented at either 20 or 22 mm from the midline. Physiological landmarks identified by microstimulation were the optic tract (located ventral to the GPi) and the internal capsule (located anterior to the GPi). The electrode tracks were oriented so that the microelectrode could sample neuronal activity in the GPe and the GPi. A representative example is shown in Figure 2.F1.

*2.1.1.b - Subthalamic nucleus*

The use of microelectrode recording to localize DBS electrode placement in the STN is described in detail elsewhere (Hutchison et al. 1998a). Briefly, functional stereotaxic surgery was undertaken to implant chronic DBS electrodes or to perform radio-frequency lesions (subthalamotomy). Similar to pallidal surgery, single unit microelectrode recordings and stimulation mapping allowed the identification of physiological landmarks and cell localization. However, greater emphasis was placed on characterization of neuronal activity because microstimulation yielded less information

than pallidal exploration due to the absence of the optic tract and, in most cases, the motor capsule. Parasagittal trajectories at either 10.5 or 12 mm from the midline passed through the thalamic reticular nucleus and/or anterior thalamus, zona incerta, STN, and the SNr. Exploration of the neuronal activity was carried out along the entire dorsal /ventral extent of STN. The main characteristics that were identified in order to localize the motor portion of the STN were neurons with tremor-related activity, neurons that responded to passive or active movements, and microstimulation effects such as tremor reduction or arrest. The anterior-posterior limits of the STN were delimited by regions with sparse neuronal activity and a reduced background noise compared to that observed within the STN. A representative example is shown in Figure 2.F2.

### *2.1.2 - Single-unit microelectrode recording*

Single-cell microelectrode recording is used to locate target regions for lesion making or DBS in patients operated at the Toronto Western Hospital. This procedure minimizes surgical risk by accurately delineating subcortical structures and provides greater accuracy than with using MRI derived coordinates alone (Lees and Smith 1983; Bakay et al. 1997; Biousse et al. 1998; Alterman et al. 1999).

#### *2.1.2.a - OR setup and Offline setup*

During surgery, single unit activity recorded from the microelectrode was amplified, high-pass filtered (200-300 Hz), and monitored on a loudspeaker and with an oscilloscope (Hutchison 1998b). In some cases, signals were amplified, filtered, and

displayed using Axon Instruments equipment (GS3000 system, Axon Instruments, Foster City, CA.). An example of a well isolated extracellular recording of a single neuron is shown in Figure 2.F3A. All neuronal data were recorded simultaneously with wrist flexor/extensor EMG and accelerometer (Acc) data to monitor muscle activity and limb movement, respectively. Data were stored on an analog videotape by a digital recorder (model S-100, Instrutech Corp., Port Washington, NY) and analyzed off-line with a similar set-up. Single unit event times were discriminated using a dual window discriminator (DDIS-1, BAK Electronics, Mount Airy, MD) and a storage oscilloscope in spike-trigger mode or by template matching spike-sorting software (Spike2, Cambridge Electronic Design, Cambridge, England).

*2.1.2.b - Regular electrode designs*

Single units were recorded using electrodes made by inserting a parylene-C coated tungsten microelectrode with an exposed tip size of 15-25 microns (Microprobe Inc.) into a 25 gauge stainless steel tube (Small Parts Inc., HTX-25 tubing) that was then covered by Kapton tubing (Micro ML Tubing, #23 polyimide tubing). These parts were glued together with epoxy. Microelectrode tips were plated with gold and platinum to reduce the impedance to about 0.2 to 0.4 MΩ at 1 kHz. This electrode was inserted through a guide tube made of 19 gauge steel tube (Small Parts, HTX-19). A schematic of the microelectrode construction is shown in Figure 2.F3B.

### *2.1.3 - Dual microelectrode / stimulation / injection apparatus*

The simultaneous recording of neuron pairs in this thesis was performed using a double electrode set-up in which two microelectrodes were inserted either as a glued pair separated by a distance of 250 to 300 um or independently in which the electrodes were separated by 600 um and each electrode was driven by a separate microdrive. The latter technique used a novel dual microelectrode/cannula assembly that was conceived and built by the author for the purposes of dual recording, electrical stimulation and neuronal recording (Dostrovsky et al. 2000), and local drug injection and neuronal recording. The assembly fits a standard Leskell stereotactic frame (model G). The assembly is capable of holding two microelectrodes, a microelectrode and an injection cannula, or a microelectrode and a macroelectrode. The two microelectrodes or the cannula and microelectrode occupied separate guide tubes (23 gauge stainless steel tubes) and the guide tubes were positioned medial-lateral to one another at a center to center distance of ~600 μm. The assembly is shown in Figure 2.F4 configured with two microelectrodes. In most cases dual electrode recordings were only obtained on one side (usually the first). The electrode used for the glued pair or in the assembly was a "thin" electrode and is discussed below.

#### *2.1.3.a - Thin electrode design*

Similar to the regular electrode design discussed above, thin electrodes were made by inserting a parylene-C coated tungsten microelectrode with an exposed tip size of 15-25 microns (Microprobe) into a 30 gauge stainless steel tube (Small Parts, HTX-30). This was covered by Kapton tubing (Micro ML Tubing, #28 polyimide tubing). These

parts were glued together by applying epoxy in the same manner as the regular electrodes discussed above. Microelectrode tips were plated with gold and platinum to reduce the impedance to about 0.2 to 0.4 MΩ at 1 kHz. Glued pairs of electrodes were carefully joined using epoxy so as to fit through a standard 19 gauge guide tube and recordings were performed using the regular stereotactic set-up. In the case of recordings performed using the assembly, thin electrodes were used individually and fit a thinner guide tube made of 23 gauge steel tube (Small Parts, HTX-23TW).

*2.1.3.b - Microinjection cannula and macroelectrode design*

Injection cannulae could also be used as macroelectrodes and were constructed from a 30 gauge stainless steel tube (Small Parts, HTX-30) which was covered by Kapton tubing so as to be insulated to 0.3-0.5 mm of the tip (Micro ML Tubing, #28 polyimide tubing). These parts were glued together by applying epoxy in the same manner as the thin electrodes discussed above. The injection/macroelectrode cannulae were used in the dual microelectrode/cannula assembly.

The injection cannula was connected to a 10-15 cm piece of polyethylene tubing (PE 50, inside diameter 0.58 mm) and sealed with epoxy glue. Substances were preloaded in the cannula and polyethylene tubing and in a 25 µL Hamilton syringe. An air bubble (~1 cm in length) was introduced in the polyethylene tubing to allow the visual determination of the movement of the solutions. The polyethylene tubing was then friction fit over the tip of the Hamilton syringe.

### *2.1.4 - Local field potential recordings*

Bipolar "macroelectrode" recordings of field potentials were performed through adjacent contacts of the DBS leads between two and seven days after implantation. The DBS leads consist of four concentric cylindrical contacts (length 1.52 mm, diameter 1.27 mm) separated by 1.5 mm. Contacts were labeled 0, 1, 2, 3 from the most ventral to the most dorsal contact respectively. Differential recordings between pairs of contacts were amplified and digitally recorded (CED1401, Cambridge Electronic Design) at a sampling rate of 1000-1200 Hz. All patients had the DBS leads internalized seven days following microelectrode surgery. In some cases, intra-operative monopolar macroelectrode recordings were made with the macroelectrode cannula used in the dual microelectrode/cannula assembly.

## 2.2 - Clinical assessments

### *2.2.1 - Intra-operative apomorphine injection*

All patients in the APO series of experiments (see Chapter 3) were challenged pre-operatively with systemic APO to establish a dose sufficient to produce an ON state, but not produce dyskinetic movements. In order to rate the clinical effect of APO, patients underwent a pre-operative partial Unified Parkinson's Disease Rating Scale motor assessment (UPDRS) (Part III) during the practically defined OFF state (12-14 hours after last medication) and during an APO induced ON state. Motor scores were determined by summing UPDRS items 18-31 (i.e. greatest possible score is 108). In

general, the higher the UPDRS score, the worse the parkinsonian symptoms (Stebbins and Goetz 1998).

Patients were studied during the stereotaxic surgery 12-14 hours after the last oral dose of levodopa and were considered to be in the OFF state (i.e. non-medicated). All patients were premedicated with domperidone (Motilium, Janssen), a peripherally acting dopamine receptor antagonist to minimize undesirable side effects (nausea, vomiting, and hypotension). The time course of the effects of APO was evaluated intra-operatively by a trained clinician. Patients were asked to report when they started to feel the effects of APO. The time and duration of limb tremor or the occurrence of drug induced dyskinetic or dystonic movements were also noted.

In each patient, a stable and well isolated single unit was found and APO was administered subcutaneously following 2-3 minutes of stable recording. These neurons were recorded for as long a period as possible, usually until there was an was an objective effect of the medication (tremor reduction, dyskinesias) and patients felt a subjective beneficial effect of medication. However, in some cases stable recordings from single neurons were lost after a shorter period of time.

### *2.2.2 - Limb tremor measurements*

Limb tremor was quantified using EMG or accelerometer (Acc) (Entran EGAX-5, Fairfield, NJ) recorded simultaneously with neuronal activity. Signals were usually recorded at 500 Hz and low passed filtered below ~55 Hz. The upper limit of 55 Hz was used to avoid any contamination due to 60 Hz line noise. An example of a rectified EMG signal of ongoing limb tremor is shown in Figure 2.F3C.

### *2.2.3 - Intra-operative microinjections*

Previous studies have shown the safety and utility of controlled microinjections of lidocaine and muscimol in the thalamus and GPi of patients with movement disorders (Dostrovsky et al. 1993; Penn et al. 1998; Pahapill et al. 1999). All injections were performed with the patients in the OFF state (12-14 hours after last anti-parkinsonian medications). In order to rate the clinical effect of microinjections, patients underwent a partial UPDRS assessment of bradykinesia (item 24), rigidity (item 22, arm/wrist), and tremor (items 20 and 21, arm/wrist). Rigidity was assessed by a trained clinician before and following injections. Tremor, bradykinesia, and dyskinesias were assessed from camera tapes by a trained clinician. When possible, bradykinesia was also assessed using quantitative tasks measuring movement time and amplitude such as wrist pronation/supination or repetitive pointing with the index finger from the patient's chest to a target placed ~50 cm in front of the patient (total trial lengths ~10s). Rigidity was also quantified in a few cases using a commercially available device (Prochazka et al. 1997). This device allows the accurate determination of rigidity by quantifying the impedance provided by a limb to an applied force imposed by the examiner.

## 2.3 - Data analysis of single neuron discharge

Tonic spontaneous single unit activity was collected with the patients at rest and without any passive joint manipulation or voluntary movements. The average neuronal discharge or firing rate per unit time (usually 1 second) was noted for all cells sampled.

The pattern of neuronal discharge was also characterized. Bursting discharge was defined as "periodic" if bursts appeared to be rhythmic in time (i.e. a constant period of time between each burst). "Aperiodic" bursting was defined as bursting activity that may have also occurred without any underlying periodicity (i.e. this term was used to describe bursting in general). Although neurons displaying oscillatory "bursting" activity can be regarded as a special case of aperiodic bursting cells, it is important to compare the effect of APO on both types of discharge patterns because these phenomena may occur with different mechanisms and may have different physiological meanings (Kaneoke and Vitek 1996). These neuronal discharge characterizations are discussed in detail below.

### *2.3.1 - Aperiodic bursting discharge*

Aperiodic or general bursting discharge was quantified using two different burst measures. (1) The Poisson "surprise" method of burst detection as described by Legendy and Salcman (Legendy and Salcman 1985) was employed to detect burst discharges with a Poisson surprise value of greater than 5. This method defines a "burst" as an improbable epoch of elevated discharge rate in a spike train. The number of spikes in burst discharges was compared to the total number of spikes sampled in each cell and the percentage of spikes in bursts was calculated (Wichmann et al. 1999). This gave a measure of the "burstiness" of each neuron since irregularly discharging neurons will have a greater proportion of spikes that participate in bursts when compared to regularly discharging neurons. (2) The spike discharge pattern of groups of neurons was further characterized by labeling each neuron as being "regular", "random", or "irregular" by comparison to a Poisson process. The method employed here is a simplified version of a

burst analysis scheme presented by Kaneoke and Vitek (1996). Briefly, the discharge density of a neuron was determined by calculating the number of spikes in an interval equal to the reciprocal of the mean firing rate. The number of occurrences of no spikes, one spike, two spikes (and so on) in each time interval was then counted and a discharge density histogram was constructed. This discharge density histogram represents the probability distribution of the neuron's discharge density and can easily be compared to a discharge density of a Poisson process with a mean of 1 by using a $\chi^2$ goodness-of-fit test. If the neuronal discharge pattern was "random", its discharge density distribution would be statistically similar to that of a Poisson process. If the neuron's discharge pattern was significantly non-random then two possibilities existed. Either the spikes occurred in a "regular" discharge pattern where the probability of finding one spike per time segment was high, or the spikes occurred in a "irregular" discharge pattern where the probability of finding no spikes or many spikes per time segment was high. Since a Poisson process with a mean of one has a variance equal to one, the former case represents a significantly non-Poisson discharge density distribution with a variance of less than one and the latter case represents a significantly non-Poisson discharge density distribution with a variance of greater than one. This method was a convenient way to characterize regular, random, and irregular spike discharge patterns between groups of neurons since the patterns of neuronal discharge between two cells with different mean tonic activity could be directly compared. It should be pointed out that the classification of neurons using these methods does not rule out the possibility that there may be subgroups of neurons within any one group that might be distinguishable on the basis of some other type of pattern analysis.

### *2.3.2 - Periodic bursting discharge*

Periodic bursting discharge was quantified using both time (auto-correlation) and frequency (spectral) domain analysis. Auto-correlation can be used to distinguish between intermittent bursting discharge and oscillatory discharge. Auto-correlations of oscillatory discharge are smoother and contain multiple evenly spaced peaks. Auto-correlations of intermittent bursting discharge typically display a large short latency peak followed by long period of inhibition. To detect and test the significance of multiple oscillation frequencies, spectral techniques were employed.

#### *2.3.2.a - Time domain analysis*

Auto-correlation histograms of spike trains were plotted for 1.0 second to 100 ms offsets using 10 ms to 0.5 ms bin widths. All correlation histograms were quantified to the units of rate (spikes/s) (Abeles 1982). Auto-correlation distributions were used to index the strength of the periodic activity. The strength of the oscillation was graded according to standard examples given by Karmon and Bergman for oscillating cells in MPTP-treated non-human primates (Karmon and Bergman 1993). For example, only TCs with a strength of five or greater were considered for further analysis. Oscillatory modulation of ongoing discharge was initially detected by locating at least two successive peaks within the auto-correlation functions. Oscillatory activity was then assessed by calculating confidence lines at ± 2 standard deviations (~95% confidence interval) or ± 2.68 standard deviations (~99% confidence interval) of the baseline firing rate (Abeles 1982). Peaks were considered significant if they were found outside the area defined by the confidence lines. The frequency of oscillation was then determined by calculating the

reciprocal of the peak-to-peak time of two successive peaks.

*2.3.2.b - Frequency domain analysis*

Spectral analysis was used to characterize the frequency content of neurons with oscillatory activity. Spike trains were transformed from a series of events to a continuous function representing the density of spikes in time (using conversion software from Spike2, Cambridge Electronic Design, Cambridge, England). This is graphically demonstrated in Figure 2.F5. The final digitization rate was 200 Hz to 1000 Hz depending on the range of oscillatory frequencies investigated. Standard spectral techniques resulted in a final frequency resolution ranging from 0.39 Hz to 1.95 Hz (Spike2 software, Cambridge Electronic Design, Cambridge, England). In general, the frequency resolution depended on the length of time that the neuron was sampled. The only limitation imposed by this procedure of spike to spike density conversion is that oscillation frequencies investigated could not be greater than the frequency of the firing rate. Graphical displays of frequency versus time were constructed by calculating the frequency content within consecutive 10 or 20 second windows and were scaled to the ratio of signal to noise. Spectral noise was defined as the average power estimate over all spectral frequencies (usually 0-35 Hz).

***2.3.3 - Receptive fields***

Only cells that had a stable baseline and were clearly distinguishable from the background noise were chosen for receptive field (RF) mapping. The time spent

investigating the somatosensory RF properties of a neuron was considerably longer than the time spent recording tonic activity when the patient was at rest. RF mapping took on the order of 3-5 minutes per cell and was carried out following tonic activity sampling. Passive movements were performed in a vigorous manner about a single joint. A positive response was indicated by a phasic excitation or inhibition of neural discharge which was robust to repeated trials. Contralateral and ipsilateral wrist, elbow, and shoulder (and sometimes ankle) manipulation were assessed. We did not check for knee and hip responses because brisk movements of the entire leg often resulted in slight movement artifacts in the microelectrode recording or loss of the neuronal recording. The responses of all of the cells tested to passive limb manipulation were divided into the following categories: no response, single joint, double joint, and multiple joint responses (more than two joints or bilateral responses). Some limitations of this RF testing is that we did not distinguish between muscle and joint receptive fields, that biarticulate muscle responses may have accounted for some of the double or multiple joint responses, and that cells with inhibition or activation responses were not discriminated and may have provided more information (Boraud et al. 2000).

### *2.3.4 - Statistical comparisons of populations of single neurons*

Statistical analyses on the firing rates or bursting properties of populations of neurons were carried out using ANOVA followed by an All Pairwise Multiple Comparison Procedure (Student-Newman-Keuls) for normally distributed data. In cases of non-normality, data were compared using an ANOVA on ranks procedure (Kruskal-Wallis) followed by an All Pairwise Multiple Comparison Procedure (Dunn's Method).

Differences in proportions of cells in different categories were evaluated using $\chi^2$ tests. Statistical significance was assigned at $p < 0.05$ (i.e. $\alpha = 0.05$). Unless indicated otherwise, all errors are reported as standard errors of the mean (SE).

## 2.4 - Data analysis of the discharge of pairs of single neurons

Correlations between separate spike trains can arise from functional connections between pairs of neurons that include "direct" synaptic connections and/or "indirect" connections such as common input from presynaptic sources (Moore et al. 1970). Data analysis on pairs of neurons used both time domain and frequency domain analysis. Although there is some overlap in these analyses, cross-correlograms can indicate coincident discharges in time and thereby assess short latency interactions such as direct synaptic connections. Furthermore, cross-correlation analysis can detect aperiodic synchronization (e.g. between two non-rhythmic bursting neurons) and this is displayed as a single symmetric or asymmetric peak in the correlogram. Coherence analysis is a reliable and conservative method that allows us to detect the statistical significance of the similarity between two oscillatory signals. Only well isolated single neurons recorded from different electrodes were examined thereby avoiding the difficulties of interpreting cross-correlograms constructed from multiunit recordings (several undiscriminated cells recorded on a single electrode) (Bedenbaugh and Gerstein 1997; Bar-Gad et al. 2001).

### *2.4.1 - Time domain analysis*

Cross-correlation analysis was used to detect coincident activity between pairs of

neurons and detect and grade the rhythmic neuronal activity within these pairs. Correlation histograms of spike trains were plotted for 1.0 second to 100 ms offsets using 10 ms to 0.5 ms bin widths. All correlation histograms were quantified to the units of rate (spikes/s) (Abeles 1982). Aperiodic synchronization of a neuron pair was assessed by detecting single peaks or troughs in the cross-correlograms that consisted of at least three or more consecutive bins with values outside a 99% confidence interval about the mean firing rate (Abeles 1982). Oscillatory synchronization of the neuron pair discharge was initially detected by locating at least two successive peaks within the cross-correlation functions. Peaks were considered significant if they were found outside a 99% confidence interval about the mean firing rate (Abeles 1982). The frequency of oscillation was then determined by calculating the reciprocal of the peak-to-peak time of two successive peaks. Phase shifts were determined by calculating the time of the highest peak (typically the peak closest to zero time) divided by the oscillation period. Joint peri-stimulus time histogram analysis (JPSTH) was employed to correlate the discharge activity of a pair of neurons in conjunction with a movement (Gerstein and Perkel 1972). A JPSTH plot is a scatter diagram of the joint occurrences of spikes from each neuron relative to the times of stimulation. In a JPSTH plot, dependence of spike trains on the stimulus appear as vertical or horizontal bands of increased or decreased point density while functional connections between the pair of neurons appear as diagonal bands of increased or decreased point density.

### *2.4.2 - Frequency domain analysis*

The similarity in oscillatory frequency content of two oscillatory signals was calculated using coherence techniques. Coherence is a function of frequency and is calculated from the cross-spectral density between the two waveforms normalized by the power spectral density of each waveform. Coherence values can range from 0 if the spike trains are not linearly related to a value of 1 if the spike trains have a perfectly linear relationship. Since coherence is a measure of linear similarity, the phase shift must be constant and the amplitudes of the two waveforms must have a constant ratio to be completely coherent at a particular frequency over a given time range. A statistically significant coherence value between the discharge of two neurons was used to indicate the presence of oscillatory synchronization. A $100 \cdot \beta\%$ confidence level was determined by calculating a coherence value given by $\text{Coherence} = 1 - (1 - \beta)^{1/(L-1)}$, where $\beta = 0.99$ and L = number of windows used (Rosenberg et al. 1989). This value or greater was considered to indicate a significant probability ($p<0.01$) of a linear relationship between two cells. Phase relations were also assessed for those pairs of neurons that had a significant coherence at some frequency $f_i$ using $\text{Phase}(f_i) = \arctan(-Q(f_i) / L(f_i))$, where $f_i$ is the $i^{th}$ spectral estimate, Q is the real part and L is the imaginary part of the cross-spectra between a pair of neurons (Glaser and Ruchkin 1976). Graphical displays of coherence or phase versus time were constructed by calculating the coherence or phase within consecutive 10 second windows.

## 2.5 - Data analysis of the local field potentials

Macroelectrode signals recorded post-operatively were low passed filtered (<100 Hz) and then down sampled to a common sampling rate of 200 Hz to facilitate comparisons between the power spectra of different patients and of different trials. Standard spectral techniques resulted in 256 spectral estimates between 0 and 100 Hz thereby yielding a frequency resolution of 0.39 Hz (unless otherwise indicated). Statistical significance of spectral peaks was assessed by comparing each macroelectrode recording to a white noise signal with the same mean power in the range 0-55 Hz (i.e. mean spectral "noise"). The upper limit of 55 Hz was used to avoid any contamination due to 60 Hz line noise. Spectral estimates were deemed significant if they were equal to or greater than the upper bound of a $100 \cdot (1-\alpha)\%$ confidence interval about this white noise signal. The upper bound was given by $2N \cdot f(\omega) / \chi^2_{2N,1-\alpha/2}$ where $f$ is the power, $\omega$ is the frequency, 2N is the effective degrees of freedom, and N is the number of sampling windows (Chatfield 1996). Plots of frequency versus time displayed normalized spectra where each spectral estimate was divided by the spectral noise in the respective window. In addition, the signal-to-noise ratio of significant peaks in the frequency spectra was calculated by averaging the signal-to-noise ratio over the range of frequencies given by the width of the peak at half the maximum peak value.

**Table 2.T1**

A list of all of the patients studied in each section of the Results. Data from some patients were used in more than one section.

*Patients studied in each section of the Results*

| Chapter 3 Section 1 | Chapter 3 Section 2 | Chapter 3 Section 3 | Chapter 4 | Chapter 5 Section 1 | Chapter 5 Section 2 | Chapter 5 Section 3 |
|---|---|---|---|---|---|---|
| n = 14 | n = 6 | n = 13 | n = 6 | n = 9 | n = 12 | n = 15 |
| 2018 | 2019 | 2153 | 2181 | 2196 | 2196 | 2194 |
| 2019 | 2028 | 2154 | 2182 | 2198 | 2198 | 2195 |
| 2023 | 2041 | 2157 | 2194 | 2201 | 2200 | 2198 |
| 2027 | 2042 | 2169 | 2209 | 2202 | 2203 | 2201 |
| 2028 | 2047 | 2173 | 2230 | 2206 | 2208 | 2202 |
| 2030 | 2068 | 2174 | 2231 | 2209 | 2210 | 2206 |
| 2039 | | 2176 | | 2210 | 2214 | 2209 |
| 2041 | | 2179 | | 2211 | 2215 | 2211 |
| 2042 | | 2181 | | 2214 | 2232 | 2212 |
| 2047 | | 2183 | | | 2233 | 2214 |
| 2049 | | 2194 | | | 2237 | 2217 |
| 2060 | | 2196 | | | 2248 | 2218 |
| 2067 | | 2198 | | | | 2225 |
| 2068 | | | | | | 2227 |
| | | | | | | 2241 |

Table 2.T1

**Figure 2.F1**

An example of microelectrode trajectories through the globus pallidus (sagittal section at 20 mm from the midline). Each vertical line represents the trajectory of a micrelectrode. A DBS electrode is shown positioned in the most anterior track. GPe = globus pallidus externus; GPi = globus pallidus internus; IC = internal capsule; OT = optic tract; V = visual response to microstimulation; M = motor response to microstimulation.

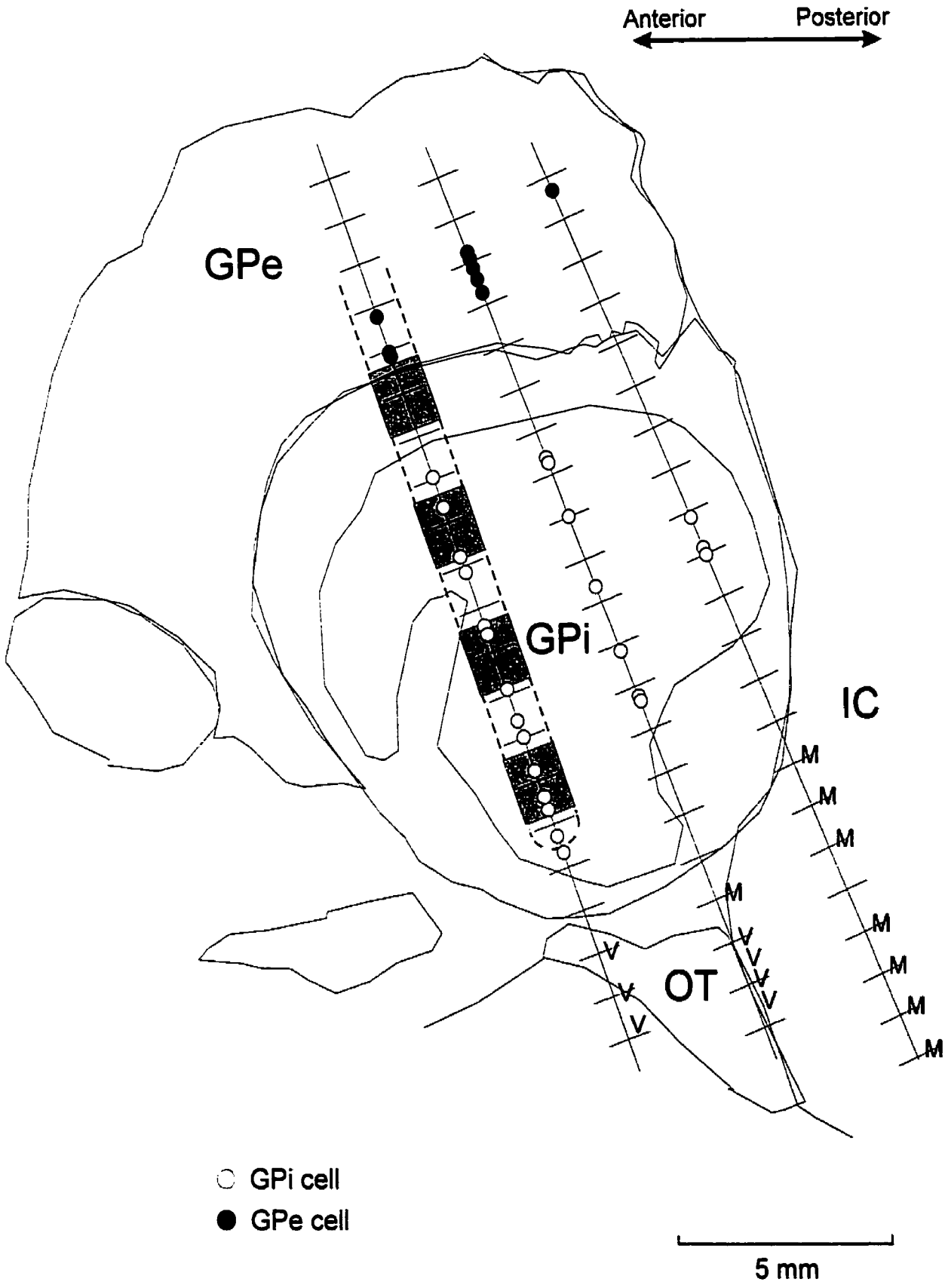

Anterior
Posterior
GPe
GPi
IC
M
M
M
M
M
M
M
V
V
V
V
V
V
OT
GPi cell
GPe cell
5 mm

Figure 2.F1

**Figure 2.F2**

An example of microelectrode trajectories through the subthalamic nucleus (sagittal section at 12 mm from the midline). Each vertical line represents the trajectory of a micrelectrode. A DBS electrode is shown positioned in the middle track. rTh = reticular thalamus; Voa = nucleus ventro-oralis anterior; Vop = nucleus ventro-oralis posterior; STN = subthalamic nucleus; SNr = substantia nigra pars reticulata.

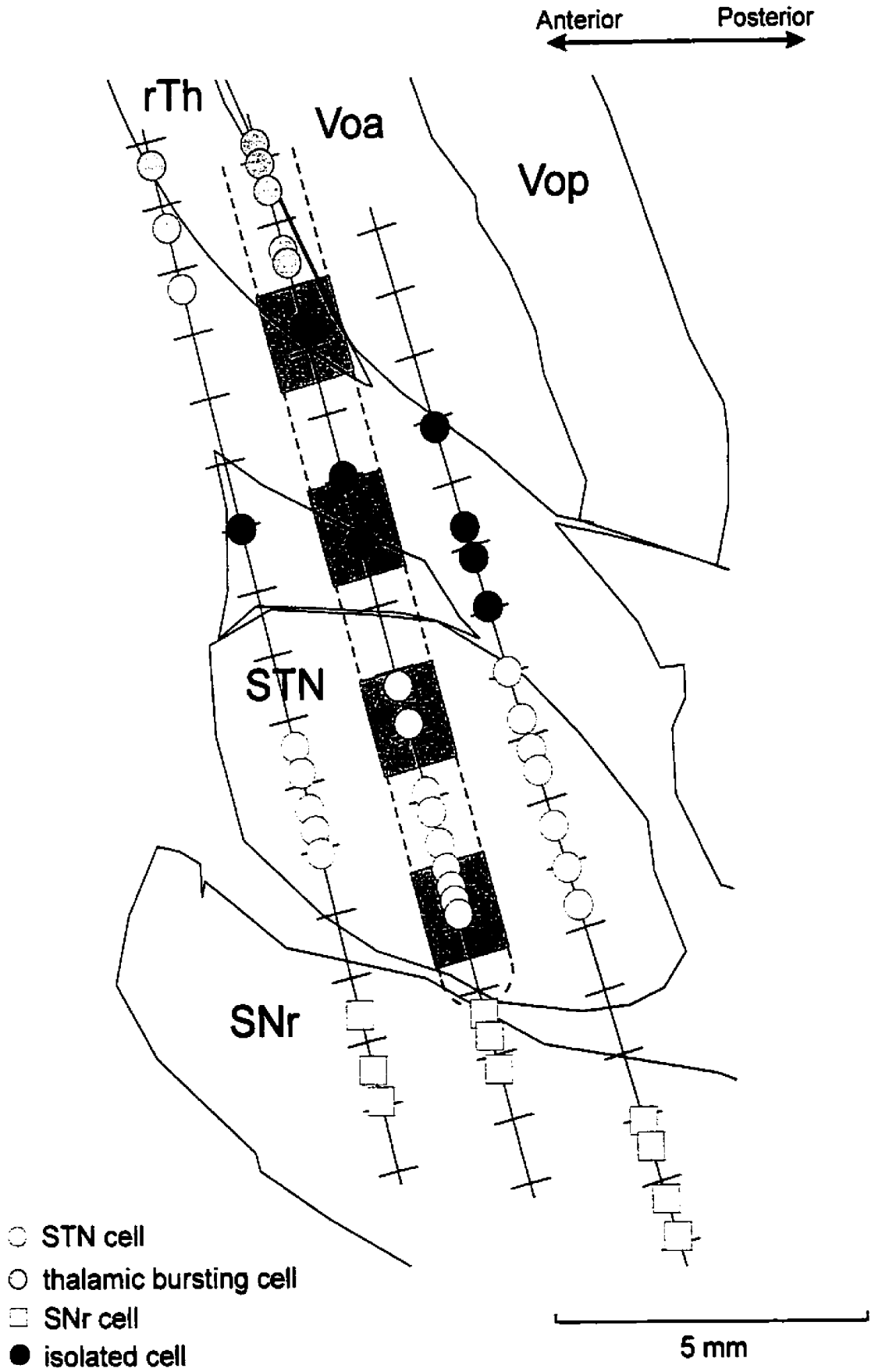

Anterior
Posterior
rTh
Voa
Vop
STN
SNr
STN cell
thalamic bursting cell
SNr cell
isolated cell
5 mm

Figure 2.F2

**Figure 2.F3**

Microelectrode design and physiological signals from cells and muscles. A: Extracellular recording of a single neuron recorded with a microelectrode. This is an example of a raw trace from a well isolated STN neuron. B: Schematic of a regular microelectrode. C: An example of a rectified EMG trace of limb tremor.

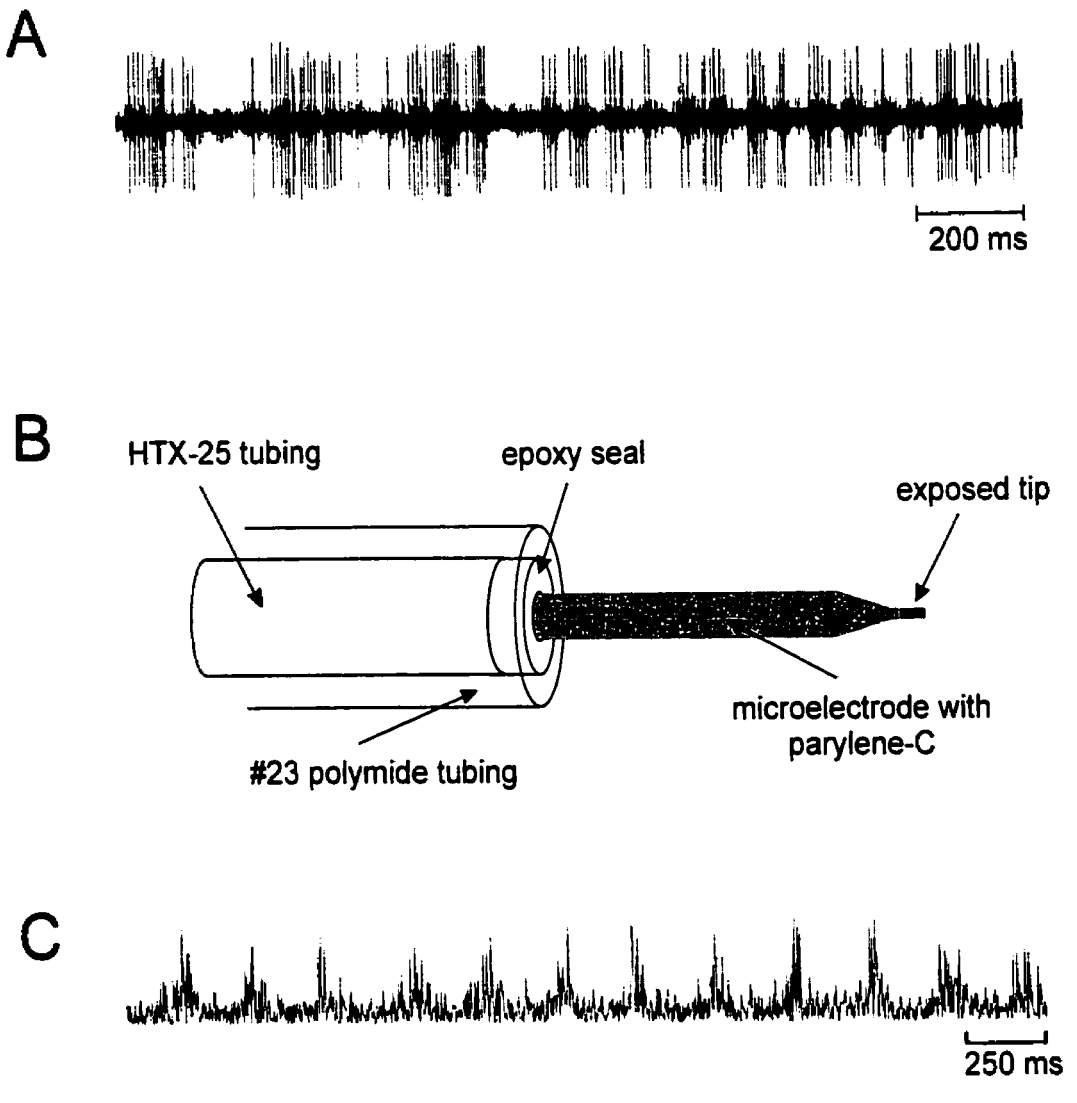
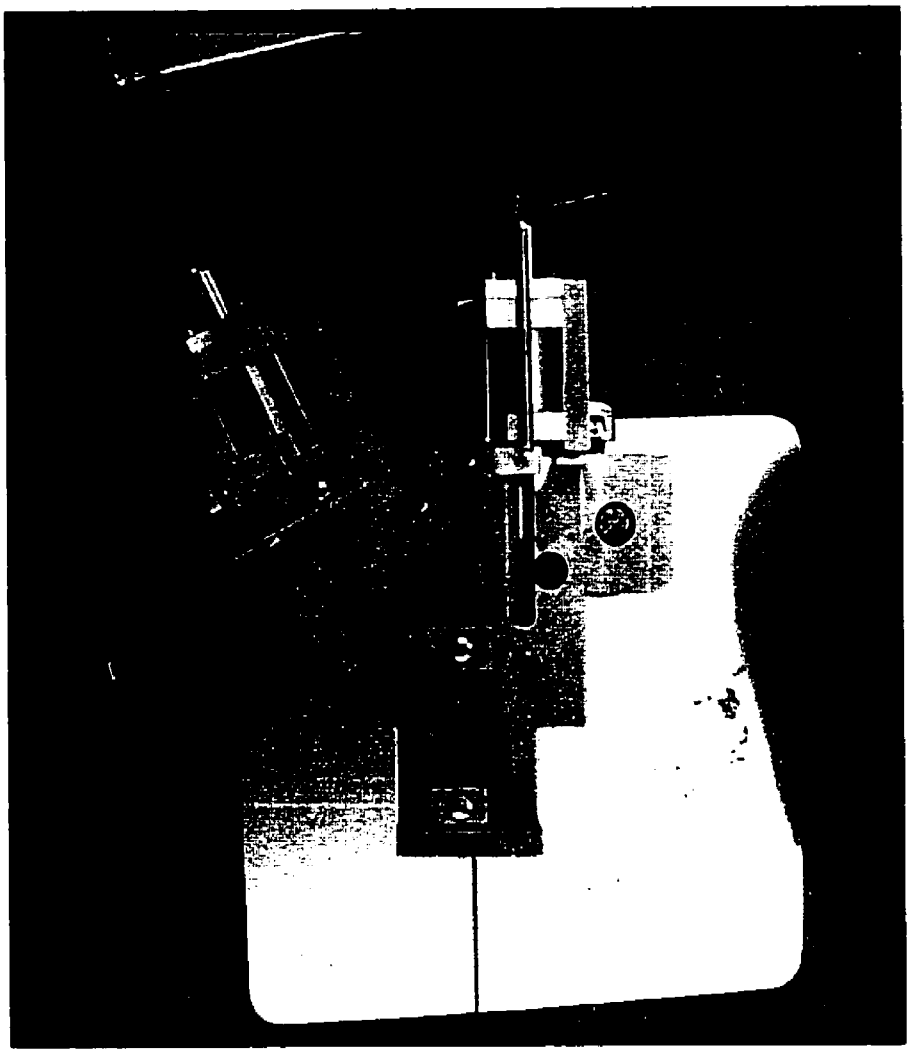

A
200 ms
B
HTX-25 tubing
epoxy seal
exposed tip
microelectrode with
parylene-C
#23 polymide tubing
C
250 ms

Figure 2.F3

**Figure 2.F4**

The dual microelectrode/cannula assembly built by the author. A: A picture of the head stage showing the angled positioning the microdrive slave cylinders. The assembly is configured with two microelectrodes. B: A picture of the two microelectrodes protruding from the end of the assembly. The diameter of the coin is 19 mm.

A



B

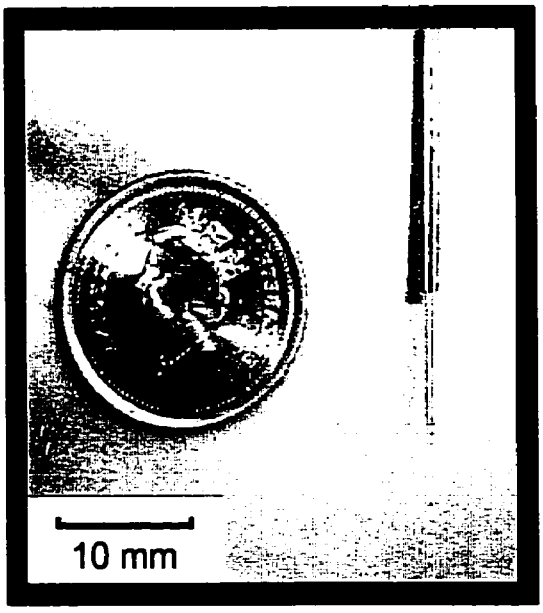



Figure 2.F4

**Figure 2.F5**

Spike trains were transformed from a series of events to a continuous function by replacing each spike with a raised cosine with unit area under the curve and a width of 10 ms. Each vertical line represents a single spike. Summation resulted in a smooth continuous function representing the density of spikes in time that was used in subsequent Fast Fourier transform analysis.

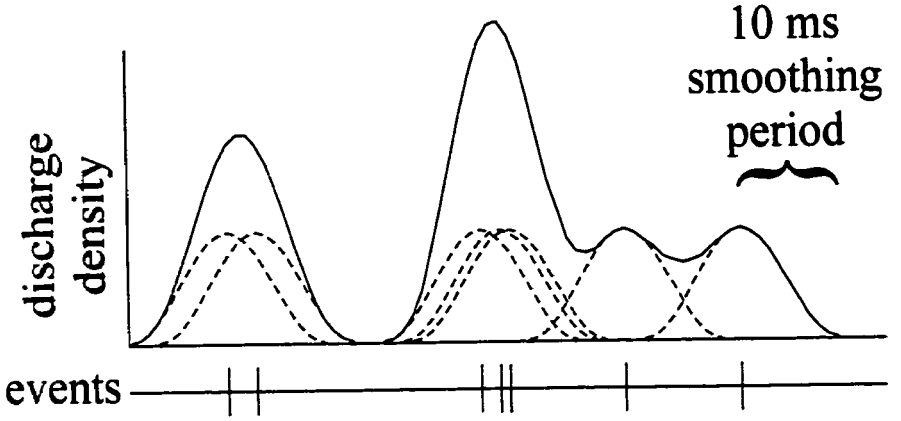



Figure 2.F5

## CHAPTER 3 - APOMORPHINE ALTERS NEURONAL ACTIVITY IN THE GLOBUS PALLIDUS AND SUBTHALAMIC NUCLEUS

The degeneration of the neurons in the SNc leads to the loss of the dopaminergic innervation of the striatum. In animal models of PD, this dopamine-depleted state has been associated with an excessive tonic inhibition of thalamic motor and brainstem nuclei (DeLong 1990) by the GPi (Miller and DeLong 1987; Filion and Tremblay 1991). Inhibition of thalamic motor and brainstem nuclei is believed to result in the cardinal symptoms of rigidity, bradykinesia, and tremor (DeLong 1990). The amelioration of parkinsonian symptoms following lesions of the GPi or STN is consistent with the view that both these nuclei are hyperactive and/or display aberrant discharge patterns in parkinsonian monkeys and patients with PD (Bergman et al. 1990; Aziz et al. 1991; Lozano et al. 1995; Lang et al. 1997; Obeso et al. 1997a; Gill and Heywood 1997).

Since changes in the neuronal activity of the basal ganglia are secondary to a decrease in striatal dopamine, it is possible that the antiparkinsonian effect of dopaminergic medication may be related to a reversal of these pathological patterns and rates of activity. The aim of this chapter was to test the hypothesis that changes in neuronal firing rates and patterns and receptive field responses in the basal ganglia occur concurrently with observed improvements in the clinical features of PD patients due to the administration of APO, a nonselective dopamine receptor agonist.

## 3.1 - Effects of apomorphine on discharge rates in the globus pallidus

*Abstract*

This study examines the effect of APO, a non-selective $D_1$- and $D_2$-dopamine receptor agonist, on the mean firing rates of neurons in the GPi and GPe of patients with PD. Single unit microelectrode recordings were conducted in 14 patients undergoing a pallidotomy. Following baseline recordings from a single neuron, APO was administered and the activity of the neuron followed for an average of 15 minutes. Other neurons sampled during the course of the procedure were included in a population study. Injections of APO during single unit recordings decreased the firing rate of 10/12 GPi neurons while increasing the firing rate of 3/3 GPe neurons. Similar results were also observed when the mean firing rates of separate populations of GPi and GPe neurons were calculated. Before APO administration, the mean firing rate of 200 GPi neurons was 74±1.3 Hz (SE) and the mean firing rate of 85 GPe neurons was 45±1.6 Hz (SE). Maximal changes in mean firing rates occurred at 25-35 minutes after APO administration. During this period, the mean firing rate of 33 GPi neurons was 36±3.4 Hz (SE) and the mean firing rate of 7 GPe neurons was 72±6.6 Hz (SE). These results indicate that the APO-induced amelioration of parkinsonian symptoms is related to a decrease in the spontaneous discharge of GPi neurons and an increase in the spontaneous discharge of GPe neurons as predicted by the current model of basal ganglia function in PD.

### *3.1.1 - Introduction*

The administration of APO decreases the mean spontaneous discharge of the GPi in monkeys rendered parkinsonian with MPTP (Filion et al. 1991). This decrease occurs concurrently with the improvement in bradykinesia within the time course of the behavioral "ON" period associated with the medication. An APO induced decrease of GPi activity is hypothesized to result from two separate striatal influences, (1) driving of the direct GABAergric striatopallidal pathway and (2) inhibition of the glutamatergic drive from the STN to the GPi (Miller and DeLong 1987; Bergman et al. 1994). The latter influence is believed to be due to stimulation of striatal dopamine $D_2$ receptors resulting in disinhibition of the GABAergic GPe projections to the STN (Albin et al. 1989a). An increase in GPe activity following APO administration has been reported in MPTP treated monkeys (Filion et al. 1991). The aim of this section was to examine the changes in mean firing rates in the GPi and GPe following the administration of APO and an improvement in clinical symptoms.

### *3.1.2 - Methods*

APO was administered subcutaneously during 14 stereotactic pallidotomy procedures for the treatment of idiopathic PD. Pallidotomy is described in detail in the General Methods (sections 2.1.1.a) and single-unit microelectrode recording is described in detail in the General Methods (section 2.1.2). Briefly, stereotactic single unit microelectrode mapping of the GP allowed the identification of physiological landmarks and characterization of regional cellular activity (Lozano et al. 1996). All patients withheld antiparkinsonian medication for 12 hours previous to surgery and were

considered to be in the "OFF" state. APO administration is described in the General Methods (section 2.2.1). In each patient APO was given after a stable and isolated single unit recording was found. The cell's activity was monitored for up to a total time of 30 minutes. Other neurons included in this study were sampled for at least 20 seconds before or after APO administration and were included in a population study. A simple burst index was calculated by dividing the reciprocal of the modal interval (i.e. the peak of the inter-spike interval histogram) by the mean firing rate. Higher values of this burst index are taken to indicate that the neuronal discharge was more "bursty". The time when patients reported feeling the effects of medication or the time of the appearance of drug-induced dyskinesias were noted.

Cells were grouped according to their locations in GPe or GPi, the latter being subdivided into GPie and GPii based on the reconstructions of microelectrode track trajectories (Hutchison et al. 1994a).

### *3.1.3 - Results*

*Clinical effects of APO*

All patients were challenged pre-operatively with APO and total motor scores of the UPDRS (Part III) were assigned. This is shown in Table 3.1.T1. The doses of APO given intra-operatively gave rise to clinical improvements in the total motor scores of the UPDRS which were highly significant ($p < 0.01$).

*APO effects on single units (peri-injection effects)*

A total of 12 GPi and 3 GPe units were followed for 10 to 30 minutes after APO administration. Figure 3.1.F1 shows examples of the changes in firing rates and patterns of a GPi and a GPe neuron. The time course of the mean firing rates (average taken over 60 second intervals) of the 12 GPi cells are shown in Figure 3.1.F2A and the 3 GPe cells are shown in Figure 3.1.F2B. Of the 12 GPi cells studied, 10 showed a significant decrease ($p < 0.0001$, paired t-test) in firing rate at 10 minutes and all 3 GPe neurons had increases in their firing rate after APO injection.

The mean normalized inter-spike interval histograms of 5 GPi and 3 GPe neurons before and 15 minutes after APO injection are displayed in Figure 3.1.F3A and Figure 3.1.F3B, respectively. The plot for the GPi cells indicates that the reduction of mean firing rates was due to a decrease in shorter intervals and an increase in longer intervals, suggesting that the cells discharge with more bursts. The plot for the GPe cells indicates that the increase of mean firing rates was due to an increase in shorter intervals and a decrease in longer intervals. However, the simple burst index calculated for the 12 GPi cells was 3.3±1.7 (SD) before APO and 4.3±1.1 (SD) at 10 minutes after APO which was not significantly different ($p = 0.37$, paired t-test). The simple burst index for the GPe cells was 4.7±2.3 (SD) before APO and 2.4±0.1 (SD) 15 minutes after APO ($p = 0.14$, paired t-test).

*Apomorphine effects on separate populations of pallidal neurons*

The total number of cells sampled in all patients before the administration of APO was 312 and the results of the population study are shown in Table 3.1.T2. The regional mean firing rates were similar to those reported in another group of patients with PD

(Hutchison et al., 1994a). The locations of units sampled before and after APO administration is given in Figure 3.1.F4. Pre- and post-APO distributions within each nucleus were similar and it is unlikely that the observed changes in cellular activity were a result of differences in the location of neurons in the pallidal nuclei.

There were 184 neurons sampled after the administration of APO. The mean firing rates of neurons in each region as a function of time (5 minute bins) after APO injection are displayed in Figure 3.1.F5. There were 8 patients that reported feeling ON (i.e. the effects of APO) at 6 to 15 minutes after APO dosing, while 3 patients were noted to be dyskinetic within 16 to 23 minutes. Recovery to baseline values for all three regions (GPii, GPie, GPe) occurred at about 80 minutes. There was no significant difference between firing rates of neurons in GPie and GPii over time and these two groups were lumped together for statistical analysis. For GPi cells, firing rates were significantly decreased versus baseline values 15 minutes after APO administration ($p < 0.001$, one-way ANOVA). The distribution of firing rates occurring before APO and 25 to 35 minutes after APO for the GPi and GPe are shown in Figure 3.1.F6A and Figure 3.1.F6B, respectively.

**Table 3.1.T1**

Patient characteristics and pre-operative effects of APO on Unified Parkinson's Disease Rating Scale (UPDRS) Motor Scores.

*The clinical effects of APO in 14 patients with PD*

| | APO dose (mg) | Age at operation (years) | Disease duration (years) | UPDRS Total Motor Score OFF | UPDRS Total Motor Score ON (after APO) | Difference OFF - ON |
|---|---|---|---|---|---|---|
| mean | 4.1 | 58.8 | 14.3 | 44.9 | 15.1 | 28.6* |
| range | 2 - 10 | 45 - 71 | 5 - 19 | 26 - 67 | 5 - 34 | 10 - 52 |

*Significantly different from zero ($p<0.01$, z-test).

Table 3.1.T1

**Figure 3.1.F1**

The effects of APO on GPi (A) and GPe (B) single unit discharge. Rate histograms were calculated using 1 second bins. Samples of the discharge patterns before and after APO administration are shown below each rate histogram. Each vertical line represent one action potential.

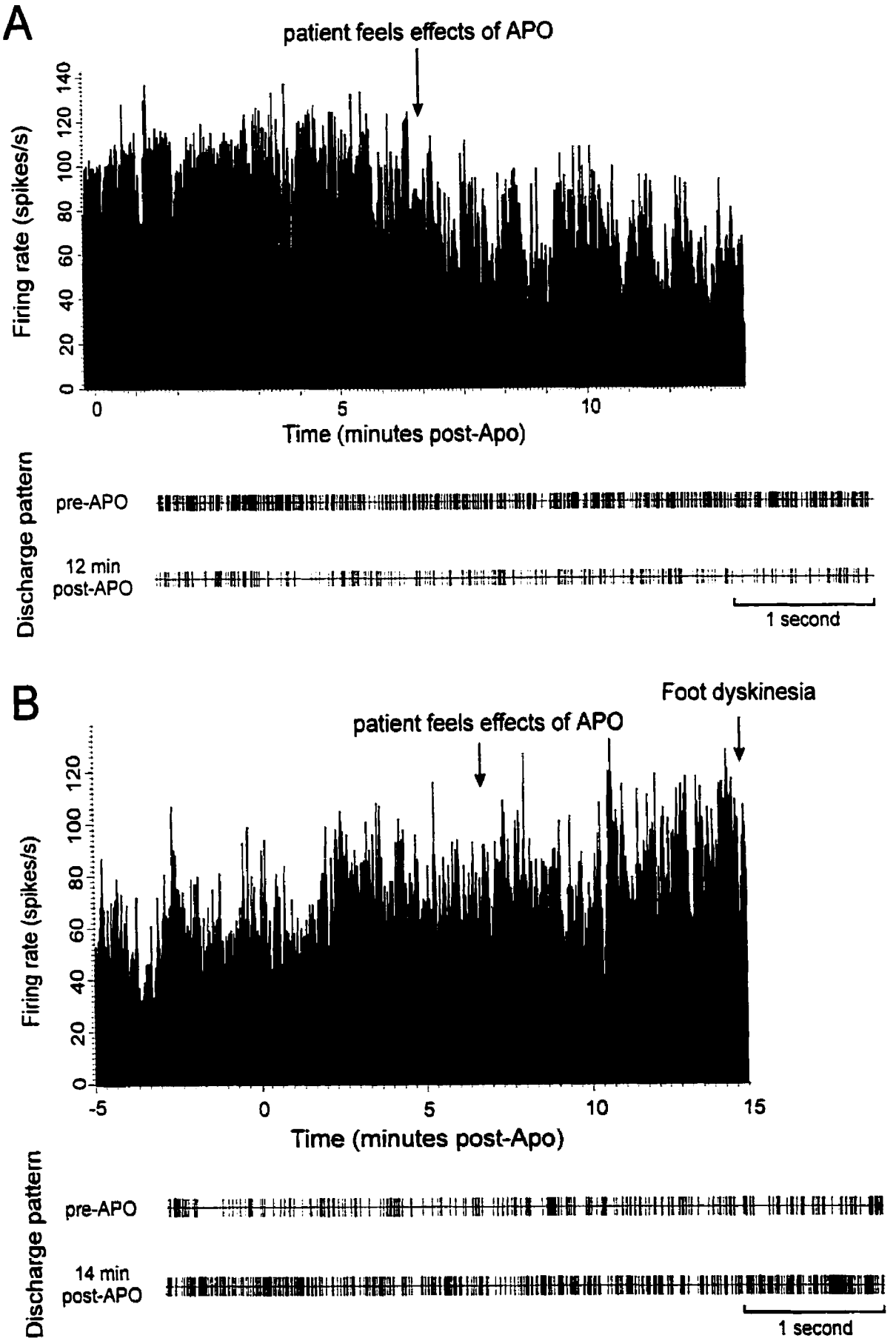

A
patient feels effects of APO
Firing rate (spikes/s)
0
20
40
60
80
100
120
140
0
5
10
Time (minutes post-Apo)
Discharge pattern
pre-APO
12 min
post-APO
1 second
B
Foot dyskinesia
patient feels effects of APO
Firing rate (spikes/s)
0
20
40
60
80
100
120
-5
0
5
10
15
Time (minutes post-Apo)
Discharge pattern
pre-APO
14 min
post-APO
1 second

Figure 3.1.F1

**Figure 3.1.F2**

The effects of APO on the spontaneous discharge of all followed GPi (A) and GPe (B) neurons. Means of single units were calculate using 1 minute bins.

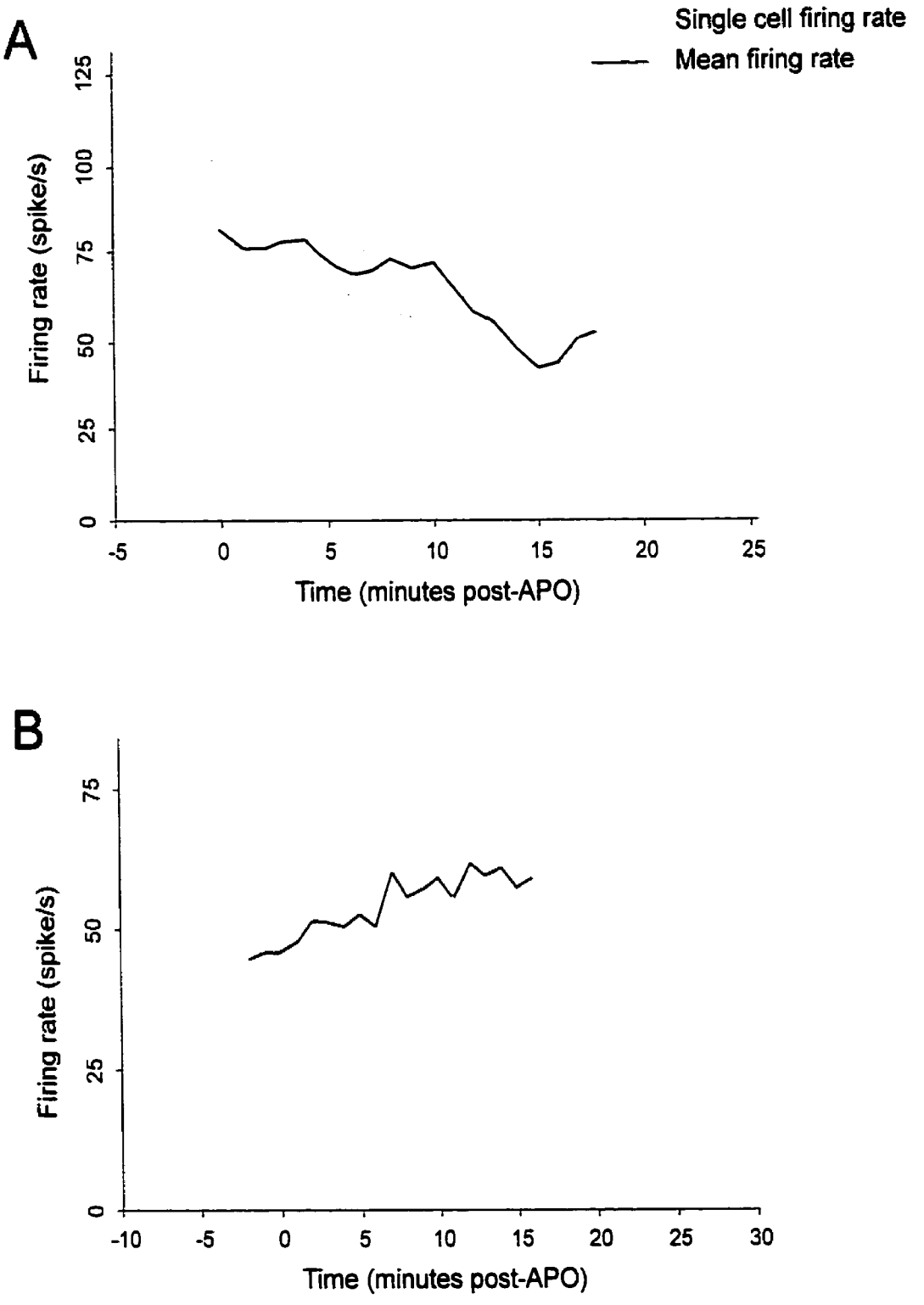

A
Single cell firing rate
Mean firing rate
Firing rate (spike/s)
0
25
50
75
100
125
-5
0
5
10
15
20
25
Time (minutes post-APO)
B
Firing rate (spike/s)
0
25
50
75
-10
-5
0
5
10
15
20
25
30
Time (minutes post-APO)

Figure 3.1.F2

**Figure 3.1.F3**

The mean normalized inter-spike interval histograms of the GPi (A) and GPe (B) neurons. Inter-spike interval histograms were calculated using 0.5 ms bins and normalized by the total number of inter-spike intervals for each cell.

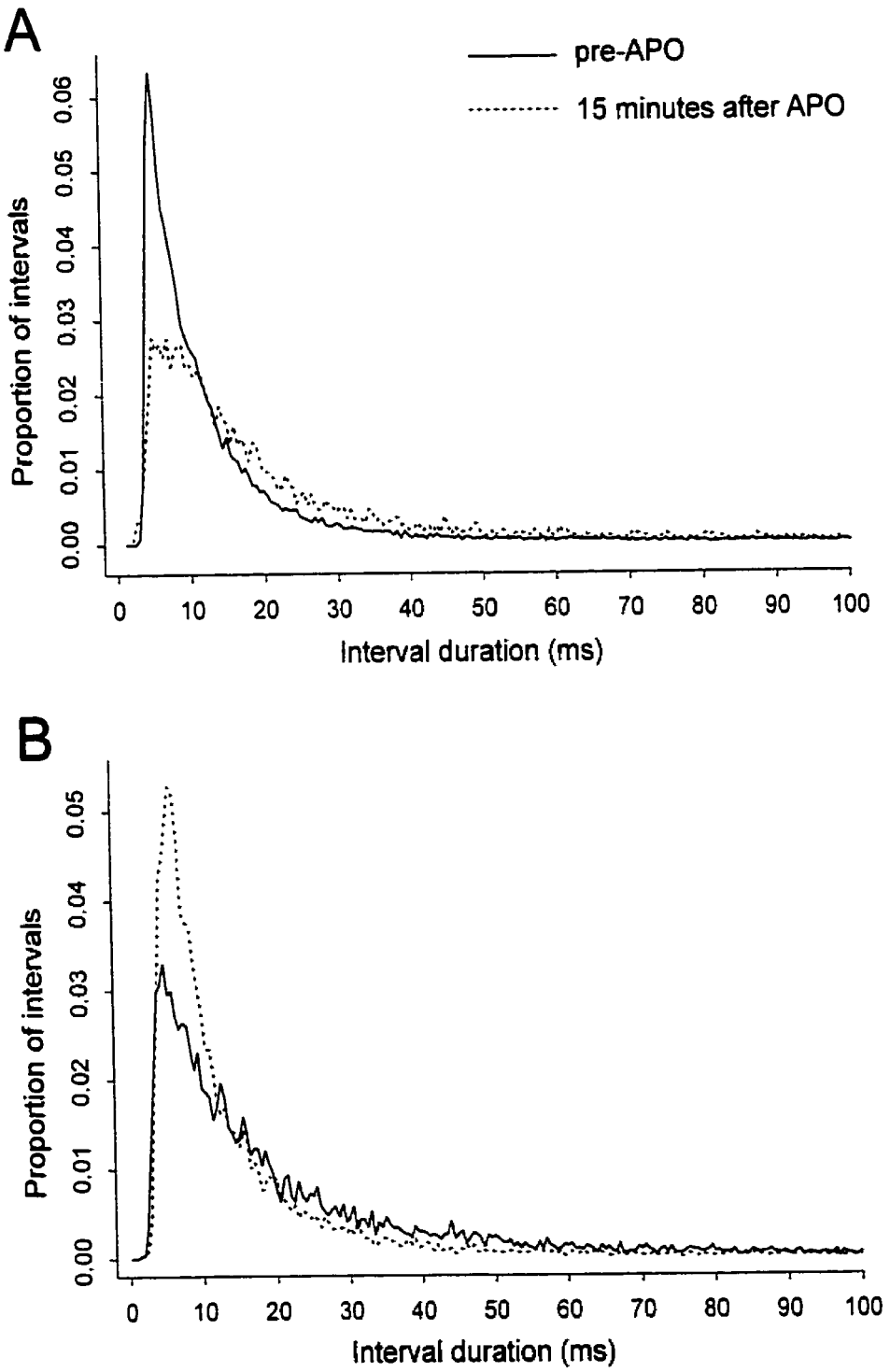

A
pre-APO
15 minutes after APO
Proportion of intervals
0.00
0.01
0.02
0.03
0.04
0.05
0.06
0
10
20
30
40
50
60
70
80
90
100
Interval duration (ms)
B
Proportion of intervals
0.00
0.01
0.02
0.03
0.04
0.05
0
10
20
30
40
50
60
70
80
90
100
Interval duration (ms)

Figure 3.1.F3

**Table 3.1.T2**

The mean firing rates of pallidal neurons sampled before the administration of APO. SD = standard deviation.

*Mean firing rates of pallidal neurons before APO administration*

| | GPe | GPie | GPii |
|---|---|---|---|
| Mean firing rate (Hz) | 45.0 | 66.9 | 85.2 |
| S.D. | 15.0 | 14.1 | 18.6 |
| n | 85 | 125 | 75 |

**Table 3.1.T2**

**Figure 3.1.F4**

Sagittal sections (at 17, 20, and 22 mm from the midline) based on the Schaltenbrand and Wahren stereotactic atlas (standardized to the patients anterior-posterior commissural distance) displaying the locations of pallidal neurons sampled before and after APO administration.

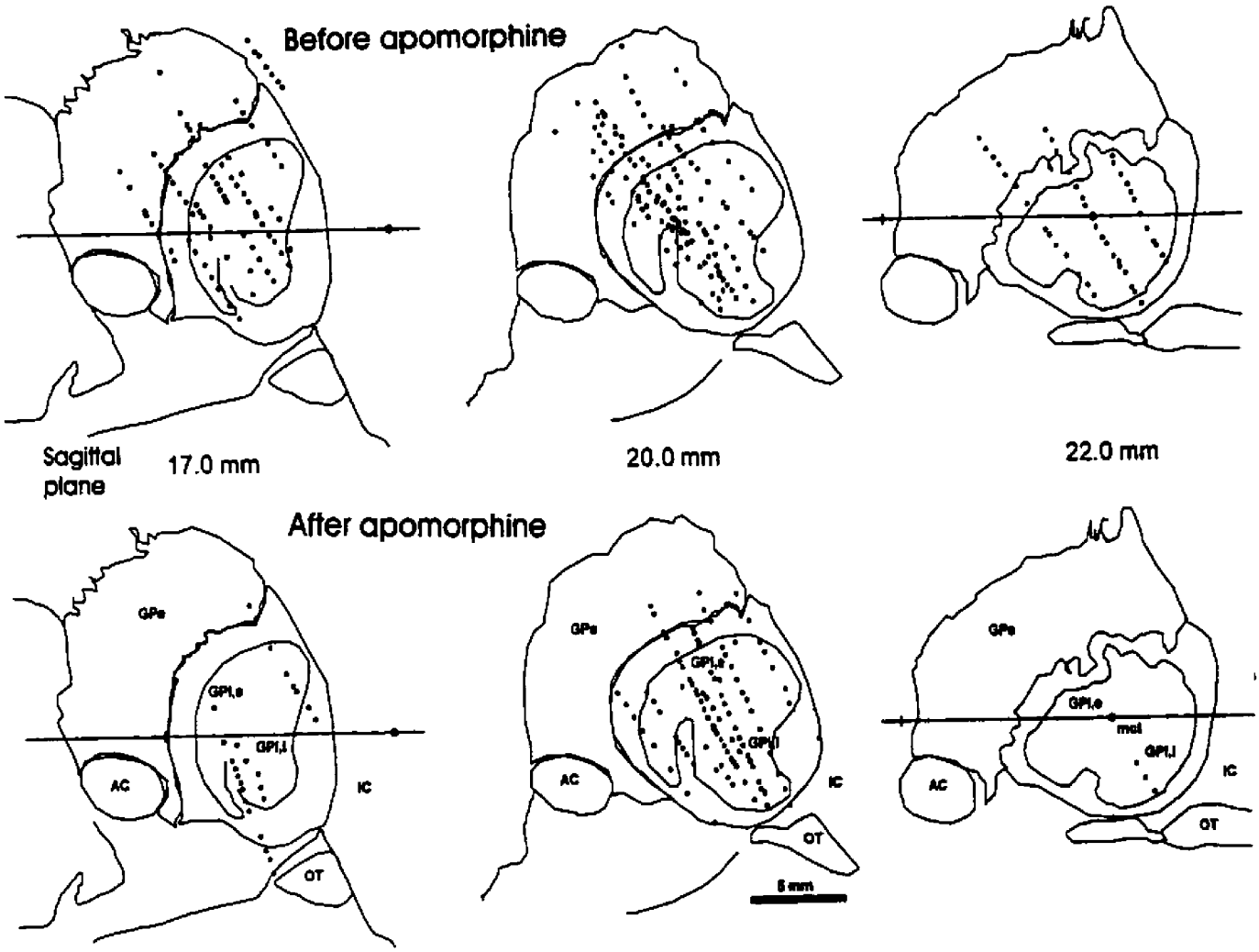

Before apomorphine
Sagittal plane
17.0 mm
20.0 mm
22.0 mm
After apomorphine
GPe
GPi,e
GPi,l
AC
IC
OT
5 mm
mcl

Figure 3.1.F4

**Figure 3.1.F5**

The effect of APO on the mean firing rates of separate populations of pallidal neurons.

Means were calculated using 5 minute bins.

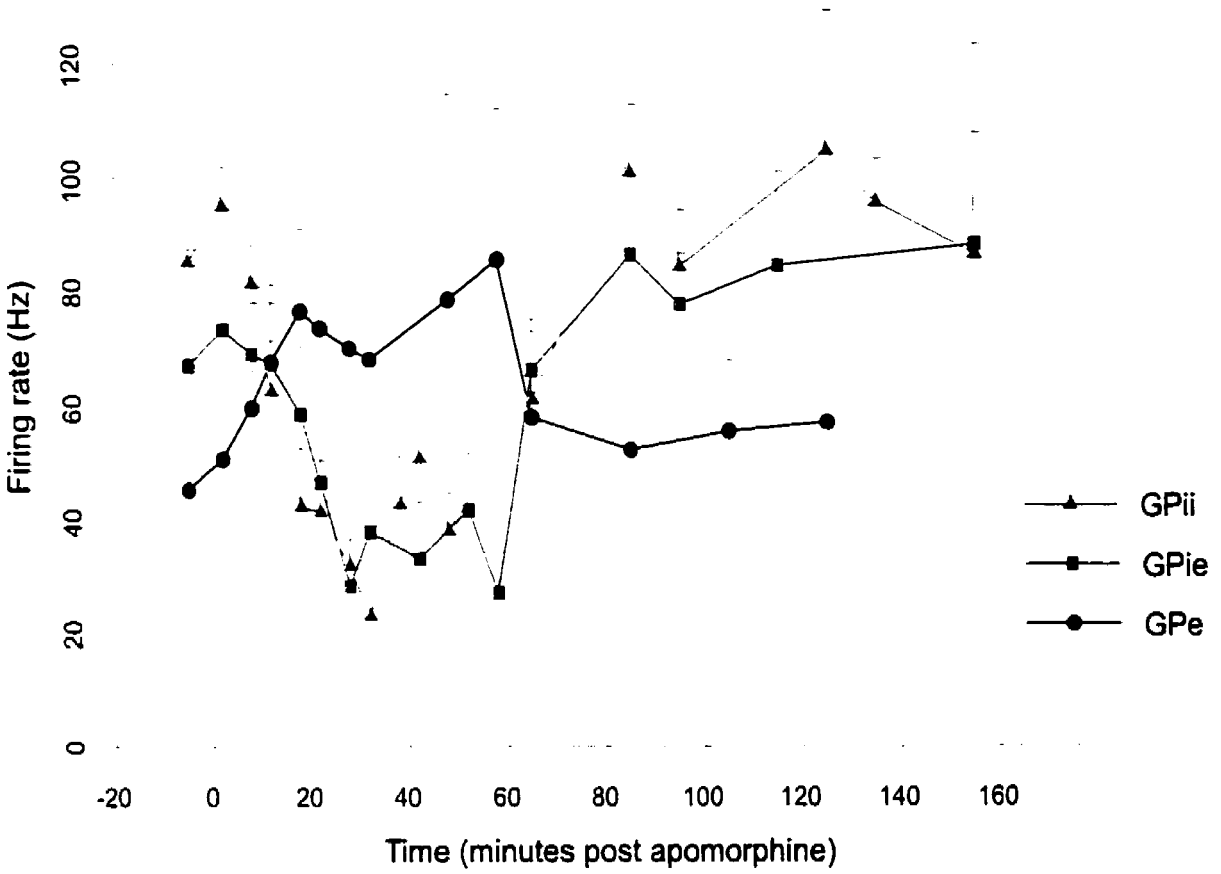

Firing rate (Hz)
0
20
40
60
80
100
120
-20
0
20
40
60
80
100
120
140
160
Time (minutes post apomorphine)
GPii
GPie
GPe
Time over which 8 patients begin to report feeling ON
Time over which 3 patients begin getting dyskinesias

Figure 3.1.F5

**Figure 3.1.F6**

The distributions of firing rates from separate populations of GPi (A) and GPe (B) neurons sampled before and 25-35 minutes after APO administration.

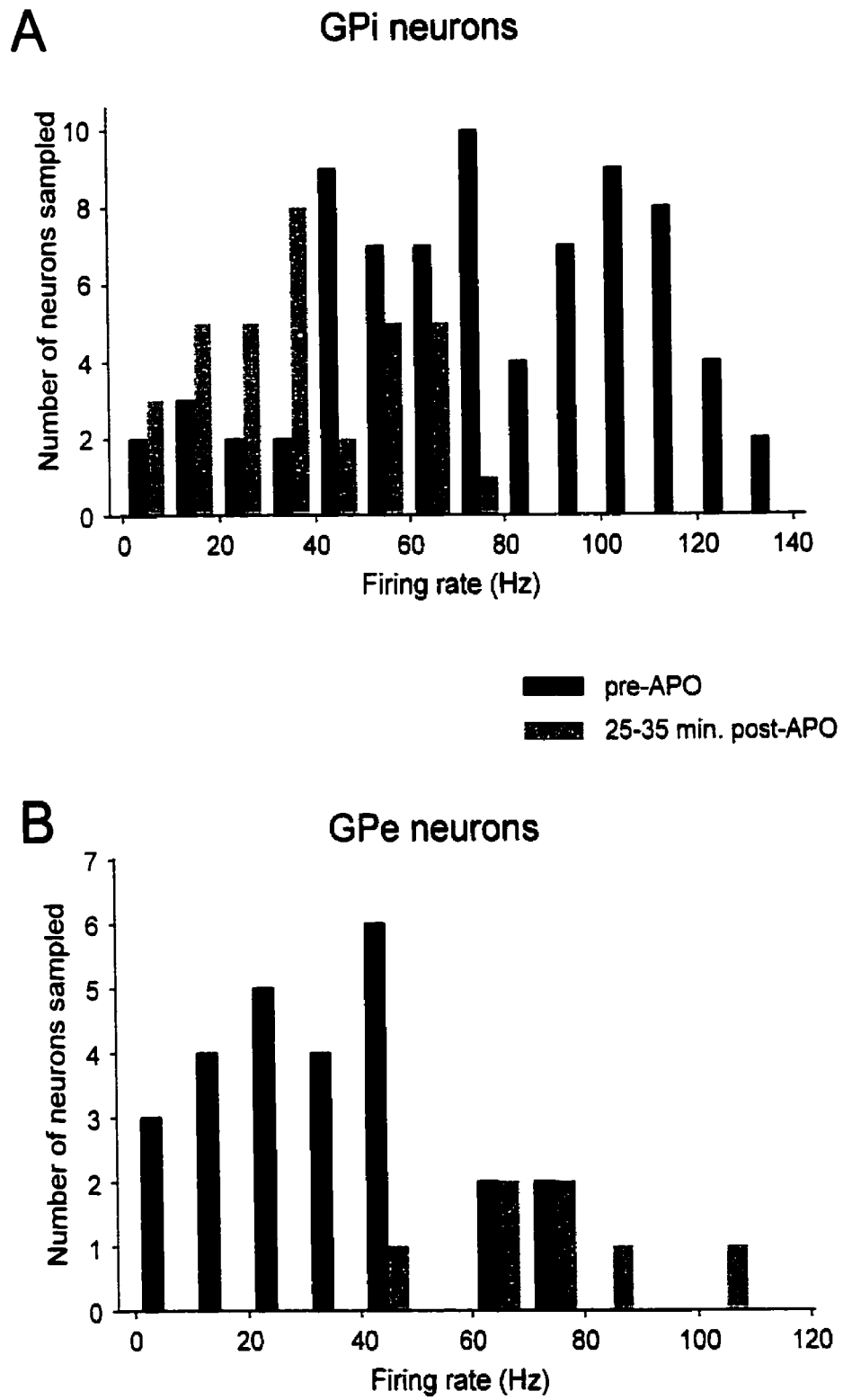

A
GPi neurons
Number of neurons sampled
0
2
4
6
8
10
0
20
40
60
80
100
120
140
Firing rate (Hz)
pre-APO
25-35 min. post-APO
B
GPe neurons
Number of neurons sampled
0
1
2
3
4
5
6
7
0
20
40
60
80
100
120
Firing rate (Hz)

Figure 3.1.F6

### *3.1.4 - Discussion*

This section demonstrated that the administration of APO led to a decrease in the activity of neurons in the GPi and increased the activity of those in the GPe. The APO-induced changes in mean firing rates occurred in the GPi and GPe at both the single cell and population level. The observed changes in mean firing rates occurred concurrently with the onset and duration of clinical effects of APO (Gancher, 1995). These results support similar observations in MPTP-treated monkeys (Filion et al. 1991; Boraud et al. 1998) and suggest that the anti-parkinsonian effect of APO is due, in part, to a normalization of the mean firing rates in the GPi and GPe. An APO-induced decrease in the firing rates of GPi neurons in parkinsonian patients have now been confirmed by other groups of researchers (Stefani et al. 1997; Merello et al. 1999).

The reduction in akinesia and bradykinesia, the main therapeutic effect of APO (Gancher, 1995), is possibly due to a disinhibition of the motor thalamus secondary to a decrease in the mean spontaneous activity in the GPi as predicted by the box model of the pathophysiology of the basal ganglia in PD (Albin et al. 1989a; Delong 1990). An APO-induced reduction in the firing rates of GPi neurons may be mediated by activity in the direct pathway and/or indirect pathway as discussed in section 1.4.1. APO-induced changes in the firing pattern of GPi and GPe neurons were also observed. A detailed analysis of the effects of APO on firing patterns and somatosensory responses of neurons in the GPi and STN is given in the next two sections of this chapter.

## 3.2 - Effects of apomorphine on discharge patterns in the internal segment of the globus pallidus

*Abstract*

This study examines the effect of APO on the discharge patterns and somatosensory responses of neurons in the GPi of patients with PD. Single unit microelectrode recordings were conducted in 6 patients undergoing a pallidotomy. Doses of APO (2.5-8 mg) were sufficient to produce an ON state, but not intended to induce dyskinetic movements. Following baseline recordings from a single neuron, APO was administered and the activity of the neuron followed for an average of 15 minutes. The spontaneous discharge of GPi neurons encountered before (n=309), during (n=146, 10-60 minutes), and after the effect of APO had waned (n=127, >60 minutes) was also sampled and the response to passive joint movements was noted. APO significantly decreased the overall firing rates of GPi neurons ($p<0.01$), produced an increase in the overall proportion of spikes in burst discharges (as detected with Poisson "surprise" analysis) and led to a greater proportion of cells with an irregular discharge pattern. Concurrent with a reduction in limb tremor, the percentage of TCs was found to be significantly reduced from 14% to 0% following APO administration. During the OFF state, more than 15% of neurons tested (63 cells tested) responded to passive movement of two or more joints. After APO, this proportion decreased significantly to 4% of GPi cells (26 cells tested). These findings demonstrate that APO produces dramatic changes in the discharge patterns of GPi neurons and indicate that the anti-parkinsonian effect of APO is probably not solely due to a decrease in overall activity in the GPi as predicted by the current model of basal ganglia function in PD.

### *3.2.1 - Introduction*

It has been observed that following the depletion of striatal dopamine, the pattern of neuronal discharge in the GPi is altered. In MPTP-treated monkeys, GPi neurons display increased bursting activity (Filion and Tremblay 1991; Wichmann et al. 1999). Periodic bursting or "oscillatory activity" that is time locked to limb tremor is also observed in MPTP monkeys (Bergman et al. 1994; Nini et al. 1995) and PD patients (Hutchison et al. 1997). GPi neurons in parkinsonian animals also have exaggerated responses and multi-limb receptive fields (Filion et al. 1988). The aim of this section was to test the hypothesis that changes in the pattern of neuronal activity and somatosensory responses in the GPi following the administration of APO are related to parkinsonian symptoms.

### *3.2.2 - Methods*

The recording procedures for the GPi are described in the General Methods (sections 2.1.1.a and 2.1.2). The patients in this study were those undergoing pallidotomy. The indications for pallidotomy were akinetic-rigid parkinsonian syndromes with fluctuating on-off periods and drug-induced dyskinesias (Lozano et al. 1996). This group consisted of 6 of the 14 patients in whom APO-induced changes in mean firing rates were previously reported (see Chapter 3, section 1). Further analysis of changes in firing patterns, receptive fields, and TCs are now reported here. Unless otherwise stated, errors are reported as standard errors of the mean (SE). These 6 patients received an

average of 3.7±0.6 mg (SE) of APO during their pallidotomy. The protocol for APO injection is described in the General Methods (section 2.2.1). In each patient, a stable and well isolated single unit was found and APO was administered subcutaneously following 2-3 minutes of stable recording. The peri-injection activity of these neurons were then monitored. Other neurons sampled before and after APO administration were included in a population study if they were well isolated (i.e. a high signal-to-noise ratio of the action potential versus the background noise) and stable. In this study, the median sampling time of each neuron was 30.1 seconds (n=261, minimum=28 seconds) and the median number of discriminated action potentials per neuron was 1880.

All neuronal data were subdivided into three groups. The "pre-APO time" block group included all cells sampled before the administration of APO, the "APO period" time block group included all cells sampled between 10 and 60 minutes after the administration of APO, and the "post-APO" time block group comprised all cells sampled at 60 minutes or more following APO administration. This breakdown followed the time course of GPi and GPe cells following APO administration used in the preceding section and matched the time course of the clinical effects in the pre-operative APO trials of the 13 STN patients (see Chapter 3, section 3). It has also been reported that APO is rapidly absorbed following subcutaneous injection, with peak levels achieved within 5-10 minutes in most patients (Gancher 1995). Data analysis of single unit activity is described in the General Methods (section 2.3). Neuronal responses to somatosensory stimulation were carried out by noting the receptive fields (RF) of neurons to passive movements of the limbs and is described in the General Methods (section 2.3.3).

### *3.2.3 - Results*

*Clinical effects of APO*

There was a significant pre-operative beneficial effect of APO administration in the group of 6 patients with median UPDRS motor scores improving from 46.0 to 16.5 ($p<0.01$, Wilcoxon signed rank test). Following the intra-operative administration of APO, two patients reported that they were becoming ON at 6 and 11 minutes but they did not display APO induced involuntary movements. At the start of the procedure three patients had a pronounced limb tremor and the administration of APO was found to abolish limb tremor and to produce dyskinesias. The remaining patient did not report feeling ON yet this patient developed mild drug-induced dyskinesias.

*Single unit studies*

Three GPi neurons were recorded for at least 10 minutes following the administration of APO. The change in firing rates (top panel) and the corresponding change in the proportion of spikes in bursts as detected with Poison surprise analysis (lower panel) are shown in Figure 3.2.F1. All three patients felt the effects of the medication during this time (time of occurrence indicated by black dots) which corresponded to a reduction from the pre-APO baseline firing rates (mean decrease ~30%). These decreases in firing rate were associated with increases in the proportion of spikes in bursts. One patient became mildly dyskinetic after a 40% decrease in the firing rate of the single cell (dashed line, indicated by x). The cell had a discharge rate of ~ 60 spikes/sec during episodes of mild dyskinesias. In another patient (dotted line), there was a marked reduction in spontaneous discharge that coincided with a cessation of ongoing

limb tremor at 5 minutes after the APO dosing (indicated by †) and the appearance of dyskinetic movements 4 minutes after the end of the single unit recording.

*Population analysis - firing rates and pattern*

The distributions of the average neuronal firing rates and the discharge firing patterns of GPi neurons are shown in Figure 3.2.F2. There was a significant decrease of the average neuronal firing rate to 39 Hz (±2.5, n=51) during the APO period compared to both pre-APO (72 Hz (±2.9), n=93) and post-APO periods (82 Hz (±4.1), n=53) (†$p<0.01$, ANOVA on ranks) (leftmost panel). The proportion of neurons that discharged in an irregular or random pattern significantly increased during the APO period (*$p<0.01$, $\chi^2 = 16.2$, n=197). The proportion of spikes in bursts was also increased from 16.2% (±1.2) to 26.1% (±2.4) during the APO period (†$p<0.01$, ANOVA on ranks). There was no difference in the change of the mean firing rates from pre-APO values between the patients with and without dyskinesias. In addition, the mean firing rates of cells recorded in the four patients during time periods with dyskinetic movements (n=30, 40.5 Hz (±5.0)) to those recorded in the two patients without dyskinesias during the APO period (n=18, 39.6 Hz (±5.2)) were not different ($p=0.45$, ANOVA on ranks). There was no difference in the proportion of spikes in bursts between the two groups ($p=0.40$, ANOVA on ranks).

*Population analysis - oscillatory cells*

Before the administration of APO, 14% (13/93) of all GPi neurons examined displayed tremor-related activity. These cells were located in four patients (3 of whom

had a pronounced limb tremor at the start of the procedure). The average firing rate of the TCs was 84.5 Hz (±7.3) and was significantly higher than the firing rate of the non-oscillatory GPi neurons in these 4 patients (65.3 Hz (±3.1), n=54 cells, $p<0.01$). Only 2 GPi neurons with a high-frequency oscillation (>10 Hz oscillation) were encountered in all 6 patients. The distribution of oscillatory frequencies of GPi neurons sampled during pre-APO period, APO period, and post-APO period is shown in Figure 3.2.F3. There were no TCs encountered in the GPi during the APO period (51 neurons examined in the six patients). During the post-APO period 22.6% (12/53) of the neurons were TCs. These neurons were located in the same 4 patients who displayed TC activity before the administration of APO. The firing rate of the 12 TCs was 96.0 Hz (±8.9). This was significantly higher than the firing rate of non-oscillatory cells found in this group of 4 patients (78.8 Hz (±4.5), n=37, $p<0.05$).

*Population analysis - Receptive fields*

The proportions of neurons that had no detectable RF and those that responded to movements about one, two or more joints are displayed in Figure 3.2.F4. The administration of APO decreased the proportion of cells that responded to limb movement from 54% to 20% ($p<0.01$, $\chi^2 = 9.43$, n=102). APO decreased the proportion of cells that responded to passive movement of two joints from 10% to 4%. During the APO period, there were no neurons with a multiple or bilateral RF encountered. The relative proportions of single RFs to double and multiple RFs did not significantly change during this period or during the post-APO period ($p=0.11$, $\chi^2 = 4.50$, n=46). There were no significant differences between firing rates, bursting, or oscillatory behavior of cells

that did not have a detectable RF and those that did have detectable RFs nor was there any significant differential effects of APO on the neuronal activity of these groups.

**Figure 3.2.F1**

Plots of firing rate (top panel, 2 minute bins) and the proportion of spikes in bursts (lower panel, 2 minute bins) of three GPi neurons. One patient (indicated by dotted line) had a cessation of limb tremor at 5 minutes following dosing and became dyskinetic 4 minutes after the end of the single unit recording. Another patient had a loss of limb tremor and reported feeling ON at 7 minutes after dosing. The patient also became dyskinetic at 10 minutes. The patient was still ON at 45 minutes and the limb tremor recurred at 63 minutes (indicated by dashed line).

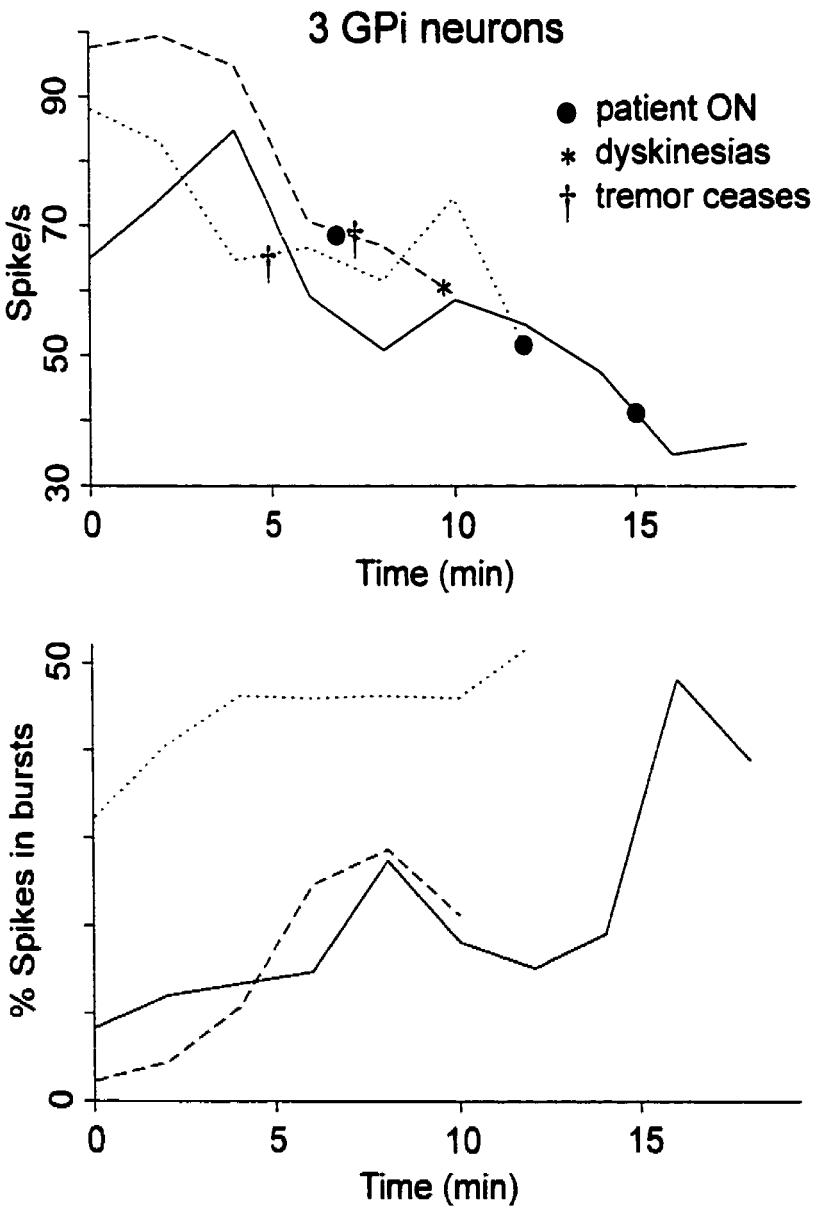

3 GPi neurons
patient ON
dyskinesias
tremor ceases
Spike/s
90
70
50
30
0
5
10
15
Time (min)
% Spikes in bursts
50
0
0
5
10
15
Time (min)

Figure 3.2.F1

**Figure 3.2.F2**

Graphs and plots showing the effects of APO on populations of neurons in the GPi. Population firing rate distributions are shown in the leftmost panel (10 Hz bins). The downward arrows in this graph represent the mean of the corresponding distribution. Numbers in parentheses at the bottom of the left set of vertical bars (i.e. proportion of random, irregular, and regular discharges) indicate the number of cells within each group. Data from the same cells were used to construct the firing rate distributions and the right bar graphs. APO reduced the mean firing rate of GPi neurons from pre-APO values and post-APO means (†$p<0.01$, ANOVA on ranks). APO significantly increased the proportion of neurons with irregular or random firing patterns (*$p<0.01$, $\chi^2 = 16.2$, $n=197$) and the proportion of spikes in bursts of GPi neurons (†$p<0.01$, ANOVA on ranks).

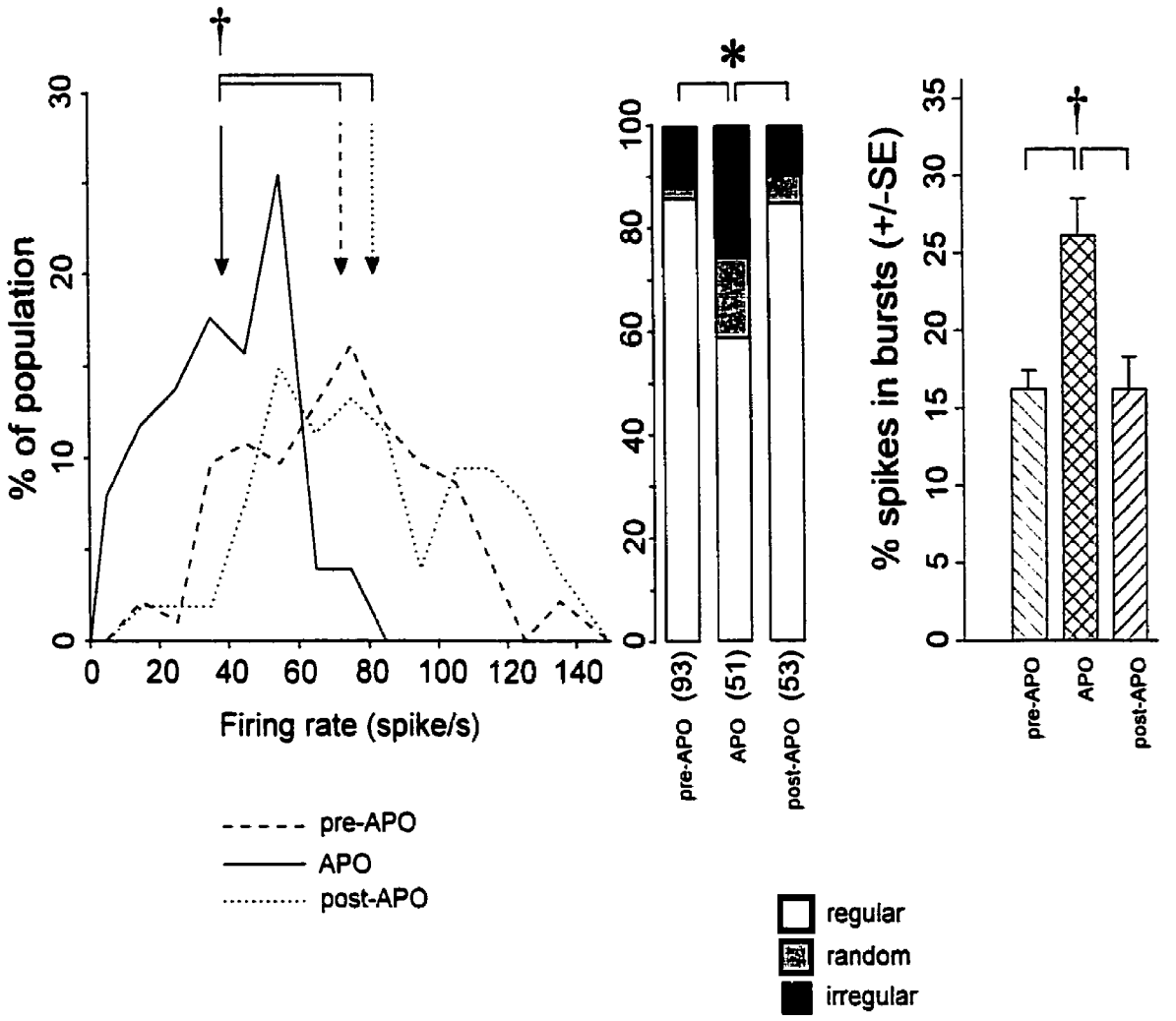

†
% of population
30
20
10
0
0 20 40 60 80 100 120 140
Firing rate (spike/s)
pre-APO
APO
post-APO
*
100
80
60
40
20
0
pre-APO (93)
APO (51)
post-APO (53)
regular
random
irregular
% spikes in bursts (+/-SE)
35
30
25
20
15
10
5
0
†
pre-APO
APO
post-APO

Figure 3.2.F2

**Figure 3.2.F3**

Distribution of oscillation frequencies of cells in the GPi. Total number of cells sampled is given in upper left of each panel. Cells with tremor activity or a high-frequency oscillatory component are represented by gray squares.

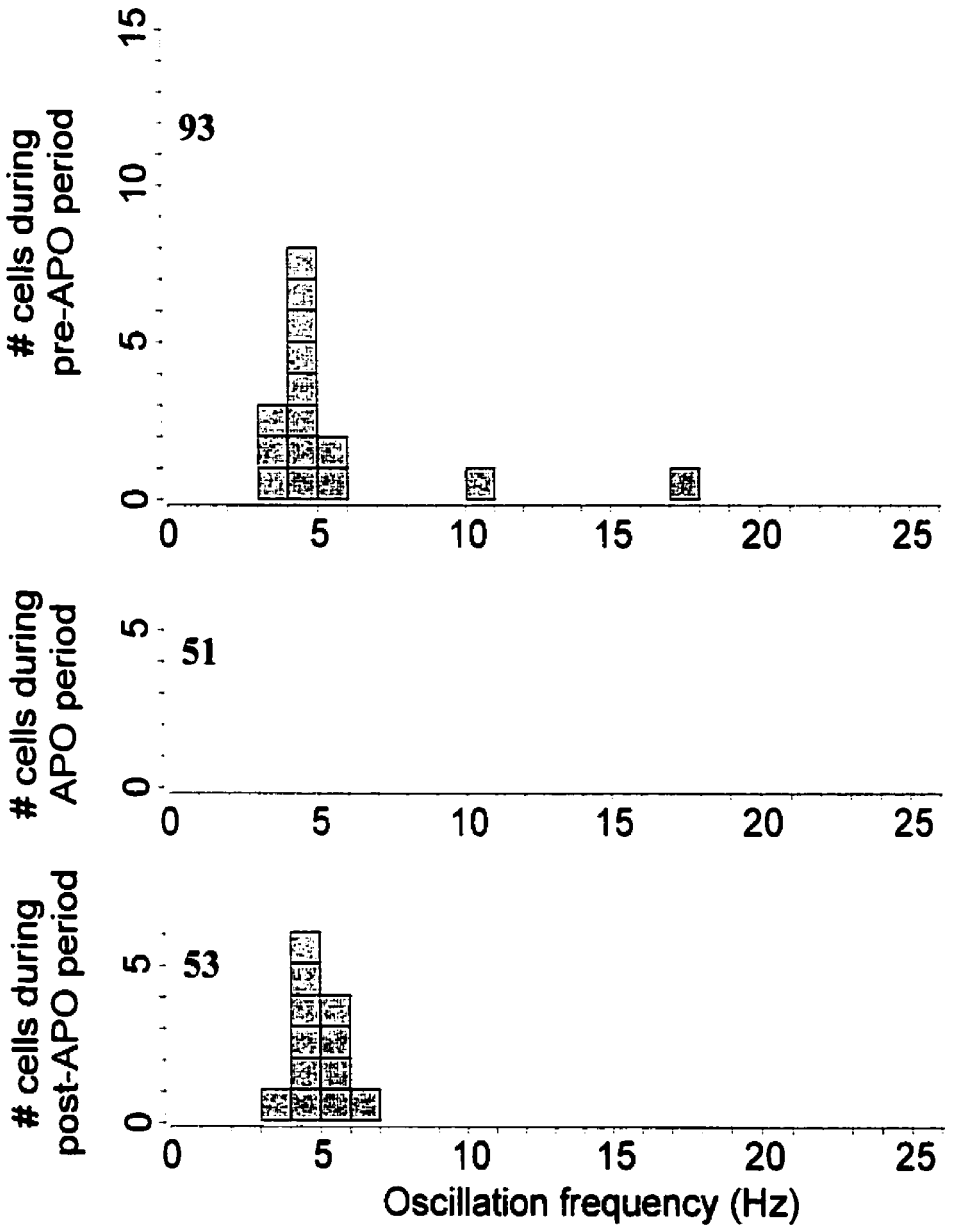

# cells during pre-APO period
93
# cells during APO period
51
# cells during post-APO period
53
0
5
10
15
20
25
Oscillation frequency (Hz)

Figure 3.2.F3

**Figure 3.2.F4**

Bar graphs showing the proportions of neurons that had no response (no detectable RF), and single, double, and multiple RFs before APO administration (pre-APO), during the APO period (APO), and during the post-APO period (post-APO) in the GPi. Significant differences from the proportion of cells with no response before and after the APO period are indicated by ** ($p<0.01$). Numbers under grouped vertical bars indicate the ratio of the total number of cells versus the number of patients in which these cells were sampled.

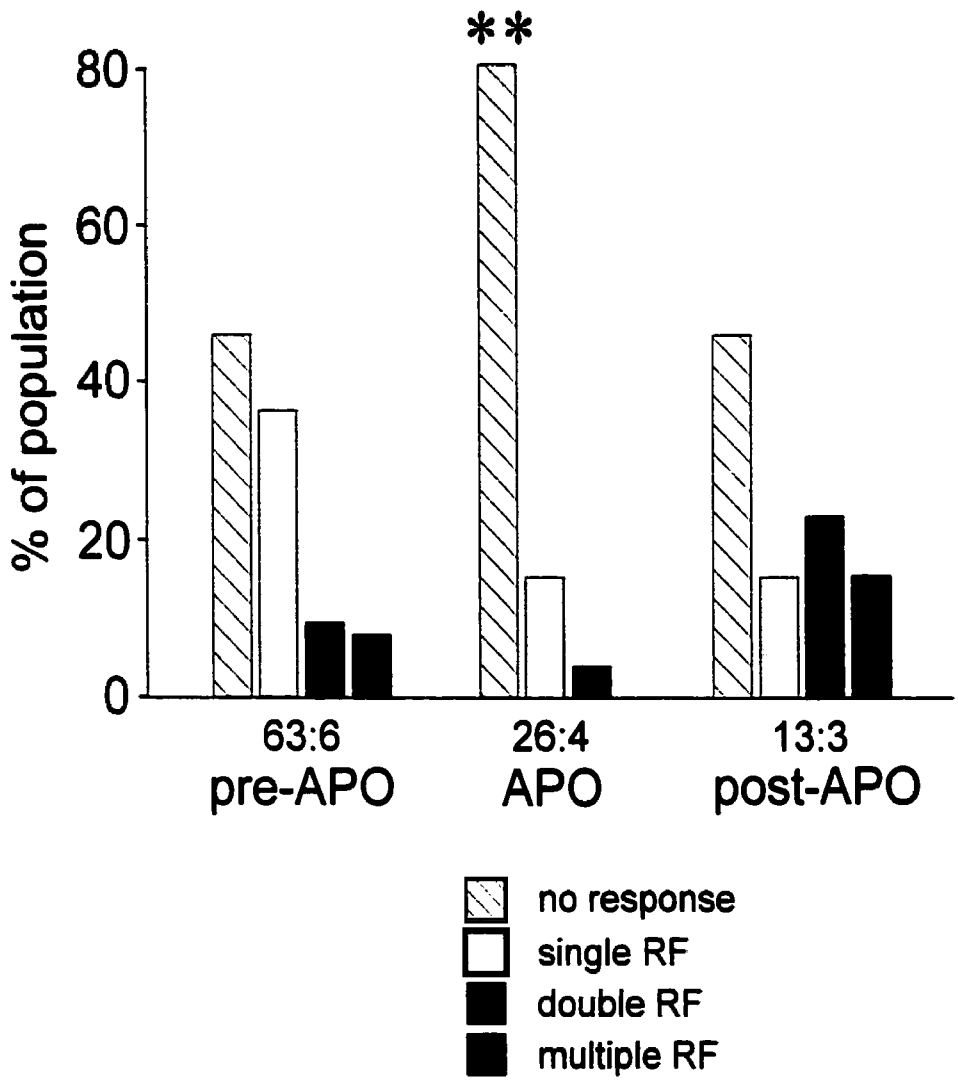

**
80
60
40
20
0
% of population
63:6
pre-APO
26:4
APO
13:3
post-APO
no response
single RF
double RF
multiple RF

Figure 3.2.F4

### *3.2.4 - Discussion*

This section demonstrated that the administration of APO produces alterations in the pattern of neuronal activity in the GPi and many of these changes can be directly related to the clinical antiparkinsonian effect of this dopaminergic medication. APO administration, in addition to decreasing mean firing rates, brought about changes in discharge patterns and somatosensory responses of neurons in the GPi. The demonstration of tremor related activity in this nuclei is consistent with previous reports of TCs in the GPi of parkinsonian patients in the OFF state (i.e. no anti-parkinsonian medication) (Hutchison et al. 1997; Hurtado et al. 1999). This is the first report of the effects of dopaminergic medication on tremor-related activity in the BG of parkinsonian patients. Following APO administration, a decrease in the proportion of GPi TCs was observed and was related to the APO-induced decrease in limb tremor.

Therefore, the alterations in firing pattern produced by APO might have, in addition to decreasing the firing rates of GPi neurons, contributed to the therapeutic effects of the drug. Indeed, it has been suggested that increased irregularity of discharge and bursting in the GPi and STN contribute to the development of the disorders of movement seen in PD (Filion and Tremblay 1991; Miller and DeLong 1987; Bergman et al. 1994; Wichmann et al. 1999). Specifically, these changes in firing patterns involve an increase in the proportion of (1) aperiodic bursting cells and (2) oscillatory cells or periodic bursting cells such as GPi TCs. Although neurons displaying oscillatory "bursting" activity can be regarded as a special case of aperiodic bursting cells, it is important to compare the effect of APO on both types of discharge patterns because these

phenomena may occur with different mechanisms and may have different physiological meanings (Kaneoke and Vitek 1996).

Surprisingly, this study demonstrated that bursting discharge was increased in the GPi during the period of time in which APO reduced the patient's parkinsonism, in apparent contradiction to the notion that increased bursting contributes to the parkinsonian pathophysiology. However the results from previous studies examining the effect of dopaminergic medication in the GPi of parkinsonian monkeys or patients with PD are unclear. In MPTP-treated monkeys, Filion et al. (1991) reported that APO administration was associated with a more regular firing pattern in the GPi, even when APO induced only a moderate decrease in firing rate but still produced a dyskinetic state. This is in contrast to Boraud et al. (1998) who found no significant decrease in the number of GPi bursting cells with L-dopa administration in MPTP-treated monkeys. In agreement with our results, Merello et al. (1999) reported that previously high frequency tonic discharge neurons in the GPi displayed reduced tonic firing rates and burst-like discharges during APO-induced dyskinesias in patients with PD.

In the 4/6 GPi patients presenting mild dyskinesias, the mean activity of the GPi was not significantly lower than in those GPi patients without dyskinesias. It is however possible that the neurons in this sample were not related to the area of the body in which the dyskinesias occurred. A recent study by Papa et al. (1999) found that GPi neurons in MPTP-treated monkeys were nearly silenced during episodes of drug-induced dyskinesias. However, the dyskinesias were produced by administration of oral carbidopa/levodopa doses that were at least twice as high as those used to reverse parkinsonian disability without producing dyskinesias. It has been reported that MPTP-

treated monkeys or patients with PD can develop APO-induced dyskinesias even when the firing rates of GPi neurons are not dramatically reduced (Filion et al. 1991; Merello et al. 1999).

The somatosensory responses observed in this section are consistent with several studies that have noted that following MPTP treatment and the emergence of parkinsonian symptoms, GPi neuronal responses to passive limb movement increase in magnitude and lose specificity (Filion et al. 1988; Boraud et al. 2000a). Although the effect of APO on somatosensory responses from the leg was not determined (and therefore underestimated the number of "leg" responsive neurons), the results for the upper extremities are nonetheless highly relevant because of the anti-parkinsonian effect of APO on these body regions (as demonstrated with the preoperative effect of APO on UPDRS motor scores).

## 3.3 - Effects of apomorphine on discharge rates and patterns in the subthalamic nucleus

*Abstract*

This study examines the effect of APO on the discharge patterns and somatosensory responses of neurons in patients with PD. Single unit microelectrode recordings were conducted in 13 patients undergoing implantation of DBS electrodes in STN. Doses of APO (2.5-8 mg) were sufficient to produce an ON state, but not intended to induce dyskinetic movements. Following baseline recordings from a single neuron, APO was administered and the activity of the neuron followed for an average of 15 minutes. The spontaneous discharge of other neurons encountered before (n=309), during (n=146, 10-60 minutes), and after the effect of APO had waned (n=127, >60 minutes) was also sampled and the response to passive joint movements was noted. Although APO produced a clear therapeutic benefit, there was no change in the overall firing rate of STN neurons ($p=0.68$). However, APO increased the overall proportion of spikes in burst discharges (as detected with Poisson "surprise" analysis) and a greater proportion of cells with an irregular discharge pattern was observed. In contrast, the mean firing rates of STN neurons during APO-induced movements (choreic or dystonic dyskinesias) that occurred in 4 patients were significantly lower than OFF-period baseline values ($p<0.05$). Concurrent with a reduction in limb tremor, the percentage of TCs was found to be significantly reduced from 19% to 6% following APO administration. APO also decreased the firing rate of STN TCs ($p<0.05$). During the OFF state, more than 15% of neurons tested (93 cells tested) responded to passive movement of two or more joints. After APO, this proportion decreased significantly to 7% of STN cells (28 cells tested).

These findings demonstrate that the anti-parkinsonian effect of APO administration is associated with changes in the pattern of neuronal discharge in the STN rather than changes in overall mean firing rate.

### *3.3.1 - Introduction*

Similar to observations in the GPi, the pattern of neuronal discharge in the STN is also altered following the depletion of striatal dopamine. In monkeys made parkinsonian with MPTP, increased bursting and tremor-related oscillatory activity is observed in the STN (Bergman et al. 1994). Tremor-related oscillatory activity is also observed in patients with PD (Rodriguez et al. 1998). Since the GPi receives direct afferent input from the STN, it is possible that APO-induced changes in discharge rate and pattern of GPi neurons, as described in the preceding sections, is also present in the STN. For example, in rats made parkinsonian with 6-hydroxydopamine-induced lesions of the nigrostriatal pathway, APO has been shown to decrease the firing rates of STN neurons (Kreiss et al. 1997). The effect of APO on the STN in parkinsonian monkeys or humans is not known. The aim of this section was to test the hypothesis that changes in the rate and pattern of neuronal activity and somatosensory responses in the STN following the administration of APO are related to parkinsonian symptoms.

### *3.3.2 - Methods*

Studies of the STN were performed in 13 individuals undergoing microelectrode guided placement of bilateral DBS electrodes for the treatment of the symptoms of PD.

The group consisted of 7 females and 6 males and at the time of operation had a mean age of 62.8 years (range 46–76). The average duration of the disease was 15.9 years (±1.2 SE) and all had PD for at least 10 years. The median OFF Hoehn and Yahr rating of the patients was IV (range II–V). One patient had a previous pallidotomy and only cells from the non-lesioned side were included. Two other patients were given the anaesthetic propofol when the burr holes were drilled and only data from cells recorded at least 30 minutes after propofol had completely worn off were included. A subsequent comparison between these two individuals and the other STN patients confirmed that there were no differences in the neuronal discharge characteristics. The indications for STN DBS are bilateral limb and axial manifestations of PD, medication-refractory motor fluctuations and levodopa-induced dyskinesias (Kumar et al., 1998b).

The recording procedures for the STN are described in the General Methods (sections 2.1.1.b and 2.1.2). The protocol for APO injection is described in the General Methods (section 2.2.1). In each patient, a stable and well isolated single unit was found and APO was administered subcutaneously following 2-3 minutes of stable recording. The peri-injection activity of these neurons were then monitored. Other neurons sampled before and after APO administration were included in a population study if they were well isolated (i.e. a high signal-to-noise ratio of the action potential versus the background noise) and stable. The median sampling time of each neuron was 28.5 seconds (n=611, minimum=20 seconds) and the median number of discriminated action potentials per neuron was 1100. Patients were always at rest when tonic activity was sampled.

Similar to the preceding section on GPi discharge patterns, all neuronal data were subdivided into three groups. The "pre-APO time" block group included all cells sampled before the administration of APO, the "APO period" time block group included all cells sampled between 10 and 60 minutes after the administration of APO, and the "post-APO" time block group comprised all cells sampled at 60 minutes or more following APO administration. Data analysis of single unit activity is described in the General Methods (section 2.3). Neuronal responses to somatosensory stimulation were carried out by noting the receptive fields of neurons to passive movements of the limbs and is described in the General Methods (section 2.3.3).

### *3.3.3 - Results*

*Clinical effects of APO*

Pre-operative APO administration significantly improved the median UPDRS motor scores from 44.5 to 15.5 ($p<0.01$, Wilcoxon signed rank test). All of the 13 patients in the STN group were given an intra-operative amount of APO that was intended to produce an ON state without dyskinesia (determined from the pre-operative APO trials). However, in 3 patients this dose was insufficient and a supplemental APO injection was administered (1/2 the original dose). 11 patients reported feeling ON at a mean time of 18.9±9.0 minutes (SD) after the APO injection (the second injection for the 3 patients receiving a supplemental dose). Conditions in the operating room such as the stress and anxiety for the patient as well as a prolonged drug holiday likely led to the fact that some patients displayed APO induced dyskinetic movements and others required higher doses than pre-operative amounts. The two patients that did not report feeling ON

were not given a supplemental dose of APO since they displayed drug-induced movements (dystonic dyskinesias). In total, there were 4 patients who became dyskinetic. In all cases, dyskinetic (choreic or dystonic) movements were mild, intermittent, and involved low amplitude movements. Limb tremor was significantly reduced or abolished at 20±5 minutes (SD) in the 6 of the 9 patients who had limb tremor at the beginning of surgery.

*Single unit studies*

A single neuron was continuously recorded before and following the administration of APO in 10 patients. These neurons were recorded for at least 9 minutes and a mean time of 14.7 minutes (±4.6SD) after APO administration. The left panel of Figure 3.3.F1A demonstrates that there were varied changes in the firing rates of 10 STN neurons following APO administration. The upper right and lower right panels of Figure 3.3.F1A show the percent change versus baseline values of the firing rates and the proportion of spikes in bursts, respectively. Decreases in the average firing rate of greater than 30% with a concurrent increase in the proportion of spikes in bursts were observed in 4 neurons; three of these patients reported feeling the effects of the medication during the period of the recordings. A firing rate histogram of one of these neurons (indicated by the thick dashed line) is displayed in the left panel of Figure 3.3.F1B and examples of the pattern of firing of this neuron are shown in the right panel. This patient became mildly dyskinetic during 14-43 minutes post-APO. Dyskinesias also appeared during the period of recording in one other case. In both cases firing rates were

more than 30% below the pre-APO value at the time the dyskinesias appeared (indicated with an x in Figure 3.3.F1A).

Changes in tonic firing rate were also associated with the emergence of tremor-related activity and concurrent limb tremor in one cell. Figure 3.3.F1C shows the changes in the auto-correlogram (calculated over non-overlapping 2 minute time segments) of the STN neuron that, following an initial increase, was seen to decrease its firing rate by 40% (marked by the thick dotted line in part A). The patient developed prominent bilateral tremor in the upper extremities shortly after the administration of APO. This is seen in some patients and has been termed "beginning-of-dose deterioration" (Merello and Lees 1992). The development of bilateral tremor matched the time course of the increase in tonic firing rate and the appearance of 4 Hz oscillatory neural discharge. Furthermore, a subsequent decrease in firing rate was accompanied by a decrease in the oscillatory neural activity and limb tremor.

*Population analysis - firing rates and pattern*

There were 216, 95, and 74 cells examined during the pre-APO period, APO period, and post-APO time period respectively. The distribution of the average neuronal firing rates and the discharge firing patterns of STN neurons are shown in Figure 3.3.F2. The means of the firing rate distributions were not significantly different from the baseline value of 37.1 Hz (±1.1) during the APO period or post-APO period ($p=0.68$, ANOVA on ranks) (Figure 3.3.F2, leftmost panel). Note also that there was no change in the shape of the population firing rate distribution. However there was an increase in the proportion of neurons that discharged in an irregular or random manner (*$p<0.05$, $\chi^2 =$

4.75, n=311). These changes in discharge firing patterns were accompanied by an increase in the overall proportion of spikes in bursts from 20.2% (±0.8) to 25.6% (±1.6) during the APO period (†$p<0.01$, ANOVA on ranks) and remained elevated at 23.8% (±1.5) during the post-APO period. In four of the patients with APO-induced dyskinesias, there was a significant decrease from the baseline mean firing rate of 38.3 Hz (±1.7, n=63) to 28.1 Hz (±1.8, n=25) ($p<0.05$, ANOVA on ranks) and the proportion of spikes in bursts increased from 19.8% (±1.3) to 23.8% (±1.8) ($p<0.05$, ANOVA on ranks) for cells recorded during the time period when these movements were present.

*Population analysis - oscillatory cells*

Before the administration of APO, 19% (42/216) of all STN neurons examined displayed significant tremor-related activity. These cells were found in 10 patients, 9 of whom had limb tremor at the beginning of the surgery. TCs were observed during episodes with limb tremor and also during episodes with no noticeable limb tremor. An example of a typical autocorrelogram and power spectrum for an STN TC is given in Figure 3.3.F3A. The average overall firing rate of these cells was 43.5 Hz (±2.2). Oscillatory frequencies other than within the limb tremor frequency range were also observed. There were 18 neurons that displayed a high-frequency oscillatory component that was between 10 to 30 Hz. An example is shown in Figure 3.3.F3B. The average firing rate of these high-frequency oscillatory cells was 43.6 Hz (±4.7). Neurons with high-frequency oscillatory components were located in areas containing TCs; 12/18 high-frequency oscillatory cells were located within 1 mm of TCs. In addition, six of the TCs were also observed to have a high-frequency oscillatory component (>10 Hz). An

example of an STN neuron with multiple frequency oscillatory behavior is shown in Figure 3.3.F3C. Both TCs and high-frequency oscillatory cells were found to have significantly higher firing rates than non-oscillatory cells (34.6 HZ (±1.2), n=156) ($p<0.01$, t-test). The distribution of oscillatory frequencies of STN neurons sampled during pre-APO period, APO period, and post-APO period is shown in Figure 3.3.F4.

Following the administration of APO, the proportion of TCs encountered was significantly reduced from 19% to 6.3% (6/95 neurons sampled in 11 patients) ($p<0.01$, $\chi^2 = 9.34$, n=311). In the six patients in whom APO significantly reduced or abolished limb tremor (49 neurons sampled), only 1 TC and 8 neurons with high-frequency oscillatory activity were encountered and they were all in one patient (see Figure 3.3.F4, middle panel). The mean firing rate of the 6 TCs was 24.6 Hz (±5.0) and was significantly lower than the mean firing rate of TCs before the administration of APO ($p<0.05$, ANOVA). Neurons with high-frequency oscillatory activity had similar firing rates during APO to those encountered before APO dosing (43.2 Hz (±5.3)). APO did not affect the firing rates of non-oscillatory STN cells (n=76) but these cells did have a greater proportion of spikes in bursts when compared to pre-APO period values (n=156)($p<0.01$, t-test).

During the post-APO period, the proportion of the TCs (14/74) was the same as that found before the administration of APO ($p=0.95$, $\chi^2 = 0.34$, n=290). These TCs were found in 6 patients (limb tremor was abolished and no TCs were found during the APO period in 3 of these). The mean firing rate of the TCs was 44.0 Hz (±5.9) which was significantly higher than that found during the APO period and the same as the mean TC firing rate of the pre-APO period ($p<0.05$, ANOVA).

*Population analysis - Receptive fields*

The proportion of neurons that responded to movements about one, two or more joints or had no detectable RFs (i.e. no response) are displayed in Figure 3.3.F5. The administration of APO was found to decrease the proportion of cells that had a response to limb movement from 56% to 25% and decrease the proportion that responded to two joints from 13% to 7% ($p<0.05$, $\chi^2 = 8.31$, $n=150$). There were no neurons with multiple or bilateral RFs found during the APO period. During the post-APO period, the proportion of cells with no detectable RFs decreased to 52% (n=14). The relative proportions of single RFs to double and multiple RFs did not significantly change in either the APO period or the post-APO period ($p=0.71$, $\chi^2 = 0.66$, $n=74$). When the average firing rates, bursting, or oscillatory patterns were compared between groups of cells that had no response, single, double, or multiple RFs no significant differences were evident and APO did not preferentially affect any of these groups.

**Figure 3.3.F1**

The effects of APO on the firing rates and discharge firing patterns of single neurons in the STN. A: The left panel shows the firing rates of 10 STN neurons following the administration of APO (2 minute bins). An x indicates the time that patients became dyskinetic during these recordings. The thick dashed line indicates the neuron shown in part B while the dotted line indicates the neuron shown in part C. The upper right panel shows the percent change of firing rates versus baseline values. Horizontal thin dotted lines represent 30% increases/decreases from baseline. The lower right panel shows the percent change of the proportion of spikes in bursts versus baseline values of these 10 neurons (2 minute bins). B: The left panel shows an example of the firing rate of an STN neuron that decreased its mean firing rate concurrent with the APO induced ON effect. The right panel of part B shows examples of firing patterns of this neuron revealing increased irregularity and longer pauses in the discharge pattern during the ON period. C: A composite plot showing mean firing rate and autocorrelograms for an STN neuron that first displayed an increase in its firing rate concurrent with the appearance of severe bilateral tremors. The limb tremors subsided as the firing rate decreased and the patient felt the effects of APO. The oscillatory activity of the cell is shown using auto-correlograms (750 ms time lag, 10 ms bin width) that were calculated over 2 minute periods. All auto-correlograms were quantified to the units of firing rate (spikes/s) and each was constructed using at least 4500 event intervals.

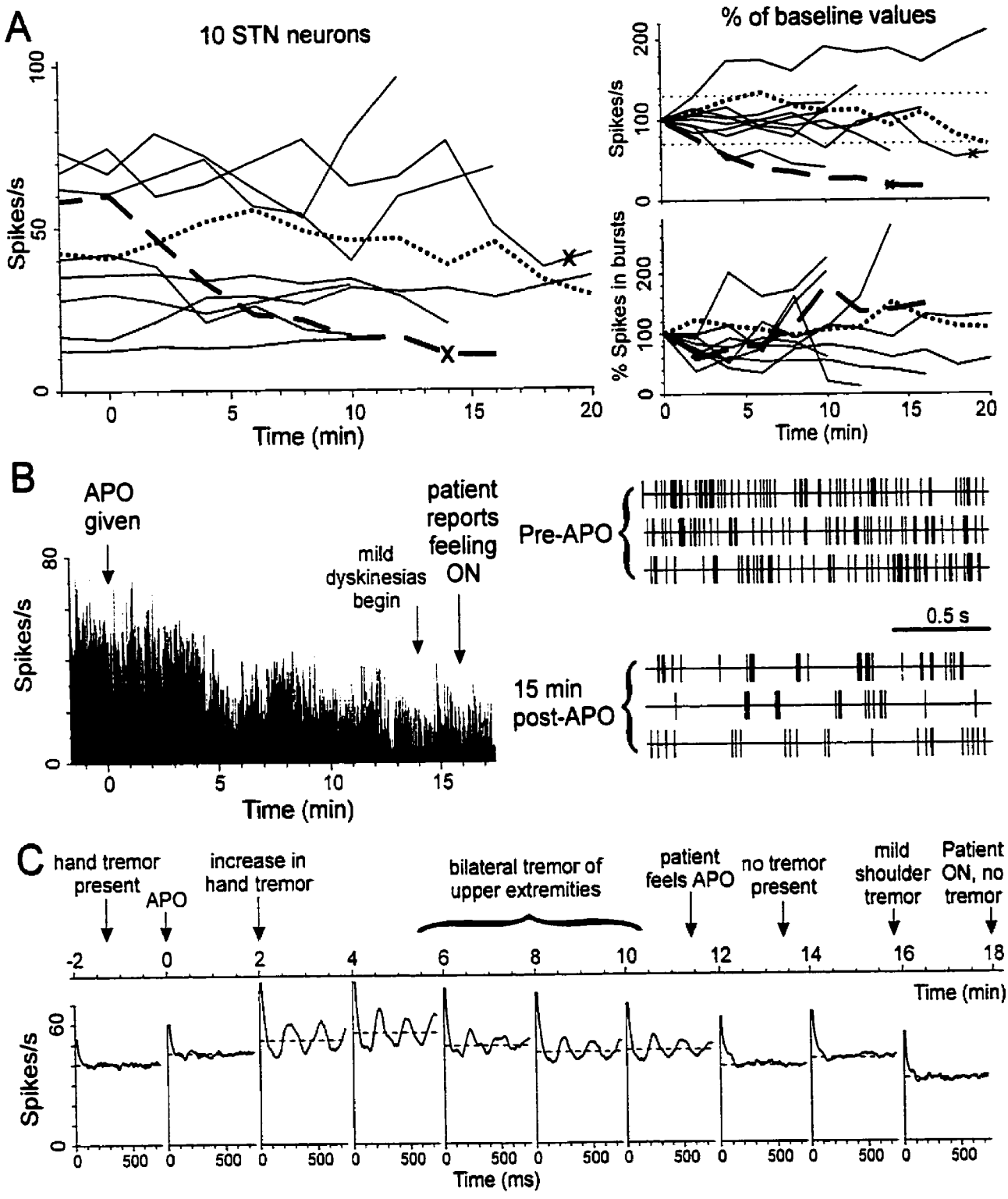

A
10 STN neurons
Spikes/s
Time (min)
% of baseline values
Spikes/s
% Spikes in bursts
Time (min)
B
APO given
mild dyskinesias begin
patient reports feeling ON
Spikes/s
Time (min)
Pre-APO
0.5 s
15 min post-APO
C
hand tremor present
APO
increase in hand tremor
bilateral tremor of upper extremities
patient feels APO
no tremor present
mild shoulder tremor
Patient ON, no tremor
Time (min)
Spikes/s
Time (ms)

Figure 3.3.F1

**Figure 3.3.F2**

Graphs and plots showing the effects of APO on populations of neurons in the STN. Population firing rate distributions are shown in the leftmost panel (10 Hz bins). The downward arrows in this graph represent the means of the corresponding distributions. Numbers in parentheses at the bottom of the left set of vertical bars (i.e. proportion of random, irregular, and regular discharges) indicate the number of cells within each group. Data from the same cells were used to construct the firing rate distributions and the right bar graphs. There was no significant difference in the mean firing rate of neurons in the STN due to APO administration but the proportion of cells with a regular discharge pattern decreased during the APO period (*- $p<0.05$, $\chi^2 = 4.75$, $n=311$). APO also significantly increased the proportion of spikes in bursts in STN neurons when compared to pre-APO values (†$p<0.01$, ANOVA on ranks).

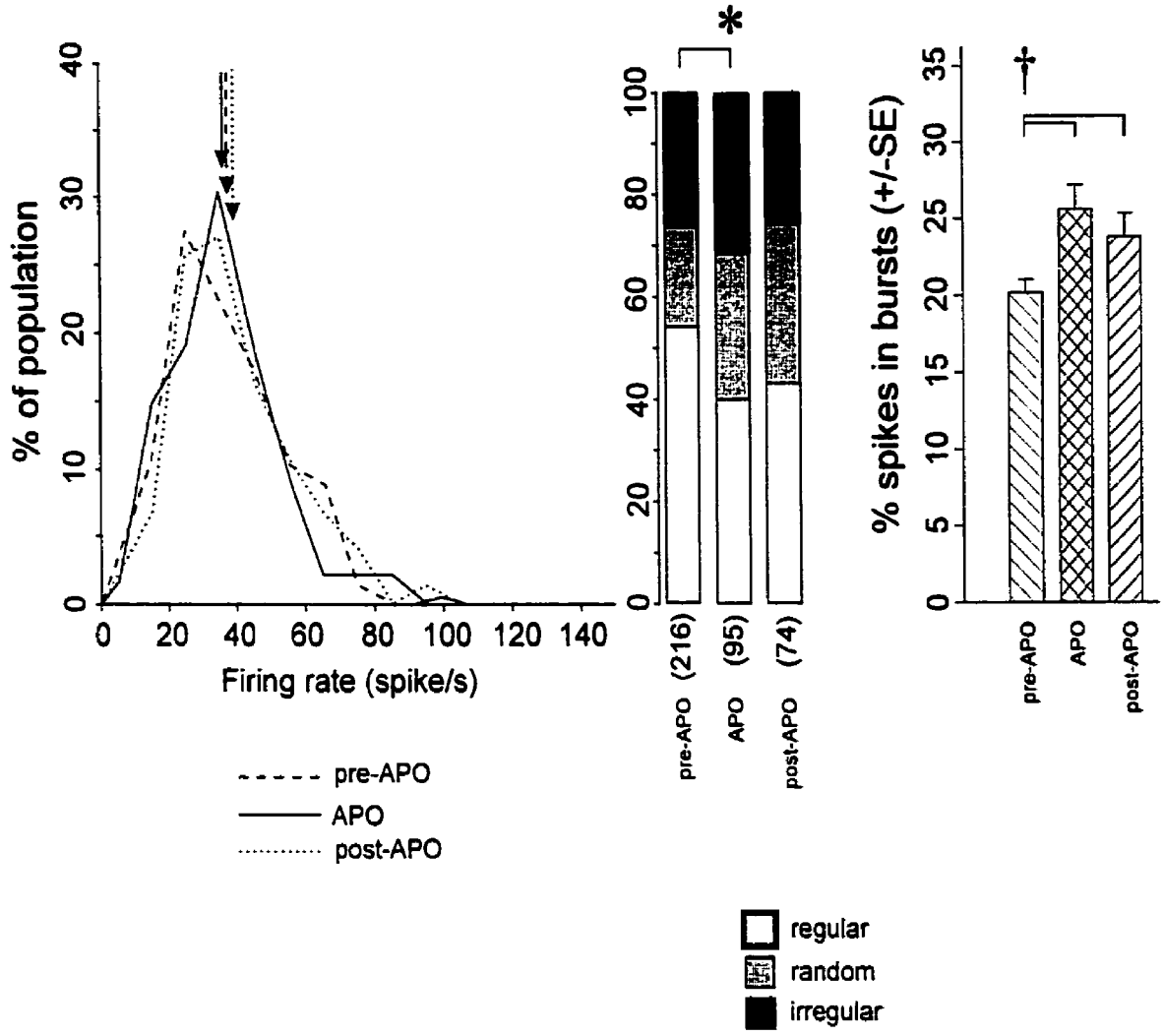

% of population
Firing rate (spike/s)
pre-APO
APO
post-APO
(216)
(95)
(74)
*
% spikes in bursts (+/-SE)
†
regular
random
irregular

Figure 3.3.F2

**Figure 3.3.F3**

Examples of oscillatory activity in STN neurons (A-C) with three types of periodic oscillatory activity before the administration of APO. Each row shows a smoothed autocorrelogram (time base of 750 ms and bin width is 1 ms) of the neuronal discharge, power spectrum of the spike signal (0.39 Hz resolution), and an inter-spike interval histogram (ISI) for a single neuron (1 ms bins). A: An STN neuron with tremor related activity. Patient was tremulous at this time. A strong single peak at ~4 Hz is evident in the power spectrum. B: STN neuron with high-frequency oscillatory activity centered around 16 Hz. The ISI histogram is single peaked and nearly symmetrical suggesting that the oscillatory pattern is not due to intermittent bursting activity. C: STN neuron with multiple frequency oscillatory behavior. The power spectrum gives one peak at 4 Hz and another at ~18 Hz. Dashed horizontal lines in autocorrelograms are the average discharge rate. The number at the bottom right corner is the number of events used to construct the autocorrelogram. The signal-to-noise ratio of peaks in the power spectrum is indicated by the number above each peak. The arrows in the inter-spike interval histograms indicate the median inter-spike interval.

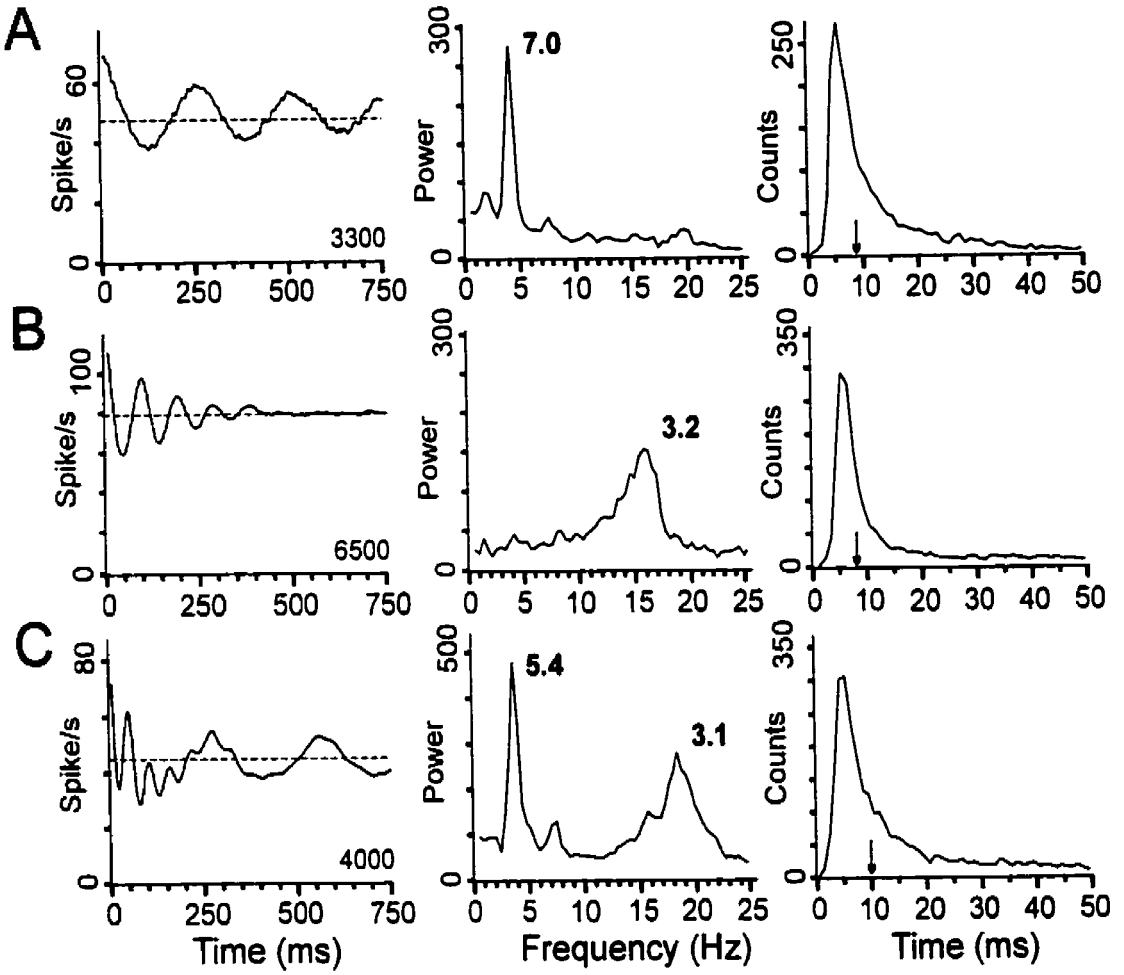

A
B
C
Spike/s
Power
Counts
7.0
3.2
5.4
3.1
3300
6500
4000
Time (ms)
Frequency (Hz)
Time (ms)

Figure 3.3.F3

**Figure 3.3.F4**

Distribution of oscillation frequencies of cells in the STN. Total number of cells sampled is given in upper left of each panel. Cells with tremor activity or a high-frequency oscillatory component are represented by gray squares. Cells with tremor activity and a high frequency component are represented by white squares (i.e. both frequencies are denoted so that each cell is represented by two squares). The squares with a dot represent a group of cells all recorded in one patient during the ON period (see Results of Chapter 3, section 3).

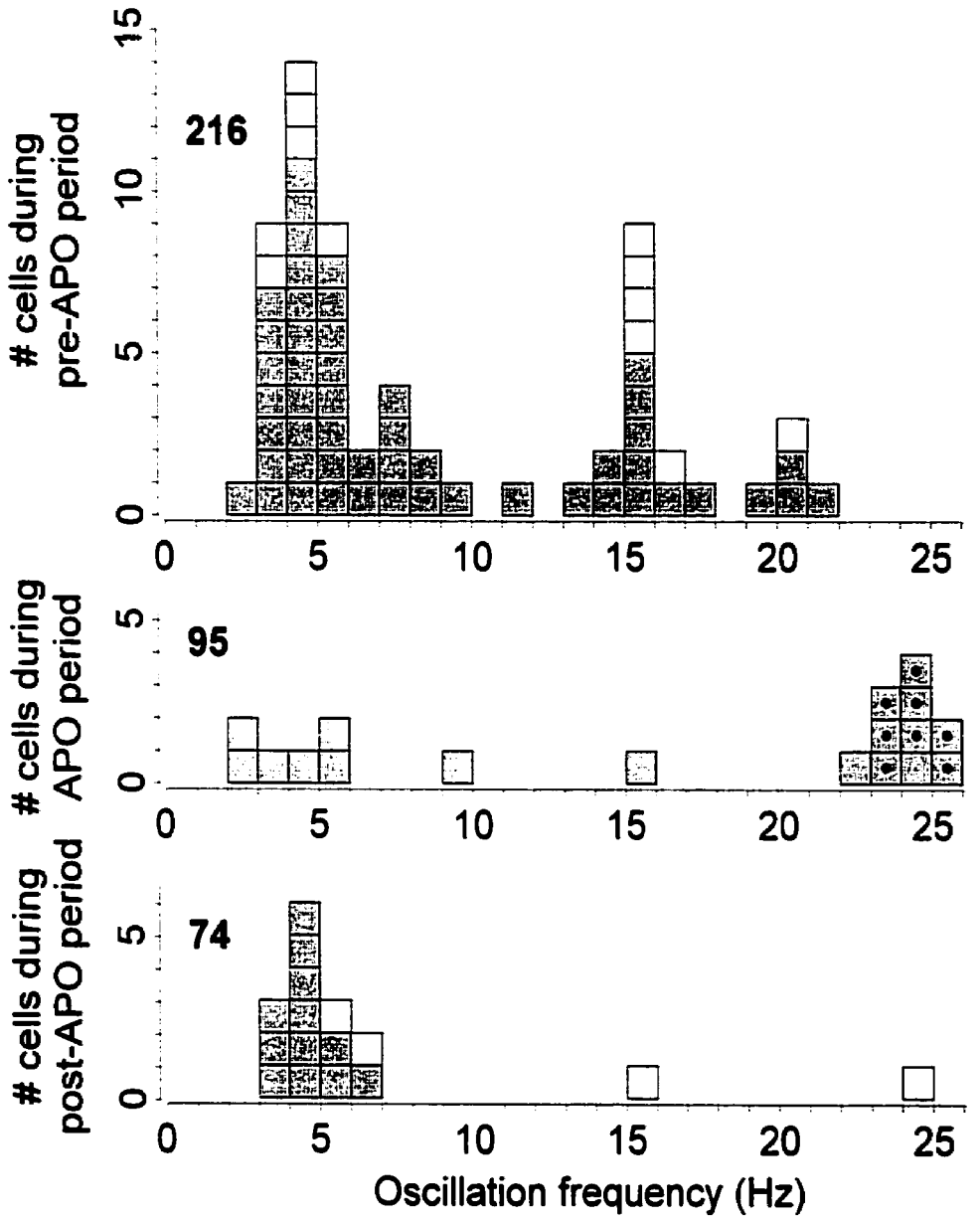

216
95
74
# cells during pre-APO period
# cells during APO period
# cells during post-APO period
0
5
10
15
20
25
Oscillation frequency (Hz)

Figure 3.3.F4

**Figure 3.3.F5**

Bar graphs showing the proportions of neurons that had no response (no detectable RF), and single, double, and multiple RFs before APO administration (pre-APO), during the APO period (APO), and during the post-APO period (post-APO) in the STN. Significant differences from the proportion of cells with no response before and after the APO period are indicated by * ($p<0.05$). Numbers under grouped vertical bars indicate the ratio of the total number of cells versus the number of patients in which these cells were sampled.

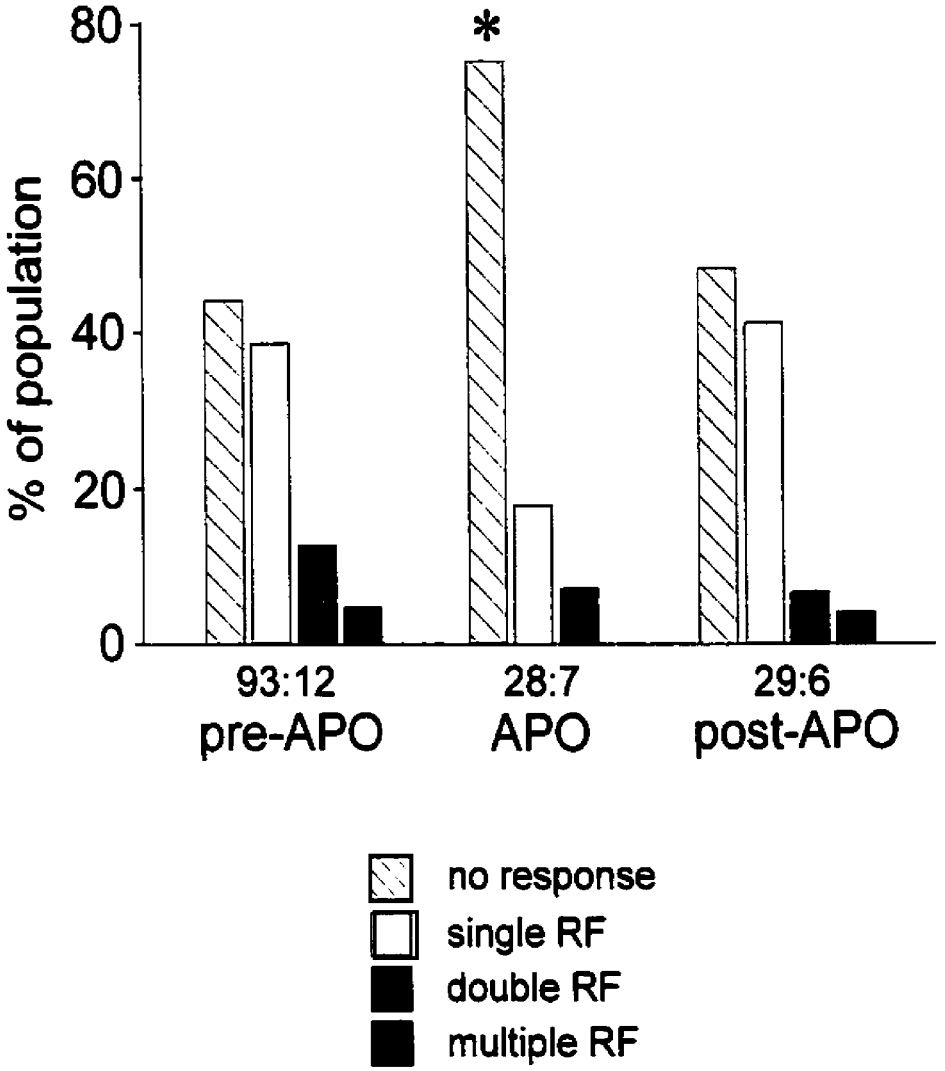

80
60
40
20
0
% of population
*
93:12
pre-APO
28:7
APO
29:6
post-APO
no response
single RF
double RF
multiple RF

Figure 3.3.F5

### *3.3.4 - Discussion*

This is the first demonstration of the effects of APO in the primate STN. According to the current model of the basal ganglia, systemic administration of APO is predicted to decrease the mean firing rates of STN neurons (Miller and DeLong 1987; Bergman et al. 1994). However, evidence supporting this prediction is unclear. APO has been shown to decrease the spontaneous discharge of STN neurons in 6-OHDA-treated rats (Kreiss et al. 1997), but contrary to predictions APO increases the firing rates of STN neurons in intact rats (Kreiss et al. 1997). In the present study, both increases and decreases were observed in the mean firing rates of single STN neurons following APO administration. It is unlikely that this was simply due to the fact the cells were monitored for only a short period of time. In 5 STN cells monitored for 15 minutes or more no mean overall increase or decrease was observed although the patients started to experience the effects of APO during the recording period (Figure 3.3.F1A). In addition, in contrast to GPi (see Chapter 3, section 1), there was no significant difference in the overall mean firing rate of STN neurons recorded in the APO period when compared to the pre-APO period. Since the APO period did not consist of a true steady state in terms of clinical effect and blood levels, it is possible that significant changes in mean firing rate related to a particular state might have been missed in this analysis. It is interesting that the increase in GPi firing rates following the induction of parkinsonism by MPTP in monkeys is much greater than the increase in the firing rates of neurons in the STN (Miller and DeLong 1987; Bergman et al. 1994), and may explain why APO, when producing a therapeutic benefit, had a much larger and more consistent effect on GPi neurons than STN neurons.

The variability in the effect of APO on the firing rates of single STN neurons observed in this study may be due to sampling of functionally different neurons that have different connectivity and sensitivity to APO. Heterogeneity in the function of STN neurons is suggested by the diversity of brain regions that provide afferent input to the STN. As well as input from GPe, the STN receives massive input from the cerebral cortex (Carpenter et al. 1981; Canteras et al. 1990). The STN forms reciprocal projections with the PPN (Hammond et al. 1983; Lavoie and Parent 1994) and receives input from the parafascicular nucleus of the thalamus (Mouroux et al. 1995; Orieux et al. 2000). In a recent study by Orieux et al. (2000), it was demonstrated that STN hyperactivity in the 6-hydroxydopamine treated rat model of PD is due in part to an increase of excitatory input arising from both these nuclei. Dopaminergic agonists can also influence STN activity by acting on dopaminergic cells projecting to the STN (Meibach and Katzman 1979; Campbell et al. 1985; Descarries et al. 1987; Hassani et al. 1997; Francois et al. 2000) and at dopamine receptors within the STN itself (Campbell et al. 1985; Bouthenet et al. 1987; Kreiss et al. 1996; Hassani and Feger 1999; Mehta et al. 2000).

The demonstration of tremor-related oscillatory activity is also consistent with previous reports of TCs in the STN of parkinsonian patients (Hutchison et al. 1998a; Rodriguez et al. 1998; Magarinos-Ascone et al. 2000). The mean firing rates of TCs in both the STN and the GPi (as shown in section 3.2) before APO administration were significantly greater than the mean firing rates of neurons with no oscillatory components and this is similar to the findings of previous studies in PD patients (Hutchison et al. 1994b) and in MPTP-treated monkeys (Bergman et al. 1994). These findings suggest

that excessive neuronal activity in these nuclei might promote tremorgenesis. Interestingly, APO related changes in mean firing rates of STN neurons were closely associated with changes in tremor-related activity (see Figure 3.3.F1C).

A novel finding was that a significant number of STN neurons have high-frequency oscillatory activity and that some neurons concurrently display a tremor frequency component. Similar observations have been reported in the STN and GPe of tremulous MPTP-treated monkeys (Bergman et al. 1994; Raz et al. 2000). In the present study, many neurons with high-frequency oscillations were found in regions that contained TCs and apart from a single patient who displayed high-frequency oscillations (and 1 TC) in the ON state, the incidence of these neurons following APO administration was reduced along with the proportion of TCs. Yet unlike TCs, the firing rate of neurons with high-frequency oscillations was not changed due to APO, suggesting that tremor oscillations and high-frequency oscillations in the STN might be due to separate mechanisms.

Lastly, this section demonstrated that, similar to the results obtained for the GPi (see section 3.2), bursting activity was increased in the STN during the period of time in which APO reduced the patient's parkinsonism. The APO-induced changes in somatosensory responses in the STN were also similar to those observed in the GPi. Unlike TC activity which has a clinical correlate (i.e. limb tremor) and may be related to hyperpolarization of thalamic target of the GPi (Jahnsen and Llinas 1984), the functional significance of the change in bursting that is not rhythmical or changes in somatosensory responses is not predicted by the box model. It is possible that changes in bursting discharge or somatosensory responses may be related to changes in the parallel

organization of the BG as discussed in section 1.4.2. Therefore, the role of bursting activity and somatosensory responses will be examined with more powerful methodology such as simultaneous recording techniques that can assess the degree of correlation of spikes between basal ganglia neurons and the effect of dopaminergic medication (see chapter 5).

## CHAPTER 4 - INACTIVATION OF THE SUBTHALAMIC NUCLEUS REVERSES PARKINSONIAN SYMPTOMS


### *Abstract*

Inactivation of neurons in the STN of the MPTP-treated monkey model of PD has been shown to relieve parkinsonian motor symptoms. In patients with PD, neurons in the STN display hyperactive firing rates and rhythmic discharge activity such as tremor-related oscillations (3-8 Hz) and high-frequency oscillations (15-30 Hz). In this study, microinjections of lidocaine (n = 4) and muscimol (a $GABA_A$ receptor agonist)(n = 2) were performed in the STN of 6 patients with PD to determine whether the focal suppression of STN neuronal activity can lead to an improvement in tremor, bradykinesia, and rigidity. The first use of microelectrode recording of the effects of microinjections on neuronal activity in the human brain (n = 2) is also reported. Microinjections of 10-23 μL of lidocaine produced striking improvements in bradykinesia, limb tremor, and rigidity in 3/3 patients. These improvements were correlated with good therapeutic effects of subsequent STN DBS performed in the same microelectrode trajectories as these injections. The most dramatic observation following lidocaine injections was the appearance of dyskinetic limb movements. In one patient, simultaneous microelectrode recording during an injection of 3.5 μL of lidocaine demonstrated a suppression of neuronal activity at distances of < 0.9 mm from the injection site but no suppression was observed at ≥ 1.2 mm from the injection site. Microinjections of 5-10 μL of muscimol in a region with tremor-related activity resulted in suppression of limb tremor in 2/2 patients. Interestingly in one of these patients, 4 Hz oscillatory activity was diminished in a neuron recorded 1.3 mm from the injection site,

but there was no reduction in the mean firing rate or 20 Hz oscillatory activity. These results demonstrate that inactivation of neuronal activity in the STN of patients with PD improves motor symptoms. These findings also suggest that a focal block of the STN might alter the oscillatory activity of neurons located beyond the inhibited region.

### *4.1 - Introduction*

Local inactivation of neuronal activity in the STN in the MPTP-treated non-human primate model of PD has been shown to ameliorate parkinsonian symptoms (Bergman et al. 1990; Wichmann et al. 1994b; Guridi et al. 1996). This therapeutic effect is consistent with the notion of STN hyperactivity or dysfunction in parkinsonism (Miller and DeLong 1987; Bergman et al. 1994). Intentional lesion making in the STN of patients with PD has usually been avoided because of the possible risk of causing severe ballism. However, recent reports have demonstrated good therapeutic effects of subthalamotomy in patients with PD without significant adverse effects (Gill and Heywood 1997; Obeso et al. 1997a; Muthane et al. 1998; Alvarez et al. 2001; Barlas et al. 2001). STN DBS has also been shown to be highly effective in treating parkinsonian symptoms (Limousin et al. 1995b; Kumar et al. 1998a; Krack et al. 1998a). To determine the therapeutic and neuronal effects of blocking STN activity in patients with PD, microinjections of the local anesthetic lidocaine and muscimol, a γ-aminobutyric acid-A receptor agonist ($GABA_A$) were carried out in the STN. Lidocaine has the effect of non-selectively blocking axonal fibers of passage as well as neurons while muscimol selectively inhibits the cell bodies of neurons.

Elucidating the population behavior of STN neurons and its role in the dynamics of the basal ganglia is essential to extending our understanding of the pathophysiology of PD (Ryan et al. 1992; Plenz and Kital 1999; Magill et al. 2000). The neuronal population in the STN has been shown to exhibit synchronous oscillatory activity (Plenz and Kital 1999; Magill et al. 2000; Marsden et al. 2001; Brown et al. 2001) and it has been suggested that increased oscillatory synchronization in the basal ganglia underlies the development of parkinsonian limb tremor in MPTP-treated monkeys (Bergman et al. 1998a; Raz et al. 2000). Synchronized 3-8 Hz tremor-related activity has also been shown in the GPi (Hurtado et al. 1999) and in the motor thalamus of parkinsonian patients with PD (Levy et al. 1999). Therefore, if parkinsonian limb tremor is due in part to an elevated level of oscillatory synchronization between basal ganglia subcircuits (Bergman et al. 1998a), it is conceivable that pharmacological blocks, in addition to inactivating local neuronal activity, might influence the oscillatory behavior of neurons beyond the region directly affected by the block. In theory, invasive surgical therapies could act to reduce limb tremor by desynchronizing pathological oscillations in the basal ganglia-thalamo-cortical network (Bergman et al. 1998a; Deuschl et al. 2000). In the present chapter, this issue was addressed by recording the activity of a STN neuron that displayed both tremor-related and high-frequency oscillations and was located outside of a region of pharmacologically blocked TCs. This is the first demonstration of the use of simultaneous microelectrode recording to assess the effects of microinjection of substances in the human brain.

### *4.2 - Methods*

*Patient group*

Studies of muscimol and lidocaine microinjections into the STN were performed in 7 PD patients undergoing microelectrode-guided placement of DBS electrodes (n=5) or a STN lesion (n=2) for the treatment of the symptoms of PD. The results for one of these patients is not presented because post-operative MRI revealed that microinjections were performed at the ventral border of the STN. Results for the rest of the patients are presented here. This group consisted of 2 females and 4 males who at the time of operation had a mean age of 55 years (range 48-67). The average duration of the disease was 12.2 years (±1.8 SE) and all had PD for at least 7 years. All patients gave informed consent and the studies were approved by the Human Experimentation Committee of the Toronto Hospital.

*Injections*

Lidocaine (2% Xylocaine, Astra Pharma Inc.; 20 mg/ml without preservative) and muscimol (Sigma, St Louis, MO; 1 mg/ml [8.8 mM] in sterile saline, 0.2 μm filter sterilized) were injected into the STN through a stereotactically placed 30 gauge injection cannula. The construction of the injection cannula is described in the General Methods (section 2.1.3.b). Substances were injected at a rate ≤ 1.25 μL per minute except in one patient in whom lidocaine was injected at 2.5 μL per minute (patient C). The injection cannula was left in the brain for 20-25 minutes after microinjection to reduce the likelihood of an injected solution diffusing back up the cannula track. In one case, two injections (saline followed by muscimol) were carried out by employing two fixed

parallel injection cannulae (~350 μm apart) with two separate Hamilton syringes. This technique avoided the need to remove a single injection cannula in order to insert a second cannula filled with a different solution, and thereby reduced the likelihood of backflow along the cannula track.

*Determination of the target area for microinjection in STN*

The recording and localization procedures for the STN are described in the General Methods (sections 2.1.1.b and 2.1.2). Briefly, parasagittal trajectories at either 10.5 or 12 mm from the midline passed through the thalamic reticular nucleus and/or anterior thalamus, zona incerta, STN, and the SNr (Schaltenbrand and Wahren 1977). Microinjections were performed in the same microelectrode track that would later be used to insert the DBS electrode (5 patients). Microinjection in the one patient undergoing a subthalamotomy was performed at a location that was 3 mm anterior to the center of a subsequent lesion (see Figure 4.F1). The assessment of clinical changes due to microinjections is described in the General methods (section 2.2.3). Post-operative MRI was carried out in 4 patients to identify the placement of DBS electrodes or lesion in the STN and to confirm that microinjections were performed in the desired location in the STN (see Table 4.T1). All patients underwent post-operative UPDRS assessment of the clinical improvement due to lesion or DBS (in the OFF drug state).

*Simultaneous microinjection and microelectrode recording of neuronal activity*

In two patients (patients A and F), simultaneous microelectrode recording of neuronal activity during microinjection was performed using a second independently

driven microelectrode that was inserted in parallel with the injection cannula at a center to center distance of ~600 μm. This set-up is described in detail in the General Methods (section 2.1.3). Microelectrode recordings were performed posterior-ventral to the injection site (i.e. microelectrode was advanced ahead of the injection site). Spectral analysis of single-neuron discharge activity is described in detail in the General Methods (section 2.3.2.b). 512 spectral estimates were made between 0 and 500 Hz thereby yielding a frequency resolution of 0.98 Hz. Statistical significance of spectral peaks was assessed by comparing spectra to a white noise signal with the same mean power in the range 0-40 Hz (i.e. mean spectral "noise"). Spectral estimates were deemed significant if they were equal to or greater than the upper bound of a $100\cdot(1-\alpha)\%$ confidence interval about this white noise signal. The upper bound was given by $2N\cdot f(\omega) / \chi^2_{2N,1-\alpha/2}$ where $f$ is the power, $\omega$ is the frequency, 2N is the effective degrees of freedom, and N is the number of sampling windows (Chatfield 1996).

### *4.3 - Results*

*Localization of injections*

Figure 4.F1 displays digitized parasagittal plates (Schaltenbrand and Wahren 1977) of the STN (standardized to the patients anterior-posterior commissural distance) to show the location of the microelectrode trajectories and to provide information about the neuronal activity and the location of the individual microinjections. In all patients, microinjections were performed in regions of the STN populated by neurons with movement-evoked activity, tremor-related activity, or neurons characteristic of those

found in the motor portion of the STN (Hutchison et al. 1998a). As shown in Table 4.T1, STN DBS in 5 patients and the subthalamotomy in the remaining patient (patient A) resulted in a dramatic improvement in contralateral bradykinesia, tremor and rigidity. Post-operative MRI was available in 4 patients and confirmed that the interventions were performed in the STN.

*Lidocaine injections*

The diffusion of lidocaine was examined in patient A by simultaneously recording neural activity close to the injection cannula. These data are shown in Figure 4.F2. After 3.5 μL of lidocaine was injected over a 5 minute period, there was a dramatic decrease in neural activity recorded 0.6 mm from the injection site. When the recording electrode was moved to another cell 0.78 mm away (relative to the tip of the injection cannula), neural discharge at this site decreased approximately 30 seconds later. However, neural activity 1.2 mm away was not blocked at 5 minutes after the end of the injection period. No change in contralateral arm rigidity, tremor, or bradykinesia was observed at 13 minutes after the injection (data not shown).

A marked anti-parkinsonian effect was observed in 3 patients (patients B, C, D). All these patients received ≥10μL of lidocaine and the results are displayed in Figure 4.F3. In all three patients there was a decrease in rigidity and this reached a minimum value ~10-20 minutes after the start of injection. Recovery of rigidity to baseline values was observed in two patients (B, C). There were no "recovery" data available for patient D because lidocaine was injected near the end of the stereotaxic procedure. Lidocaine microinjections into regions of the STN with tremor-related activity reduced contralateral

arm tremor in the two patients with tremor during the procedure (patients B and D). Accelerometer traces at the bottom of Figure 3 show that the baseline resting tremor of patient D was intermittent with brief (~10 second) periods of tremor. At 6 minutes, tremor amplitude was decreased and the residual tremor was more intermittent. Patients B and D performed quantitative movement tasks. There was a significant decrease in the time required for patient B to perform repetitive chest to button board pointing after the injection (displayed in the upper right bar graph in Figure 4.F3, see Methods). In patient D, the amplitude of wrist pronation/supination movements increased after lidocaine injection (traces shown to the right of UPDRS ratings).

Following lidocaine injections, dyskinesias were observed in all 3 patients. Patient B developed low amplitude choreoathetotic movements of the ipsilateral foot (indicated by dashed arrow in Figure 4.F3). Patient C developed dystonic contralateral wrist movements at 15 minutes after injection. These movements interfered with the patient's ability to perform hand-gripping movements (filled squares in Figure 4.F3, middle panel, UPDRS item 24). Patient D displayed dystonic dyskinesias (i.e. a sustained posturing) of the contralateral foot at 6 minutes following injection. At 9 minutes following injection, myoclonic jerking movements were also observed. Dyskinetic movements in the foot were also observed when the patient performed wrist pronation/supination movements during this period (11 minutes after initial injection).

*Muscimol injections*

A marked anti-parkinsonian effect following muscimol injections was observed in patients E and F. Figure 4.F4 demonstrates that muscimol but not saline (both injected at

a rate of 1 μL per minute) injected into an area of the STN with tremor-related activity in patient E caused a dramatic reduction in contralateral resting tremor within 5 minutes after the start of injection. This was also observed using an accelerometer placed on the index finger of the contralateral hand (bottom traces in Figure 4.F4). The patient was asked to perform mental arithmetic throughout the sampling period to enhance spontaneous resting tremor. Muscimol also improved the performance of wrist pronation/supination movements.

An injection of 5 μL of muscimol into a region with tremor-related activity also decreased resting tremor in patient F. The changes in hand tremor and the discharge activity of a neuron that was located 1.3 mm from the injection site are shown in Figure 4.F5. A 5 Hz resting tremor of the hand was measured with an accelerometer (Acc) placed on the contralateral index finger (Figure 4.F5A). There was no elbow tremor and pill rolling movements were not observed. There was no other detectable tremor on the side contralateral to the recording. The patient had a resting tremor of the ipsilateral hand/wrist and ipsilateral foot. Changes in rigidity and bradykinesia were not assessed in this patient because of the need to maintain a stable microelectrode recording from the single neuron. Microstimulation along this microelectrode trajectory produced tremor arrest in the contralateral hand (1 mm above to 3 mm below injection site in Figure 4.F1). The left panel of Figure 4.F5B demonstrates that before the injection of muscimol, the neuron displayed two peaks in the frequency spectra, one peak at 4 Hz and another at 20 Hz. The lower frequency oscillatory component of the recorded neuron was not coherent with the contralateral wrist flexor EMG or the accelerometer signal at any time (not shown). Following the injection of muscimol, the lower frequency oscillatory component

decreased concurrent with a reduction in contralateral hand tremor (Figure 4.F5B, right panel). No change was observed for ipsilateral tremor. Interestingly, there was no suppression in the firing rate of the neuron (see Figure 4.F5A) or the 20 Hz oscillatory activity. Time-frequency analysis revealed that the reduction of 4 Hz oscillatory neuronal discharge was due to a decrease in all oscillatory activity < 10 Hz rather than an increase in the moment-to-moment variability of a peak within this frequency band. Contralateral hand tremor reappeared approximately 5 minutes after the end of the injection period and at that time, the recorded neuron started to display a lower frequency oscillatory component in addition to the 20 Hz high-frequency oscillatory component.

**Figure 4.F1**

Sagittal sections from the Schaltenbrand and Wahren stereotactic atlas at 12 mm from the midline displaying the microelectrode trajectories, neuronal activity, and location of microinjection in the 6 patients (definitions of the symbols used are at the bottom of the figure). DBS electrodes were placed in the same microelectrode trajectory as the microinjection in patients B-F. The lesion in patient A was placed 3mm posterior to the location of the lidocaine microinjection. The diameter of the injection cannula was 0.3 mm but is drawn as 0.2 mm so as not to obscure data in the figure. Simultaneous recording of neuronal activity during microinjection was performed in patients A and F (see Methods). STN = subthalamic nucleus; Thal = thalamus; SNr = substantia nigra pars reticulata; H2 = Fields of Forel; rTh = reticular nucleus of the thalamus; Voa = nucleus ventralis oralis anterior; Vop = nucleus ventralis oralis posterior; Vim = ventrointermedius. The dashed line represents the anterior-posterior commissural line; RF = receptive field (a neuron that responded to passive or active limb movement).

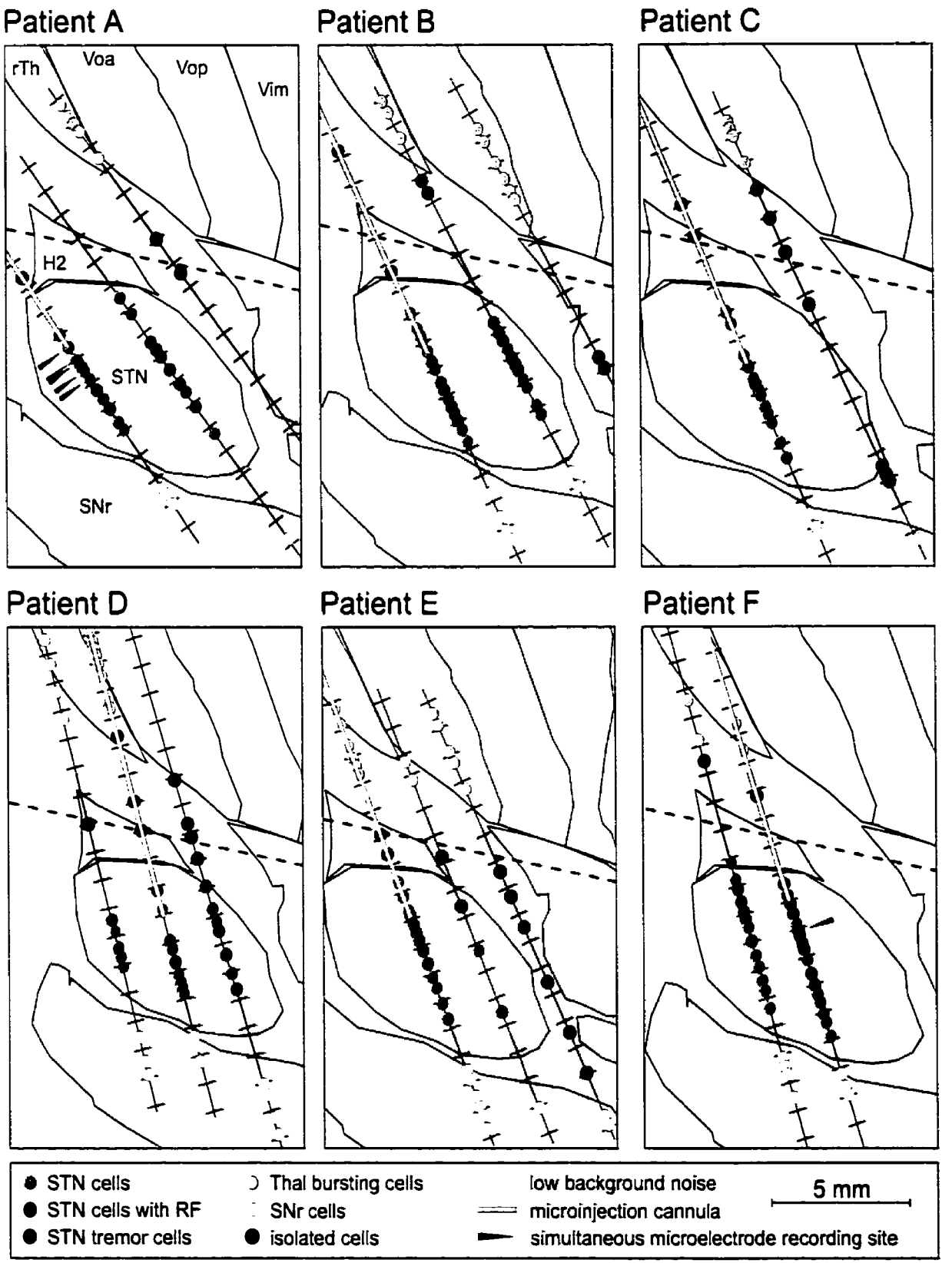

Patient A
Patient B
Patient C
Patient D
Patient E
Patient F
rTh
Voa
Vop
Vim
H2
STN
SNr
STN cells
STN cells with RF
STN tremor cells
Thal bursting cells
SNr cells
isolated cells
low background noise
microinjection cannula
simultaneous microelectrode recording site
5 mm

Figure 4.F1

**Table 4.T1**

All patients were assessed in the OFF drug condition (following an overnight drug holiday). For patients B-F, data reported as the UPDRS score for DBS OFF / DBS ON (DBS at optimal parameters and contacts). For patients A, data reported as the UPDRS for pre-operative score / post-operative score. Scores are reported for the body side contralateral to the side of injection in the STN. *Stimulation used and post-operative time of assessment is indicated in parenthesis. †Tremor is calculated as the sum of UPDRS items 20 and 21 (unilateral scores; maximum possible score of 12). ‡Rigidity is calculated from UPDRS item 22 (unilateral scores; maximum possible score of 8). §Bradykinesia is calculated as the sum of UPDRS items 23-26 (unilateral scores; maximum possible score of 16).

*The clinical effects of microinjections and STN DBS or subthalamotomy*

| Patient | STN side, substance injected | Clear therapeutic benefit of injection? | Procedure* | contra-lateral UPDRS tremor† | contra-lateral UPDRS rigidity‡ | contra-lateral UPDRS brady-kinesia§ | Post-operative MRI targeting |
|---|---|---|---|---|---|---|---|
| A | left, 3.5μL lidocaine | no | left STN lesion (1 week) | 6/1 | 5/1 | 13/5 | Centered in left STN |
| B | right,10μL lidocaine | yes | bilateral DBS (1 month) | 2/0 | 5/3 | 14/4 | not available |
| C | right, 23μL lidocaine | yes | bilateral DBS (3 months) | 3/0 | 6/3 | 11/7 | Effective contacts in STN |
| D | left, 10μL lidocaine | yes | unilateral DBS (3 weeks) | 7/0 | not available | 14/10 | Effective contacts in STN |
| E | left, 10μL muscimol | yes | bilateral DBS (1 month) | 4/2 | 6/5 | 8/5 | Effective contacts in STN |
| F | left, 5 μL muscimol | yes | bilateral DBS (3 weeks) | 4/1 | 4/0 | 5/1 | not available |

Table 4.T1

**Figure 4.F2**

Microelectrode recording of neuronal activity during the microinjection of lidocaine in patient A. Lidocaine was injected at the volumes (μL, bold numbers in gray boxes) and times indicated by the gray boxes to the left side of vertical timeline. The relative distance from the tip of the injection cannula to the tip of microelectrode is indicated by the numbers on the left hand side of the figure. Neuronal recordings were sampled at the time indicated by position of traces with respect to timeline.

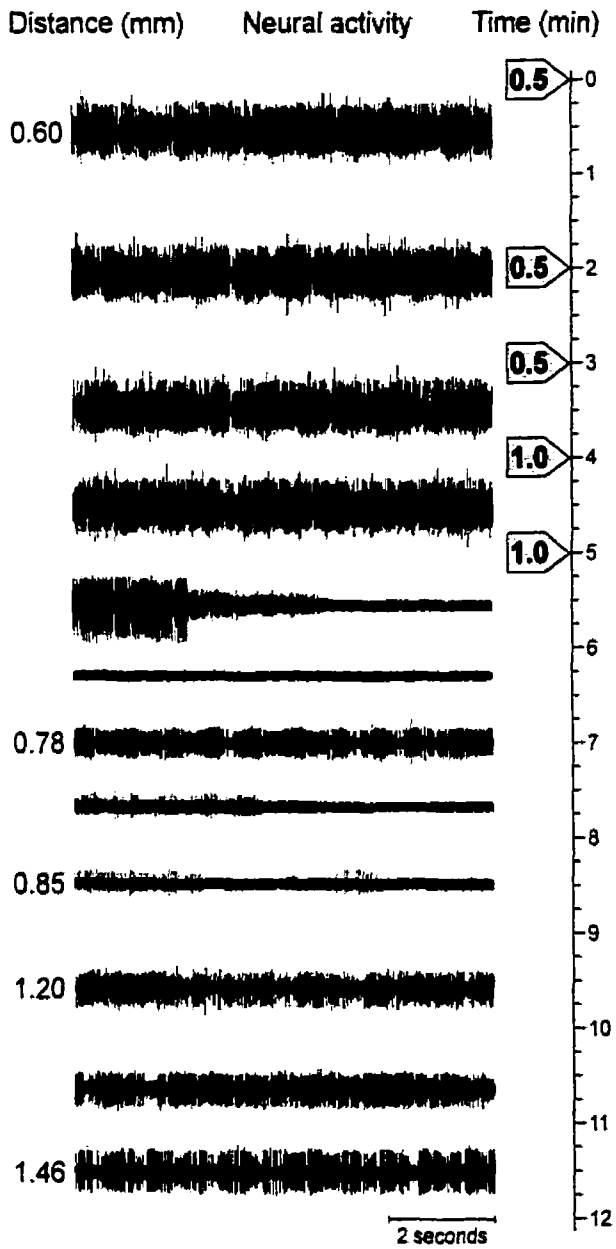

Distance (mm)
Neural activity
Time (min)
0.60
0.78
0.85
1.20
1.46
0.5
0.5
0.5
1.0
1.0
0
1
2
3
4
5
6
7
8
9
10
11
12
2 seconds

Figure 4.F2

**Figure 4.F3**

The effects of lidocaine injections in the STN of three patients. The 3 plots show the effects of lidocaine injection on the UPDRS measures of tremor, rigidity, and hand grips and the rigidity meter readings (see box at bottom right for distinction of graph symbols, values for the body side contralateral to the injected STN). The gray bars show time period over which lidocaine was injected, the volume of lidocaine in μL is given by the numbers in the bars. Lidocaine resulted in a decrease in rigidity in all three patients and the rigidity in two of these patients (B, C) was observed to recover to baseline values. Lidocaine reduced limb tremor in patients B and D (patient C did not have limb tremor during the procedure). Traces at the bottom of the figure are accelerometer traces of 90 seconds of resting tremor of patient D (traces were sampled starting at the times indicated to the left). The bar graph at the top right shows that lidocaine injections in patient B resulted in improved performance on a movement time task (see Methods, $*P < 0.05$, ANOVA on ranks). The traces at the bottom right show the improvement in repetitive wrist pronation/supination movements (WPS) in patient D following lidocaine injections. The time of appearance of dyskinetic movements is indicated by downward dashed arrows. Following lidocaine injections, all three patients developed dystonic or dyskinetic movements (see Results).

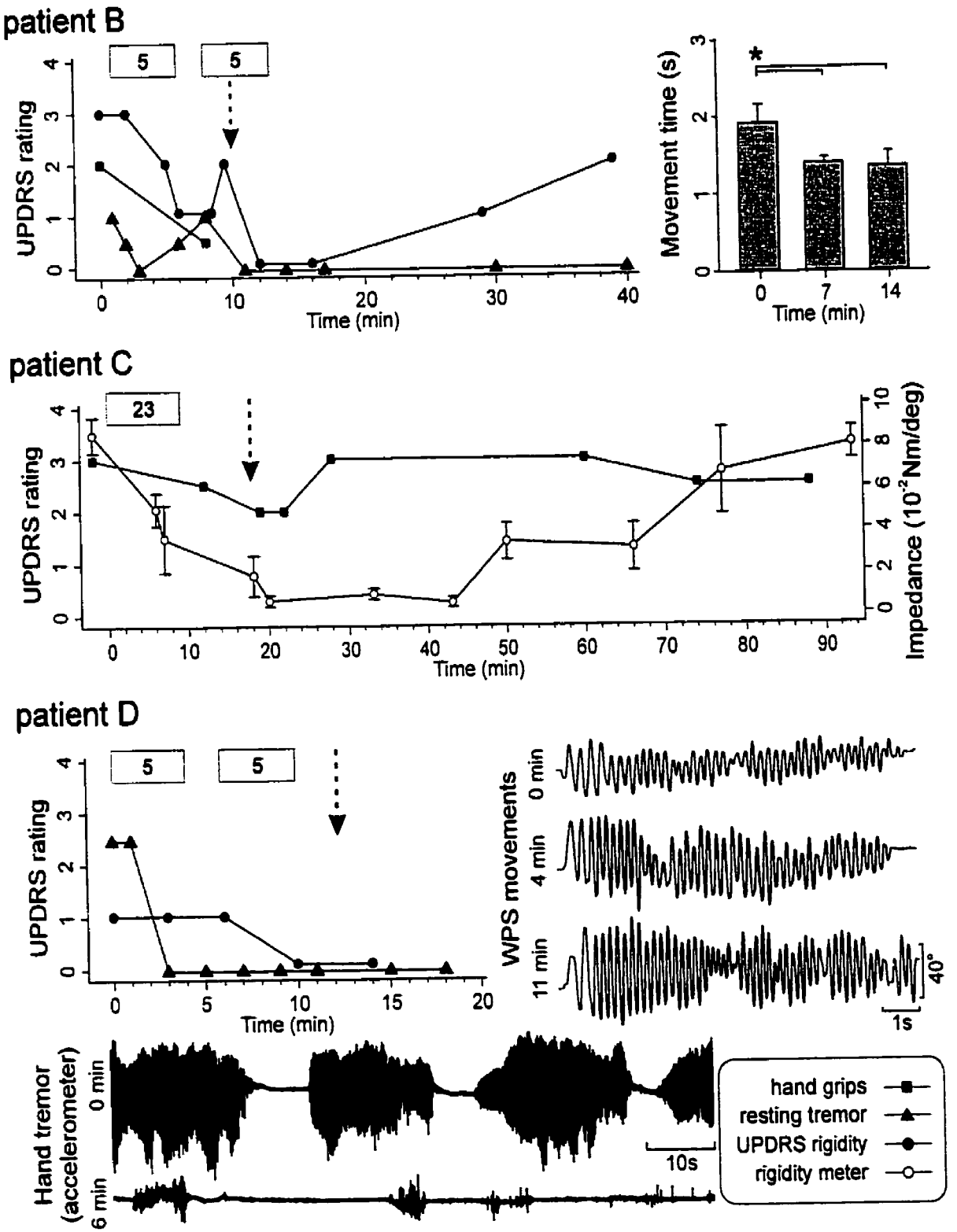

patient B
5
5
UPDRS rating
Time (min)
Movement time (s)
*
0
7
14
Time (min)
patient C
23
UPDRS rating
Impedance ($10^{-2}$Nm/deg)
Time (min)
patient D
5
5
UPDRS rating
Time (min)
WPS movements
0 min
4 min
11 min
40°
1s
Hand tremor (accelerometer)
0 min
6 min
10s
hand grips
resting tremor
UPDRS rigidity
rigidity meter

Figure 4.F3

**Figure 4.F4**

The effect of muscimol injection in the STN on clinical symptoms in patient E. The plot at the top left shows the effect of muscimol on bilateral resting tremor and rigidity (UPDRS scores, see box at bottom right for distinction of graph symbols). The gray bar (muscimol) and the white bar (saline) show time period over which each substance was injected and the volume of substance in μL in the bars. The plot shows that contralateral but not ipsilateral UPDRS resting tremor was reduced by a muscimol injection into an area of the STN with tremor-related activity (see Figure 1). Muscimol also improved the performance of wrist pronation/supination (WPS) movements (traces at top right). The traces at the bottom of the figure demonstrate that muscimol but not saline reduced spontaneous resting tremor recorded with an accelerometer (see Results).

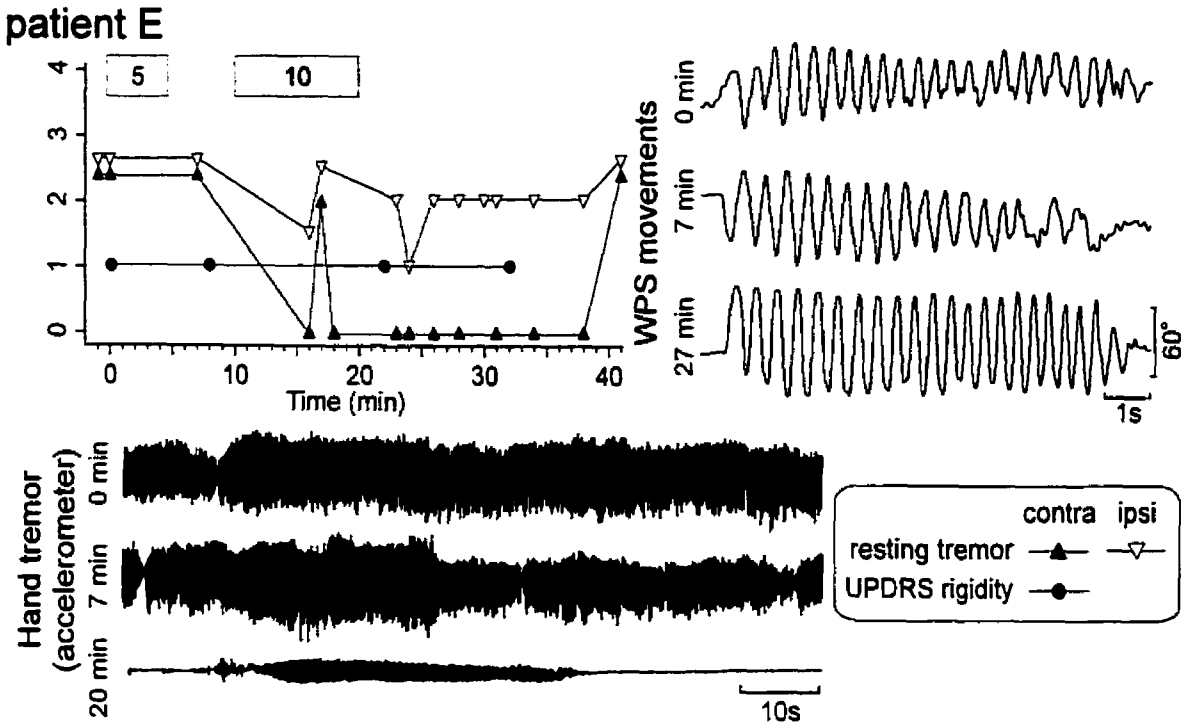

patient E
5
10
0
1
2
3
4
0
10
20
30
40
Time (min)
WPS movements
0 min
7 min
27 min
60°
1s
Hand tremor (accelerometer)
0 min
7 min
20 min
10s
contra
ipsi
resting tremor
UPDRS rigidity

Figure 4.F4

**Figure 4.F5**

Effects of muscimol injection in the STN of patient F. A: The top trace shows the accelerometer recording of the hand/wrist tremor (accelerometer was placed on index finger, Acc). The histogram shows the firing rate (20 second bins) of an STN neuron recorded during the injection and located 1.3 mm from the cannula tip. The gray bar represents the time period over which the 5 μL of muscimol was injected. B: Power spectra of oscillatory neuronal discharge recorded before (left panel, 0-3 minutes) and after (right panel, 9-12 minutes) muscimol injection (0.24 Hz resolution). The inset in each plot shows the frequency spectra of the accelerometer over each time period (0.39 Hz resolution). C: Time-frequency analysis of oscillatory neuronal discharge (0.98 Hz resolution x 20 second bins). The color legend indicates those spectral estimates with signal-to-noise ratios (green to light green) that were greater than a 99.8% confidence interval about the mean spectral noise. These plots demonstrate that the lower frequency oscillatory activity of the recorded neuron but not firing rate or 20 Hz oscillatory activity was reduced concurrent with a reduction in hand tremor.

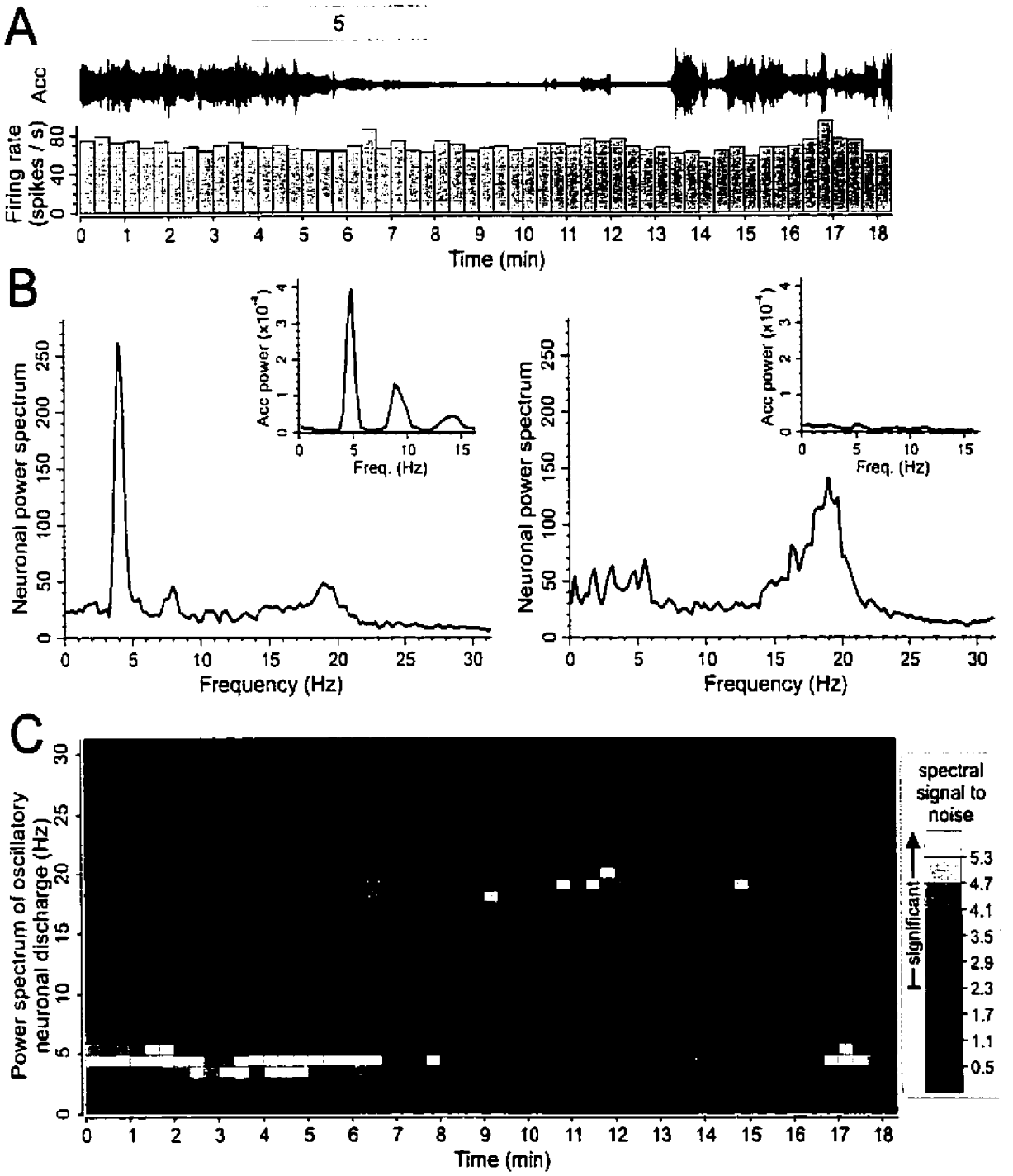

A
5
Acc
Firing rate (spikes / s)
0 40 80
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Time (min)
B
Neuronal power spectrum
0 50 100 150 200 250
Acc power (x10⁻⁴)
0 1 2 3 4
0 5 10 15
Freq. (Hz)
0 5 10 15 20 25 30
Frequency (Hz)
C
Power spectrum of oscillatory neuronal discharge (Hz)
0 5 10 15 20 25 30
spectral signal to noise
significant
5.3
4.7
4.1
3.5
2.9
2.3
1.7
1.1
0.5
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Time (min)

Figure 4.F5

### *4.4 - Discussion*

This is the first report of microinjections of muscimol and lidocaine in the STN of humans. This study demonstrates that local inactivation of the STN using pharmacological blocking agents results in a transient improvement in akinesia, rigidity, and limb tremor in patients with PD. These results support the current model of basal ganglia pathophysiology that predicts that a reduction of excessive activity in the STN of patients with PD should produce a therapeutic benefit (DeLong 1990). These results in humans are consistent with previous observations made in the non-human primate MPTP model of parkinsonism (Bergman et al. 1990; Aziz et al. 1991, 1992; Guridi et al. 1994; Wichmann et al. 1994b).

Although subthalamotomy and STN DBS in patients with PD improves all parkinsonian cardinal motor signs (Limousin et al. 1995b; Obeso et al. 1997a; Gill and Heywood 1997; Alvarez et al. 2001), it is unknown if these effects are due solely to inactivation of STN neurons rather than an action on fibers passing through or near the affected region. The anti-parkinsonian effect of muscimol in this study confirms that suppression of STN sensorimotor-related neuronal activity, as opposed to possible alterations in nearby pallidofugal fibers, results in a therapeutic benefit.

Since lidocaine acts on fibers passing through the blocked volume of cell bodies, it can indirectly affect other STN regions by preventing transmission through both inhibitory and excitatory afferent inputs and excitatory efferent projections. Although inhibition of GABAergic afferent fibers from the GPe would be predicted to enhance STN activity (Rouzaire-Dubois et al. 1980), it has been suggested that the increased activity of the STN in PD is due primarily to excitatory drive (Hassani et al. 1996; Levy

et al. 1997). As well as input from GPe, the STN receives massive glutamatergic input from the cerebral cortex (Monakow et al. 1978; Rouzaire-Dubois and Scarnati 1985; Canteras et al. 1990; Nambu et al. 1996), forms reciprocal projections with the pedunculopontine nucleus (Hammond et al. 1983; Lavoie and Parent 1994) and receives input from the centromedian-parafascicular complex of the thalamus (Sadikot et al. 1992b; Mouroux et al. 1995; Orieux et al. 2000). Inhibition by lidocaine of these excitatory afferent projections to other regions of the STN, in addition to the inhibition of just STN neurons, would also be predicted to have an anti-parkinsonian effect. Equivalently, inhibition of efferent axonal projections from other STN neurons (whose somata are not within the blocked area) by lidocaine would also act to decrease glutamatergic excitatory outflow from the STN. Therefore, it is possible that the functional volume of the STN that is blocked using lidocaine is larger than the volume of the affected cell bodies. Since muscimol specifically inhibits cell bodies, the anti-parkinsonian effects of muscimol observed is this study are likely due to the focal inhibition of excitatory output from the blocked region only.

The involvement of the STN in the pathogenesis of dyskinesias is supported by many studies (Crossman 1990). Dyskinesias and dystonic postures are observed in normal monkeys following excitotoxic cell-specific lesions (Hamada and DeLong 1992b) or electrical stimulation of the STN (Beurrier et al. 1997). Dyskinesias can also be induced by injection of the GABA antagonist bicuculline in the GPe (Matsumura et al. 1995) and disinhibition of the GPe should lead to decreases in STN activity. In MPTP-treated monkeys, inactivation of the STN results in transient dyskinesias in addition to improving parkinsonism (Bergman et al. 1990; Aziz et al. 1991, 1992; Wichmann et al.

1994b; Guridi et al. 1994). In patients with PD, choreic or dystonic dyskinesias are sometimes observed during penetration of the STN target by microelectrodes or DBS electrodes or during lesion making (Benabid et al. 2000; Alvarez et al. 2001).

Limousin et al. (1996) demonstrated that STN DBS at higher voltages than those required to control parkinsonism could also induce dyskinesias in patients with PD. It was suggested that because the anti-parkinsonian effect and dyskinetic effect occurred with different stimulation parameters, the mechanisms responsible for these two effects might be distinct. In the present study, $\geq 10\mu L$ of lidocaine reduced parkinsonian symptoms and produced dyskinesias in 3 patients while in the remaining patient (patient A), no motor benefit was obtained and no dyskinesias were observed following an injection of 3.5 $\mu L$ of lidocaine. These results suggest that in parkinsonian patients, the dyskinetic effect requires a greater degree of STN inactivation than does the anti-parkinsonian effect. This would explain why injections of muscimol did not produce dyskinesias in this study but did produce an anti-parkinsonian effect, if the volume of the STN inactivated by muscimol produced only a threshold anti-parkinsonian effect, but was not large enough to produce dyskinesias. It is also of interest that both choreic and dystonic dyskinesias were observed in the present study. These types of dyskinesias were typical of those seen during levodopa-induced dyskinesias (Fahn 2000) and support the finding that the neuronal activity of the STN in patients with PD is reduced during APO-induced dyskinesias (as demonstrated in Chapter 3, section 3).

The location of microinjections into the STN in this study was determined using microelectrode techniques and post-operative MRI verification of DBS electrode or lesion position relative to the STN. In addition, DBS in the same microelectrode tracks

as the injections resulted in an improvement in tremor, rigidity, and bradykinesia. The simultaneous recording of neuronal activity in two patients was also used to confirm that injections were performed in the STN. This technique is the most direct way to assess the effectiveness and spread of inactivating agents (Malpeli 1999), and was especially important with regard to patient A because it demonstrated that the lidocaine injection was well targeted and that the injection effectively inactivated neuronal tissue although no clinical effect was observed.

By recording neuronal activity at multiple distances from the injection site, it was possible to assess the spread of lidocaine and the size of the effective block. It took ~5 minutes for 3.5 μL of lidocaine to block neuronal activity within ~1mm from the injection site in the posterior-ventral direction (i.e. below the cannula, see Figure 4.F1). Our results are comparable to those of Martin and Ghez (1999). They demonstrated, using autoradiographic monitoring of glucose uptake/metabolism, that following an injection of 1 μL of lidocaine a reduction in glucose uptake within ~1mm of the injection center was attributable to drug spread. Other observations of diffusion distances in rat thalamic and spinal tissue have demonstrated that a 1 μL injection of lidocaine would result in a block of neuronal activity in a spherical region of radius 0.8 mm at 10 minutes after injection (Myers 1966; Sandkuhler et al. 1987). Although 3.5 μL was injected in the present study whereas these studies injected 1 μL of lidocaine, there are many factors that could account for variability in diffusion distances. For example, it is assumed that the distribution of lidocaine is spherical in shape in nuclear and cortical regions (Myers 1966; Martin and Ghez 1999) but there is significant anisotropy in the direction and extent of diffusion from the injection site in regions containing fibers of passage

(Sandkuhler et al. 1987). Some of the injected lidocaine might have also preferentially diffused up along the cannula shaft and therefore reduced the diffusion distances observed with our simultaneous microelectrode recording set-up. Hupe et al. (1999) demonstrated that with pressure injections, inactivation is more efficient above than below the pipette tip and that the volume of inactivation has an ellipsoidal form centered above the tip of the pipette. Other factors contributing to the observed differences in diffusion distances include: the volume of the extracellular space, the diffusibility of the drug through the extracellular space, the homogeneity of the medium of diffusion (white matter versus gray matter), the vascularization of the tissue surrounding the injection cannula (which would affect the washout of the drug), how fast the drug is degraded, and the rate of drug delivery (Sandkuhler et al. 1987; Malpeli 1999).

One caveat of this study is the inability to completely rule out that the observed effects were not due to diffusion of lidocaine or muscimol into neighboring structures (especially when simultaneous recording was not performed), most notably the SNr. The effects of these agents on this nearby structure might have a similar effect to STN inactivation since increased neuronal activity and abnormal discharge patterns of the SNr is observed in the MPTP monkey model of PD (Wichmann et al. 1999).

Although the injection rates used in this study (1-2.5 μL per minute) were greater than those used in animals (0.1μL to 2μL per minute)(Myers 1966; Demer and Robinson 1982; Duncan et al. 1993; Wichmann et al. 1994b; Burbaud et al. 1998), there are several factors that indicate that volume effects did not produce the observed clinical effects. (1) Simultaneous recording of neuronal activity was quite stable during the period of injection and indicates that tissue was not being deformed at distances ≥ 0.6 mm from the

injection site when substances were injected at a rate of ~1 μL per minute. (2) It is unlikely that the effects observed were due to a volume effect since there was a delay in the anti-parkinsonian effect produced by these injections. For example, in patient C (23 μL injected at 2.5 μL per minute), a marked decrease in rigidity did not occur until 20 minutes following injection. In contrast, the subsequent insertion of the DBS electrode in this patient resulted in an immediate improvement in rigidity (not shown) (n.b. if the maximum length of the DBS electrode (1.27 mm in diameter) in the STN is ~7 mm (see Figure 4.F1), the volume of the STN tissue displaced by the DBS electrode is ~9 μL). Benabid et al. (2000) have also reported that a significant decrease in akinesia and rigidity, along with the emergence of ballistic or choreoballistic movements, occur at the time of insertion of the DBS electrode in patients with PD. However, Demer and Robinson (1982) demonstrated that injections of more than 12 μL and/or at rates > 1 μL per minute produced irreversible damage in a region within ~ 0.7 mm from the injection site that was marked by gliosis and fiber loss. Therefore, it cannot be ruled out that tissue damage did not occur due to higher rates of injection (especially in patient C). Yet, it is unlikely that the observed clinical effects were due to permanent tissue damage because there was a return to baseline parkinsonism in all patients in whom recovery data were available.

The time course of the clinical effects of the lidocaine and muscimol injections, beginning 5 to 10 minutes following injection and lasting 30-50 minutes, closely matched those seen in animals (Sandkuhler et al. 1987; Wichmann et al. 1994b; Martin and Ghez 1999). In contrast, recovery to baseline tremor following a 5 μL muscimol injection (patient F) was observed ~5 minutes after the end of the injection. This time course is

similar to the time course of tremor suppression observed following injections of a similar volume of muscimol in the thalamus of patients with essential tremor (Pahapill et al. 1999). These results are consistent with studies using GABA that demonstrate that the duration of neuronal inactivation is proportional to the volume of substance injected (Hupe et al. 1999). These data suggest that the potential clinical application of microinjections to aid in the determination of the optimal target for lesions or DBS is limited. A significant advantage of the use of stimulation techniques over the use of microinjections as described in the present work is that intra-operative stimulation decreases tremor or rigidity with a very short latency (less than one minute) and is highly reproducible (Rodriguez et al. 1998).

Following MPTP-treatment in monkeys, there is a prominent increase in the number of STN neurons that display oscillatory activity (Bergman et al. 1994) and limb tremor reduction has been demonstrated following muscimol injections in the STN (Wichmann et al. 1994b). In the present study, injections of muscimol into regions of the STN with tremor-related activity caused a reduction in limb tremor. Our results support the view that oscillatory activity in the STN is important in the mediation of parkinsonian limb tremor (Bergman et al. 1994). It is interesting that the latency of the effect of muscimol or lidocaine on limb tremor was short. Five minutes after the start of a 5 μL lidocaine injection, a reduction of limb tremor in patients B and D and in patients E and F after 5 μL of muscimol was observed. Although a long period of time did not elapse after the saline injection in patient E, it was observed that saline did not affect tremor. The effect of muscimol occurred immediately after 5 μL of muscimol was injected while there was no immediate effect of saline (both were injected at 1 μL per minute). Since

tremor suppression occurred with small volumes of inactivating agents and with a short latency, our results suggest that tremor suppression can be accomplished by silencing the activity of a small region of STN containing TCs. Evidence from simultaneous microelectrode recording techniques has indicated that potential tremor-generating circuits in the basal ganglia can occupy a relatively small volume (< 1 $mm^3$) (Hurtado et al., 1999). Our results are also consistent with those of Rodriguez et al. (1998) who demonstrated that microstimulation in STN regions containing TCs reduces tremor with a very short latency. It has been suggested that microstimulation affects a small volume of tissue at currents equal to or less than 100 μA, the maximum generally possible with microelectrodes (Dostrovsky et al. 2000).

In this section, the simultaneous recording of neuronal activity during microinjection allowed the direct assessment of the time course of the effect of a pharmacological block in an area not directly deactivated by the block. It was demonstrated that the 4 Hz discharge oscillation in a neuron located outside a blocked region of TCs was reduced concurrent with a reduction in limb tremor. However the firing rate and 20 Hz oscillatory activity remained unchanged. This result suggests that a block of neuronal activity can modify the neuronal discharge of cells located beyond the blocked area. There are several possible ways that this result might be interpreted.

First, if the recorded neuron received proprioceptive input from the tremulous contralateral hand/wrist, reduction of limb tremor could account for a reduction in the lower frequency oscillatory activity of the recorded neuron (Krack et al. 1998b). However, at no time was the oscillatory activity of the neuron coherent with wrist flexor EMG or the accelerometer signal which would be expected if its firing was dependent on

sensory input. Second, if the recorded neuron received 4 Hz oscillatory input directly from cells at the injection site, inactivation of these cells would also lead to a reduction in the lower frequency component of the recorded neuron (Martin and Ghez 1999). Yet although intrinsic axon collaterals in the STN are frequent in the rat (Kita et al. 1983), they are rare in primates (Yelnik and Percheron 1979; Sato et al. 2000). Furthermore, coincident discharge between pairs of STN neurons in patients with PD is not observed suggesting that STN TCs do not directly drive the activity of other STN TCs (see Chapter 5, section 1). Third, muscimol might have affected the activity of the recorded neuron by acting on a dendrite extending within the blocked region. For example, it has been shown that the dendritic fields of neurons located centrally in the STN can extend over nearly two thirds of the structure (Sato et al. 2000). However this would likely result also in a decrease in the overall spontaneous discharge of the neuron and this was not observed. Fourth, both parkinsonian limb tremor (Scholz and Bacher 1995) and tremor-related activity in the basal ganglia (Bergman et al. 1998b; Hurtado et al. 1999; Raz et al. 2000) have been shown to exhibit fluctuations in rhythmic activity. However, it is unlikely that both the decrease in 4 Hz oscillations of the recorded neuron and a decrease in 5 Hz limb tremor are merely due to spontaneous variability, because these oscillations decreased and reappeared with a similar time course. Lastly, suppression of limb tremor could arise as a result of, in addition to direct inactivation of tremor-related discharge, the "desynchronizing" effect of a small block of the STN upon neighboring subcircuits in the cortico-basal ganglia-thalamic loop (Bergman et al. 1998a; Deuschl et al. 2000).

# CHAPTER 5 - NEURONAL SYNCHRONIZATION IN THE SUBTHALAMIC NUCLEUS AND GLOBUS PALLIDUS

In monkeys treated with MPTP, degeneration of the SNc and subsequent depletion of striatal dopamine is related to the emergence of periodic or "oscillatory" neuronal activity in the STN and GPi and increases in the somatosensory responses and bursting activity in these nuclei (Miller and DeLong 1987; Filion et al. 1988; Filion and Tremblay 1991; Bergman et al. 1994; Boraud et al. 1998, 2000a). These changes in the activity of basal ganglia neurons due to parkinsonism cannot be explained in terms of alterations in mean firing rate (Delong 1990). It has been proposed that a breakdown of the functional segregation between parallel re-entrant subcircuits of the basal ganglia-thalamo-cortical system (Alexander et al. 1990; Alexander and Crutcher 1990; Hoover and Strick 1993) might underlie parkinsonian pathophysiology (Filion et al. 1994; Nini et al. 1995), especially with regards to the pathogenesis of limb tremor (Bergman et al. 1998a; Deuschl et al. 2000). This notion is supported by studies using simultaneous microelectrode recording techniques to demonstrate that periodic or "oscillatory" bursting in GPi neurons of tremulous MPTP-treated monkeys is synchronized (Nini et al. 1995; Bergman et al. 1998b; Raz et al. 1996, 2000). The aim of this chapter was to test the hypothesis that synchronized activity between neurons in the basal ganglia is related to the clinical features of PD.

## 5.1 - High frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor


*Abstract*

It has been hypothesised that in PD there is increased synchronization of neuronal firing in the basal ganglia. This study examines the discharge activity of 121 pairs of STN neurons in 9 PD patients undergoing functional stereotactic mapping. There were 4 patients with a previous pallidotomy. A double microelectrode set-up was used to simultaneously record from two neurons separated by distances as small as 250 μm. In the 6 patients that had limb tremor during the recording session (n=76 pairs), the discharge pattern of 12 pairs of TCs were found to be coherent at the frequency of the limb tremor. Both in-phase and out-of-phase relationships were observed between TCs. Interestingly, in these 6 patients, 63/129 single neurons displayed 15 to 30 Hz oscillations while 36/76 pairs were coherent in this frequency range. Although the oscillatory frequencies were variable between patients, they were highly clustered within a patient. The phase difference between these pairs was found to be close to 0. High frequency synchronization was observed during periods of limb tremor as well as during intermittent periods with no apparent limb tremor. In contrast, in the three patients without limb tremor during the recording session, only 1/84 neurons had high frequency oscillatory activity and no TCs or synchronous high frequency oscillatory activity was observed (n=45 pairs). These findings demonstrate that in PD patients with limb tremor many STN neurons display high frequency oscillations with a high degree of in-phase synchrony. The results suggest that high frequency synchronized oscillatory activity may be associated with the pathology that gives rise to tremor in PD patients.

### *5.1.1 - Introduction*

The role of the STN in the pathogenesis of parkinsonian symptoms has gained prominence since the demonstration of the anti-parkinsonian effect of injections of fiber sparing neurotoxins into the STN of MPTP treated non-human primates (Bergman et al. 1990). DBS or lesions (Limousin et al. 1995b; Obeso et al. 1997a; Gill and Heywood 1997) of the STN in PD patients have been shown to be an effective treatment for rigidity, akinesia, and especially tremor (Krack et al. 1998b; Kumar et al. 1998b). In PD patients, the reduction of tremor by STN DBS is comparable to the response obtained by thalamic stimulation for tremor (Krack et al. 1997). As in the thalamus (Lenz et al. 1988a), groups of STN neurons display tremor related spontaneous activity which is periodic at limb tremor frequency (Hutchison et al. 1998a) and microstimulation in these regions has been shown to reduce resting tremor (Rodriguez et al. 1998).

It has been hypothesized that in PD, limb tremor is the result of tremor-related neuronal discharge synchronization due to a reduction in the independence of functionally segregated parallel circuits in the basal ganglia secondary to a loss of striatal dopamine (Bergman et al. 1998a). To assess whether synchronous activity between neurons in the STN underlies differences in parkinsonian pathophysiology, this study examined the discharge activity of pairs of neurons in PD patients with and without limb tremor. It is demonstrated that groups of STN neurons oscillate in-phase at high frequencies (15-30 Hz) in PD patients with limb tremor, but are not found in those patients without limb tremor.

### *5.1.2 - Methods*

*Subjects*

Nine patients underwent microelectrode guided placement of bilateral DBS electrodes for the treatment of the symptoms of PD. These patients had a mean age of 51 years (±2.4 SE, range 34–66) at the time of operation. The average duration of the disease was 12 years (±1.5 SE) and all had PD for at least 7 years. Individual patient characteristics are listed in Table 5.1.T1. All patients were pre-operatively assessed using the UPDRS. In both the pre-operative assessment and during surgery, patients were studied in the practically defined OFF state, 12-14 hours after the last oral dose of levodopa. The mean motor UPDRS score (motor subsection III) was 50 (±2 SE) (maximum possible score is 108). UPDRS OFF period tremor score (maximum value is 28) was calculated as the sum of UPDRS item 20 (resting tremor of right hand, left hand, right leg, left leg, face) and item 21 (action tremor of right hand, left hand). Using the following criteria, patients were divided into two groups. Those with any resting tremor of the limbs during the microelectrode recording session were assigned to a "tremor" group (n=6). Patients without any discernable resting tremor of the limbs during the microelectrode recording session were assigned to a "non-tremor" group (n=3). There were four patients who had previously undergone a unilateral pallidotomy (see Table 5.1.T1). In these patients, pallidotomy was indicated for disabling drug-induced dyskinesia. Two of these patients were in the "tremor" group and two were in the "non-tremor" group. In both the "tremor" group patients (patients A, F), pallidotomy led to a moderate decrease in contralateral limb tremor at 6 months following surgery. However, the tremor reduction was not maintained at the time of the STN recordings (33 and 28

months post pallidotomy). One of the two "non-tremor" group patients (patient I) did have mild facial tremor prior to and at 6 months post pallidotomy but this tremor was not present at the time of the STN recordings. Since it is possible to induce or enhance parkinsonian resting limb tremor by having patients perform a cognitive task that demands their attention, patients were periodically asked to perform mental arithmetic during some of the microelectrode recordings.

*Recording procedure and apparatus*

The use of microelectrode recording to localize DBS electrode placement in the STN has previously been described (Hutchison et al. 1998a) and is described in the General Methods (sections 2.1.1.b and 2.1.2). The simultaneous recording of neuron pairs is described in the General Methods (section 2.1.3). Recorded neurons were included if they were well isolated, stable, and were sampled for at least 20 seconds or at least 1000 action potentials. In this study, the average number of action potentials recorded per cell was 2830±130 (SE) over an average sample time of 62±3 seconds (SE).

*Data analysis*

Spontaneous ongoing discharge (tonic activity) analyzed in this study was collected with the patient at rest and without any passive joint manipulation or voluntary movements. The average neuronal firing rate and the median inter-spike interval were calculated for each cell. Statistical analysis of group values was carried out using Student's t-tests. In cases of non-normality, the Wilcoxon Signed Rank Test or Mann-

Whitney Rank Sum Test was employed. Statistical significance was assigned at $p < 0.05$ (i.e. $\alpha = 0.05$; two-tailed).

Time domain analysis of single-neuron discharge activity is described in the General Methods (section 2.3.2.a). Spectral analysis of single-neuron discharge activity is described in the General Methods (section 2.3.2.b). Time domain analysis of the discharge between two neurons employed the cross-correlation technique and is described in the General Methods (section 2.4.1). Spectral analysis used the coherence technique. Coherence analysis was used to compare the linear correlation between two signals over a range of frequencies and is described in the General Methods (section 2.4.2).

### *5.1.3 - Results*

*Oscillatory activity of single neurons in the STN*

A total of 213 single neurons (from 121 pairs) was recorded from the STN of the 9 patients. Three types of rhythmic activities were identified over the range of the rhythmic frequencies investigated: 1) TCs (4% of total STN population, n=8) which displayed rhythmic activity at tremor frequency concurrently with limb tremor (Figure 5.1.F1A), 2) cells with high (>10 Hz) frequency oscillations (20% of total STN population, n=44) (Figure 5.1.F1B), and 3) cells with both tremor frequency and high frequency oscillation components (6% of total STN population, n=12) (Figure 5.1.F1C). The median firing rate of all STN neurons was 45.7 Hz (25% = 34.7, 75% = 61.7). Cells with no oscillatory discharge had a median firing rate of 43.1 Hz (25% = 32.4, 75% = 61.1) while cells that displayed oscillatory activity had a median firing rate of 53.4 Hz

(25% = 40.2, 75% = 64.4) which was significantly greater ($p<0.05$, Mann-Whitney Rank Sum Test) (Figure 5.1.F1D). There was no significant difference in the FRs of TCs and cells with high frequency oscillatory activity.

Almost all (63/64) of the neurons with tremor frequency activity (i.e. TCs) and/or high frequency oscillations were found in the 6 patients of the "tremor" group (129 single neurons examined) including the two patients (A, F) with a pallidotomy (ipsilateral to the recordings). In the 3 patients of the "non-tremor" group, only 1/84 STN neurons was found to have a high frequency oscillation. Figure 5.1.F1E shows box plots of the frequency distributions of the high frequency oscillatory neurons in the "tremor" group (frequency calculated from auto-correlograms). Each of the 6 patients had high frequency oscillations that were tightly centered about one frequency in the range from 15 to 25 Hz. In one patient high frequency oscillatory activity was recorded on both sides and the frequency was similar on the two sides. Three of the patients in the "tremor" group had TCs and the distribution of TC frequencies is also shown in Figure 5.1.F1E. For cells which had both a tremor frequency oscillation and a high frequency oscillation (n=12), the ratio of the mean high frequency oscillatory component to the mean frequency of the tremor component was 4.0 (±0.1 SE).

*Highly synchronous high frequency oscillatory activity in the STN of "tremor" group patients*

A total of 121 neuron pairs was recorded in the STN. Single short latency peaks in the cross-correlogram that would indicate short-interval interactions between STN neurons were never observed. However, 44/76 pairs of neurons were found to have a

significant cross-correlation at high frequencies (>10 Hz) in the "tremor" group. High frequency oscillatory activity was more evident in cross-correlograms than in auto-correlograms of single neurons (55/129 single STN neurons with high frequency oscillatory activity in the "tremor" group). The oscillation strength ratings were stronger for cross-correlation (7.4 (±0.1 SE)) than for auto-correlation (6.9 (±0.1 SE)) (two-tailed t-test, $p<0.01$). Figure 5.1.F2A shows the spontaneous ongoing discharge of two simultaneously recorded STN neurons and Figure 5.1.F2B shows the corresponding correlograms and spectra for this pair. Although the spectral signal to noise ratio of the high frequency oscillation of unit 2 is lower than for unit 1, there is a statistically significant coherence between the pair. Figure 5.1.F2C shows examples of cross-correlograms and coherence functions of neuron pairs with synchronous high frequency oscillatory activity from 4 patients in the "tremor" group; these pairs all oscillated in-phase but each patient had a unique oscillation frequency. Furthermore, 36/76 pairs of STN neurons were found to have a significant coherence at a high frequency (mean sample time for the pairs of neurons was 79.3 s (±9.3 SE)). Coherence analysis revealed that fast oscillatory cells were also in synchrony for long periods of time. For example, eight of these pairs were seen to be coherent and in-phase for longer than 2 minutes.

Figure 5.1.F2D is a plot of the proportion of the pairs that displayed high frequency oscillatory cross-correlation in each patient to each patient's pre-surgical UPDRS tremor rating score. There was a roughly linear relationship between the amount of high frequency synchronous activity and the patients' tremor ($r^2=0.67$, $p<0.01$). Data obtained from those patients in whom TCs were encountered during the time of surgery are indicated by triangles. Although all 6 of the "tremor" group patients had limb tremor

during the procedure, the high frequency rhythmic firing was also present during some episodes when these patients did not have any noticeable tremor. TCs were found in 3 of the 6 "tremor" group patients. The TCs encountered appeared to be localized to regions that also contained cells with a high frequency oscillatory component (see Figure 5.1.F5). There were 9 instances of recording a TC on one electrode and no discernible TC frequency component for the other neuron; 3 of these pairs showed significant high frequency coherence. There were 9 instances in which two TCs were recorded simultaneously, and the tremor oscillation in 8 of these pairs was found to be coherent over the total amount of time sampled.

Figure 5.1.F2E demonstrates that the phase relationship between high frequency oscillatory pairs (detected from the cross-correlograms) was not dependent on the distance between the recording sites. There were 61 pairs of STN neurons investigated that were separated by 250 um and 60 STN pairs which were separated by distances greater than 600 um. Figure 5.1.F2E shows that fast frequency pairs were synchronous and in-phase (absolute phase difference) over distances up to 1.5 mm.

Temporal relationships between limb tremor and neural pair synchronization were analysed in detail by using time-frequency plots. Figure 5.1.F3A displays individual power spectrums of two STN units (scaled to the ratio signal / noise) and the coherence between them as a function of time during ongoing wrist tremor. Unit 1 was a STN TC with a high frequency component while unit 2 predominantly displayed high frequency oscillatory activity. During a period of limb tremor (40-70 seconds), both cells were coherent at tremor frequency and at 20 Hz. When wrist tremor was suppressed by an examiner holding the patient's wrist, the pair of units displayed an even stronger high

frequency synchronization (as indicated by the value of the coherence). In contrast to this type of modulation, high frequency synchronization in several pairs was observed by inducing or enhancing resting tremor. Figure 5.1.F3B shows the changes in coherence between two cells where, following a rest period and some repetitive passive and voluntary movements (see accelerometer trace - Acc), resting tremor was induced by asking the patient to mentally count backwards. It can been seen that when no tremor was present there was no coherence between the two cells but during ankle tremor (approximately 3.3 Hz) there was a strong high frequency oscillatory synchronization. Due to the limited time resolution it is not possible to ascertain whether coherence precisely coincides with the limb tremor. However at 83 seconds, the ankle tremor was suppressed by having an examiner hold the patient's ankle for approximately 5 seconds and then releasing thereby letting tremor re-appear. At this point (preceding the high frequency synchronization) the two cells were coherent at tremor frequency. Note also that these cells were not coherent during the passive arm movements but did show coherence at 26-28 Hz during voluntary ankle movements. There was one other example in a different patient where the high frequency synchronization appeared during limb tremor (not shown). The issue of whether high frequency oscillatory synchronization occurred during activity other than tremor was not fully explored. There were some neuron pairs that had ongoing high frequency oscillatory synchronization during repetitive voluntary limb movements such as pointing with one hand and tapping with the other hand. An example is shown in Figure 5.1.F4A where the pair displayed synchronization of their 24-28 Hz oscillation during passive repetitive elbow movements. Synchronization within this frequency range was absent during the voluntary pointing

and tapping movements but synchronization at about 15 Hz remained or became even stronger. These data indicate that high frequency synchronization between STN neurons is dynamic and depends on the state of limb tremor and/or passive/voluntary movements.

*Phase relationships of pairs of STN oscillatory neurons.*

Figure 5.1.F4A also demonstrates that the pair of STN neurons with a high frequency coherence had a stable phase relationship for a long period of time (>3 minutes). This is in contrast to pairs of STN TCs. An example of the phase variability of two TCs is shown in Figure 5.1.F4B. These cells go from being in-phase at 50-60 s to nearly out-of-phase at 70-80 s. It is conceivable that lower coherence values were obtained in the tremor activity frequency range versus the high frequency activity range due to differences in phase variability between TC activity and high frequency oscillatory activity (i.e. a high coherence value is related to a stable phase relationship, see Methods).

The tremor oscillations in pairs of TCs within the same patients were also observed to have variable phase relationships. Figure 5.1.F5 shows the spatial distribution of oscillatory activity in a single patient in which two independent electrodes were used. During these recordings the patient had a robust 4-5 Hz resting tremor in both the contralateral hand and foot. The first STN cell was encountered at 3.2 mm, while the last STN cell (a TC) was found at -1.0 mm. The schematic illustrates the oscillatory behavior of single units and the distances between the pairs of neurons. As indicated by the cross-correlograms and the corresponding coherence functions, some pairs of TCs were in phase (e.g. pair 0.6 x 1.1) while others were out of phase (e.g. pair 0.2 x 0.0). It

can also be seen that the phase relationships between neighboring TCs could be out-of-phase even at distances as small as 200 um between neurons (e.g. cells in track 2 at 0.9 mm and 1.1 mm versus cell 0.6 mm in track 1). Furthermore, not all pairs of TCs studied in this patient were coherent (e.g. pair 1.3 x 1.7). Synchronization between neurons with high frequency oscillations was, in contrast to TC activity always close to 0. The mean phase difference between the high frequency oscillatory pairs in the two microelectrode tracks was only 8.7 degrees (±4.4 SE, maximum value is 31 degrees). Differences in coherence values between TCs and high frequency oscillatory neurons observed in Figure 5.1.F5 could also be due to differences in sampling time. That is, over a long sampling time (i.e. pair 1.3 x 1.7 was sampled for 130 seconds) lower coherence values might be obtained for pairs of TCs with a variable phase relationship. Close inspection of Figure 5.1.F5 also reveals that it was possible to detect oscillatory synchrony from the cross correlograms even if there was no significant oscillation in the auto-correlogram of one of the pair of neurons (e.g. pair 1.6 x 1.8, and pair 0.6 x 0.9).

**Table 5.1.T1**

Patient characteristics. *Age and years with PD at time of STN recording. † UPDRS scores calculated from pre-operative values (see Methods). ‡ Patients with a pallidotomy. Value in parentheses indicates number of months after pallidotomy.

*Patient characteristics*

| Patient | age* | sex | years with PD* | UPDRS motor score† | UPDRS tremor score† | body side of sampled STN neurons | body side of pallidotomy‡ | limb tremor during the procedure? | assigned group |
|---|---|---|---|---|---|---|---|---|---|
| A | 49 | f | 11 | 50 | 6 | left | left (33) | yes | "tremor" |
| B | 57 | f | 17 | 42 | 10 | right | - | yes | "tremor" |
| C | 66 | m | 13 | 53 | 14 | right | - | yes | "tremor" |
| D | 50 | f | 7 | 57 | 14 | right, left | - | yes | "tremor" |
| E | 55 | m | 18 | 45 | 19 | right | - | yes | "tremor" |
| F | 53 | m | 7 | 54 | 13 | right | right (27) | yes | "tremor" |
| G | 34 | f | 9 | 39 | 6 | left | - | none | "non-tremor" |
| H | 50 | m | 10 | 54 | 1 | right | left (40) | none | "non-tremor" |
| I | 49 | m | 17 | 55 | 1 | right, left | right (51) | none | "non-tremor" |

Table 5.1.T1

**Figurel 5.1.F1**

The oscillatory behavior of single neurons in the STN of PD patients. A-C: Examples of autocorrelograms (left column; dashed line is mean discharge rate) and frequency spectra (right column; numbers above peaks are the signal to noise ratio of the peak) for three types of oscillatory STN neurons. A: Cell with only a tremor frequency component (from patient D; see panel E). B: Cell with only a high frequency oscillatory component (from patient B). C: Cell with both oscillatory components (from patient B). D: Distribution of firing rates of oscillatory and non-oscillatory STN neurons (10 Hz bins, data normalized by total cell number in each group). The mean spontaneous firing rate of cells with an oscillatory component (n=64) was significantly higher than the firing rate of cells without any oscillatory components (n=149) ($p<0.05$). E: Box plot of frequencies of high frequency oscillations (gray boxes, top) and of tremor frequency oscillations (open boxes, bottom) of patients in "tremor" group. Arrows indicate the mean limb tremor frequency during the stereotaxic procedure. Numbers above patient letter designations indicate total number of single STN neurons that were sampled in each patient. Numbers above boxes show the number of single STN neurons in each group. In the box plot, the box indicates the $25^{th}$, $50^{th}$ (median), and $75^{th}$ percentiles, the error bars indicate the $10^{th}$ and $90^{th}$ percentiles, and the dots represent outliers.

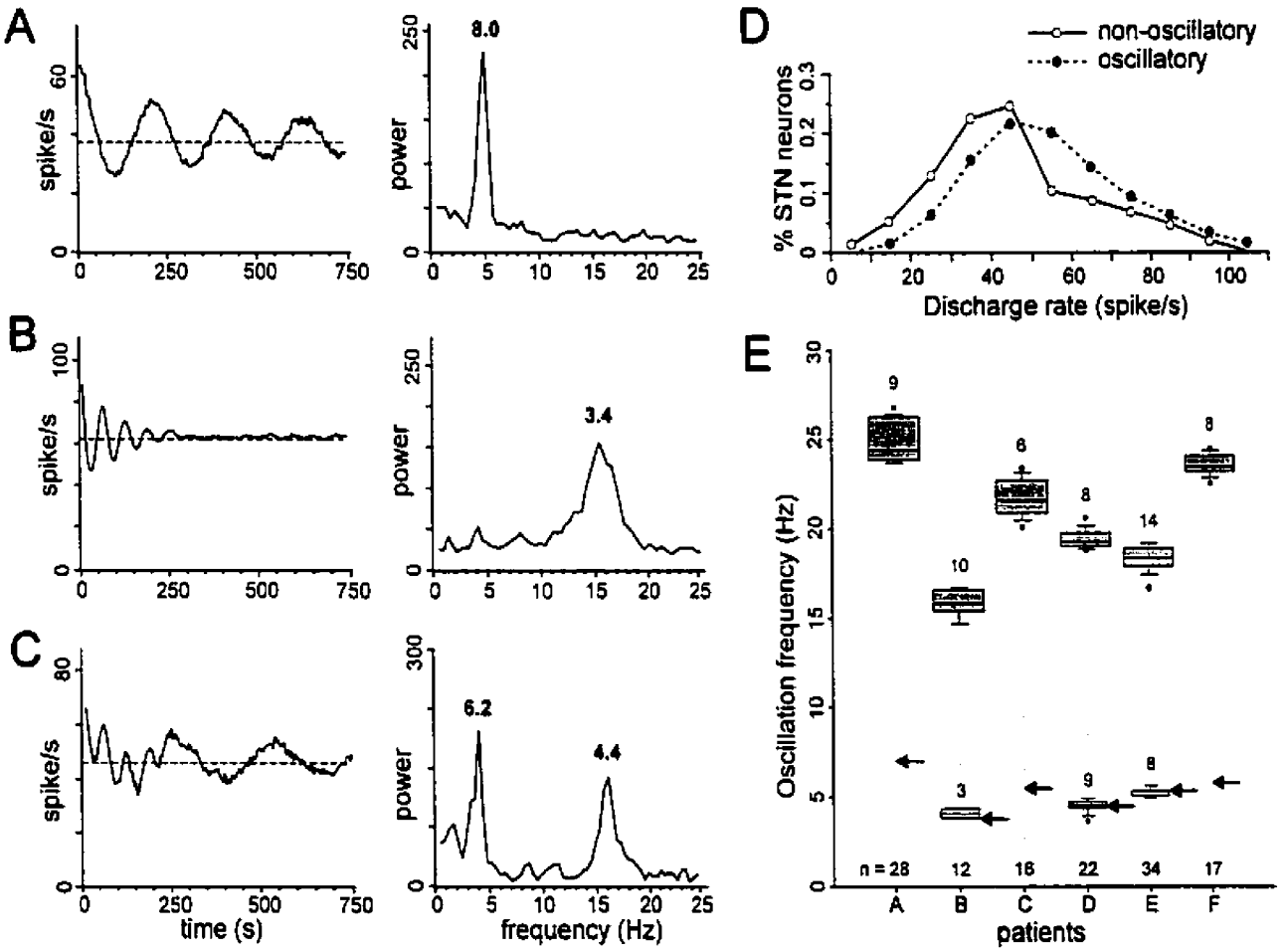

A
spike/s
power
8.0
B
3.4
C
6.2
4.4
time (s)
frequency (Hz)
D
non-oscillatory
oscillatory
% STN neurons
Discharge rate (spike/s)
E
Oscillation frequency (Hz)
n = 28
12
16
22
34
17
patients

Figure 5.1.F1

**Figure 5.1.F2**

Synchronization of STN neurons with high frequency oscillations. A: Traces 2 and 3 show the discharge activity of two simultaneously recorded neurons during wrist tremor (patient E). The top trace is the recording of rectified wrist extensor electromyographic activity (EMG). Note that the two neurons tend to fire in synchrony with each other. B: Corresponding correlograms (top row) and spectra (bottom row) of the traces shown in A (the total sample time used to construct these plots was 29 seconds). In all correlograms, the lines indicate mean FR. In the cross-correlogram (right panel of top row) unit 1 is used as the trigger. The thick dashed line in the coherence function indicates the level of significant coherence and number by the peak is the phase difference (right panel of bottom row, see Methods). C: Examples of cross-correlograms (left column, the dashed lines indicate mean ± 2SD) and coherence functions (right column) of pairs of STN neurons with a high frequency oscillatory component from 4 separate patients (A, D, B, F respectively). D: Linear regression analysis of percentage of pairs of STN neurons with a high frequency cross-correlation as a function of amount of total limb tremor (UPDRS: sum of action tremor and rest tremor) measured pre-operatively. The triangles indicate those patients in whom TCs were also found. E: Linear regression analysis of the phase relationship between pairs of fast oscillatory STN neurons as a function of the distance between the microelectrodes (phase calculated from cross-correlograms).

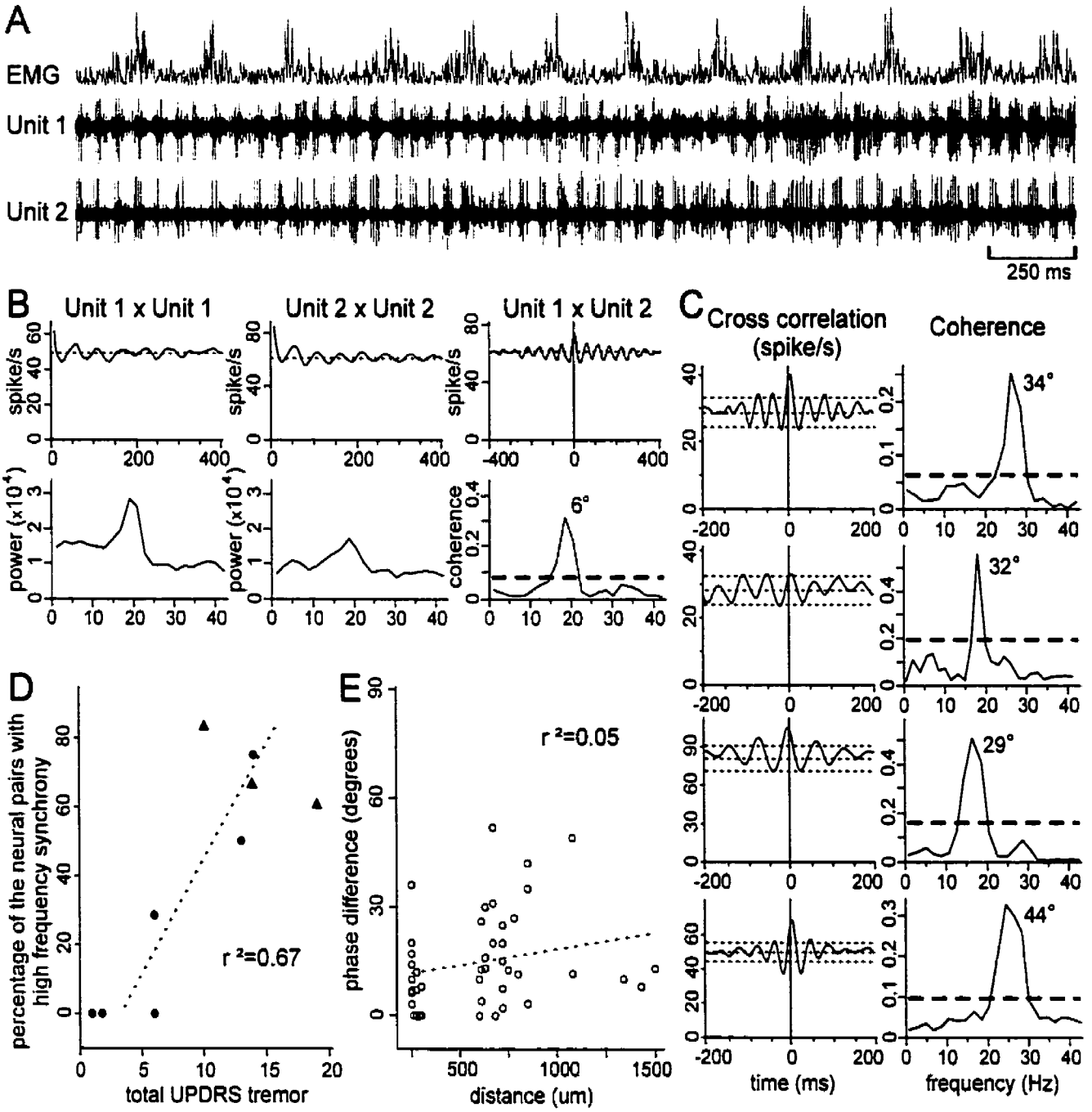

A
EMG
Unit 1
Unit 2
250 ms
B
Unit 1 x Unit 1
Unit 2 x Unit 2
Unit 1 x Unit 2
spike/s
power (x10⁴)
coherence
6°
C
Cross correlation (spike/s)
Coherence
34°
32°
29°
44°
time (ms)
frequency (Hz)
D
percentage of the neural pairs with high frequency synchrony
r²=0.67
total UPDRS tremor
E
r²=0.05
phase difference (degrees)
distance (um)

Figure 5.1.F2

**Figure 5.1.F3**

Examples of the dynamic relationship between high frequency oscillatory synchronization and limb tremor. A: Two STN neurons recorded from patient D. Bottom 2 panels show the power spectrums for each neuron, scaled to the ratio of signal to total noise (see Methods). Top panel shows the coherence between the two neurons. The top trace shows the electromyographic activity (EMG) from the patient's wrist flexors smoothed to give an estimate of the strength of the tremor (shown in detail at the top right of the figure for the 60-64 second period). Each unit displays both frequency components. However, the power spectrum of unit 1 shows that unit 1 has a larger tremor component oscillation while power spectrum of unit 2 shows that unit 2 has a larger high frequency component oscillation. Note that high frequency coherence between unit 1 and unit 2 becomes maximal when the wrist is held. B: Two STN neurons recorded from patient B. Power spectrums (bottom two panels) and coherence plot between two STN neurons during periods of ankle tremor, voluntary and passive ankle movements and rest. The two cells are synchronized at 15 Hz during resting limb tremor of approximately 3.3 Hz. Due to the time resolution of the coherence plot, it is unclear as to whether this synchronization precedes or follows limb tremor. After the ankle is released, tremor amplitude increases and the neuron pair resynchronizes at the same oscillation frequency. Top trace shows foot accelerometer (Acc) output. Coherence and auto-spectra plots were constructed by analysing consecutive 10 second sections of non-overlapping data.

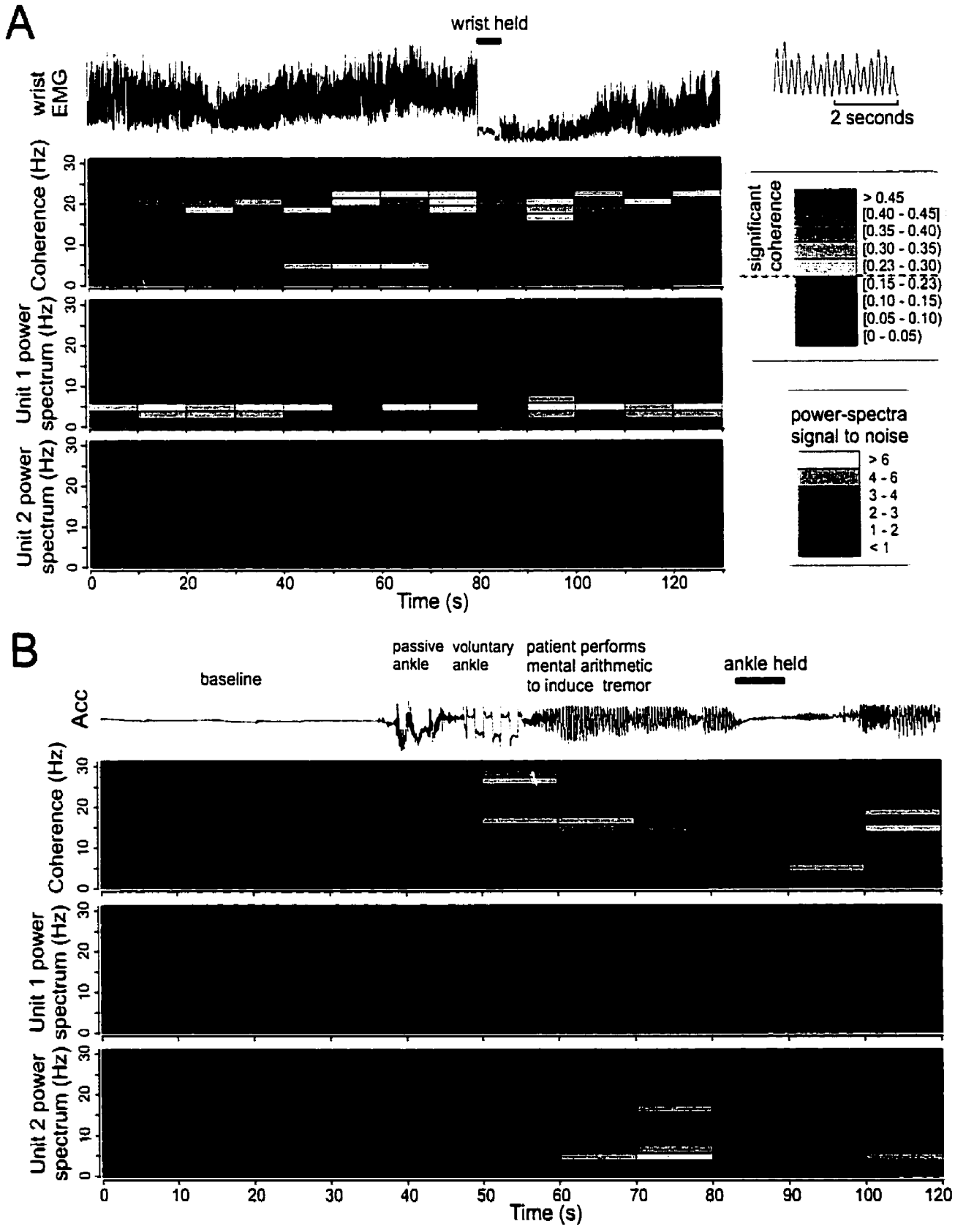

A
wrist held
wrist EMG
2 seconds
Coherence (Hz)
Unit 1 power spectrum (Hz)
Unit 2 power spectrum (Hz)
0
10
20
30
0
20
40
60
80
100
120
Time (s)
significant coherence
> 0.45
[0.40 - 0.45]
[0.35 - 0.40)
[0.30 - 0.35)
[0.23 - 0.30)
[0.15 - 0.23)
[0.10 - 0.15)
[0.05 - 0.10)
[0 - 0.05)
power-spectra signal to noise
> 6
4 - 6
3 - 4
2 - 3
1 - 2
< 1
B
baseline
passive ankle
voluntary ankle
patient performs mental arithmetic to induce tremor
ankle held
Acc
Coherence (Hz)
Unit 1 power spectrum (Hz)
Unit 2 power spectrum (Hz)
0
10
20
30
40
50
60
70
80
90
100
120
Time (s)

Figure 5.1.F3

**Figure 5.1.F4**

Changes in phase relationship between oscillatory STN neurons over time. A: Power spectrums, coherence, and phase (at ~17 Hz) between two STN neurons during a long sampling period containing passive and voluntary movements of elbow and arm (patient B). Note that the phase remains constant over the 3 minute sampling period. Coherence during passive repetitive elbow movements was at around 17 Hz and 24-28 Hz. Coherence during voluntary pointing and tapping with the opposite hand was limited to approximately 17 Hz. Top trace shows hand accelerometer (Acc) output. Same legend as in Figure 5.1.F3. B: Same plots as in A showing that the phase relationship between two STN TCs varies over time (patient D). The top left trace shows the smoothed EMG from the patient's wrist extensors. Phase at ~5 Hz was calculated for time periods in which the pair of TCs displayed significantly coherent activity at this frequency.

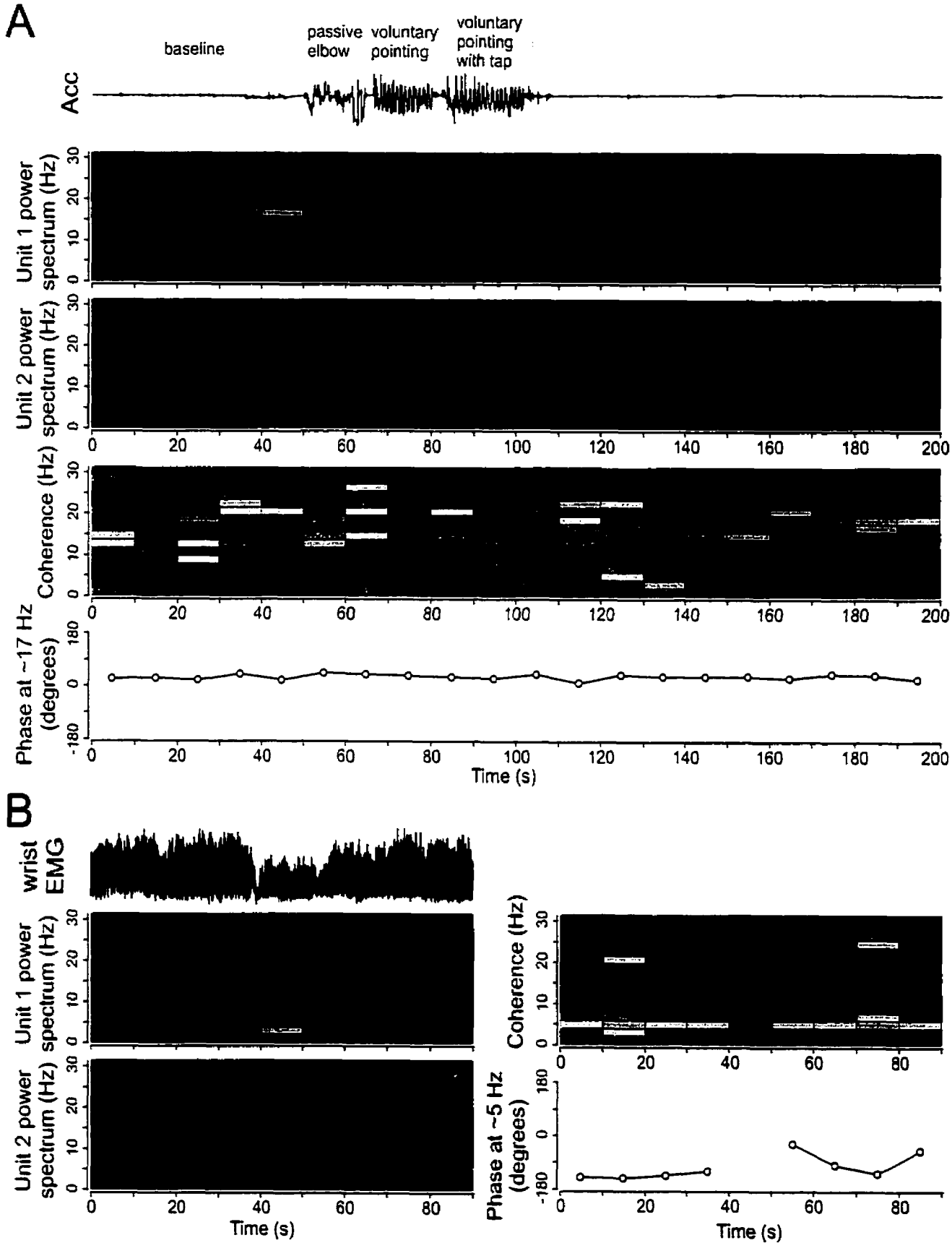

A
baseline
passive elbow
voluntary pointing
voluntary pointing with tap
Acc
Unit 1 power spectrum (Hz)
Unit 2 power spectrum (Hz)
Coherence (Hz)
Phase at ~17 Hz (degrees)
Time (s)
B
wrist EMG
Unit 1 power spectrum (Hz)
Unit 2 power spectrum (Hz)
Coherence (Hz)
Phase at ~5 Hz (degrees)
Time (s)

Figure 5.1.F4

**Figure 5.1.F5**

The central box shows a reconstruction of simultaneously recorded neuron pairs from 2 microelectrode tracks in a single patient (patient D). Pairs of neurons are denoted by their location along each track (track 1 x track 2). The meaning of the symbol shape and shading are indicated at the bottom. The strength of the high frequency component is: none = <6, weak = 6-7, strong = 8-10 (see Methods). This patient had a 4-5 Hz resting tremor in the hand and foot during these recordings. The first column of each pair of columns is the cross-correlogram and the second column is the corresponding coherence function (resolution 1.95 Hz, dashed line indicates significance level) between each pair of neurons. The numbers at top left of each pair of plots indicate the depth of the pair of neurons in track 1 and 2 respectively. The numbers in parentheses indicate sampling time in seconds. The numbers beside each significant peak in the coherence function indicate the phase difference in degrees.

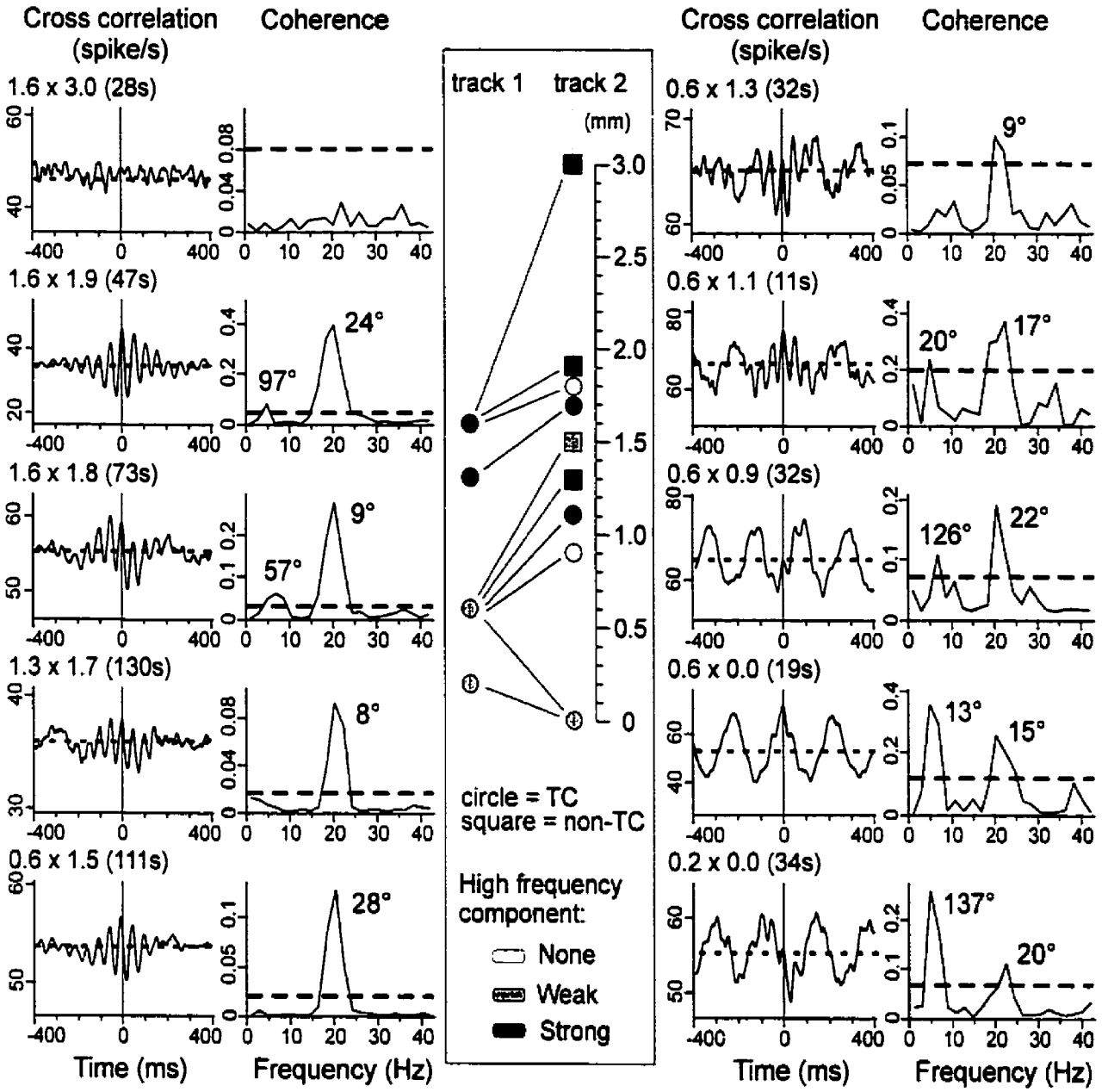

Cross correlation (spike/s)
Coherence
1.6 x 3.0 (28s)
1.6 x 1.9 (47s)
97°
24°
1.6 x 1.8 (73s)
57°
9°
1.3 x 1.7 (130s)
8°
0.6 x 1.5 (111s)
28°
Time (ms)
Frequency (Hz)
track 1
track 2
(mm)
circle = TC
square = non-TC
High frequency component:
None
Weak
Strong
Cross correlation (spike/s)
Coherence
0.6 x 1.3 (32s)
9°
0.6 x 1.1 (11s)
20°
17°
0.6 x 0.9 (32s)
126°
22°
0.6 x 0.0 (19s)
13°
15°
0.2 x 0.0 (34s)
137°
20°
Time (ms)
Frequency (Hz)

Figure 5.1.F5

### *5.1.4 - Discussion*

The existence of tremor related activity in the STN in some of the PD patients in this study supports previous findings by our group and others (Rodriguez et al. 1998; Hutchison et al. 1998a; Krack et al. 1998b). This study provides the first demonstration of neurons with high frequency oscillatory activity in the STN of PD patients and associates the synchronization of these neurons with TC activity and limb tremor. High frequency oscillatory activity was better detected from cross-correlograms or coherence functions than from auto-correlograms or auto- spectra suggesting that high frequency oscillatory behavior of the STN reflects population synchronization rather than individual neuron behavior. Our study found that the median discharge rate of cells with no rhythmic discharge was lower (43 Hz) than that for neurons with rhythmic discharge (53 Hz). This is opposite to the findings of Rodriguez et al. (1998) who reported that the mean firing rate for TCs was 25 Hz and 49 Hz for other neurons. However, data from the present study are consistent with findings from MPTP monkeys that indicate that there are differences in the spontaneous discharge rate of oscillatory versus non-oscillatory STN cells (Bergman et al. 1994). Following MPTP treatment in African green monkeys, there was an increase in the overall spontaneous discharge of STN neurons from 19 to 26 Hz while tremor related neurons showed an even more prominent increase in firing rate to 35 Hz. In addition, the mean firing rates of oscillatory neurons was greater than the firing rates of other neurons in all 3 parkinsonian monkeys. Our observations support the hypothesis that the STN is hyperactive in PD patients, especially those patients with significant limb tremor.

The relationship between oscillatory neural activity and limb tremor has been explored in various monkey species in which limb tremor is differentially present following MPTP treatment. In a study by Bergman et al. (1998b), neuronal oscillations in the GPi were synchronized and more in-phase in tremulous MPTP-treated vervet (African green) monkeys than in nontremulous parkinsonian rhesus monkeys (i.e. MPTP-treated rhesus monkeys display short episodes of 10-16 Hz postural/action tremor). Parkinsonian African green monkeys have a 3-5 Hz limb tremor that closely resembles that found in patients with PD. It has also been demonstrated that the induction of limb tremor in the MPTP African green monkey model not only brings about low frequency tremor related activity in the STN, but also high frequency oscillations in the frequency range of 8 to 20 Hz (Bergman et al. 1994). The present study supports these observations and further demonstrates that TCs and cells with high frequency oscillations in the STN of PD patients discharge in oscillatory synchrony. One caveat to this study is that the precise nature of the temporal relationship between limb tremor and high frequency synchronization was not ascertained. In some pairs of STN neurons in the "tremor" group, the appearance of limb tremor coincided with high frequency synchronization while others displayed increases in oscillatory synchronization when limb tremor was suppressed (see Figure 5.1.F3). However, there was a paucity of single neurons with oscillatory activity and no synchronous oscillations between pairs of STN neurons in the three patients that did not have significant limb tremor (45 neuron pairs examined). For the group of 9 patients the proportion of high frequency synchronized neuron pairs encountered during the stereotaxic mapping was correlated to the pre-operative UPDRS tremor score. Together these findings indicate that limb tremor and TC activity are

associated with synchronized high frequency oscillations. These results also imply that in those patients with rigidity or akinesia but little tremor, oscillatory synchronization is not an underlying factor. That is, different neuronal activity patterns at the level of the STN are present in PD patients expressing different clinical features. The present study also demonstrated that in each patient, not all STN TCs were coherent with each other and therefore supports the hypothesis that there are independent "tremor-generating" circuits in the basal ganglia (Alberts et al. 1965; Hurtado et al. 1999; Raethjen et al. 2000). Pairs of TCs were found to be coherent and out-of-phase at distances as small as ~250 um suggesting that each "tremor-generating" circuit could occupy a relatively small volume of the STN. Our finding of variability in phase differences over time between pairs of STN TCs is also consistent with the hypothesis that parkinsonian tremor is non-stationary (Bergman et al. 1998b; Hurtado et al. 1999).

The STN plays a central role in basal ganglia circuitry (Alexander and Crutcher 1990). In this study, no neuron pairs were found that displayed a single short latency peak in the cross-correlogram. This indicates that oscillatory synchronization is likely not due to intra-nuclear interactions as a result of recurrent collaterals (Kita et al. 1983) or possible interneurons (Rafols and Fox 1976) although the existence of interneurons in the STN remains unclear (Yelnik and Percheron 1979; Van Der Kooy and Hattori 1980; Ryan et al. 1992). The main difference between neural synchronization that occurred at the tremor frequency compared to high frequency synchronization was that all high frequency oscillatory activity was consistently in-phase and independent of the distance between recording sites. Pairs of neurons with high frequency oscillatory synchronization displayed constant phase differences over long sampling periods while

pairs of TCs did not. Also, the distribution of high frequency oscillations was tightly centered about a frequency that was unique to each patient. These findings imply that the underlying mechanisms of the two types of oscillatory synchrony are different. It is likely that the in-phase high frequency synchronization observed in the STN of PD patients is due to synchronous activity occurring in other areas. Two likely candidates are the GPe and the cerebral cortex, both of which send massive input to the STN (Carpenter et al. 1981; Canteras et al. 1990). These two areas are integral to cortico-striatal-GPe-STN-GPi ("indirect" pathway) and cortico-STN-GPi-thalamic circuitry, respectively (Alexander and Crutcher 1990).

The STN sends excitatory output to GPe and also receives GABAergic input from the GPe, and thus the GPe may provide feedback inhibition to the STN (Rouzaire-Dubois et al. 1980). It has been shown that the GPe influences the firing rate and discharge pattern as well as the degree of correlated firing of adjacent STN neurons in the rat (Ryan et al. 1992). In a study by Plenz and Kital (1999), evidence from *in vitro* rat organotypic brain slices of the STN and the GPe suggests that together these nuclei form a central pacemaker capable of sustained synchronous in-phase and out-of-phase oscillations. However, synchronized oscillations between STN neurons occurred at frequencies that were significantly lower (<4 Hz) than those reported in this study. Yet it was also demonstrated that a few GPe neurons have a considerable control over synchronized activity in the STN. It is therefore possible that synchronization could occur in the GPe or the striatum. It has also been shown that tonically active neurons (TANs; cholinergic interneurons) in the striatum of monkeys display synchronized high frequency oscillatory

activity (~15 Hz) following the depletion of dopamine due to MPTP treatment (Raz et al. 1996).

The STN receives a substantial excitatory glutamatergic input from the cortex (Rouzaire-Dubois and Scarnati 1985; Afsharpour 1985b) and it has been shown that neighboring STN neurons share common cortical inputs (Ryan et al. 1992). Furthermore, the increase in the firing rates of the STN in 6-OHDA treated rats is not solely dependent on GPe (Hassani et al. 1996) suggesting that direct cortico-subthalamic connections could be involved in the pathology of the parkinsonian STN. The response of the STN to cortical stimulation can be shaped by the GPe (Ryan and Clark 1991; Mouroux et al. 1995). The interaction between the STN and GPe is intimately related to cortical activity and rhythmic oscillatory activity in STN-GPe may be driven by cortex (Magill et al. 2000). Direct cortico-STN input can also modulate the inhibitory influence of the direct striato-nigral pathway on SNr neurons (Maurice et al. 1999). It is therefore possible that the source of the overt synchronization of high frequency activity in the STN of PD patients with limb tremor is due to disturbances in cortical synchrony. The involvement of the cortex in parkinsonian tremor has been well documented (Parker et al. 1992). Daffau et al. (1996) showed that during periods of limb tremor in PD patients, there were increases in the normalized regional cerebral blood flow in areas which were also modulated by voluntary repetitive arm movements. In patients with PD, cortical tremor related network oscillations have been observed using magnetoencephalography (Volkmann et al. 1996) and electroencephalography (Alberts et al. 1969). Disturbances in cortical synchronization of parkinsonian patients at frequencies other than limb tremor frequencies have also been reported (Makela et al. 1993; Neufeld et al. 1994; Brown and

Marsden 1999). These disturbances are hypothesized to result from the inability of the parkinsonian basal ganglia to release cortical elements from low frequency "idling" rhythms, such as alpha (~10 Hz) and beta (15-30 Hz), and allow for synchronization in the gamma range (30 to 50 Hz) (Brown and Marsden 1998).

In summary, highly synchronous in-phase oscillatory activity is present in the STN of PD patients with tremor predominant symptoms. Synchronized high frequency activity in the STN is likely involved in the pathophysiology of PD tremor and might in itself contribute to the expression of limb tremor.

## 5.2 - Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity


***Abstract***

It has been proposed that an increase in synchronization between neurons in the basal ganglia contributes to the clinical features of PD. To examine this hypothesis, we looked for correlations in the discharge activity of 163 pairs of neurons in the GPi, GPe, and the SNr. Recordings were performed in PD patients undergoing functional stereotactic mapping for pallidotomy (8 patients) or STN DBS (4 patients). A double microelectrode set-up was used to simultaneously record from neurons separated by distances as small as 250 um. In the 5 pallidotomy patients without limb tremor during the procedure, none of the 73 GPi pairs and 15 GPe pairs displayed synchronous activity. In the 3 pallidotomy patients with limb tremor, 6/21 GPi pairs and 5/29 GPe pairs displayed oscillatory synchronization in the frequency range of the ongoing limb tremor (3-6 Hz) or at higher frequencies (15-30 Hz). Synchronized activity was not observed in the SNr (10 pairs) and pallidal border neurons were not synchronized with each other or GP neurons (15 pairs). JPSTH analysis of pairs of GP neurons during a voluntary pointing task (7 pairs) or limb tremor (5 pairs) did not reveal synchronous spiking activity during any phase of these movements. These results indicate that neuronal synchronization is limited to tremor-related oscillatory activity and is not associated with the pathology that gives rise to akinesia or rigidity in patients with PD.

### *5.2.1 - Introduction*

Akinesia, limb tremor, and rigidity are the main motor symptoms of PD (Lang and Lozano 1998a) and have been associated with an excessive inhibition of thalamic motor and brainstem nuclei by the GPi, the major output nucleus of the basal ganglia (Miller and DeLong 1987; Albin et al. 1989a; DeLong 1990). In addition to an augmentation of GPi firing rates, monkeys rendered parkinsonian with MPTP display an increase in the bursting activity of GPi, GPe, and SNr neurons (Miller and DeLong 1987; Filion and Tremblay 1991; Boraud et al. 1998) that may be partially explained by the presence of tremor-related activity (Bergman et al. 1994; Wichmann et al. 1999). As demonstrated in the preceding section (Chapter 5, section 1), tremor-related periodic bursting or "oscillatory" activity is synchronized in the STN. The GPi receives substantial excitatory input from the STN (Parent and Hazrati, 1995a) and also displays synchronized oscillatory activity that is related to limb tremor (Nini et al. 1995; Bergman et al. 1998b; Raz et al. 1996, 2000; Hurtado et al. 1999).

However, the functional significance of the increase in aperiodic bursting in parkinsonism is unclear (Wichmann and DeLong 1996) and similar to oscillatory tremor-related activity may be due in part to an increase in synchronization between basal ganglia neurons (Vitek and Giroux 2000). Therefore, it was postulated that neurons in the GPi, GPe, and SNr might discharge in a temporally synchronous manner and that this population behavior would contribute to such non-tremulous symptoms as bradykinesia, akinesia or rigidity in patients with PD. To test this hypothesis, the degree of correlation was assessed between the discharge of pairs of neurons in these nuclei in patients with PD.

### *5.2.2 - Methods*

*Subjects*

Neurons were recorded during microelectrode guided placement of a unilateral pallidotomy (8 patients) or bilateral DBS electrodes in the STN (4 patients). The indications for pallidotomy were akinetic-rigid parkinsonian syndromes with fluctuating on-off periods and drug-induced dyskinesias (Lozano et al. 1996). Similarly, the indications for STN DBS were bilateral limb and axial manifestations of PD, medication-refractory motor fluctuations and drug-induced dyskinesias (Kumar et al. 1998b). All patients were studied during the stereotaxic surgery 12-14 hours after the last dose of anti-parkinsonian medication and all were typically akinetic/rigid with some patients displaying limb tremor (see Results). The patients had a mean age of 59 years (range 49–69) and the average duration of the disease was 14 years (range 7–20) at the time of operation.

*Recording procedure and apparatus*

Detailed descriptions of the use of microelectrode recording to localize the GPi are given in the General Methods (sections 2.1.1.a and 2.1.2) and to localize the STN are given in the General Methods (sections 2.1.1.b and 2.1.2). The simultaneous recording of neuron pairs is described in the General Methods (section 2.1.3). In this study, the mean number of action potentials recorded per cell was 6776±530 (SE) over an average sample time of 73±4.3 seconds (SE). Only well isolated single neurons recorded from different electrodes were examined.

*Data analysis*

Spontaneous ongoing discharge (tonic activity) analyzed in this study was collected with the patient at rest and without any passive joint manipulation or voluntary movements. Bursting discharge was quantified using the Poisson surprise method of burst detection as described in the General Methods (section 2.3.1). Time domain analysis of single-neuron discharge activity is described in the General Methods (section 2.3.2.a). Spectral analysis of single-neuron discharge activity is described in the General Methods (section 2.3.2.b). Time domain analysis of the discharge between two neurons employed the cross-correlation technique and is described in the General Methods (section 2.4.1). Spectral analysis of used the coherence technique. Coherence analysis was used to compare the linear correlation between two signals over a range of frequencies and is described in the General Methods (section 2.4.2).

The effects of voluntary movement on neuronal synchronization were assessed using JPSTH analysis which is described in the General Methods (section 2.4.1). For a voluntary task, patients performed chest to target reaching movements. Following a go cue indicated with a light, patients made three movements back and forth between their chest and a button board located ~50 cm in front of their chest. Patients were required to press 1 of 5 buttons (also indicated with a light) each time they reached the button board. The maximum distance between the furthest two buttons was 20 cm and the buttons were oriented in a horizontal row. Multiple trials were performed. Pairs of neurons were analyzed only if both neurons were modulated by voluntary movement. Synchronization between neuron pairs with tremor-related oscillations was also assessed using JPSTH

analysis by triggering off each cycle of the limb tremor (as detected with an accelerometer).

### *5.2.3 - Results*

There were 163 pairs of neurons recorded. Figure 5.2.F1 displays digitized parasagittal plates (Schaltenbrand and Wahren 1977) of the GP (top two rows of panels) and the SNr (bottom row of panels) to show the location of the microelectrode trajectories and to provide information about the neuronal activity and the locations of the simultaneously recorded neuron pairs in each patient. There were 3/8 pallidotomy patients and 3/4 STN DBS patients with limb tremor at the time of the recordings and oscillatory neuronal activity was limited to these patients. Examples of spike trains from 3 GPi neurons with oscillatory bursting discharge, aperiodic bursting discharge, and non-bursting discharge are shown in Figure 5.2.F2A. All three spike train segments (top, middle, and bottom) had similar firing rates (130, 111, and 124 spike/s) but differed in the percentage of spikes in bursts (25, 47, and 0 %). It can be observed that the bursts of spikes are periodic (~4 Hz) in the oscillatory bursting discharge example. The mean firing rate and percentage of spikes in bursts of single neurons in each nucleus is given in Figure 5.2.F2B. These mean firing rates of neurons in these nuclei were similar to those reported in other patient groups (Hutchison et al. 1994a, 1998a). The percentage of spikes in bursts in the GPi was also similar to that reported in another patient group analyzed in Chapter 3 (section 2) and was significantly lower than the percentage of spikes in bursts found in the GPe.

In the 5 non-tremulous patients, single GP neurons did not display oscillatory activity and all of the cross-correlograms in the GPe (15 pairs) and GPi (73 pairs) were flat. An example of cross-correlograms from 20 pairs of GPi neurons recorded from a single non-tremulous patient is displayed in Figure 5.2.F2C (this is the patient whose electrode tracks are shown in the top right panel of Figure 5.2.F1). The percentage of spikes in bursts of single GPi neurons in these pairs was 12.3% (±1.4 SE), similar to that found in the GPi of all pallidotomy patients. There were 15 pairs of neurons in which one or both neurons of the pair was a pallidal border cell (BOR, neurons located at the periphery of the pallidal segments (DeLong 1971)) and no synchronized activity was observed irrespective of whether the patient had limb tremor or not (7 BOR-GPi pairs, 6 BOR-GPe pairs, and 2 BOR-BOR pairs were studied). Synchronized activity was also not observed in the SNr (10 pairs). In the 3/4 patients who had limb tremor at the time of the SNr recordings (see Figure 5.2.F1), STN cells displayed synchronized oscillations at tremor frequency or 15-30 Hz.

In those pallidotomy patients (3 patients) with limb tremor during the microelectrode recordings, a majority of the cross-correlograms in the GPe (23/29 pairs) and GPi (15/21 pairs) were also flat. There were 12/41 GPi and 2/47 GPe single neurons (that were sampled from pairs) that displayed oscillations in the tremor frequency range (3-7 Hz). An example of a single GPi neuron that showed a strong coherence with resting tremor of the hand (as measured with an accelerometer) is shown in Figure 5.2.F3A. Coherence between the GPi neuron firing and the limb movement was limited to the period of time with limb tremor. All non-flat cross-correlograms between GP neuron pairs in tremulous patients were oscillatory (with the exception of one pair, see

below). Coherence analysis revealed that 5/6 pairs of GPi TCs displayed significant tremor-related synchronization. Neurons in each of these pairs were located 250-1000μm from one another. Two examples of tremor-related coherence are displayed in Figure 5.2.F3B (these are from the patient whose electrode tracks are shown in the top left panel of Figure 5.2.F1). Variable phase relationships (i.e. 0-180°) were observed between neurons with tremor frequency synchronization.

In one of the 3 tremulous pallidotomy patients, 1 pair of GPi neurons and 5 pairs of GPe neurons also displayed coherent high-frequency oscillatory activity. The mean frequency of the oscillatory synchronization was 20.6 Hz (range 19-22) with a mean absolute phase difference of 16.0° (range 3-35). Examples of high-frequency coherence in a pair of GPe and GPi neurons are shown in Figure 5.2.F3C. In the same patient, 1 pair of GPe neurons displayed an asymmetric trough in the cross-correlogram that was centred at ~2 ms, likely indicating a direct inhibitory connection from one neuron to the other (see Figure 5.2.F3D) (Perkel et al. 1967).

The effect of voluntary movement on simultaneous neuronal activity was assessed in 6 pairs of GPi and 1 pair of GPe neurons. Although all single neurons studied were modulated by the task, no coincident discharge activity between neurons was observed during any time period of the task (as ascertained by JPSTH analysis). Figure 5.2.F4A and 5.2.F4B shows an example of peri-stimulus time histograms and a JPSTH plot, respectively, for a pair of GPi neurons during the voluntary pointing task. Both neurons were modulated in a similar manner by the task (i.e. inhibition during arm extension to the button press). In the JPSTH plot displayed in Figure 5.2.F4B, activity related solely to the stimulus (JPSTH aligned to the button presses) appears as horizontal and vertical

bands while coincident spiking activity between the neuron pair, which would be observed as a diagonal band, is not observed. Similarly, JPSTH analysis of the 5 pairs of GPi neurons with tremor-related coherence did not reveal direct or indirect synchronized activity. Figure 5.2.F4C shows two GPi TCs (same pair as cell 1 x cell 2 in Figure 5.2.F3B). It can be observed that the out-of-phase oscillatory synchronization of these two TCs is not due to an inhibitory interconnection between the two neurons since there are no diagonal bands. For comparison, Figure 5.2.F4D shows the appearance of indirect and direct synchronization in a JPSTH plot of two thalamic neurons in a tremulous parkinsonian patient. There is a narrow diagonal band of increased point density located on the principal diagonal (the diagonal passing through the origin) that is indicative of a common excitatory input to both cells. Another diagonal band of decreased point density can be observed offset from the principal diagonal and indicates a direct inhibitory connection between the pair of neurons (i.e. neuron 2 synaptically inhibits neuron 1).

**Figure 5.2.F1**

Sagittal sections based on the Schaltenbrand and Wahren stereotactic atlas (standardized to the patients anterior-posterior commissural distance) displaying the microelectrode trajectories (dashed lines) and neuronal activity in the 12 patients (definitions of the symbols used are at the bottom of the figure). The distance from the midline is given in the upper right hand corner of each panel. The horizontal distance separating neurons in pairs recorded in the same trajectory has been slightly expanded for clarity (actually < 600 μm, see Methods). GPi = globus pallidus internus; GPe = globus pallidus externus; IC = internal capsule; OT = optic tract; STN = subthalamic nucleus; SNr = substantia nigra pars reticulata; H2 = Fields of Forel. Simultaneously recorded pairs of neurons are joined by lines. OT and IC responses were obtained using microstimulation.

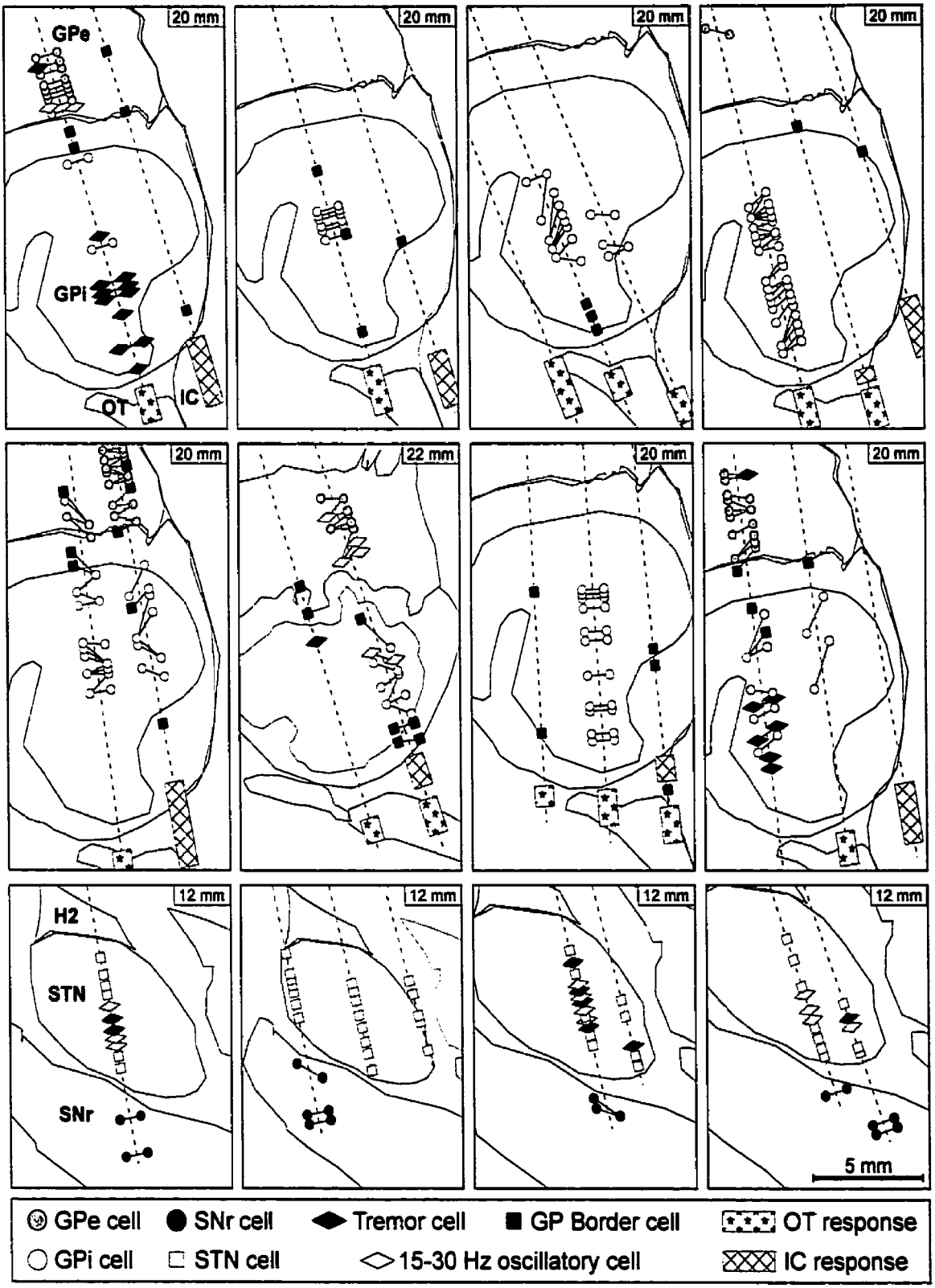

GPe
GPi
OT
IC
H2
STN
SNr
20 mm
22 mm
12 mm
5 mm
GPe cell
SNr cell
Tremor cell
GP Border cell
OT response
GPi cell
STN cell
15-30 Hz oscillatory cell
IC response

Figure 5.2.F1

**Figure 5.2.F2**

Patterns of neuronal discharge and an example of cross-correlograms in a non-tremulous patient. A: Examples of spike trains from 3 GPi neurons showing oscillatory bursting discharge, aperiodic bursting discharge, and non-bursting discharge (each action potential is represented by a vertical line). B: Mean firing rate and percentage of spikes in bursts (*$p<0.05$, ANOVA on Ranks). BOR = pallidal border cell. C: Example of cross-correlograms from 20 GPi pairs recorded in a non-tremulous patient (all correlograms were construct using 5 ms bins, normalized to baseline firing rate and scaled to the 99% CI).

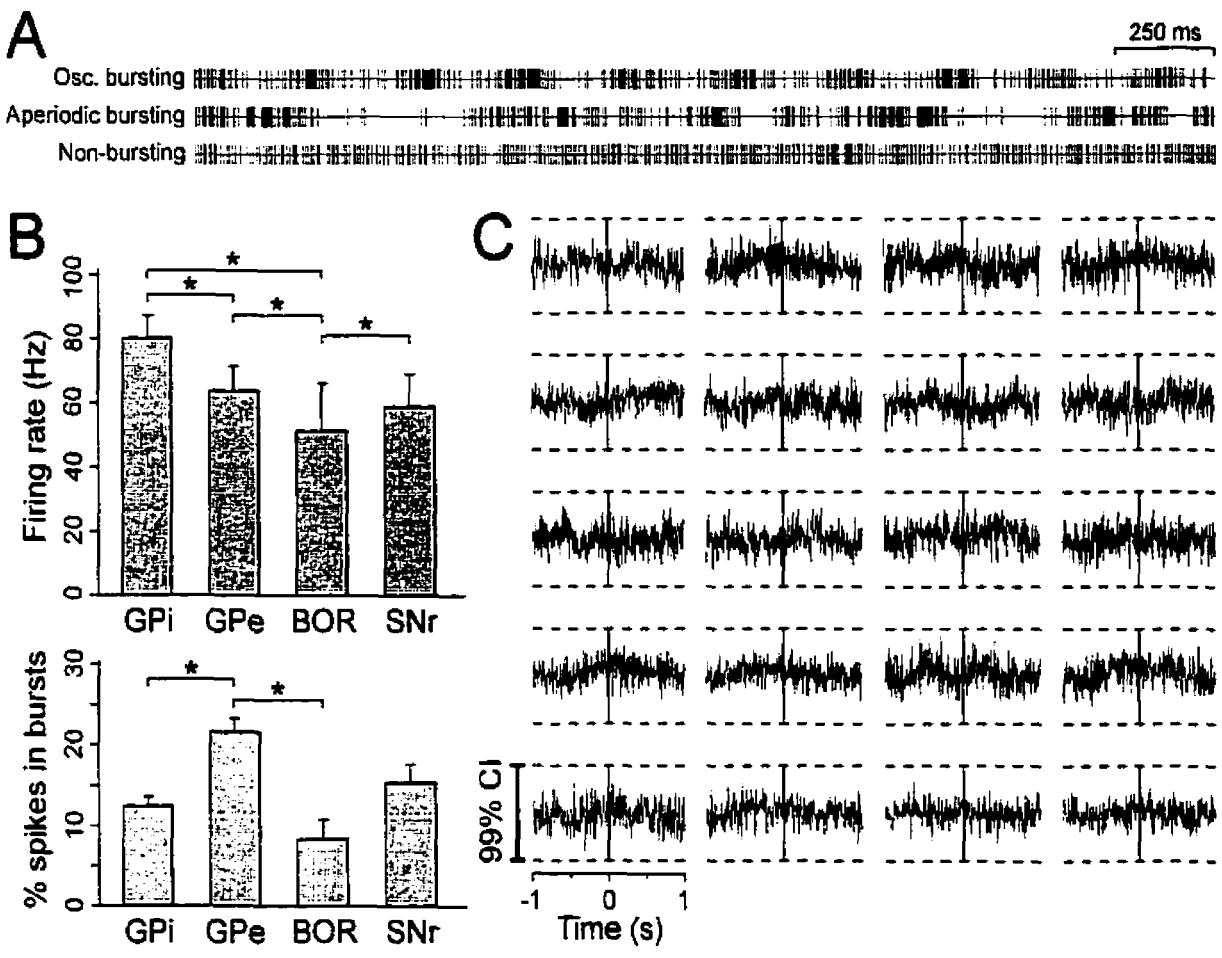

A
250 ms
Osc. bursting
Aperiodic bursting
Non-bursting
B
Firing rate (Hz)
0
20
40
60
80
100
GPi
GPe
BOR
SNr
% spikes in bursts
0
10
20
30
GPi
GPe
BOR
SNr
C
99% CI
-1
0
1
Time (s)

Figure 5.2.F2

**Figure 5.2.F3**

Synchronized activity between pairs of neurons in tremulous patients. A: Example of coherence between contralateral hand tremor (measured with an accelerometer, Acc) and GPi cell activity. The left panel shows the coherence during 30 s with no tremor and the right panel shows the coherence during a subsequent 30 s with limb tremor (0.98 Hz resolution, number beside peak is the phase difference in degrees, dashed horizontal line is $p<0.01$). B: Example of power spectra (insets) and coherence of 2 pairs of GPi TCs from a single patient (0.49 Hz resolution, calculated using 30 s of data for each pair, number beside peak is the phase difference in degrees, dashed horizontal line is $p<0.01$ for coherence). These plots demonstrate tremor-related synchronization and phase variability in the GPi of a tremulous patient. Neurons in each pair were separated by 250 μm and pairs were located ~200μm from one another. C: Examples of coherence plots showing high-frequency oscillatory synchronization in the GPe (left) and GPi (right) of a tremulous pallidotomy patient (calculated from 30 s of data, 0.98 Hz resolution, number beside peak is the phase difference in degrees, dashed horizontal line is $p<0.01$). D: A non-flat cross-correlogram in a tremulous pallidotomy patient that is indicative of an inhibitory connection between a pair of GPe neurons (0.5 ms bins, 7010x9252 events, horizontal lines indicate the 99% CI about the mean).

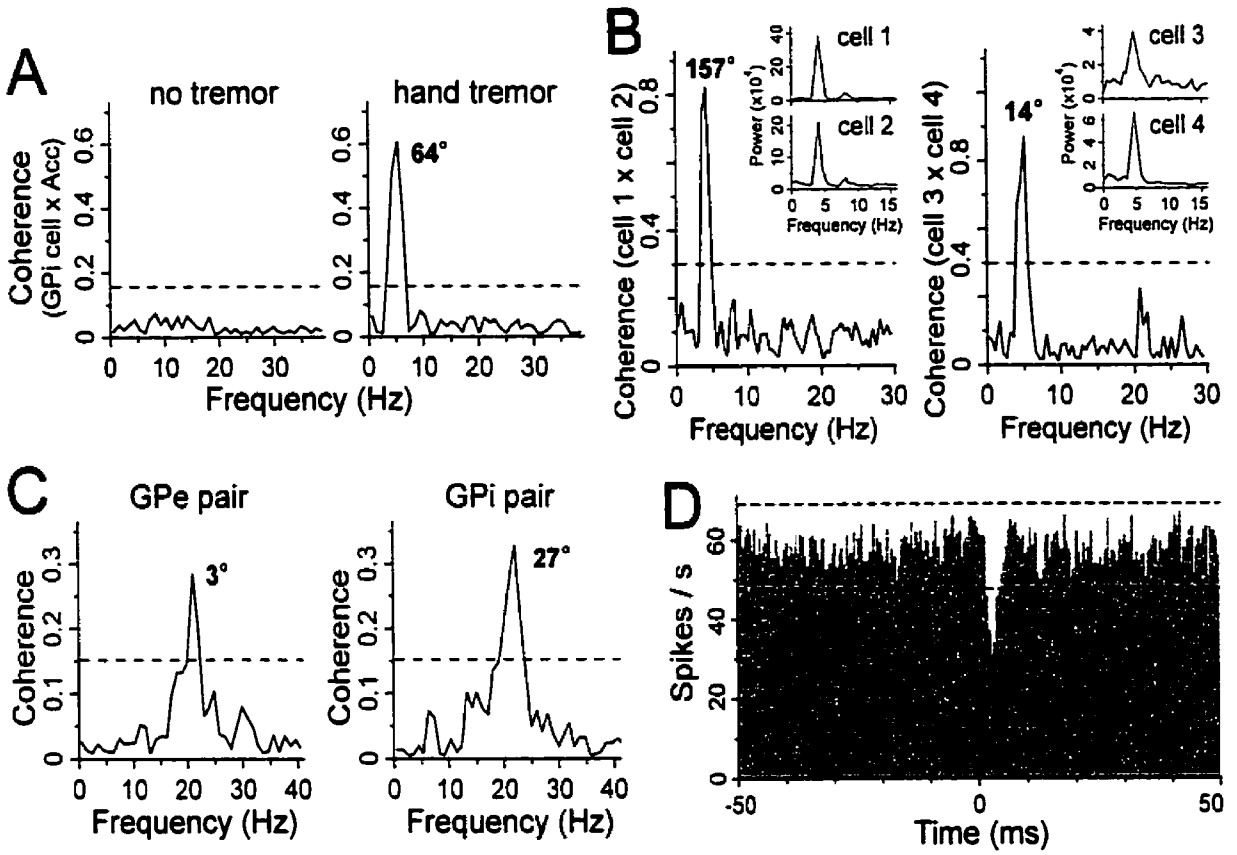

A
no tremor
hand tremor
64°
Coherence (GPi cell x Acc)
Frequency (Hz)
B
157°
cell 1
cell 2
Coherence (cell 1 x cell 2)
Power (x10⁴)
Frequency (Hz)
14°
cell 3
cell 4
Coherence (cell 3 x cell 4)
C
GPe pair
GPi pair
3°
27°
Coherence
Frequency (Hz)
D
Spikes / s
Time (ms)

Figure 5.2.F3

**Figure 5.2.F4**

The effects of voluntary movement and tremor activity on synchronization. A: The top trace is the voltage trace for the average button press. Twelve button presses were performed and all data was aligned to the beginning of the button press. The two peri-stimulus time histogram plots below demonstrated that both neurons were modulated by the task. B: The JPSTH plot of the pair of GPi neurons that are displayed in part A. The absence of diagonal bands indicates that the similar behavior of both these neurons is not due to coincident or synchronous spiking activity. C: A JPSTH of two GPi TCs (triggered off hand tremor, 10 s of tremor). Tremor-related oscillations appear as horizontal and vertical bands. No diagonal bands are present. D: A JPSTH plot (triggered off hand tremor, 30 s of tremor) of two ventral thalamic cells showing characteristic diagonal patterns of excitatory common input and neuron to neuron inhibition. Neuron 1 is a TC (note horizontal bands of increased point density). Compare with JPSTH plots in 5.2.F4B and 5.2.F4C.

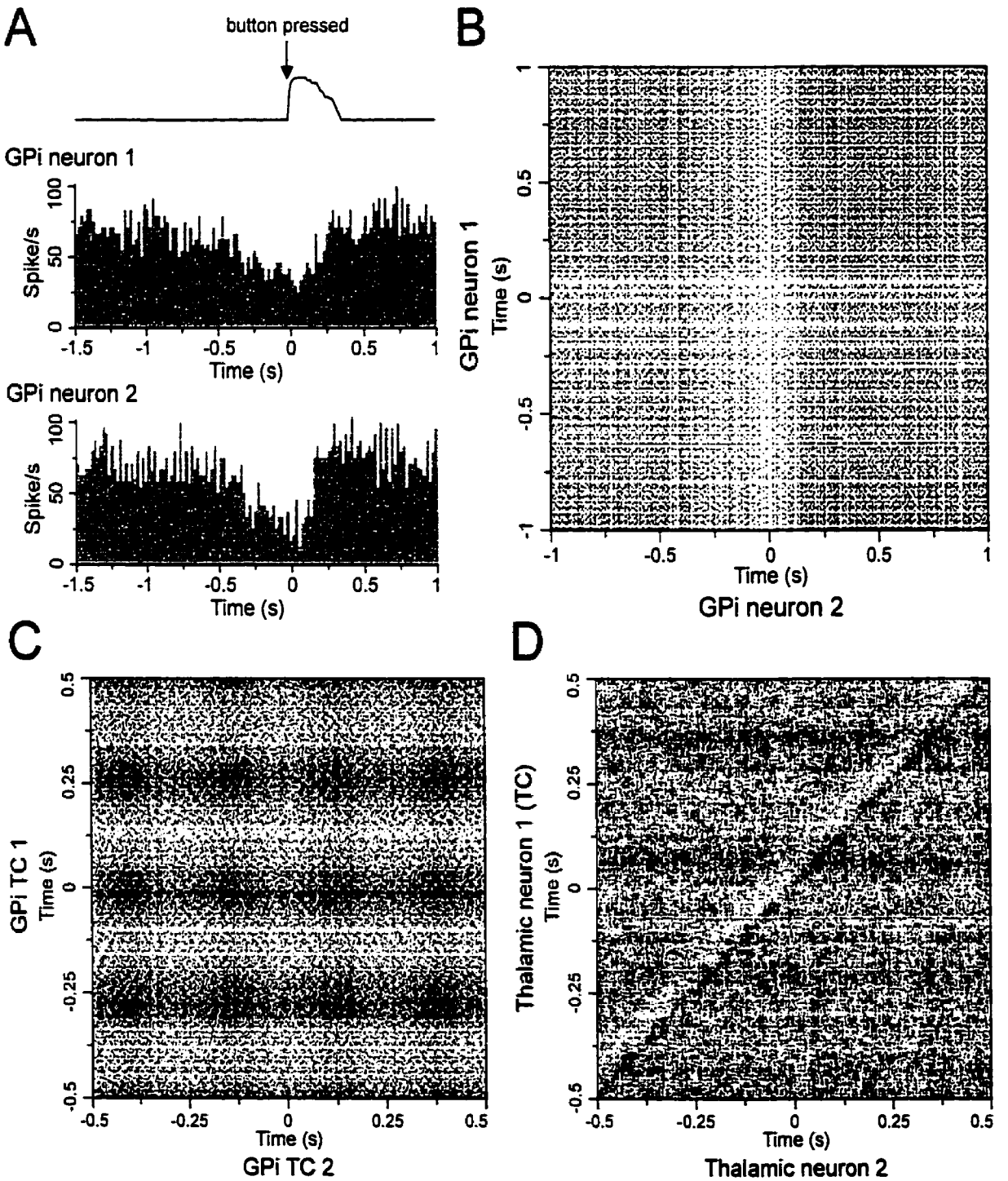

A
button pressed
GPi neuron 1
Spike/s
100
50
0
-1.5
-1
-0.5
0
0.5
1
Time (s)
GPi neuron 2
Spike/s
100
50
0
-1.5
-1
-0.5
0
0.5
1
Time (s)
B
GPi neuron 1
Time (s)
1
0.5
0
-0.5
-1
-1
-0.5
0
0.5
1
Time (s)
GPi neuron 2
C
GPi TC 1
Time (s)
0.5
0.25
0
-0.25
-0.5
-0.5
-0.25
0
0.25
0.5
Time (s)
GPi TC 2
D
Thalamic neuron 1 (TC)
Time (s)
0.5
0.25
0
-0.25
-0.5
-0.5
-0.25
0
0.25
0.5
Time (s)
Thalamic neuron 2

Figure 5.2.F4

### *5.2.4 - Discussion*

The loss of segregation hypothesis predicts that dopamine depletion in PD results in a breakdown of the independent activity in sub-circuits of the basal ganglia (Filion et al. 1994; Nini et al. 1995; Bergman et al. 1998a; Vitek and Giroux 2000). This study and the data concerning the STN from the preceding section (Chapter 5, section 1) demonstrate that in parkinsonian patients, discharge synchronization between pairs of neurons in the GPi, GPe, and STN is limited to oscillatory activity in patients with limb tremor and is indicative of common rhythmic drive to neuron pairs rather than to direct interaction between pairs of neurons in the basal ganglia. In all non-tremulous patients examined, synchronization was not observed and does not account for such clinical features as bradykinesia, akinesia, or rigidity. These results also indicate that the increase in the aperiodic bursting activity in the GPi, GPe, SNr, and STN in parkinsonism (Miller and DeLong 1987; Filion and Tremblay 1991; Bergman et al. 1994; Boraud et al. 1998; Wichmann et al. 1999) is not due to an increase in the synchronization of pairs of basal ganglia neurons. These conclusions are consistent with the findings of studies in monkeys that examined the simultaneous activity of pairs of GPi, GPe, STN, and striatal tonically active neurons and failed to find an increase in aperiodic synchronization following MPTP-induced parkinsonism (Bergman et al. 1994; Nini et al. 1995; Raz et al. 1996, 2000, 2001).

In only 1/44 pairs of GPe neurons was there evidence of a direct functional connection (inhibitory synaptic connection, see Figure 5.2.F3D). This observation is consistent with a recent study by Raz et al. (2000) in intact monkeys in which ~1% of the cross-correlograms of GPe neurons displayed a significant trough. It has been observed

that (GABAergic) GPe neurons emit short, intranuclear axon collaterals (Oertel et al. 1984; Smith et al. 1987; Sato et al. 2000) and could account for the observed inhibition in the cross-correlogram.

SNr neurons with oscillatory activity were not encountered in this study even though 3/4 patients displayed limb tremor and tremor-related oscillations were observed in the STN. This is consistent with the observation in MPTP-treated monkeys that tremor-related activity is not as prominent in the SNr as it is in the GPi or STN (Wichmann et al. 1999). In our experience in patients with PD, the proportion of TCs in the STN and GPi in tremulous patients is approximately equal (~20%) (see Chapter 3, sections 2 and 3), while the proportion of TCs in the SNr is considerably less (only ~2%) (same patient group as STN patients, unpublished observations). However, it is possible that differences in sampling (i.e. motor-related neurons in GPi versus non-motor related neurons in SNr) in parkinsonian patients might account for the lack of tremor-related oscillatory activity in SNr. The SNr neurons sampled in this study may not have been in the motor area of the SNr because this region is believed to be in the more intermediate and lateral portion of the nucleus (DeLong et al. 1983; Schultz 1986b; Hutchison et al. 1998a). It has also been suggested that the GPi contains a greater proportion of neurons with motor-related activity than the SNr and so the changes in discharge activity due to parkinsonism may be greater in the GPi than the SNr (Wichmann et al. 1999).

It is feasible that overt neuronal synchronization in parkinsonism is displayed during active or passive movements. It has been shown that after MPTP-treatment in monkeys, there is an increase in the number of GPi neurons responding to passive movement and neurons tend to display exaggerated responses and multi-limb receptive

fields (Filion et al. 1988; Boraud et al. 2000a), suggesting that dopaminergic mechanisms regulate gain and sensitivity in the basal ganglia. This idea is supported by evidence from parkinsonian patients in whom following the administration of APO, a smaller proportion of GPi and STN neurons respond to passive movements and with a greater selectivity to movements about individual joints (see Chapter 3, sections 2 and 3). In intact rhesus monkeys performing voluntary movements, less than 2% of cross-correlations of GPi neuron pairs display weakly significant cross-correlogram peaks during a spatial delayed release paradigm and these correlations are not found in any specific behavioural epoch (Nini et al. 1995). In the present study, by examining JPSTH plots for a voluntary task in which both neurons were modulated, it was demonstrated that there was no synchronization between the two neurons during the task. That is, no diagonal bands (parallel to the principal diagonal) were observed that would indicate shared input or direct synaptic interaction in some period during the movement (Gerstein and Perkel 1972). However, caution should be taken with this finding since the activity of relatively few pairs of pallidal neurons was examined (7 pairs), and it is possible that only a small population of pallidal neurons have synchronized activity during some phase of this task. Equivalently, it is possible that a different task might produce different results. Mushiake and Strick (1995) showed that GP neurons in normal monkeys encode the detailed spatio-temporal characteristics of a sequential movement since ensembles of GP neurons show phase-specific responses. It was suggested that these responses were acquired as part of the process of learning movement sequences and it was improbable that naive, untrained animals (or patients in this case), have a substantial number of pallidal neurons with phase-specific responses. Therefore, it might be more appropriate

to examine neuronal synchronization in more complex tasks or tasks involving a learned component.

The main limitation of this study is the possibility that cross-correlation between pairs of neurons cannot detect weak neuronal synchronization that might involve a larger population of neurons. For example, Brown et al. (2001) demonstrated that 15-30 Hz synchronization between the GPi and STN could be detected in parkinsonian patients by recording local field potentials in these nuclei. Another drawback of cross-correlation analysis is that it is less sensitive for inhibitory than it is for excitatory functional connectivity (of comparable strength) and therefore it is possible that some neuron to neuron inhibition would have failed to be detected using this technique (Aertsen and Gerstein 1985).

An obvious difference between studies comparing synchronization in MPTP-treated monkeys and patients with PD is that patients undergo chronic levodopa therapy over a number years and develop drug-induced dyskinesias (excessive abnormal involuntary movements) while parkinsonian monkeys are not treated with dopaminergic medication. It has been proposed that parkinsonian drug-induced dyskinesias and other involuntary hyperkinetic disorders such as dystonia and hemiballismus may result from increased synchronization in the GPi (Vitek and Giroux 2000). This is an attractive hypothesis because if tremor, dyskinesias, and co-contractions in dystonia are due to synchronization in the basal ganglia, then it is feasible that invasive surgical therapies such as lesions that act to reduce these involuntary movements (Lozano et al. 1997, 1998; Vitek et al. 1999) might do so by desynchronizing pathological neuronal activity in the basal ganglia-thalamo-cortical network (Bergman et al. 1998a; Deuschl et al. 2000). The

results of this study do not exclude this possibility and this idea should be explored in greater detail in MPTP-treated monkeys with drug-induced dyskinesias (Papa et al. 1999).

Our results of GPi TC synchronization are consistent with a previous report in a single tremulous parkinsonian patient and in studies in MPTP-treated monkeys with resting tremor and/or postural/action tremor (vervet versus rhesus monkeys) (Nini et al. 1995; Bergman et al. 1998b; Hurtado et al. 1999; Raz et al. 2000). The use of JPSTH analysis in this study revealed that tremor-related synchronization of GPi TCs is not due to common single afferent inputs or direct synaptic mechanisms between TCs. This study also described the novel finding of in-phase 15-30 Hz ("high-frequency") neuronal oscillatory synchronization in the pallidum of a patient with tremor and supports microelectrode findings in MPTP-treated vervet monkeys (Bergman et al. 1998b) and field potential analysis in parkinsonian patients (Brown et al. 2001). Our observations in the GPe are consistent with the demonstration in tremulous MPTP-treated monkeys that pairs of GPe cells exhibit high-frequency oscillatory synchronization with phase differences that are centered around 0 degrees (Raz et al. 2000) similar to the findings in the STN of tremulous parkinsonian patients that were reported in the preceding section (Chapter 5, section 1). It is likely that pallidal high-frequency oscillations are secondary to high-frequency oscillations transmitted via the cortico-STN pathway (Marsden et al. 2001). These observations suggest that the GPe-STN network (Plenz and Kital 1999; Magill et al. 2000) might be involved in maintaining in-phase high-frequency oscillatory synchronization in patients with limb tremor.

## 5.3 - Dependence of subthalamic nucleus oscillations on movement and dopamine in Parkinson's disease


***Abstract***

Pairs of neurons and local field potentials in the STN of patients with PD show synchronized high-frequency oscillations (HFOs) at 15-30 Hz. This study explores how these synchronized HFOs are modulated by voluntary movements and by dopaminergic medication. We examined 15 patients undergoing implantation of bilateral deep brain stimulating electrodes using microelectrode recordings of pairs of STN neurons (8 patients) and macroelectrode recordings of local field potentials from the STN (14 patients). Synchronized HFOs between STN neurons were observed in 28/37 pairs in 5 patients who had tremor in the operating room and 0/45 pairs in 3 patients who did not. Active movement suppressed synchronized HFOs in 3/5 pairs of neurons, independent of changes in firing rate. HFOs observed in the frequency spectra of local field potentials in 9/14 patients were reduced with voluntary movement in 6/8 patients tested. Dopaminergic medication decreased the incidence of synchronized HFOs in STN neuron pairs, reduced HFO synchrony in a pair of TCs concurrent with a reduction in firing rate and limb tremor, and decreased HFOs of local field potentials in the STN. These results demonstrate that HFO synchronization in the STN is reduced by voluntary movements and by exogenous dopaminergic medication. A mechanism for neuronal oscillatory synchronization in basal ganglia is proposed. It is suggested that the firing of STN neurons can be synchronized by 15-30 Hz cortical "idling rhythm" activity particularly when dopamine deficiency results in a higher background firing rate of STN neurons, and that this synchronization contributes to parkinsonian pathophysiology.

### *5.3.1 - Introduction*

Several lines of evidence indicate that the STN is involved in the pathogenesis of PD. Degeneration of the SNc and subsequent depletion of striatal dopamine and extrastriatal dopamine in MPTP-treated monkeys leads to the emergence of STN neurons with increased spontaneous activity and periodic bursting or "oscillatory" activity such as TCs (Bergman et al. 1994). Lesions or DBS of the STN dramatically reduce the symptoms of parkinsonism in MPTP-treated monkeys (Bergman et al. 1990; Benazzouz et al. 1993; Wichmann et al. 1994b; Guridi et al. 1996) and in patients with PD (Limousin et al. 1995b; Obeso et al. 1997a; Gill and Heywood 1997; Krack et al. 1998; Rodriguez et al. 1998; Kumar et al. 1998b).

Synchronous neuronal discharge oscillations in the cortex play an important role in normal motor processing and are associated with such functions as binding of neuronal activity in disparate motor areas, recruitment of motor-unit discharge, reduction of computational effort or processing load, and modifying motor states (Conway et al. 1995; Salenius et al. 1997; Baker et al. 1997, 1999; Volkmann 1998; Donoghue et al. 1998; Kilner et al. 2000). The STN receives a substantial excitatory glutamatergic input from the cortex (Rouzaire-Dubois and Scarnati 1985; Afsharpour 1985b) and motor-related cortical areas can modulate the activity of subthalamic efferent targets via the cortico-subthalamic pathway (Nambu et al. 2000). Furthermore, synchronous oscillatory activity in the STN-GPe network is intimately related to rhythmic cortical activity (Magill et al. 2000). Since the STN receives direct excitatory input from the primary motor cortex and the supplementary motor area (Nambu et al. 2000), it is likely that

voluntary movements which modulate oscillatory phenomena in the cortex (Crone et al. 1998; Pfurtscheller and Lopes da Silva 1999) might influence oscillatory synchronization in the STN.

It has been suggested that the STN might play a role in synchronizing oscillatory activity in the GPe (Plenz and Kital 1999) and the GPi (Wichmann et al. 1994b) and that an increase in 3-8 Hz oscillatory synchronization underlies the development of parkinsonian limb tremor (Nini et al. 1995; Bergman et al. 1998b; Hurtado et al. 1999; Raz et al. 2000). Recent reports have demonstrated that STN shows synchronized oscillatory activity at 15-30 Hz (Levy et al. 2000; Marsden et al. 2000; Brown et al. 2001). These synchronized "high-frequency" oscillations are closely associated with tremor-related neuronal activity in the basal ganglia of tremulous parkinsonian patients and MPTP-treated monkeys (Bergman et al. 1994; Levy et al. 2000; Raz et al. 2000). Dopaminergic medication has also been shown to modulate oscillatory activity in the STN and thus may play a role in the pathology of akinesia and rigidity, in addition to limb tremor, by affecting oscillatory synchronization in the basal ganglia (Allers et al. 2000; Levy et al. 2001; Marsden et al. 2001; Brown et al. 2001).

In the present study we used simultaneous microelectrode recordings of pairs of STN neurons and macroelectrode recordings of local field potentials in the STN to demonstrate that synchronous 15-30 Hz or "high-frequency" oscillations in the STN (Levy et al. 2000) are reduced by voluntary activity and dopaminergic medication. It is proposed that synchronous high-frequency oscillations in the STN are the result of rhythmic cortical input to the STN that is present when patients are at rest but not during

active movement and that this mechanism promotes synchronous oscillations in the basal ganglia-thalamo-cortical loop in the dopamine deficient state.

### *5.3.2 - Methods*

*Patient group*

Fifteen patients with PD participated in this study. The group consisted of 4 females and 11 males and at the time of operation had a mean age of 55 years (range 34-67). The average duration of the disease was 12 years (range 7-19). There were 5 who had a prior pallidotomy and 1 who had a prior thalamotomy. The mean time since these previous procedures was 44 months (range 24-74). All patients gave free and informed consent and procedures conformed to guidelines set down by Canadian Institute of Health Research policy on Ethical Conduct for Research Involving Humans.

*Microelectrode and macroelectrode recording procedures*

All 15 patients underwent microelectrode guided placement of bilateral DBS electrodes in the STN for the treatment of their parkinsonian symptoms. The localization procedure of the STN using microelectrode recording is described in the General Methods (sections 2.1.1.b and 2.1.2). There were 8 patients in whom pairs of STN neurons were recorded during the stereotaxic procedure using a dual microelectrode assembly. Recordings were performed in the "OFF" drug state (i.e. following a 12 hour holiday from parkinsonian medications). In one of these patients APO was administered at a dose determined during pre-operative assessment to provide significant motor benefit

and relief of limb tremor (see Chapter 3). Microelectrode recording procedures for neuron pairs have been described in the General Methods (section 2.1.3).

Bipolar "macroelectrode" recordings of field potentials in the STN were performed in 13 patients through adjacent contacts of the DBS leads between two and seven days after implantation. Macroelectrode recordings procedures of field potentials are described in the General Methods (section 2.1.4). In one other patient, simultaneous macroelectrode recording of field potential activity and microelectrode recording of single neuron activity was also performed during stereotactic mapping. This was accomplished by recording single neurons with a microelectrode (described in General Methods (section 2.1.3.a)) that was inserted in parallel with a macroelectrode cannula (described in General Methods (section 2.1.3.b)) at a center to center distance of 600 μm. Monopolar recording was performed through the exposed tip of the macroelectrode. Therefore, the total number of patients in whom macroelectrode recording of field potentials in the STN was obtained was 14.

*Task conditions*

Neuronal recordings during microelectrode surgery were performed with the patients at rest. Movement-related modulation of synchronous neuronal oscillations was examined by having four patients perform voluntary chest to target reaching movements. Following a go cue indicated with a light, patients made three movements back and forth between their chest and a button board located ~50 cm in front of their chest. Patients kept their hand at their chest until 1 of 5 buttons was lit, then reached out and pressed the button indicated and brought their hand back to their chest. There was a 2 second delay

between buttons being lit. The maximum distance between the furthest two buttons was 20 cm and the buttons were oriented in a horizontal row. Multiple trials were performed.

During the week following DBS insertion, macroelectrode recordings of field potentials were performed in all patients during the rest condition. Patients participated in as many trials of each voluntary activity as they wished, but tests were terminated if the patient became tired. Therefore not all tasks were tested in all patients. The length of each trial was 60 seconds. Patients performed maintained isometric contractions of the wrist extensors or self-paced hand tapping movements contralateral to the side of the macroelectrode recordings. Tasks were always alternated with trials in which macroelectrode activity was recorded with the patients at rest. In most cases spontaneous limb tremor was absent due to the acute subthalamotomy effects of the DBS electrode in the week following the stereotaxic procedure.

*Data analysis*

The analysis of the signals from the macroelectrode recordings is described in the General Methods (section 2.5). Spectral analysis of single-neuron discharge activity is described in the General Methods (section 2.3.2.b). Coherence analysis was used to compare the linear correlation between two signals over a range of frequencies and is described in the General Methods (section 2.4.2). Analysis of the task-dependent modulation of oscillatory neuronal discharge involved segmenting the discharge density waveform into 1.024 second non-overlapping windows. These windows had a fixed temporal relationship to the beginning of the voluntary movement as indicated with an accelerometer placed on the dorsum of the index finger or wrist extensor

electromyography (EMG). Application of a 1024 point fast Fourier transform then gave a frequency resolution of 0.98 Hz. Spectral estimates and coherence plots were derived from windows sharing the same relative time delay to the start of movement.

### *5.3.3 - Results*

*Neuron pair and field potential "high-frequency" oscillations (15-30 Hz) recorded during rest*

Synchronized 15-30 Hz oscillatory activity was observed in 28/82 pairs of neurons that were sampled in 8 patients. All 28 pairs were found in those patients with limb tremor in the operating room. Synchronized 15-30 Hz activity was present during time periods with limb tremor but also during some periods without any noticeable limb tremor. There was no effect of previous pallidotomy on synchronized activity in the STN. An example of intra-operative simultaneous microelectrode recordings of two STN TCs with high-frequency oscillations is shown in Figure 5.3.F1A. The corresponding frequency spectra of the neuronal firing and the coherence between these two signals are displayed below the two traces. Coherence between the oscillatory discharge of the two neurons is significant only for the high-frequency components ($p<0.01$).

Local field potential recordings were obtained from 14 patients. An example of a bipolar field potential recording between adjacent contacts of the DBS electrode is shown in Figure 5.3.F1B. In this example there was significant high-frequency activity centered at ~18 Hz ($p<0.01$). Field potential recordings revealed three characteristic spectra that are displayed in Figure 5.3.F2. Data from multiple trials are shown in the representative examples. Three patients had broad bandwidth oscillations in the macroelectrode

recordings centered between ~20-35 Hz (Figure 5.3.F2A). There were 11 patients who displayed significant low-frequency oscillations (lower than ~12Hz) (Figures 5.3.F2B and 5.3.F2C) and 6 of these patients also displayed a significant high-frequency component (Figure 5.3.F2C). The spectral profiles were always similar on both sides in 8 patients in whom bilateral recordings were performed. There were no obvious differences in the frequency spectra due to previous pallidal lesions when recordings from lesioned and non-lesioned sides were compared. The graphs at the bottom of Figure 5.3.F2 show that only the signal-to-noise ratio of the high-frequency oscillations were greatest at one pair of DBS contacts ($p<0.01$).

To examine the relationship between high-frequency oscillatory discharge recorded from single neurons and high-frequency oscillations in the field potentials, simultaneous microelectrode and macroelectrode recordings were performed in one patient (patient N). The tip of the microelectrode was located ~350 μm from the surface of the macroelectrode. As shown in Figure 5.3.F1C, the STN neuron recorded with the microelectrode had oscillations at tremor frequency (~5 Hz) and at 20 Hz (left plot). This patient was at rest but during the period of these recordings was experiencing bilateral limb tremor. The macroelectrode recording of the field potential had a high-frequency peak centered at ~20 Hz (middle plot). There was a striking coherence at ~20 Hz between the neuron and the macroelectrode recording and both these oscillatory signals were in-phase throughout the recording period (right plot).

Comparisons of intra-operative microelectrode data and intra/post-operative field potential activity (recorded with the patients at rest) were made in 7 patients and are shown in Table 5.3.T1. In the patients in whom pairs of single neurons showed a

significant high-frequency coherence (M, A, K, N), the signal-to-noise ratio of the high-frequency peak recorded with the macroelectrode was greater than in those patients who did not display high-frequency coherence between pairs of neurons (patients J, G, B). High-frequency neuron pair synchronization was consistently in-phase (maximum absolute phase difference was 30°) and occurred at frequencies that were similar to those from the macroelectrode recordings in patients A, K, and N. In patient M, the neuron pair oscillatory synchronization frequency was half of the frequency of that recorded from the macroelectrode recording.

*Voluntary movement suppresses neuron pair and field potential high-frequency oscillations*

Simultaneous microelectrode recordings were made from 5 pairs of STN neurons that displayed a modulation of their firing rates with voluntary movements in addition to displaying synchronized high-frequency oscillations. For 3 pairs, the synchronized high-frequency oscillatory activity between the pair of neurons was reduced during the period of voluntary movements. Two examples from separate patients are shown in Figure 5.3.F3 (right column vs. left column). Both of these patients performed chest to target reaching movements (see Methods). In Figures 5.3.F3A and 5.3.F3C, it can be observed that the spontaneous firing rate was decreased in three neurons and increased in the fourth (*$p<0.05$). Corresponding power spectra plots are displayed at the top and middle of Figures 5.3.F3B and 5.3.F3D and coherence plots are displayed at the bottom. High-frequency oscillations in all four neurons were reduced during the movement and high-frequency coherence between neuron pairs was only significant before and after the task.

The effects of voluntary movement on field potential oscillations were examined in 7 patients. Figure 5.3.F2 displays examples of movement-related suppression of high-frequency field potential activity. Data from multiple trials of each task are shown for these patients. It was consistently observed that high-frequency peaks were largest during the rest condition in all patients. In only those patients displaying both low and high-frequency oscillations (see Figure 5.3.F2C), sustained isometric contractions (patients M, I) or tapping (L, J, K) decreased high-frequency activity (five patients tested). Voluntary movement did not modulate the field potential spectra of those patients with only high-frequency oscillations (two patients tested, see Figure 5.3.F2A). In those patients displaying only low frequency oscillations, there was no noticeable effect of voluntary movement on frequencies below 12 Hz with one exception. In patient G, isometric contraction of the wrist extensors suppressed a discrete peak at 10 Hz (not shown). Although two of the patients with only low-frequency field potential oscillations (patients G, H) did not display statistically significant high-frequency activity, small high-frequency peaks can be observed and sustained contraction of the wrist extensor muscles did cause a clear and reproducible reduction of high-frequency activity (see Figure 5.3.F2B, alternate trials of rest versus contraction for patient H).

*Reduction of neuron pair and field potential high-frequency oscillations with dopaminergic medication*

The effects of dopaminergic medication were examined on neuron pairs in one patient and on field potential activity in another. Single neuron discharge oscillations were examined by administering APO to a patient while performing simultaneous

microelectrode recordings of neurons with synchronized high-frequency oscillations. The changes in firing rate and oscillatory activity of a pair of STN TCs with high-frequency oscillations following a subcutaneous injection of 6.5 mg of APO are displayed in detail in Figure 5.3.F4. In-phase coherent oscillations between the two neurons at their high-frequency components occurred throughout the OFF period (bottom two plots of Figure 5.3.F4B, $p<0.01$). In contrast, several periods without any coherence in the tremor frequency range were observed during this time (i.e. before ~500 seconds). Following APO administration, there was a decrease in the firing rates of both neurons concurrent with a loss of limb tremor and the patient reported that he felt the effects of medication (Figure 5.3.F4A). It can be observed that a decrease in high-frequency oscillations and a loss of synchronization precede the effect of APO on firing rates and was maintained during the period of recording when the patient was "ON". High-frequency synchronization was not present during the ON period. Figure 5.3.F5 shows coherence plots of other neuron pairs in this patient recorded before and after APO administration. Before the administration of APO (non-medicated or "OFF" state), three pairs of TCs displayed high-frequency synchronization (Figure 5.3.F5A). In 4 pairs of neurons recorded 15-29 minutes after APO administration, only 1 pair showed high-frequency coherence (Figure 5.3.F5B). All pairs recorded before and after APO were located less than 2 mm from one another.

Field potential recordings were made in one patient (patient H, see Figure 5.3.F2B) before and after levodopa administration and are shown in Figure 5.3.F5C. High-frequency activity was observed in the OFF state but was not present in the levodopa-induced ON state. Isometric wrist extensor contraction reduced high-frequency

activity in the OFF state (2 alternate trials with rest condition shown).

**Figure 5.3.F1**

Examples of an intra-operative recording from a pair of microelectrodes (A), a post-operative recording from a DBS electrode (B), and the spectral analysis of an intra-operative simultaneous recording from microelectrode and a macroelectrode (C). The dashed line in the plots represents the significance level for the power spectra estimates ($p<0.01$) and for the coherence function ($p<0.01$). The number beside the peak in the coherence spectrums is the phase difference in degrees. A: Raw traces of extracellular microelectrode recordings of two simultaneously recorded STN TCs with high-frequency oscillations. The tips of the two microelectrodes were separated by 670 μm. The frequency spectrum of the neuronal oscillatory discharge and the corresponding coherence function are shown below (1.95 Hz resolution). Spectra and coherence were calculated over a 10 second interval that included the period shown in the recordings. B: A segment of a bipolar recording of STN field potentials from a pair of DBS contacts (low pass filtered below 55 Hz). The frequency spectrum of this signal is shown to the right (0.78 Hz resolution) and was calculated from 10 seconds of data containing this segment. C: Simultaneous microelectrode and macroelectrode intra-operative recordings in patient N. The tips of the electrodes were positioned 2 mm within the dorsal border of the STN. The left and middle plots show the power spectrums (0.98 Hz resolution) for the single STN neuron recorded with the microelectrode and a monopolar field potential recorded through a 30 gauge cannula, respectively (see Methods). The right plot shows the coherence between the two signals. Spectra and coherence were calculated over a 70 second period. Coherence between the macroelectrode recording and the single unit was limited to the high frequency component of each signal.

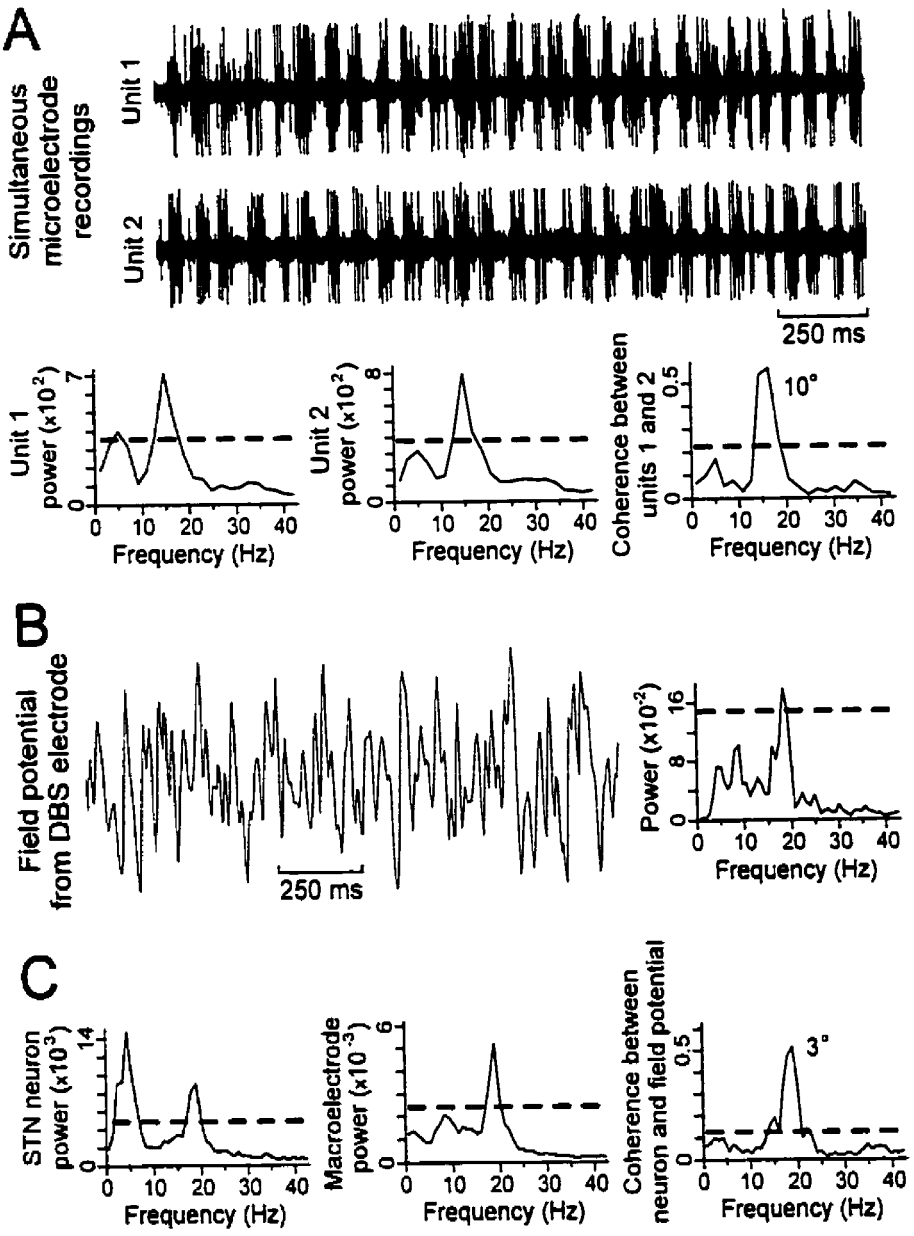

A
Simultaneous microelectrode recordings
Unit 1
Unit 2
250 ms
Unit 1 power (x10$^{-2}$)
Unit 2 power (x10$^{-2}$)
Coherence between units 1 and 2
10°
Frequency (Hz)
B
Field potential from DBS electrode
250 ms
Power (x10$^{-2}$)
C
STN neuron power (x10$^{-3}$)
Macroelectrode power (x10$^{-3}$)
Coherence between neuron and field potential
3°

Figure 5.3.F1

**Figure 5.3.F2**

Representative examples of STN field potential spectra recorded from two patients displaying only high-frequency oscillations (A), only low-frequency oscillations (<12 Hz) (B), and significant low and high-frequency field potential oscillations (recorded during rest) (C). High-frequency field potential activity was reduced by voluntary movements (tapping or sustained isometric contraction of wrist extensors) only in patients displaying spectra with both low and high-frequency activity. Labels in each graph such as "left 01" indicate that bipolar recordings of the field potentials were performed between contact 0 and contact 1 of the left STN. The dashed horizontal line in each graph represents the upper bound for a 99.8% confidence interval with respect to the mean spectral noise (calculated between 0-55 Hz from the recordings performed with the patients at rest). Spectral estimates above this line indicate statistically significant frequencies. PAL = previous pallidotomy; THAL = previous thalamotomy. The two graphs located at the bottom of the figure demonstrate that the signal-to-noise ratio of the high-frequency (left graph) and low frequency (right graph) peaks recorded from the DBS contacts when the patients were at rest was greatest at one pair of contacts (all recorded sides shown). Values from the same DBS electrode are joined by a line and multiple trials were averaged. Data was aligned with respect to the location of the greatest signal-to-noise ratio from each side. The mean signal-to-noise ratio is indicated by a filled circle (*$p<0.05$, One way ANOVA). The relative distance between the bipolar recordings from adjacent DBS contacts was 3 mm.

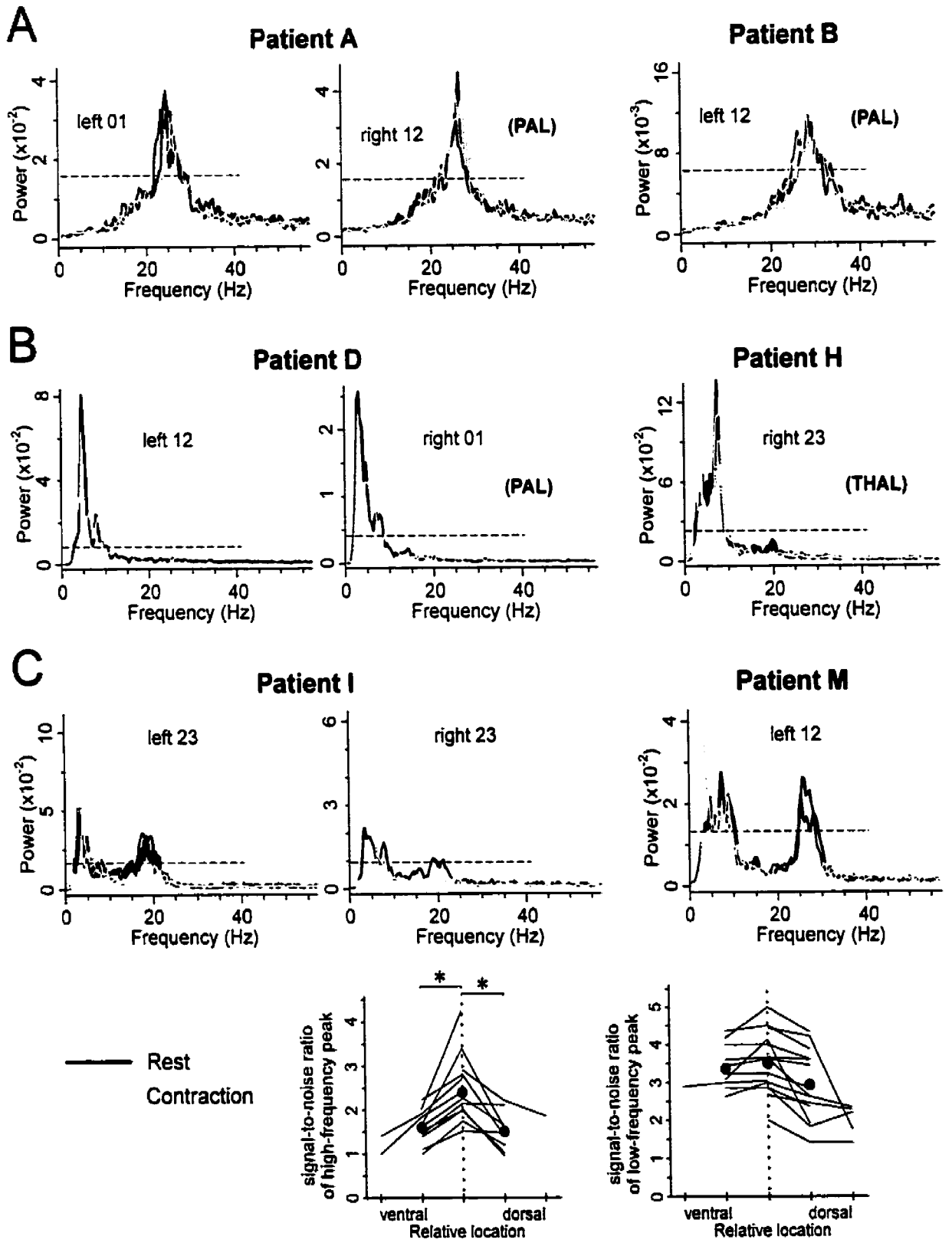

A
Patient A
left 01
right 12
(PAL)
Patient B
left 12
(PAL)
Power (x10-2)
Power (x10-3)
Frequency (Hz)
B
Patient D
left 12
right 01
(PAL)
Patient H
right 23
(THAL)
C
Patient I
left 23
right 23
Patient M
left 12
Rest
Contraction
signal-to-noise ratio of high-frequency peak
signal-to-noise ratio of low-frequency peak
ventral
dorsal
Relative location

Figure 5.3.F2

**Table 5.3.T1**

§The label in the parenthesis indicates the side and DBS contacts used for the macroelectrode recordings (see Methods). *Values in parenthesis indicates the frequency range given by width of peak at half the maximum peak value. †Monopolar macroelectrode recording performed intra-operatively in this patient only and patient was OFF medication. ‡Macroelectrode recordings were not available on the side where single unit pairs recorded, peak frequencies from the other side are reported.

*The relationship between high-frequency activity from microelectrode and macroelectrode recordings*

| Patient | Neuron pairs with high frequency synchronization / total pairs sampled | Mean synchronization frequency of STN neuron pairs (±SE) | Signal-to-noise ratio of high-frequency peak in macroelectrode recordings § | Mean frequency of the high-frequency field potential oscillation from the macroelectrode recordings * |
|---|---|---|---|---|
| J | 0/28 (right side) | - | 1.7 (right12) | 23 Hz (18 - 26) |
| G | 0/5 (left side) | - | - | non-significant |
| B | 0/8 (right side)<br>0/4 (left side) | - | 2.1 (right 12)<br>2.3 (left 12) | 32 Hz (25-40)<br>29 Hz (23-35) |
| M | 5/6 (right side) | 15.7±0.3 Hz | 2.5 (right 23) | 27 Hz (24-30) |
| A | 5/10 (right side) | 23.6±0.4 Hz | 2.9 (right 12) | 26 Hz (23-29) |
| K‡ | 6/8 (right side) | 21.3±0.5 Hz | 3.4 (left 12) | 18 Hz (15-21) |
| N† | 9/10 (left side) | 19.6±0.1 Hz | 5.8 (left) | 19 Hz (18-20) |

Table 5.3.T1

**Figure 5.3.F3**

The suppression of synchronized high-frequency oscillations of pairs of STN neurons during voluntary pointing movements in two patients (right column vs. left column). Data were calculated with respect to the onset of movement (0 seconds in plots, see Methods). The top trace of both columns is the rectified and averaged accelerometer signal (Acc). A, C: Plots of the mean firing rate of each neuron (1.024 s bins, ±SE). The patient whose data are displayed in the left column performed 15 trials of the task and the patient whose data are displayed in the right column performed 8 trials of the task. The firing rates of all four neurons were modulated by the movement (*$p<0.05$, ANOVA, versus discharge from 5.12 to 0 seconds before the onset of movement). B, D: Time-frequency plots of the spectra of each neuron (top and middle) and the coherence between them (bottom, 1.024 s bins). Both pairs of neurons displayed a movement related desynchronization and post-movement synchronization of their high-frequency oscillations (i.e. significant coherence before and after the movement). The legends for these plots are located at the bottom of each column.

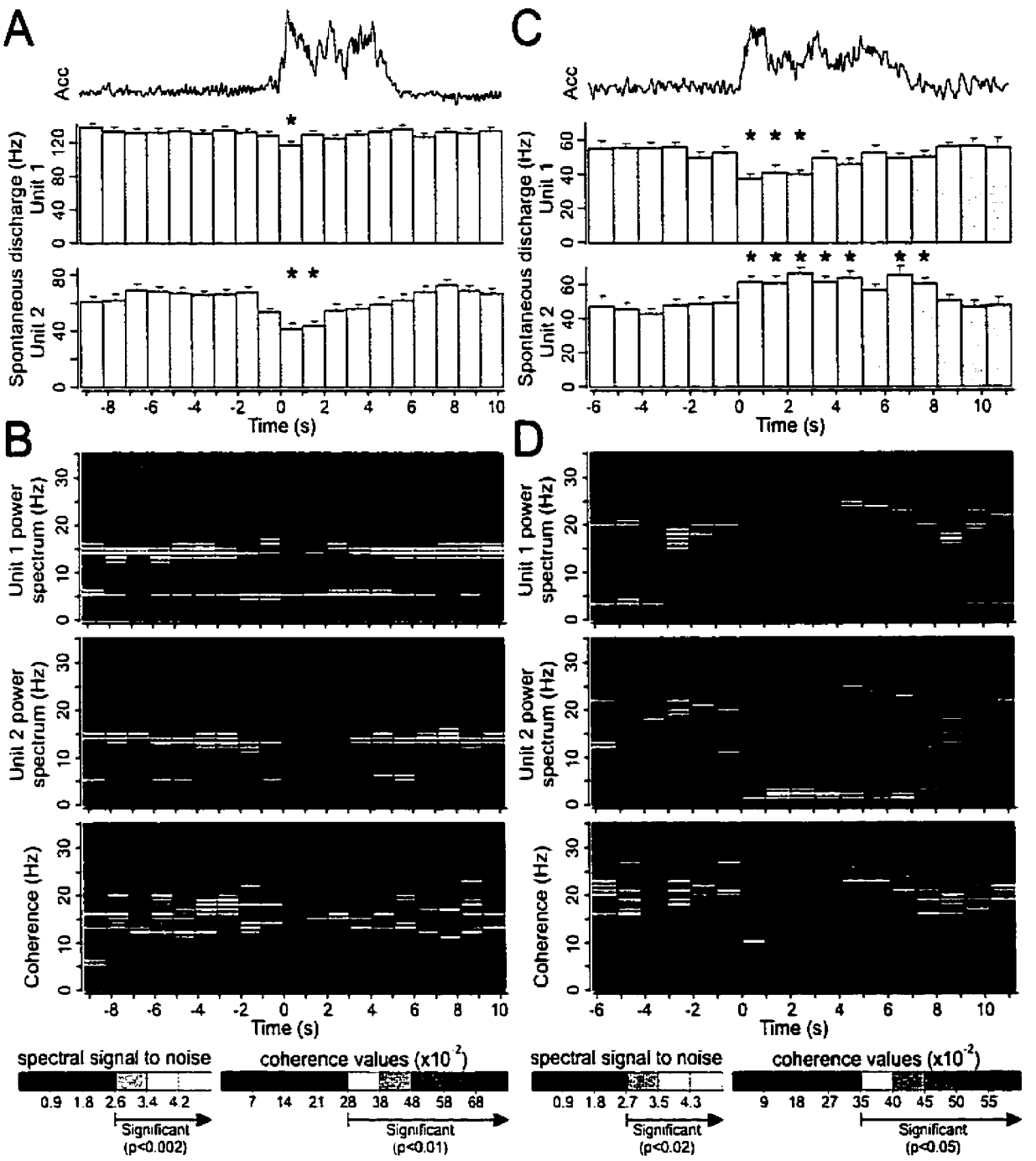

A
Acc
Spontaneous discharge (Hz)
Unit 1
Unit 2
Time (s)
C
B
D
Unit 1 power spectrum (Hz)
Unit 2 power spectrum (Hz)
Coherence (Hz)
spectral signal to noise
coherence values (x10 -2)
0.9 1.8 2.6 3.4 4.2
Significant (p<0.002)
7 14 21 28 38 48 58 68
Significant (p<0.01)
0.9 1.8 2.7 3.5 4.3
Significant (p<0.02)
9 18 27 35 40 45 50 55
Significant (p<0.05)

Figure 5.3.F3

**Figure 5.3.F4**

The effect of APO administration on neuronal activity of a pair of STN TCs with high-frequency oscillations. A: Histograms of the firing rate of the pair of STN neurons (10 second bins) demonstrate that APO reduced the spontaneous discharge of the two neurons. B: Abolition of high-frequency synchronization of the same pair of STN TCs following the administration of APO. The top two panels show the power spectra (1.95 Hz resolution) over the same time period and bin size as the firing rate histograms in part A. Both neurons displayed tremor-related activity and high-frequency oscillations before the administration of APO. The third plot shows the coherence between the oscillatory activity of the two neurons. The bottom panel is the phase of significantly coherent oscillations at tremor frequency (~5 Hz) and at high frequency (~15 Hz).

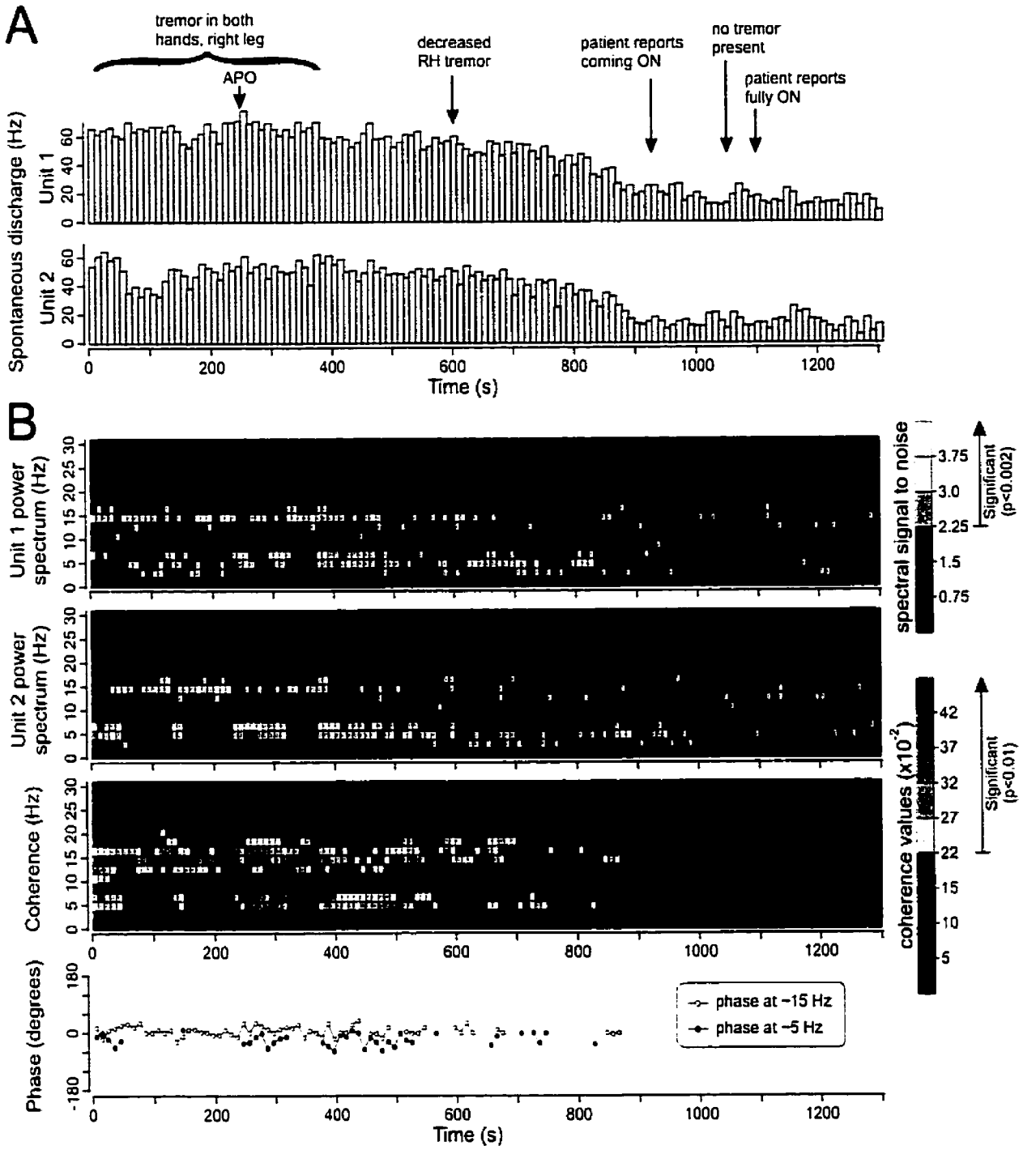

A
tremor in both hands, right leg
APO
decreased RH tremor
patient reports coming ON
no tremor present
patient reports fully ON
Spontaneous discharge (Hz)
Unit 1
Unit 2
0 20 40 60
0 200 400 600 800 1000 1200
Time (s)
B
Unit 1 power spectrum (Hz)
Unit 2 power spectrum (Hz)
Coherence (Hz)
Phase (degrees)
0 5 10 15 20 25 30
180
0
-180
spectral signal to noise
3.75
3.0
2.25
1.5
0.75
Significant (p<0.002)
coherence values (x10^-2)
42
37
32
27
22
15
10
5
Significant (p<0.01)
phase at -15 Hz
phase at -5 Hz
0 200 400 600 800 1000 1200
Time (s)

Figure 5.3.F4

**Figure 5.3.F5**

Dopaminergic modulation of high-frequency synchronized oscillations in neuron pairs recorded before (A) and after (B) APO administration and in field potential activity in another patient (C). A: Coherence plots (0.98 Hz resolution) of 3 pairs of STN neurons recorded before APO administration. All neurons displayed tremor-related activity and 2 pairs (right and left plots) were synchronized in the tremor frequency range (~3-8 Hz). The dashed line in the plots is the significance level for the coherence function ($p<0.01$). The number beside the peaks is the phase difference in degrees. All neuron pairs in parts A and B were sampled for 3 minutes. B: Coherence plots of 4 pairs of STN neurons recorded after APO administration when the patient was "ON" (the time of recording after APO dosing is indicated above each plot). C: Effect of levodopa on high-frequency field potential signals recorded from patient H. The high-frequency oscillations recorded during the OFF levodopa state were localized to the dorsal contacts of the DBS electrodes. Note the reduction of high-frequency activity during the levodopa-induced ON period or with contraction in the OFF state (2 alternate trials of 60 seconds each).

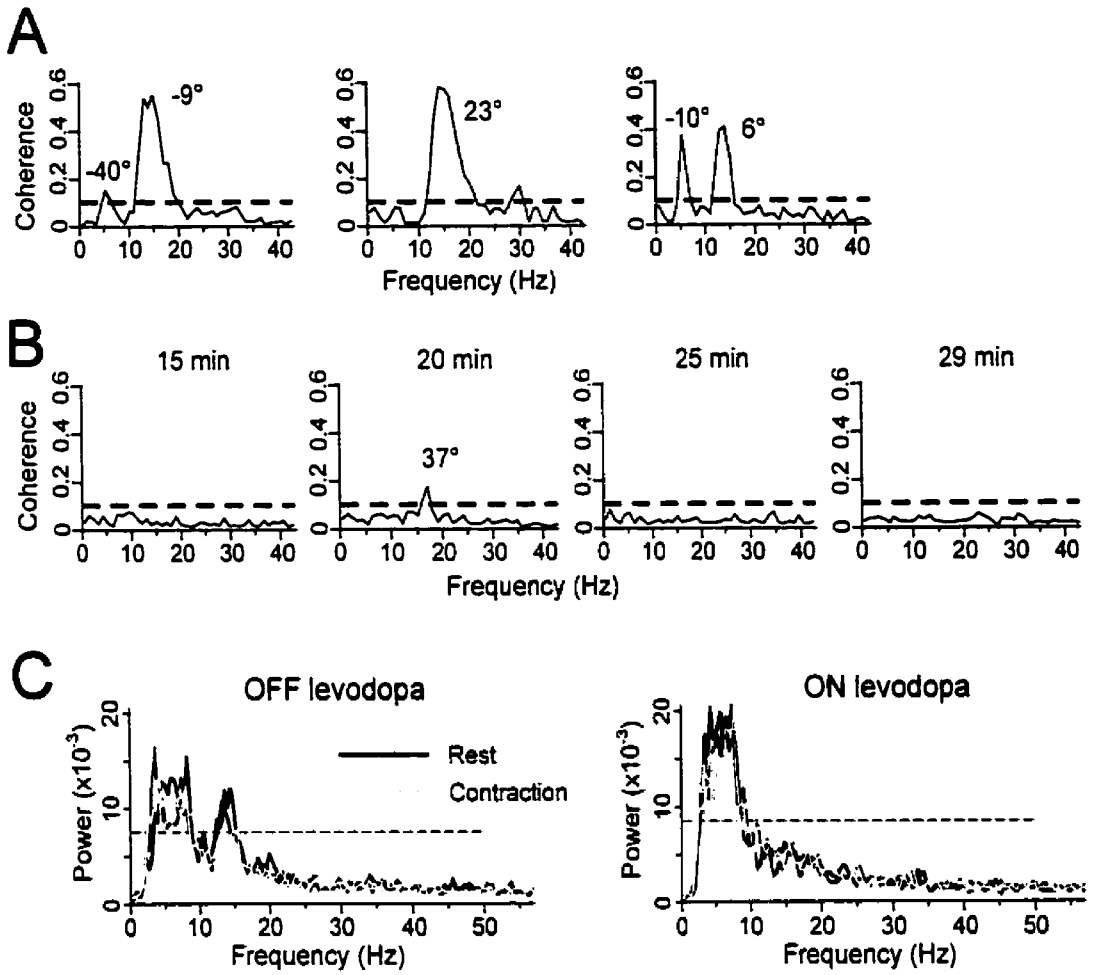

A
Coherence
-40°
-9°
23°
-10°
6°
Frequency (Hz)
B
15 min
20 min
25 min
29 min
37°
Coherence
Frequency (Hz)
C
OFF levodopa
ON levodopa
Rest
Contraction
Power (x10⁻³)
Frequency (Hz)

Figure 5.3.F5

### *5.3.4 - Discussion*

This study demonstrates that the 15-30 Hz local field potential activity that can be recorded from the contacts of DBS electrodes in STN (Brown et al. 2001; Marsden et al. 2001) is the result of in-phase synchronous 15-30 Hz oscillatory discharge activity in STN neurons. Similar observations between neurons with oscillatory synchronization and local field potentials have been made in the sensorimotor cortex of monkeys (Murthy and Fetz 1996b). In addition, our results indicate that these synchronous high-frequency oscillations are reduced by voluntary movements. The suppression of STN single unit high-frequency oscillatory discharge with movement occurred independently of increases or decreases in firing rate suggesting that the modulation of high-frequency activity reflects a change in the pattern of input to the STN. Our observations of the reduction of 15-30 Hz field potential oscillations in the STN during voluntary movement (6/8 patients in total) support and complement the findings of Brown et al. (2001) who reported that the 15-30 Hz coherence between STN and GPi local field potentials is not as high during tonic contractions as during rest.

Cortical input to the STN (Monakow et al. 1978; Carpenter et al. 1981; Afsharpour 1985b; Rouzaire-Dubois and Scarnati 1985; Canteras et al. 1990) from the primary motor cortex and the supplementary motor area is somatotopically arranged (Nambu et al. 1996) and many STN neurons display both tremor and voluntary movement-related activity suggesting that there is sensory-motor convergence within the STN (Magarinos-Ascone et al. 2000). Short latency cortical input is relayed by the STN to other basal ganglia nuclei (Wichmann et al. 1994a; Nambu et al. 1996; Levy et al. 1997; Nambu et al. 2000; Magill et al. 2000). The STN can strongly influence neuronal

activity in the basal ganglia (Carpenter and Strominger 1967; Smith et al. 1990; Hamada and DeLong 1992a; Hazrati and Parent 1992; Parent and Hazrati 1995a; Ni et al. 2000) and plays a role in synchronizing oscillatory population behavior (Wichmann et al. 1994b; Plenz and Kital 1999; Brown et al. 2001). Similar to our results in the STN, comparable changes in cortical rhythms during voluntary movements are also observed. The 15-30 Hz cortical beta sensorimotor oscillation is called an "idling rhythm" because it is observed during periods of rest and is suppressed during tasks activating the sensorimotor cortex (Pfurtscheller 1981; Salmelin and Hari 1994; Pfurtscheller et al. 1996; Crone et al. 1998; Pfurtscheller and Lopes da Silva 1999). Therefore, it is possible that the synchronous 15-30 Hz STN oscillations observed in this study are due to cortical beta idling rhythm input transmitted via the cortico-subthalamic pathway.

It has been hypothesized that the cortico-subthalamic pathway synchronizes oscillatory activity in the basal ganglia (Bergman et al. 1994; Wichmann et al. 1994b; Hurtado et al. 1999; Magill et al. 2000; Deuschl et al. 2000) and that a high level of oscillatory synchronization of the whole basal ganglia in the parkinsonian state underlies the clinical features of PD (Raz et al. 2001). An association between the cortical idling rhythms and basal ganglia function has previously been demonstrated by Brown and Marsden (1998, 1999) wherein they suggested that akinesia and bradykinesia were due to an inability of the parkinsonian basal ganglia to release cortical elements from alpha (~10 Hz) and beta rhythmic idling activity during voluntary movement. Furthermore, it has recently been shown that 15-30 Hz field potential oscillations in the STN can be coherent with cortical electroencephalogram oscillations and that stimulation through DBS contacts with 15-30 Hz oscillation frequencies produces the most effective motor benefit

in patients with PD (Marsden et al. 2001). These results suggest that synchronous 15-30 Hz cortical oscillations play a role in parkinsonian pathophysiology by affecting basal ganglia function via the STN. This notion is supported by the observation that STN DBS at 15 Hz, which would be expected to synchronously drive STN neurons, worsens parkinsonian disability through an increase in akinesia (Demeret et al. 1999).

Our results also suggest that synchronized high-frequency oscillations in the STN are more pronounced in the dopamine depleted state. We observed that APO decreased the spontaneous discharge of two STN TCs concurrent with a reduction in limb tremor and a loss of synchronized high-frequency oscillatory activity. Furthermore, pairs of neurons recorded before APO administration displayed high-frequency synchronization but only weak synchrony was observed in pairs of neurons recorded during the APO-induced ON period. We also observed that levodopa administration reduced high-frequency oscillations in the field potential of another patient. These results are consistent with the findings of Brown et al. (2001) who demonstrated that 15-30 Hz synchronization between STN and GPi local field potentials is reduced by levodopa. Our results further indicate that 15-30 Hz synchronization in the STN is not dependant on the GPi because these oscillations were detected in the STN in patients with pallidal lesions. The increase in the spontaneous activity of the STN following MPTP-treatment in monkeys (Bergman et al. 1994) and presumably in parkinsonian patients (Hutchison et al. 1998a) could also act to enhance the prevalence of 15-30 Hz oscillations in the STN. It is interesting to note that in the GPi and STN of both MPTP-treated monkeys and patients with PD, neurons with oscillatory activity have a higher spontaneous discharge rate than neurons without oscillatory activity (Bergman et al. 1994; Levy et al. 2001). A possible

mechanism is that the increase in STN firing rates occurring in PD has the effect of increasing the maximum oscillatory frequency that can be transmitted by a neuronal spike train. For example, a neuron discharging at a mean firing rate of 50 spikes/s could better carry a 25 Hz oscillation than a neuron discharging at 30 spikes/s. Smaller neuronal populations would be required to express synchronized activity and/or a greater proportion of the neurons in the STN would then present higher frequency oscillations. Dopaminergic therapy has been shown to decrease STN firing rates (Kreiss et al. 1997) and thus could lessen the influence of high-frequency cortical oscillations on the basal ganglia. These ideas are supported by the demonstration that the incidence of STN neurons with high-frequency oscillations is reduced following the administration of APO in parkinsonian patients (see section 3.3).

Although oscillatory synchronization between groups of neurons is hypothesized to be necessary for limb tremor (Llinás and Paré 1995; Bergman et al. 1998a, 1998b), it is presently unclear what mechanisms might contribute to or promote TC synchrony in PD. Since the GPe-STN network can maintain low frequency (< 2 Hz) oscillatory synchronization that is driven by the STN (Plenz and Kital 1999), it is feasible that 15-30 Hz in-phase synchronous activity in the STN is also present in the GPe and that this network behavior may in turn promote tremor-related synchronization in the basal ganglia. This notion is supported by the demonstration in tremulous MPTP-treated monkeys that pairs of GPe cells exhibit high-frequency oscillatory synchronization with phase differences that are centered around 0 degrees (Raz et al. 2000) similar to our findings in the STN of parkinsonian patients (see Chapter 5 section 1). If rhythmic oscillatory activity in the STN-GP network in disease states is driven by the cortex

(Magill et al. 2000), the modulation of 15-30 Hz oscillations in the cortex and hence the STN-GPe might underlie some of the clinical features of parkinsonian rest tremor. Event-related desynchronization and rebound synchronization of 15-30 Hz cortical idling rhythms occurring during tasks activating the sensorimotor cortex (Pfurtscheller 1981; Salmelin and Hari 1994; Salmelin et al. 1995; Andrew and Pfurtscheller 1996; Pfurtscheller et al. 1996; Crone et al. 1998) may account for the common clinical observation that parkinsonian rest tremor shows a decreasing amplitude when a limb is voluntarily activated (Deuschl et al. 1998). Furthermore, synchronous oscillations in the sensorimotor cortex are affected by arousal or attention (Murthy and Fetz 1996a, 1996b) and may play a role in "enhanced tremor" whereby the amplitude of parkinsonian rest tremor increases during mental stress (i.e. enhanced tremor can be readily observed by asking patients to perform mental arithmetic) (Deuschl et al. 1998). It is interesting to note that increased coupling between muscles in a tremulous limb is observed when parkinsonian patients perform a mental arithmetic task (Hurtado et al. 2000) suggesting that tremor-related oscillations in the basal ganglia are more synchronized during this period (Bergman et al. 1998a). In addition, if the same cortical regions that are used for voluntary movement are involved in the pathogenesis of parkinsonian limb tremor (Alberts et al. 1969; Parker et al. 1992; Duffau et al. 1996; Volkmann et al. 1996; Hellwig et al. 2000) it is feasible that limb tremor could in turn lead to a reduction in sensorimotor idling rhythms (Makela et al. 1993) and this mechanism might account for the variability or intermittent nature of parkinsonian tremor observed clinically (Schwab and Cobb 1939; Scholz and Bacher 1995) or when recording from individual neurons (Bergman et al. 1998b; Hurtado et al. 1999; Raz et al. 2000; Levy et al. 2000).

In summary, this study proposes that 15-30 Hz cortical oscillations gain access to the basal ganglia through the cortico-subthalamic pathway, possibly via hyperactive STN neurons that are present in the dopamine depleted state. These synchronized high-frequency oscillations would then promote the oscillatory synchronization in the basal ganglia and contribute to parkinsonian symptoms including tremor.

## CHAPTER 6 - GENERAL SUMMARY AND SIGNIFICANCE

The results of these studies confirm some of the predictions of the box model of BG function and also suggest that the pattern of neuronal activity plays an important role in the pathogenesis of PD. In support of the box model, APO administration produced the predicted changes in the mean firing rates of neurons in the GPi, GPe, and STN and local inactivation of the STN resulted in a transient anti-parkinsonian effect. A detailed analysis of single neuron discharge patterns in the GPi and STN revealed that APO administration resulted in an increase in bursting activity, a decrease in tremor-related oscillations, and a decrease in somatosensory responses. Using simultaneous dual microelectrode recording techniques it was demonstrated that TC activity could be synchronized in the GPi and STN and was associated with neurons displaying in-phase synchronized 15-30 Hz oscillations. These 15-30 Hz oscillations were reduced during active movements or with dopaminergic medication and may influence the synchrony of tremor frequency oscillations in the BG. In contrast to oscillatory activity, synchronized neuronal activity indicative of direct connections between or common input to pairs of neurons in the GPi or STN was not observed suggesting that parallel subcircuits in the BG might remain more or less segregated in PD even in the dopamine depleted state.

According to the predictions of the box model, dopaminergic medication leads to a reduction of GPi activity and an increase in GPe activity and hence a reversal of parkinsonism (Albin et al. 1989a; DeLong 1990). A further reduction in GPi activity, either via increased activity of the direct pathway or through a decrease in the activity of the indirect pathway (as demonstrated in sections 3.1 and 3.3), should lead to dyskinetic movements as discussed in detail in the introduction (section 1.4.1). The demonstration

of dyskinesias following inactivation of the STN (chapter 4) is consistent with local inactivation studies of the STN in MPTP monkeys (Wichmann et al. 1994b) and suggests that only a reduction the glutamatergic drive of the STN on the GPi is required to produce dyskinesias, rather than an additional increase in the activity of the direct striatal projections to the GPi. A loss of balance between the direct and indirect pathways at the level of the GPi may lead to a dramatic reduction in GPi activity due to the net inhibitory effect of the direct striatal output pathway on the GPi. These findings support the involvement of the indirect pathway (GPe-STN-GPi) in the pathogenesis of dyskinesias (Crossman 1990) and indicate that the STN strongly influences neuronal activity in the GPi.

The APO-induced reduction in the proportion of TCs in the STN and GPi were quite similar. One possibility is that tremor activity in the GPi is mainly driven by the STN and a reduction in tremor activity in the STN would be reflected in the GPi. This notion is consistent with the observation that STN inactivation dramatically reduces limb tremor (see chapter 4). Another possibility is that tremor frequency oscillations in both these nuclei may simply be due to tremor-related peripheral afferent inputs. The reduction of tremor frequency oscillations would then simply be due to a reduction in tremor. However, while TCs were encountered in patients during episodes with limb tremor, TCs were also observed during episodes with no noticeable limb tremor and in one STN patient without detectable limb tremor. These observations support the notion that tremor oscillations in the basal ganglia may be present but may not result in observable limb tremor (Wichmann et al. 1994b). A possible explanation is that although tremor activity is present, it is not synchronized to a great enough extent to produce

coordinated muscle activity (Bergman et al. 1998a). Recordings from pairs of TC in the GPi or the STN revealed that TC were indeed synchronized, however in several instances, this synchronization was variable and not tightly locked to limb tremor.

In addition to oscillations in the tremor frequency range, neurons with 15-30 Hz oscillations were identified primarily in the STN and were found to display oscillatory synchronization when dual recordings were employed. Similar to tremor frequency oscillations, neurons with 15-30 Hz oscillations were found in patients with limb tremor and the proportion of these neurons were decreased with APO. Unlike tremor frequency oscillations, 15-30 Hz oscillations were in-phase to such a strong degree that they were easily detected by recording local field potentials in the STN. Furthermore, both dopaminergic medication and active movement reduced these oscillations (albeit by different mechanisms) and it was suggested that these oscillations were due to cortical input. This idea proposes that normally non-pathological cortical oscillatory phenomena might underlie the pathophysiology of rest tremor or akinesia in PD. It is likely that in the normal state of BG function, 15-30 Hz synchronized oscillatory inputs from cortex do not affect the activity of the STN however it is quite possible that in the parkinsonian state they may serve to synchronize neuronal activity in the BG, possibly via hyperactive STN neurons that are present in the dopamine depleted state.

It has been proposed that the suppression of limb tremor following a small lesion could arise as a result of, in addition to direct inactivation of tremor-related discharge, the "desynchronizing" effect of a small block upon neighboring subcircuits in the cortico-basal ganglia-thalamic loop (Bergman et al. 1998a; Deuschl et al. 2000). The use of simultaneous recording of neuronal activity during microinjection in this thesis allowed

the direct assessment of the effect of a pharmacological block in an area not directly deactivated by the block and suggests that small blocks of neuronal tissue may affect tremor related synchronization in the BG. Other evidence from this thesis that supports the notion of an increase in synchronization of the BG in PD (Filion et al. 1994; Raz et al. 1996; Bergman et al. 1998a) is the finding that the administration of APO reduced the responses of neurons in both the STN and GPi from multi-limb responses to mainly responding about individual joints. These data support the hypothesis that a loss of receptive field specificity is a characteristic of parkinsonism and that APO might reduce the funneling or convergence of information in the BG (see section 1.4.2).

Lastly, in both the GPi and the STN, APO administration was observed to increase the amount of bursting activity even when the contribution of oscillatory cells was excluded. This observation was contrary to the expectations that APO would reduce bursting activity and thereby "reverse" the increase in bursting activity observed following MPTP-induced parkinsonism in monkeys. This result suggests that the functioning of the BG in the parkinsonian state maybe significantly different than in the normal state and the spectrum of BG function between the two states may not simply rely on the single parameter dopamine. For example, dopamine may affect the STN directly during the normal state but not during parkinsonism due to a decrease in dopaminergic innervation of the STN in PD (Francois et al. 2000). Regardless of the function of bursting in the normal state, little is known about the functional significance of bursting activity in the BG during parkinsonism. But to what extent is synchronized activity between neurons in the BG related to the clinical features of PD? When patients without limb tremor were examined, neuronal synchronization was not observed and in patients

with tremor, synchronized neuronal activity was only associated with oscillatory phenomena. This suggests that a breakdown in synchronization does not account for the overall increase in bursting activity in the BG or the expansion of receptive fields that is observed following MPTP-treatment in monkeys and in patients with PD. These observations suggest that neuronal activity of the BG remains largely segregated in PD and that the "funneling" of information in the BG is relatively weak or involves coincident activity that is related to the complexity of motor and non-motor functions of the BG.

In summary, these studies indicate that the firing patterns of neurons in the STN and GPi are intimately related to parkinsonian pathophysiology. While changes in overall rate are consistent with the predictions of the box model, changes in oscillatory activity but not general bursting activity are related to the prediction of overt synchronization in the parallel model of BG function. Therefore, it is likely that both serial and parallel information processing are involved in the pathological functioning of the BG in PD and may also serve a role in the normal functions of the BG.

## REFERENCES

Aarsland, D., Larsen, J. P., Lim, N. G., Janvin, C., Karlsen, K., Tandberg, E., and Cummings, J. L. Range of neuropsychiatric disturbances in patients with Parkinson's disease. J.Neurol Neurosurg.Psychiatry 67: 492-496, 1999.

Aarsland, D., Tandberg, E., Larsen, J. P., and Cummings, J. L. Frequency of dementia in Parkinson disease. Arch Neurol 53: 538-542, 1996.

Abeles, M. Quantification, smoothing, and confidence limits for single-units' histograms. J.Neurosci.Methods 5: 317-325, 1982.

Absher, J. R., Vogt, B. A., Clark, D. G., Flowers, D. L., Gorman, D. G., Keyes, J. W., and Wood, F. B. Hypersexuality and hemiballism due to subthalamic infarction. Neuropsychiatry Neuropsychol.Behav.Neurol 13: 220-229, 2000.

Ackermann, H., Konczak, J., and Hertrich, I. The temporal control of repetitive articulatory movements in Parkinson's disease. Brain Lang 56: 312-319, 1997.

Aebischer, P. and Schultz, W. The activity of pars compacta neurons of the monkey substantia nigra is depressed by apomorphine. Neurosci.Lett. 50: 25-29, 1984.

Aertsen, A.M., Gerstein, G.L. Evaluation of neuronal connectivity: sensitivity of cross-correlation. Brain Res 340: 341-354, 1985.

Afsharpour, S. Light microscopic analysis of Golgi-impregnated rat subthalamic neurons. J.Comp Neurol 236: 1-13, 1985a.

Afsharpour, S. Topographical projections of the cerebral cortex to the subthalamic nucleus. J.Comp Neurol 236: 14-28, 1985b.

Agostino, R., Berardelli, A., Curra, A., Accornero, N., and Manfredi, M. Clinical impairment of sequential finger movements in Parkinson's disease. Mov Disord 13: 418-421, 1998.

Agostino, R., Berardelli, A., Formica, A., Accornero, N., and Manfredi, M. Sequential arm movements in patients with Parkinson's disease, Huntington's disease and dystonia. Brain 115 ( Pt 5): 1481-1495, 1992.

Akert, K. and Hartmann-von Monakow, K. Relationships of precentral premotor and prefrontal cortex to the mediodorsal and intralaminar nuclei of the monkey thalamus. Acta Neurobiol.Exp.(Warsz.) 40: 7-25, 1980.

Akkal, D., Burbaud, P., Audin, J., and Bioulac, B. Responses of substantia nigra pars reticulata neurons to intrastriatal D1 and D2 dopaminergic agonist injections in the rat. Neurosci.Lett. 213: 66-70, 1996.

Albanese, A., Bonuccelli, U., Brefel, C., Chaudhuri, K. R., Colosimo, C., Eichhorn, T., Melamed, E., Pollak, P., van Laar, T., and Zappia, M. Consensus statement on the role of acute dopaminergic challenge in Parkinson's disease. Mov Disord 16: 197-201, 2001.

Alberts, J. L., Tresilian, J. R., and Stelmach, G. E. The co-ordination and phasing of a bilateral prehension task. The influence of Parkinson's disease. Brain 121: 725-742, 1998.

Alberts, W. W., Libet, B., Wright, E. W., Jr., and Feinstein, B. Physiological mechanisms of tremor and rigidity in parkinsonism. Confin.Neurol 26: 318-327, 1965.

Alberts, W. W., Wright, E. W., Jr., and Feinstein, B. Cortical potentials and Parkinsonian tremor. Nature 221: 670-672, 1969.

Albin, R. L., Aldridge, J. W., Young, A. B., and Gilman, S. Feline subthalamic nucleus neurons contain glutamate-like but not GABA-like or glycine-like immunoreactivity. Brain Res. 491: 185-188, 1989b.

Albin, R. L., Young, A. B., and Penney, J. B. The functional anatomy of basal ganglia disorders. Trends.Neurosci. 12: 366-375, 1989a.

Aldridge, J. W., Anderson, R. J., and Murphy, J. T. Sensory-motor processing in the caudate nucleus and globus pallidus: a single-unit study in behaving primates. Can.J.Physiol Pharmacol. 58: 1192-1201, 1980a.

Aldridge, J. W., Anderson, R. J., and Murphy, J. T. The role of the basal ganglia in controlling a movement initiated by a visually presented cue. Brain Res. 192: 3-16, 1980b.

Aldridge, J. W. and Gilman, S. The temporal structure of spike trains in the primate basal ganglia: afferent regulation of bursting demonstrated with precentral cerebral cortical ablation. Brain Res. 543: 123-138, 1991.

Aldridge, J. W., Gilman, S., and Dauth, G. Spontaneous neuronal unit activity in the primate basal ganglia and the effects of precentral cerebral cortical ablations. Brain Res. 516: 46-56, 1990.

Alexander, G. E. Selective neuronal discharge in monkey putamen reflects intended direction of planned limb movements. Exp.Brain Res. 67: 623-634, 1987.

Alexander, G. E. and Crutcher, M. D. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci. 13: 266-271, 1990.

Alexander, G. E., Crutcher, M. D., and DeLong, M. R. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog.Brain Res. 85:119-46: 119-146, 1990.

Alexander, G. E. and DeLong, M. R. Microstimulation of the primate neostriatum. I. Physiological properties of striatal microexcitable zones. J.Neurophysiol. 53: 1401-1416, 1985b.

Alexander, G. E. and DeLong, M. R. Microstimulation of the primate neostriatum. II. Somatotopic organization of striatal microexcitable zones and their relation to neuronal response properties. J.Neurophysiol. 53: 1417-1430, 1985a.

Alexander, G. E., DeLong, M. R., and Strick, P. L. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu.Rev.Neurosci. 9:357-81: 357-381, 1986.

Allers, K. A., Kreiss, D. S., and Walters, J. R. Multisecond oscillations in the subthalamic nucleus: Effects of apomorphine and dopamine cell lesion. Synapse 38: 38-50, 2000.

Alterman, R. L., Sterio, D., Beric, A., and Kelly, P. J. Microelectrode recording during posteroventral pallidotomy: impact on target selection and complications. Neurosurgery 44: 315-321, 1999.

Alvarez, L., Macias, R., Guridi, J., Lopez, G., Alvarez, E., Maragoto, C., Teijeiro, J., Torres, A., Pavon, N., Rodriguez-Oroz, M. C., Ochoa, L., Hetherington, H., Juncos, J., DeLong, M. R., and Obeso, J. A. Dorsal subthalamotomy for Parkinson's disease. Mov Disord 16: 72-78, 2001.

Amalric, M., Conde, H., Dormont, J. F., Farin, D., and Schmied, A. Activity of caudate nucleus neurons in cat performing a reaction time task. Neurosci.Lett. 49: 253-258, 1984.

Anderson, M. E. and Horak, F. B. Influence of the globus pallidus on arm movements in monkeys. III. Timing of movement-related information. J.Neurophysiol. 54: 433-448, 1985.

Antal, A., Bandini, F., Keri, S., and Bodis-Wollner, I. Visuo-cognitive dysfunctions in Parkinson's disease. Clin Neurosci. 5: 147-152, 1998.

Antonini, A., Moeller, J. R., Nakamura, T., Spetsieris, P., Dhawan, V., and Eidelberg, D. The metabolic anatomy of tremor in Parkinson's disease. Neurology 51: 803-810, 1998.

Antonini, A., Schwarz, J., Oertel, W. H., Pogarell, O., and Leenders, K. L. Long-term changes of striatal dopamine D2 receptors in patients with Parkinson's disease: a study with positron emission tomography and [11C]raclopride. Mov Disord 12: 33-38, 1997.

Aosaki, T., Graybiel, A. M., and Kimura, M. Effect of the nigrostriatal dopamine system on acquired neural responses in the striatum of behaving monkeys. Science 265: 412-415, 1994b.

Aosaki, T., Kimura, M., and Graybiel, A. M. Temporal and spatial characteristics of tonically active neurons of the primate's striatum. J.Neurophysiol. 73: 1234-1252, 1995.

Aosaki, T., Kiuchi, K., and Kawaguchi, Y. Dopamine D1-like receptor activation excites rat striatal large aspiny neurons in vitro. J.Neurosci. 18: 5180-5190, 1998.

Aosaki, T., Tsubokawa, H., Ishida, A., Watanabe, K., Graybiel, A. M., and Kimura, M. Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. J.Neurosci. 14: 3969-3984, 1994a.

Apicella, P., Ljungberg, T., Scarnati, E., and Schultz, W. Responses to reward in monkey dorsal and ventral striatum. Exp.Brain Res. 85: 491-500, 1991a.

Apicella, P., Ravel, S., Sardo, P., and Legallet, E. Influence of predictive information on responses of tonically active neurons in the monkey striatum. J.Neurophysiol. 80: 3341-3344, 1998.

Apicella, P., Scarnati, E., and Schultz, W. Tonically discharging neurons of monkey striatum respond to preparatory and rewarding stimuli. Exp.Brain Res. 84: 672-675, 1991b.

Ardouin, C., Pillon, B., Peiffer, E., Bejjani, P., Limousin, P., Damier, P., Arnulf, I., Benabid, A. L., Agid, Y., and Pollak, P. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann.Neurol 46: 217-223, 1999.

Arecchi-Bouchhioua, P., Yelnik, J., Francois, C., Percheron, G., and Tande, D. 3-D tracing of biocytin-labelled pallido-thalamic axons in the monkey. Neuroreport 7: 981-984, 1996.

Arecchi-Bouchhioua, P., Yelnik, J., Francois, C., Percheron, G., and Tande, D. Three-dimensional morphology and distribution of pallidal axons projecting to both the lateral region of the thalamus and the central complex in primates. Brain Res. 754: 311-314, 1997.

Ashby, P., Strafella, A., Dostrovsky, J. O., Lozano, A., and Lang, A. E. Immediate motor effects of stimulation through electrodes implanted in the human globus pallidus. Stereotact.Funct.Neurosurg. 70: 1-18, 1998.

Augood, S. J., Hollingsworth, Z. R., Standaert, D. G., Emson, P. C., and Penney, J. B., Jr. Localization of dopaminergic markers in the human subthalamic nucleus. J.Comp Neurol 421: 247-255, 2000.

Awad, H., Hubert, G. W., Smith, Y., Levey, A. I., and Conn, P. J. Activation of metabotropic glutamate receptor 5 has direct excitatory effects and potentiates NMDA receptor currents in neurons of the subthalamic nucleus. J.Neurosci. 20: 7871-7879, 2000.

Aziz, T. Z., Peggs, D., Agarwal, E., Sambrook, M. A., and Crossman, A. R. Subthalamic nucleotomy alleviates parkinsonism in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-exposed primate. Br.J.Neurosurg. 6: 575-582, 1992.

Aziz, T. Z., Peggs, D., Sambrook, M. A., and Crossman, A. R. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov Disord 6: 288-292, 1991.

Baev, K. V. Disturbances of learning processes in the basal ganglia in the pathogenesis of Parkinson's disease: a novel theory. [Review] [21 refs]. Neurological Research 17: 38-48, 1995.

Bakay, R. A., Starr, P. A., Vitek, J. L., and DeLong, M. R. Posterior ventral pallidotomy: techniques and theoretical considerations. Clin Neurosurg. 44: 197-210, 1997.

Baker, S.N., Olivier, E., and Lemon, R.N. Coherent oscillations in monkey motor cortex and hand muscle EMG show task-dependent modulation. J Physiol (Lond) 501 ( Pt 1): 225-241, 1997.

Baker, S.N., Kilner, J.M., Pinches, E.M., and Lemon, R.N. The role of synchrony and oscillations in the motor output. Exp Brain Res 128: 109-117, 1999.

Bankiewicz, K. S., Oldfield, E. H., Chiueh, C. C., Doppman, J. L., Jacobowitz, D. M., and Kopin, I. J. Hemiparkinsonism in monkeys after unilateral internal carotid artery infusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Life Sci. 39: 7-16, 1986.

Bar-Gad, I., Ritov, Y., Vaadia, E., and Bergman, H. Failure in identification of overlapping spikes from multiple neuron activity causes artificial correlations. J.Neurosci.Methods 107: 1-13, 2001.

Barlas, O., Hanagasi, H. A., Imer, M., Sahin, H. A., Sencer, S., and Emre, M. Do unilateral ablative lesions of the subthalamic nucleu in parkinsonian patients lead to hemiballism? Mov Disord 16: 306-310, 2001.

Baron, M. S., Vitek, J. L., Bakay, R. A., Green, J., Kaneoke, Y., Hashimoto, T., Turner, R. S., Woodard, J. L., Cole, S. A., McDonald, W. M., and DeLong, M. R. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. Ann.Neurol. 40: 355-366, 1996.

Baron, M. S., Vitek, J. L., Bakay, R. A., Green, J., McDonald, W. M., Cole, S. A., and DeLong, M. R. Treatment of advanced Parkinson's disease by unilateral posterior GPi pallidotomy: 4-year results of a pilot study. Mov Disord 15: 230-237, 2000.

Barone, P., Bankiewicz, K. S., Corsini, G. U., Kopin, I. J., and Chase, T. N. Dopaminergic mechanisms in hemiparkinsonian monkeys. Neurology 37: 1592-1595, 1987.

Bassotti, G., Germani, U., Pagliaricci, S., Plesa, A., Giulietti, O., Mannarino, E., and Morelli, A. Esophageal manometric abnormalities in Parkinson's disease. Dysphagia 13: 28-31, 1998.

Baunez, C. and Robbins, T. W. Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. Eur.J.Neurosci. 9: 2086-2099, 1997.

Baunez, C. and Robbins, T. W. Effects of transient inactivation of the subthalamic nucleus by local muscimol and APV infusions on performance on the five-choice serial reaction time task in rats. Psychopharmacology (Berl) 141: 57-65, 1999.

Bazalgette, D., Zattara, M., Bathien, N., Bouisset, S., and Rondot, P. Postural adjustments associated with rapid voluntary arm movements in patients with Parkinson's disease. Adv Neurol 45: 371-374, 1987.

Beckley, D. J., Bloem, B. R., and Remler, M. P. Impaired scaling of long latency postural reflexes in patients with Parkinson's disease. Electroencephalogr.Clin Neurophysiol. 89: 22-28, 1993.

Beckley, D. J., Bloem, B. R., Van Dijk, J. G., Roos, R. A., and Remler, M. P. Electrophysiological correlates of postural instability in Parkinson's disease. Electroencephalogr.Clin Neurophysiol. 81: 263-268, 1991.

Beckley, D. J., Panzer, V. P., Remler, M. P., Ilog, L. B., and Bloem, B. R. Clinical correlates of motor performance during paced postural tasks in Parkinson's disease. J.Neurol Sci. 132: 133-138, 1995.

Bedenbaugh, P. and Gerstein, G. L. Multiunit normalized cross correlation differs from the average single- unit normalized correlation. Neural Comput. 9: 1265-1275, 1997.

Bejjani, B. P., Arnulf, I., Demeret, S., Damier, P., Bonnet, A. M., Houeto, J. L., and Agid, Y. Levodopa-induced dyskinesias in Parkinson's disease: is sensitization reversible? Ann Neurol 47: 655-658, 2000.

Benabid, A. L., Benazzouz, A., Limousin, P., Koudsie, A., Krack, P., Piallat, B., and Pollak, P. Dyskinesias and the subthalamic nucleus. Ann Neurol 47: S189-S192, 2000.

Benabid, A. L., Pollak, P., Gao, D., Hoffmann, D., Limousin, P., Gay, E., Payen, I., and Benazzouz, A. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J.Neurosurg. 84: 203-214, 1996.

Benabid, A. L., Pollak, P., Gervason, C., Hoffmann, D., Gao, D. M., Hommel, M., Perret, J. E., and de Rougemont, J. Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. Lancet 337: 403-406, 1991.

Benabid, A. L., Pollak, P., Gross, C., Hoffmann, D., Benazzouz, A., Gao, D. M., Laurent, A., Gentil, M., and Perret, J. Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease. Stereotact.Funct.Neurosurg. 62: 76-84, 1994.

Benazzouz, A., Boraud, T., Feger, J., Burbaud, P., Bioulac, B., and Gross, C. Alleviation of experimental hemiparkinsonism by high-frequency stimulation of the subthalamic

nucleus in primates: a comparison with L-Dopa treatment. Mov Disord. 11: 627-632, 1996.

Benazzouz, A., Gross, C., Dupont, J., and Bioulac, B. MPTP induced hemiparkinsonism in monkeys: behavioral, mechanographic, electromyographic and immunohistochemical studies. Exp.Brain Res. 90: 116-120, 1992.

Benazzouz, A., Gross, C., Feger, J., Boraud, T., and Bioulac, B. Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. Eur.J.Neurosci. 5: 382-389, 1993.

Benecke, R., Rothwell, J. C., Dick, J. P., Day, B. L., and Marsden, C. D. Performance of simultaneous movements in patients with Parkinson's disease. Brain 109: 739-757, 1986.

Benecke, R., Rothwell, J. C., Dick, J. P., Day, B. L., and Marsden, C. D. Disturbance of sequential movements in patients with Parkinson's disease. Brain 110: 361-379, 1987b.

Benecke, R., Rothwell, J. C., Dick, J. P., Day, B. L., and Marsden, C. D. Simple and complex movements off and on treatment in patients with Parkinson's disease. J.Neurol.Neurosurg.Psychiatry 50: 296-303, 1987a.

Bennett, D. A., Beckett, L. A., Murray, A. M., Shannon, K. M., Goetz, C. G., Pilgrim, D. M., and Evans, D. A. Prevalence of parkinsonian signs and associated mortality in a community population of older people. N.Engl.J.Med. 334: 71-76, 1996.

Bennett, K. M., O'Sullivan, J. D., Peppard, R. F., McNeill, P. M., and Castiello, U. The effect of unilateral posteroventral pallidotomy on the kinematics of the reach to grasp movement. J.Neurol Neurosurg.Psychiatry 65: 479-487, 1998.

Bentivoglio, M., van der, K. D., and Kuypers, H. G. The organization of the efferent projections of the substantia nigra in the rat. A retrograde fluorescent double labeling study. Brain Res. 174: 1-17, 1979.

Berardelli, A., Accornero, N., Argenta, M., Meco, G., and Manfredi, M. Fast complex arm movements in Parkinson's disease. J.Neurol.Neurosurg.Psychiatry 49: 1146-1149, 1986b.

Berardelli, A., Dick, J. P., Rothwell, J. C., Day, B. L., and Marsden, C. D. Scaling of the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. J.Neurol Neurosurg.Psychiatry 49: 1273-1279, 1986a.

Berardelli, A., Hallett, M., Rothwell, J. C., Agostino, R., Manfredi, M., Thompson, P. D., and Marsden, C. D. Single-joint rapid arm movements in normal subjects and in patients with motor disorders. Brain 119 ( Pt 2): 661-674, 1996a.

Berardelli, A., Rona, S., Inghilleri, M., and Manfredi, M. Cortical inhibition in Parkinson's disease. A study with paired magnetic stimulation. Brain 119 ( Pt 1): 71-77, 1996b.

Bergman, H., Feingold, A., Nini, A., Raz, A., Slovin, H., Abeles, M., and Vaadia, E. Physiological aspects of information processing in the basal ganglia of normal and parkinsonian primates. Trends Neurosci. 21: 32-38, 1998a.

Bergman, H., Raz, A., Feingold, A., Nini, A., Nelken, I., Hansel, D., Ben Pazi, H., and Reches, A. Physiology of MPTP tremor. Mov Disord. 13 Suppl 3:29-34: 29-34, 1998b.

Bergman, H., Wichmann, T., and DeLong, M. R. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 249: 1436-1438, 1990.

Bergman, H., Wichmann, T., Karmon, B., and DeLong, M. R. The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. J.Neurophysiol. 72: 507-520, 1994.

Bergstrom, D. A., Bromley, S. D., and Walters, J. R. Apomorphine increases the activity of rat globus pallidus neurons. Brain Res. 238: 266-271, 1982.

Beric, A., Sterio, D., Dogali, M., Fazzini, E., Eidelberg, D., and Kolodny, E. Characteristics of pallidal neuronal discharges in Parkinson's disease patients. Adv Neurol 69: 123-128, 1996.

Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K., and Seitelberger, F. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. J.Neurol Sci. 20: 415-455, 1973.

Beurrier, C., Bezard, E., Bioulac, B., Gross, C.. Subthalamic stimulation elicits hemiballismus in normal monkey. Neuroreport 7: 1625-1629, 1997.

Beurrier, C., Congar, P., Bioulac, B., and Hammond, C. Subthalamic nucleus neurons switch from single-spike activity to burst-firing mode. J.Neurosci. 19: 599-609, 1999.

Bevan, M. D. and Bolam, J. P. Cholinergic, GABAergic, and glutamate-enriched inputs from the mesopontine tegmentum to the subthalamic nucleus in the rat. J.Neurosci. 15: 7105-7120, 1995.

Bevan, M. D., Bolam, J. P., and Crossman, A. R. Convergent synaptic input from the neostriatum and the subthalamus onto identified nigrothalamic neurons in the rat. Eur.J.Neurosci. 6: 320-334, 1994b.

Bevan, M. D., Clarke, N. P., and Bolam, J. P. Synaptic integration of functionally diverse pallidal information in the entopeduncular nucleus and subthalamic nucleus in the rat. J.Neurosci. 17: 308-324, 1997.

Bevan, M. D., Crossman, A. R., and Bolam, J. P. Neurons projecting from the entopeduncular nucleus to the thalamus receive convergent synaptic inputs from the subthalamic nucleus and the neostriatum in the rat. Brain Res. 659: 99-109, 1994a.

Bevan, M. D., Francis, C. M., and Bolam, J. P. The glutamate-enriched cortical and thalamic input to neurons in the subthalamic nucleus of the rat: convergence with GABA-positive terminals. J.Comp Neurol 361: 491-511, 1995.

Bevan, M. D., Smith, A. D., and Bolam, J. P. The substantia nigra as a site of synaptic integration of functionally diverse information arising from the ventral pallidum and the globus pallidus in the rat. Neuroscience 75: 5-12, 1996.

Bevan, M. D. and Wilson, C. J. Mechanisms underlying spontaneous oscillation and rhythmic firing in rat subthalamic neurons. J.Neurosci. 19: 7617-7628, 1999.

Bezard, E., Boraud, T., Bioulac, B., and Gross, C. E. Compensatory effects of glutamatergic inputs to the substantia nigra pars compacta in experimental parkinsonism. Neuroscience 81: 399-404, 1997b.

Bezard, E., Boraud, T., Bioulac, B., and Gross, C. E. Presymptomatic revelation of experimental parkinsonism. Neuroreport 8: 435-438, 1997a.

Bezard, E., Boraud, T., Bioulac, B., and Gross, C. E. Involvement of the subthalamic nucleus in glutamatergic compensatory mechanisms. Eur.J.Neurosci. 11: 2167-2170, 1999.

Bezard, E. and Gross, C. E. Compensatory mechanisms in experimental and human parkinsonism: towards a dynamic approach. Prog.Neurobiol. 55: 93-116, 1998.

Bezard, E., Imbert, C., Deloire, X., Bioulac, B., and Gross, C. E. A chronic MPTP model reproducing the slow evolution of Parkinson's disease: evolution of motor symptoms in the monkey. Brain Res. 766: 107-112, 1997c.

Bezard, E., Imbert, C., and Gross, C. E. Experimental models of Parkinson's disease: from the static to the dynamic. Rev.Neurosci. 9: 71-90, 1998.

Biousse, V., Newman, N. J., Carroll, C., Mewes, K., Vitek, J. L., Bakay, R. A., Baron, M. S., and DeLong, M. R. Visual fields in patients with posterior GPi pallidotomy. Neurology 50: 258-265, 1998.

Bishop, G. H., Clare, M. H., and Price, J. Patterns of tremor in normal and pathological conditions. J.Appl.Physiol 1: 123, 1948.

Blanchet, P. J., Boucher, R., and Bédard, P. J. Excitotoxic lateral pallidotomy does not relieve L-DOPA- induced dyskinesia in MPTP parkinsonian monkeys. Brain Res. 650: 32-39, 1994.

Blandini, F., Garcia-Osuna, M., and Greenamyre, J. T. Subthalamic ablation reverses changes in basal ganglia oxidative metabolism and motor response to apomorphine induced by nigrostriatal lesion in rats. Eur.J.Neurosci. 9: 1407-1413, 1997.

Bloem, B. R. Postural instability in Parkinson's disease. Clin Neurol Neurosurg. 94 Suppl: S41-S45, 1992.

Bloem, B. R., Beckley, D. J., Remler, M. P., Roos, R. A., and Van Dijk, J. G. Postural reflexes in Parkinson's disease during 'resist' and 'yield' tasks. J.Neurol Sci. 129: 109-119, 1995.

Bloem, B. R., Beckley, D. J., and Van Dijk, J. G. Are automatic postural responses in patients with Parkinson's disease abnormal due to their stooped posture? Exp.Brain Res. 124: 481-488, 1999.

Bloem, B. R., Beckley, D. J., Van Dijk, J. G., Zwinderman, A. H., Remler, M. P., and Roos, R. A. Influence of dopaminergic medication on automatic postural responses and balance impairment in Parkinson's disease. Mov Disord 11: 509-521, 1996.

Bloem, B. R., Irwin, I., Buruma, O. J., Haan, J., Roos, R. A., Tetrud, J. W., and Langston, J. W. The MPTP model: versatile contributions to the treatment of idiopathic Parkinson's disease. J.Neurol Sci. 97: 273-293, 1990.

Bloem, B. R., Van Dijk, J. G., Beckley, D. J., Roos, R. A., Remler, M. P., and Bruyn, G. W. Altered postural reflexes in Parkinson's disease: a reverse hypothesis. Med.Hypotheses 39: 243-247, 1992.

Blond, S., Caparros-Lefebvre, D., Parker, F., Assaker, R., Petit, H., Guieu, J. D., and Christiaens, J. L. Control of tremor and involuntary movement disorders by chronic stereotactic stimulation of the ventral intermediate thalamic nucleus. J.Neurosurg. 77: 62-68, 1992.

Bloxham, C. A., Dick, D. J., and Moore, M. Reaction times and attention in Parkinson's disease. J.Neurol Neurosurg.Psychiatry 50: 1178-1183, 1987.

Bloxham, C. A., Mindel, T. A., and Frith, C. D. Initiation and execution of predictable and unpredictable movements in Parkinson's disease. Brain 107 ( Pt 2): 371-384, 1984.

Bodis-Wollner, I. Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. Trends Neurosci. 13: 296-302, 1990.

Bodis-Wollner, I., Marx, M. S., Mitra, S., Bobak, P., Mylin, L., and Yahr, M. Visual dysfunction in Parkinson's disease. Loss in spatiotemporal contrast sensitivity. Brain 110 ( Pt 6): 1675-1698, 1987.

Bolam, J. P., Powell, J. F., Totterdell, S., and Smith, A. D. The proportion of neurons in the rat neostriatum that project to the substantia nigra demonstrated using horseradish peroxidase conjugated with wheatgerm agglutinin. Brain Res. 220: 339-343, 1981.

Bolam, J. P. and Smith, Y. The striatum and the globus pallidus send convergent synaptic inputs onto single cells in the entopeduncular nucleus of the rat: a double anterograde labelling study combined with postembedding immunocytochemistry for GABA. J.Comp Neurol 321: 456-476, 1992.

Bolam, J. P., Smith, Y., Ingham, C. A., von Krosigk, M., and Smith, A. D. Convergence of synaptic terminals from the striatum and the globus pallidus onto single neurones in the substantia nigra and the entopeduncular nucleus. Prog.Brain Res. 99: 73-88, 1993.

Bond, J. M. and Morris, M. Goal-directed secondary motor tasks: their effects on gait in subjects with Parkinson disease. Arch.Phys.Med.Rehabil. 81: 110-116, 2000.

Bonuccelli, U., Piccini, P., Del Dotto, P., Rossi, G., Corsini, G. U., Muratorio, and A. Apomorphine test for dopaminergic responsiveness: a dose assessment study. Mov.Disord. 8: 158-164, 1993.

Boraud, T., Bezard, E., Bioulac, B., and Gross, C. High frequency stimulation of the internal Globus Pallidus (GPi) simultaneously improves parkinsonian symptoms and reduces the firing frequency of GPi neurons in the MPTP-treated monkey. Neurosci.Lett. 215: 17-20, 1996.

Boraud, T., Bezard, E., Bioulac, B., and Gross, C. E. Ratio of Inhibited-to-Activated Pallidal Neurons Decreases Dramatically During Passive Limb Movement in the MPTP-Treated Monkey. J.Neurophysiol. 83: 1760-1763, 2000a.

Boraud, T., Bezard, E., Bioulac, B., and Gross, C. E. Dopamine agonist-induced dyskinesias are correlated to both firing pattern and frequency alterations of pallidal neurones in the MPTP-treated monkey. Brain 124: 546-557, 2001.

Boraud, T., Bezard, E., Guehl, D., Bioulac, B., and Gross, C. Effects of L-DOPA on neuronal activity of the globus pallidus externalis (GPe) and globus pallidus internalis (GPi) in the MPTP- treated monkey. Brain Res. 787: 157-160, 1998.

Boraud, T., Bezard, E., Stutzmann, J. M., Bioulac, B., and Gross, C. E. Effects of riluzole on the electrophysiological activity of pallidal neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkey. Neurosci.Lett. 281: 75-78, 2000b.

Boussaoud, D. and Joseph, J. P. Role of the cat substantia nigra pars reticulata in eye and head movements. II. Effects of local pharmacological injections. Exp.Brain Res. 57: 297-304, 1985.

Bouthenet, M. L., Martres, M. P., Sales, N., and Schwartz, J. C. A detailed mapping of dopamine D-2 receptors in rat central nervous system by autoradiography with [125I]iodosulpride. Neuroscience 20: 117-155, 1987.

Boyce, S., Clarke, C. E., Luquin, R., Peggs, D., Robertson, R. G., Mitchell, I. J., Sambrook, M. A., and Crossman, A. R. Induction of chorea and dystonia in parkinsonian primates. Mov Disord 5: 3-7, 1990.

Britton, T. C., Thompson, P. D., Day, B. L., Rothwell, J. C., Findley, L. J., and Marsden, C. D. "Resetting" of postural tremors at the wrist with mechanical stretches in Parkinson's disease, essential tremor, and normal subjects mimicking tremor. Ann Neurol 31: 507-514, 1992.

Britton, T. C., Thompson, P. D., Day, B. L., Rothwell, J. C., Findley, L. J., and Marsden, C. D. Modulation of postural tremors at the wrist by supramaximal electrical median nerve shocks in essential tremor, Parkinson's disease and normal subjects mimicking tremor. J.Neurol Neurosurg.Psychiatry 56: 1085-1089, 1993a.

Britton, T. C., Thompson, P. D., Day, B. L., Rothwell, J. C., Findley, L. J., and Marsden, C. D. Modulation of postural wrist tremors by magnetic stimulation of the motor cortex in patients with Parkinson's disease or essential tremor and in normal subjects mimicking tremor. Ann Neurol 33: 473-479, 1993b.

Brotchie, J. M., Mitchell, I. J., Sambrook, M. A., and Crossman, A. R. Alleviation of parkinsonism by antagonism of excitatory amino acid transmission in the medial segment of the globus pallidus in rat and primate. Mov Disord 6: 133-138, 1991c.

Brotchie, P., Iansek, R., and Horne, M. K. Motor function of the monkey globus pallidus. 1. Neuronal discharge and parameters of movement. Brain 114: 1667-1683, 1991a.

Brotchie, P., Iansek, R., and Horne, M. K. Motor function of the monkey globus pallidus. 2. Cognitive aspects of movement and phasic neuronal activity. Brain 114: 1685-1702, 1991b.

Broussolle, E., Cinotti, L., Pollak, P., Landais, P., Le Bars, D., Galy, G., Lavenne, F., Khalfallah, Y., Chazot, G., and Mauguiere, F. Relief of akinesia by apomorphine and cerebral metabolic changes in Parkinson's disease. Mov Disord 8: 459-462, 1993.

Brown, P. Cortical drives to human muscle: the Piper and related rhythms. Prog.Neurobiol. 60: 97-108, 2000.

Brown, P. and Marsden, C. D. What do the basal ganglia do? Lancet 351: 1801-1804, 1998.

Brown, P. and Marsden, C. D. Bradykinesia and impairment of EEG desynchronization in Parkinson's disease. Mov Disord 14: 423-429, 1999.

Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., and Di Lazzaro, V. Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. J Neurosci 21: 1033-1038, 2001.

Brown, R. G., Dowsey, P. L., Brown, P., Jahanshahi, M., Pollak, P., Benabid, A. L., Rodriguez-Oroz, M. C., Obeso, J., and Rothwell, J. C. Impact of deep brain stimulation on upper limb akinesia in Parkinson's disease. Ann Neurol 45: 473-488, 1999.

Brown, R. G. and Jahanshahi, M. Cognitive-motor dysfunction in Parkinson's disease. Eur.Neurol. 36 Suppl 1:24-31: 24-31, 1996.

Brown, R. G., MacCarthy, B., Jahanshahi, M., and Marsden, C. D. Accuracy of self-reported disability in patients with parkinsonism. Arch.Neurol. 46: 955-959, 1989.

Brown, R. G. and Marsden, C. D. An investigation of the phenomenon of "set" in Parkinson's disease. Mov Disord. 3: 152-161, 1988b.

Brown, R. G. and Marsden, C. D. Internal versus external cues and the control of attention in Parkinson's disease. Brain 111 ( Pt 2): 323-345, 1988a.

Brown, R. G. and Marsden, C. D. Dual task performance and processing resources in normal subjects and patients with Parkinson's disease. Brain 114 ( Pt 1A): 215-231, 1991.

Bruet, N., Windels, F., Bertrand, A., Feuerstein, C., Poupard, A., and Savasta, M. High frequency stimulation of the subthalamic nucleus increases the extracellular contents of striatal dopamine in normal and partially dopaminergic denervated rats. J.Neuropathol.Exp.Neurol 60: 15-24, 2001.

Buford, J. A., Inase, M., and Anderson, M. E. Contrasting locations of pallidal-receiving neurons and microexcitable zones in primate thalamus. J.Neurophysiol. 75: 1105-1116, 1996.

Burbaud, P., Bonnet, B., Guehl, D., Lagueny, A., and Bioulac, B. Movement disorders induced by gamma-aminobutyric agonist and antagonist injections into the internal globus pallidus and substantia nigra pars reticulata of the monkey. Brain Res. 780: 102-107, 1998.

Burbaud, P., Gross, C., Benazzouz, A., Coussemacq, M., and Bioulac, B. Reduction of apomorphine-induced rotational behaviour by subthalamic lesion in 6-OHDA lesioned rats is associated with a normalization of firing rate and discharge pattern of pars reticulata neurons. Exp.Brain Res. 105: 48-58, 1995.

Burkhard, P. R., Shale, H., Langston, J. W., and Tetrud, J. W. Quantification of dyskinesia in Parkinson's disease: validation of a novel instrumental method. Mov Disord 14: 754-763, 1999.

Burleigh-Jacobs, A., Horak, F. B., Nutt, J. G., and Obeso, J. A. Step initiation in Parkinson's disease: influence of levodopa and external sensory triggers. Mov Disord 12: 206-215, 1997.

Burleigh, A., Horak, F., Nutt, J., and Frank, J. Levodopa reduces muscle tone and lower extremity tremor in Parkinson's disease. Can.J.Neurol Sci. 22: 280-285, 1995.

Burne, J. A. Reflex origin of parkinsonian tremor. Exp.Neurol. 97: 327-339, 1987.

Burns, R. S., Chiueh, C. C., Markey, S. P., Ebert, M. H., Jacobowitz, D. M., and Kopin, I. J. A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc.Natl.Acad.Sci.U.S.A 80: 4546-4550, 1983.

Buytenhuijs, E. L., Berger, H. J., van Spaendonck, K. P., Horstink, M. W., Borm, G. F., and Cools, A. R. Memory and learning strategies in patients with Parkinson's disease. Neuropsychologia 32: 335-342, 1994.

Calabresi, P., Maj, R., Mercuri, N. B., and Bernardi, G. Coactivation of D1 and D2 dopamine receptors is required for long-term synaptic depression in the striatum. Neurosci.Lett. 142: 95-99, 1992.

Caligiuri, M. P. and Peterson, S. A quantitative study of levodopa-induced dyskinesia in Parkinson's disease. Journal of Neural Transmission - Parkinsons Disease & Dementia Section 6: 89-98, 1993.

Calne, D. B. and Langston, J. W. Aetiology of Parkinson's disease. Lancet 2: 1457-1459, 1983.

Calne, D. B., Langston, J. W., Martin, W. R., Stoessl, A. J., Ruth, T. J., Adam, M. J., Pate, B. D., and Schulzer, M. Positron emission tomography after MPTP: observations relating to the cause of Parkinson's disease. Nature 317: 246-248, 1985.

Camicioli, R., Oken, B. S., Sexton, G., Kaye, J. A., and Nutt, J. G. Verbal fluency task affects gait in Parkinson's disease with motor freezing. J.Geriatr.Psychiatry Neurol 11: 181-185, 1998.

Campbell, G. A., Eckardt, M. J., and Weight, F. F. Dopaminergic mechanisms in subthalamic nucleus of rat: analysis using horseradish peroxidase and microiontophoresis. Brain Res. 333: 261-270, 1985.

Canteras, N. S., Shammah-Lagnado, S. J., Silva, B. A., and Ricardo, J. A. Somatosensory inputs to the subthalamic nucleus: a combined retrograde and anterograde horseradish peroxidase study in the rat. Brain Res. 458: 53-64, 1988.

Canteras, N. S., Shammah-Lagnado, S. J., Silva, B. A., and Ricardo, J. A. Afferent connections of the subthalamic nucleus: a combined retrograde and anterograde horseradish peroxidase study in the rat. Brain Res. 513: 43-59, 1990.

Caparros-Lefebvre, D., Blond, S., Feltin, M. P., Pollak, P., and Benabid, A. L. Improvement of levodopa induced dyskinesias by thalamic deep brain stimulation is related to slight variation in electrode placement: possible involvement of the centre median and parafascicularis complex. J.Neurol Neurosurg.Psychiatry 67: 308-314, 1999.

Caparros-Lefebvre, D., Blond, S., Vermersch, P., Pecheux, N., Guieu, J. D., and Petit, H. Chronic thalamic stimulation improves tremor and levodopa induced dyskinesias in Parkinson's disease. J.Neurol Neurosurg.Psychiatry 56: 268-273, 1993.

Caparros-Lefebvre, D., Ruchoux, M. M., Blond, S., Petit, H., and Percheron, G. Long-term thalamic stimulation in Parkinson's disease: postmortem anatomoclinical study. Neurology 44: 1856-1860, 1994.

Carlson, J. D., Pearlstein, R. D., Buchholz, J., Iacono, R. P., and Maeda, G. Regional metabolic changes in the pedunculopontine nucleus of unilateral 6-hydroxydopamine Parkinson's model rats. Brain Res. 828: 12-19, 1999.

Carlson, J. H., Bergstrom, D. A., and Walters, J. R. Stimulation of both D1 and D2 dopamine receptors appears necessary for full expression of postsynaptic effects of dopamine agonists: a neurophysiological study. Brain Res. 400: 205-218, 1987.

Carpenter, M.B. and Strominger, N.L. Efferent fibers of the subthalamic nucleus in the monkey. A comparison of the efferent projections of the subthalamic nucleus, substantia nigra and globus pallidus. Am J Anat 121: 41-72, 1967.

Carpenter, M. B., Carleton, S. C., Keller, J. T., and Conte, P. Connections of the subthalamic nucleus in the monkey. Brain Res. 224: 1-29, 1981.

Carpenter, M. B., Nakano, K., and Kim, R. Nigrothalamic projections in the monkey demonstrated by autoradiographic technics. J.Comp Neurol 165: 401-415, 1976.

Carpenter, M. B., Whittier, J. R., and Mettler, F. A. Analysis of choreoid hyperkinesia in the rhesus monkey. surgical and pharmacological analysis of hyperkinesia resulting from lesions in the subthalamic nucleus of luys. Journal of Comparative Neurology 92: 293-331, 1950.

Catalan, M. J., Ishii, K., Honda, M., Samii, A., and Hallett, M. A PET study of sequential finger movements of varying length in patients with Parkinson's disease. Brain 122 ( Pt 3): 483-495, 1999.

Ceballos-Baumann, A. O., Boecker, H., Bartenstein, P., von, F., I, Riescher, H., Conrad, B., Moringlane, J. R., and Alesch, F. A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease: enhanced movement-related activity of motor-association cortex and decreased motor cortex resting activity. Arch.Neurol. 56: 997-1003, 1999.

Ceballos-Baumann, A. O., Obeso, J. A., Vitek, J. L., DeLong, M. R., Bakay, R., Linazasoro, G., and Brooks, D. J. Restoration of thalamocortical activity after posteroventral pallidotomy in Parkinson's disease. Lancet 344: 814, 1994.

Celada, P., Paladini, C. A., and Tepper, J. M. GABAergic control of rat substantia nigra dopaminergic neurons: role of globus pallidus and substantia nigra pars reticulata. Neuroscience 89: 813-825, 1999.

Centonze, D., Gubellini, P., Picconi, B., Calabresi, P., Giacomini, P., and Bernardi, G. Unilateral dopamine denervation blocks corticostriatal LTP. J.Neurophysiol. 82: 3575-3579, 1999.

Chang, H. T., Kita, H., and Kitai, S. T. The ultrastructural morphology of the subthalamic-nigral axon terminals intracellularly labeled with horseradish peroxidase. Brain Res. 299: 182-185, 1984.

Charpier, S. and Deniau, J. M. In vivo activity-dependent plasticity at cortico-striatal connections: evidence for physiological long-term potentiation. Proc.Natl.Acad.Sci.U.S.A 94: 7036-7040, 1997.

Charpier, S., Mahon, S., and Deniau, J. M. In vivo induction of striatal long-term potentiation by low-frequency stimulation of the cerebral cortex. Neuroscience 91: 1209-1222, 1999.

Chase, T. N. Levodopa therapy: consequences of the nonphysiologic replacement of dopamine. Neurology 50: S17-S25, 1998.

Chatfield, C. The analysis of time series - an introduction. London: Chapman & Hall; 1996.

Chen, R., Kumar, S., Garg, R. R., and Lang, A. E. Impairment of motor cortex activation and deactivation in Parkinson's disease. Clin Neurophysiol. 112: 600-607, 2001.

Chergui, K., Akaoka, H., Charléty, P. J., Saunier, C. F., Buda, M., and Chouvet, G. Subthalamic nucleus modulates burst firing of nigral dopamine neurones via NMDA receptors. Neuroreport 5: 1185-1188, 1994.

Cheruel, F., Dormont, J. F., Amalric, M., Schmied, A., and Farin, D. The role of putamen and pallidum in motor initiation in the cat. I. Timing of movement-related single-unit activity. Exp.Brain Res. 100: 250-266, 1994.

Chevalier, G. and Deniau, J. M. Disinhibition as a basic process in the expression of striatal functions. Trends Neurosci. 13: 277-280, 1990.

Chevalier, G., Vacher, S., Deniau, J. M., and Desban, M. Disinhibition as a basic process in the expression of striatal functions. I. The striato-nigral influence on tecto-spinal/tecto-diencephalic neurons. Brain Res. 334: 215-226, 1985.

Chiueh, C. C., Burns, R. S., Markey, S. P., Jacobowitz, D. M., and Kopin, I. J. Primate model of parkinsonism: selective lesion of nigrostriatal neurons by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine produces an extrapyramidal syndrome in rhesus monkeys. Life Sci. 36: 213-218, 1985.

Chong, R. K., Horak, F. B., and Woollacott, M. H. Parkinson's disease impairs the ability to change set quickly. J.Neurol Sci. 175: 57-70, 2000.

Chudler, E. H., Sugiyama, K., and Dong, W. K. Multisensory convergence and integration in the neostriatum and globus pallidus of the rat. Brain Res. 674: 33-45, 1995.

Clarke, C. E., Boyce, S., Robertson, R. G., Sambrook, M. A., and Crossman, A. R. Drug-induced dyskinesia in primates rendered hemiparkinsonian by intracarotid administration

of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). J.Neurol Sci. 90: 307-314, 1989.

Clarke, C. E., Sambrook, M. A., Mitchell, I. J., and Crossman, A. R. Levodopa-induced dyskinesia and response fluctuations in primates rendered parkinsonian with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). J.Neurol Sci. 78: 273-280, 1987.

Colosimo, C., Merello, M., Hughes, A. J., Sieradzan, K., and Lees, A. J. Motor response to acute dopaminergic challenge with apomorphine and levodopa in Parkinson's disease: implications for the pathogenesis of the on-off phenomenon. J.Neurol Neurosurg.Psychiatry 60: 634-637, 1996.

Conde, H., Dormont, J. F., and Farin, D. The role of the pedunculopontine tegmental nucleus in relation to conditioned motor performance in the cat. II. Effects of reversible inactivation by intracerebral microinjections. Exp.Brain Res. 121: 411-418, 1998.

Connor, N. P., Abbs, J. H., Cole, K. J., and Gracco, V. L. Parkinsonian deficits in serial multiarticulate movements for speech. Brain 112 ( Pt 4): 997-1009, 1989.

Contin, M., Riva, R., Martinelli, P., Albani, F., and Baruzzi, A. Relationship between levodopa concentration, dyskinesias, and motor effect in parkinsonian patients: a 3-year follow-up study. Clin Neuropharmacol. 20: 409-418, 1997.

Contin, M., Riva, R., Martinelli, P., Procaccianti, G., Cortelli, P., Avoni, P., and Baruzzi, A. Response to a standard oral levodopa test in parkinsonian patients with and without motor fluctuations. Clin Neuropharmacol. 13: 19-28, 1990.

Conway, B.A., Halliday, D.M., Farmer, S.F., Shahani, U., Maas, P., Weir, A.I., and Rosenberg, J.R. Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. J Physiol (Lond) 489 ( Pt 3): 917-924, 1995.

Cools, A. R., van den Bercken, J. H., Horstink, M. W., van Spaendonck, K. P., and Berger, H. J. Cognitive and motor shifting aptitude disorder in Parkinson's disease. J.Neurol.Neurosurg.Psychiatry 47: 443-453, 1984.

Cools, A. R., van den Bercken, J. H., Horstink, M. W., van Spaendonck, K. P., and Berger, H. J. Parkinson's disease: a reduced ability to shift to a new grouping if not prompted or guided. Mov Disord. 5: 178-179, 1990.

Cooper, I. S. Intracerebral injection of procaine into globus pallidus in hyperkinetic disorders. Science 119: 417-419, 1954.

Cooper, I. S. Chemopallidectomy: An investigative technique in geriatric parkinsonians. Science 121: 217-218, 1955.

Cooper, I. S. Surgical treatment of parkinsonism. Ann.Rev.Med. 16: 309-330, 1956.

Cooper, I. S. Results of 1000 consecutive basal ganglia operations for parkinsonism. Ann.Int.Med. 52: 483-499, 1960.

Corboy, D. L., Wagner, M. L., and Sage, J. I. Apomorphine for motor fluctuations and freezing in Parkinson's disease. [Review]. Annals of Pharmacotherapy 29: 282-288, 1995.

Cossette, M., Levesque, M., and Parent, A. Extrastriatal dopaminergic innervation of human basal ganglia. Neurosci.Res. 34: 51-54, 1999.

Counihan, T. J., Shinobu, L. A., Eskandar, E. N., Cosgrove, G. R., and Penney, J. B., Jr. Outcomes following staged bilateral pallidotomy in advanced Parkinson's disease. Neurology 56: 799-802, 2001.

Crawford, T. J., Henderson, L., and Kennard, C. Abnormalities of nonvisually-guided eye movements in Parkinson's disease. Brain 112: 1573-1586, 1989.

Crone, N.E., Miglioretti, D.L., Gordon, B., Sieracki, J.M., Wilson, M.T., Uematsu, S., and Lesser, R.P. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. I. Alpha and beta event-related desynchronization. Brain 121 ( Pt 12): 2271-2299, 1998.

Crossman, A. R., Mitchell, I. J., and Sambrook, M. A. Regional brain uptake of 2-deoxyglucose in N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the macaque monkey. Neuropharmacology 24: 587-591, 1985.

Crossman, A. R., Mitchell, I. J., Sambrook, M. A., and Jackson, A. Chorea and myoclonus in the monkey induced by gamma-aminobutyric acid antagonism in the lentiform complex. The site of drug action and a hypothesis for the neural mechanisms of chorea. Brain 111 ( Pt 5): 1211-1233, 1988.

Crossman, A.R. A hypothesis on the pathophysiological mechanisms that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment. Mov Disord 5: 100-108, 1990.

Crutcher, M. D. and DeLong, M. R. Single cell studies of the primate putamen. I. Functional organization. Exp.Brain Res. 53: 233-243, 1984a.

Crutcher, M. D. and DeLong, M. R. Single cell studies of the primate putamen. II. Relations to direction of movement and pattern of muscular activity. Exp.Brain Res. 53: 244-258, 1984b.

Cummings, J. L. Depression and Parkinson's disease: a review. Am.J.Psychiatry 149: 443-454, 1992.

Cummings, J. L. and Masterman, D. L. Depression in patients with Parkinson's disease. Int.J.Geriatr.Psychiatry 14: 711-718, 1999.

Cunnington, R., Iansek, R., and Bradshaw, J. L. Movement-related potentials in Parkinson's disease: external cues and attentional strategies. Mov Disord 14: 63-68, 1999.

Cunnington, R., Iansek, R., Bradshaw, J. L., and Phillips, J. G. Movement-related potentials in Parkinson's disease. Presence and predictability of temporal and spatial cues. Brain 118 ( Pt 4): 935-950, 1995.

Cunnington, R., Iansek, R., Thickbroom, G. W., Laing, B. A., Mastaglia, F. L., Bradshaw, J. L., and Phillips, J. G. Effects of magnetic stimulation over supplementary motor area on movement in Parkinson's disease. Brain 119 ( Pt 3): 815-822, 1996.

Davis, K. D., Taub, E., Houle, S., Lang, A. E., Dostrovsky, J. O., Tasker, R. R., and Lozano, A. M. Globus pallidus stimulation activates the cortical motor system during alleviation of parkinsonian symptoms. Nat.Med. 3: 671-674, 1997.

de Bie, R. M., de Haan, R. J., Nijssen, P. C., Rutgers, A. W., Beute, G. N., Bosch, D. A., Haaxma, R., Schmand, B., Schuurman, P. R., Staal, M. J., and Speelman, J. D. Unilateral pallidotomy in Parkinson's disease: a randomised, single- blind, multicentre trial. Lancet 354: 1665-1669, 1999.

Defebvre, L., Blatt, J. L., Blond, S., Bourriez, J. L., Gieu, J. D., and Destee, A. Effect of thalamic stimulation on gait in Parkinson disease. Arch Neurol 53: 898-903, 1996a.

Defebvre, L., Bourriez, J. L., Derambure, P., Duhamel, A., Guieu, J. D., and Destee, A. Influence of chronic administration of L-DOPA on event-related desynchronization of mu rhythm preceding voluntary movement in Parkinson's disease. Electroencephalogr.Clin Neurophysiol. 109: 161-167, 1998.

Defebvre, L., Bourriez, J. L., Destee, A., and Guieu, J. D. Movement related desynchronisation pattern preceding voluntary movement in untreated Parkinson's disease. J.Neurol Neurosurg.Psychiatry 60: 307-312, 1996b.

Deiber, M.-P., Pollak, P., Passingham, R., Landais, P., Gervason, C., Cinotti, L., Friston, K., Frackowiak, R., Mauguiere, F., and Benabid, A. L. Thalamic stimulation and suppression of parkinsonian tremor. Evidence of a cerebellar deactivation using positron emission tomography. Brain 116: 267-279, 1993.

DeLong, M. R. Activity of pallidal neurons during movement. J.Neurophysiol. 34: 414-427, 1971.

DeLong, M. R. The neurophysiologic basis of abnormal movements in basal ganglia disorders. Neurobehav.Toxicol.Teratol. 5: 611-616, 1983.

DeLong, M. R. Primate models of movement disorders of basal ganglia origin. Trends Neurosci. 13: 281-285, 1990.

DeLong, M. R., Crutcher, M. D., and Georgopoulos, A. P. Relations between movement and single cell discharge in the substantia nigra of the behaving monkey. J.Neurosci. 3: 1599-1606, 1983.

DeLong, M. R., Crutcher, M. D., and Georgopoulos, A. P. Primate globus pallidus and subthalamic nucleus: functional organization. J.Neurophysiol. 53: 530-543, 1985.

DeLong, M. R., Georgopoulos, A. P., Crutcher, M. D., Mitchell, S. J., Richardson, R. T., and Alexander, G. E. Functional organization of the basal ganglia: contributions of single- cell recording studies. Ciba Found.Symp. 107:64-82: 64-82, 1984.

Demer, J.L. and Robinson, D.A. Effects of reversible lesions and stimulation of olivocerebellar system on vestibuloocular reflex plasticity. J Neurophysiol 47: 1084-1107, 1982.

Deniau, J. M. and Chevalier, G. Disinhibition as a basic process in the expression of striatal functions. II. The striato-nigral influence on thalamocortical cells of the ventromedial thalamic nucleus. Brain Res. 334: 227-233, 1985.

Descarries, L., Lemay, B., Doucet, G., and Berger, B. Regional and laminar density of the dopamine innervation in adult rat cerebral cortex. Neuroscience 21: 807-824, 1987.

Deschenes, M., Bourassa, J., and Parent, A. Two different types of thalamic fibers innervate the rat striatum. Brain Res. 701: 288-292, 1995.

Deschenes, M., Bourassa, J., and Parent, A. Striatal and cortical projections of single neurons from the central lateral thalamic nucleus in the rat. Neuroscience 72: 679-687, 1996.

Deshaies, P., Bedard, P., Falardeau, P., and Di Paolo, T. Behavioral and biochemical evidence of apomorphine-induced supersensitivity of the striatal dopamine receptors. Neuropharmacology 23: 1219-1222, 1984.

Deuschl, G., Bain, P., and Brin, M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord 13 Suppl 3: 2-23, 1998.

Deuschl, G., Raethjen, J., Baron, R., Lindemann, M., Wilms, H., and Krack, P. The pathophysiology of parkinsonian tremor: a review. J.Neurol 247 Suppl 5: V33-V48, 2000.

Dick, J. P., Rothwell, J. C., Berardelli, A., Thompson, P. D., Gioux, M., Benecke, R., Day, B. L., and Marsden, C. D. Associated postural adjustments in Parkinson's disease. J.Neurol.Neurosurg.Psychiatry 49: 1378-1385, 1986.

Dick, J. P., Rothwell, J. C., Day, B. L., Cantello, R., Buruma, O., Gioux, M., Benecke, R., Berardelli, A., Thompson, P. D., and Marsden, C. D. The Bereitschaftspotential is abnormal in Parkinson's disease. Brain 112: 233-244, 1989.

Diederich, N., Goetz, C. G., Stebbins, G. T., Klawans, H. L., Nittner, K., Koulosakis, A., Sanker, P., and Sturm, V. Blinded evaluation confirms long-term asymmetric effect of unilateral thalamotomy or subthalamotomy on tremor in Parkinson's disease. Neurology 42: 1311-1314, 1992.

Diederich, N. J., Goetz, C. G., Raman, R., Pappert, E. J., Leurgans, S., and Piery, V. Poor visual discrimination and visual hallucinations in Parkinson's disease. Clin Neuropharmacol. 21: 289-295, 1998.

Dietz, M. A., Goetz, C. G., and Stebbins, G. T. Evaluation of a modified inverted walking stick as a treatment for parkinsonian freezing episodes. Mov Disord 5: 243-247, 1990.

Dietz, V., Quintern, J., and Berger, W. Electrophysiological studies of gait in spasticity and rigidity. Evidence that altered mechanical properties of muscle contribute to hypertonia. Brain 104: 431-449, 1981.

Dogali, M., Beric, A., Sterio, D., Eidelberg, D., Fazzini, E., Takikawa, S., Samelson, D. R., Devinsky, O., and Kolodny, E. H. Anatomic and physiological considerations in pallidotomy for Parkinson's disease. Stereotact.Funct.Neurosurg. 62: 53-60, 1994.

Dogali, M., Fazzini, E., Kolodny, E., Eidelberg, D., Sterio, D., Devinsky, O., and Beric, A. Stereotactic ventral pallidotomy for Parkinson's disease. Neurology 45: 753-761, 1995.

Donoghue, J.P., Sanes, J.N., Hatsopoulos, N.G., and Gaal, G. Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. J Neurophysiol 79: 159-173, 1998.

Dormont, J. F., Conde, H., Cheruel, F., and Farin, D. Correlations between activity of pallidal neurons and motor parameters. Somatosens.Mot.Res. 14: 281-294, 1997.

Dormont, J. F., Conde, H., and Farin, D. The role of the pedunculopontine tegmental nucleus in relation to conditioned motor performance in the cat. I. Context-dependent and reinforcement-related single unit activity. Exp.Brain Res. 121: 401-410, 1998.

Dostrovsky, J. O., Levy, R., Wu, J. P., Hutchison, W. D., Tasker, R. R., and Lozano, A. M. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J.Neurophysiol. 84: 570-574, 2000.

Dostrovsky, J. O., Sher, G. D., Davis, K. D., Parrent, A. G., Hutchison, W. D., and Tasker, R. R. Microinjection of lidocaine into human thalamus: a useful tool in stereotactic surgery. Stereotact.Funct.Neurosurg. 60: 168-174, 1993.

Doudet, D., Gross, C., Lebrun-Grandie, P., and Bioulac, B. MPTP primate model of Parkinson's disease: a mechanographic and electromyographic study. Brain Res. 335: 194-199, 1985.

Doudet, D. J., Gross, C., Arluison, M., and Bioulac, B. Modifications of precentral cortex discharge and EMG activity in monkeys with MPTP-induced lesions of DA nigral neurons. Exp.Brain Res. 80: 177-188, 1990.

Drago, J., Gerfen, C. R., Lachowicz, J. E., Steiner, H., Hollon, T. R., Love, P. E., Ooi, G. T., Grinberg, A., Lee, E. J., Huang, S. P., and . Altered striatal function in a mutant mouse lacking D1A dopamine receptors. Proc.Natl.Acad.Sci.U.S.A 91: 12564-12568, 1994.

Dromey, C., Kumar, R., Lang, A. E., and Lozano, A. M. An investigation of the effects of subthalamic nucleus stimulation on acoustic measures of voice. Mov Disord 15: 1132-1138, 2000.

Dube, L., Smith, A. D., and Bolam, J. P. Identification of synaptic terminals of thalamic or cortical origin in contact with distinct medium-size spiny neurons in the rat neostriatum. J.Comp Neurol 267: 455-471, 1988.

Duffau, H., Tzourio, N., Caparros-Lefebvre, D., Parker, F., and Mazoyer, B. Tremor and voluntary repetitive movement in Parkinson's disease: comparison before and after L-dopa with positron emission tomography. Exp.Brain Res. 107: 453-462, 1996.

Duncan, G.H., Bushnell, M.C., Oliveras, J.L., Bastrash, N., and Tremblay, N. Thalamic VPM nucleus in the behaving monkey. III. Effects of reversible inactivation by lidocaine on thermal and mechanical discrimination. J Neurophysiol 70: 2086-2096, 1993.

Eblen, F. and Graybiel, A. M. Highly restricted origin of prefrontal cortical inputs to striosomes in the macaque monkey. J.Neurosci. 15: 5999-6013, 1995.

Ebmeier, K. P., Potter, D. D., Cochrane, R. H., Crawford, J. R., Stewart, L., Calder, S. A., Besson, J. A., and Salzen, E. A. Event related potentials, reaction time, and cognitive performance in idiopathic Parkinson's disease. Biol.Psychol. 33: 73-89, 1992.

Edley, S. M. and Graybiel, A. M. The afferent and efferent connections of the feline nucleus tegmenti pedunculopontinus, pars compacta. J.Comp Neurol 217: 187-215, 1983.

Ehringer, H. and Hornykiewicz, O. Verteilung von noradrenalin und dopamin (3-hydroxytyramin) im gehirn des menschen und ihr verhalten bei erkrankungen des extrapyramidalen systems. Klin.Wschr. 38: 1236-1239, 1960.

Eidelberg, D., Moeller, J. R., Ishikawa, T., Dhawan, V., Spetsieris, P., Silbersweig, D., Stern, E., Woods, R. P., Fazzini, E., Dogali, M., and Beric, A. Regional metabolic correlates of surgical outcome following unilateral pallidotomy for Parkinson's disease. Ann.Neurol. 39: 450-459, 1996.

Eidelberg, D., Moeller, J. R., Kazumata, K., Antonini, A., Sterio, D., Dhawan, V., Spetsieris, P., Alterman, R., Kelly, P. J., Dogali, M., Fazzini, E., and Beric, A. Metabolic correlates of pallidal neuronal activity in Parkinson's disease. Brain 120: 1315-1324, 1997.

Elble, R. J. Central mechanisms of tremor. J.Clin Neurophysiol. 13: 133-144, 1996.

Elizan, T. S. and Casals, J. The viral hypothesis in parkinsonism. J.Neural Transm.Suppl 19: 75-88, 1983.

Ellaway, P. H., Davey, N. J., Maskill, D. W., and Dick, J. P. The relation between bradykinesia and excitability of the motor cortex assessed using transcranial magnetic stimulation in normal and parkinsonian subjects. Electroencephalogr.Clin.Neurophysiol. 97: 169-178, 1995.

Elsworth, J. D., Deutch, A. Y., Redmond, D. E., Taylor, J. R., Sladek, J. R., and Roth, R. H. Symptomatic and asymptomatic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated primates: biochemical changes in striatal regions. Neuroscience 33: 323-331, 1989.

Elsworth, J. D., Deutch, A. Y., Redmond, D. E., Jr., Sladek, J. R., Jr., and Roth, R. H. Differential responsiveness to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine toxicity in sub-regions of the primate substantia nigra and striatum. Life Sci. 40: 193-202, 1987b.

Elsworth, J. D., Deutch, A. Y., Redmond, D. E., Jr., Sladek, J. R., Jr., and Roth, R. H. Effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on catecholamines and metabolites in primate brain and CSF. Brain Res. 415: 293-299, 1987a.

Elsworth, J. D., Taylor, J. R., Sladek, J. R., Collier, T. J., Redmond, D. E., and Roth, R. H. Striatal dopaminergic correlates of stable parkinsonism and degree of recovery in old-world primates one year after MPTP treatment. Neuroscience 95: 399-408, 2000.

Erro, E., Lanciego, J. L., and Gimenez-Amaya, J. M. Relationships between thalamostriatal neurons and pedunculopontine projections to the thalamus: a neuroanatomical tract-tracing study in the rat. Exp.Brain Res. 127: 162-170, 1999.

Fahn, S. The spectrum of levodopa-induced dyskinesias. Ann Neurol 47: S2-S9, 2000.

Feger, J., Mouroux, M., Benazzouz, A., Boraud, T., Gross, C., and Crossman, A. The subthalamic nucleus: A more complex structure than expected. In Percheron, G. ed. The basal ganglia IV. New York, Plenum Press. 1994, 371-382.

Filion, M. Effects of interruption of the nigrostriatal pathway and of dopaminergic agents on the spontaneous activity of globus pallidus neurons in the awake monkey. Brain Res. 178: 425-441, 1979.

Filion, M. and Tremblay, L. Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res. 547: 142-151, 1991.

Filion, M., Tremblay, L., and Bedard, P. J. Abnormal influences of passive limb movement on the activity of globus pallidus neurons in parkinsonian monkeys. Brain Res. 444: 165-176, 1988.

Filion, M., Tremblay, L., and Bedard, P. J. Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res. 547: 152-161, 1991.

Filion, M., Tremblay, L., Matsumura, M., and Richard, H. Dynamic focusing of informational convergence in basal ganglia. Rev.Neurol (Paris) 150: 627-633, 1994.

Findley, L. J., Gresty, M. A., and Halmagyi, G. M. Tremor, the cogwheel phenomenon and clonus in Parkinson's disease. J.Neurol Neurosurg.Psychiatry 44: 534-546, 1981.

Flaherty, A. W. and Graybiel, A. M. Corticostriatal transformations in the primate somatosensory system. Projections from physiologically mapped body-part representations. J.Neurophysiol. 66: 1249-1263, 1991.

Flaherty, A. W. and Graybiel, A. M. Two input systems for body representations in the primate striatal matrix: experimental evidence in the squirrel monkey. J.Neurosci. 13: 1120-1137, 1993.

Flaherty, A. W. and Graybiel, A. M. Input-output organization of the sensorimotor striatum in the squirrel monkey. J.Neurosci. 14: 599-610, 1994.

Flowers, K. A. and Robertson, C. The effect of Parkinson's disease on the ability to maintain a mental set. J.Neurol.Neurosurg.Psychiatry 48: 517-529, 1985.

Forno, L. S., Langston, J. W., DeLanney, L. E., Irwin, I., and Ricaurte, G. A. Locus ceruleus lesions and eosinophilic inclusions in MPTP-treated monkeys. Ann Neurol 20: 449-455, 1986.

Francois, C., Savy, C., Jan, C., Tande, D., Hirsch, E. C., and Yelnik, J. Dopaminergic innervation of the subthalamic nucleus in the normal state, in MPTP-treated monkeys, and in Parkinson's disease patients. J.Comp Neurol 425: 121-129, 2000.

Francois, C., Yelnik, J., and Percheron, G. Golgi study of the primate substantia nigra. II. Spatial organization of dendritic arborizations in relation to the cytoarchitectonic boundaries and to the striatonigral bundle. J.Comp Neurol 265: 473-493, 1987.

Fujimoto, K. and Kita, H. Response characteristics of subthalamic neurons to the stimulation of the sensorimotor cortex in the rat. Brain Res. 609: 185-192, 1993.

Gancher, S. Pharmacokinetics of apomorphine in Parkinson's disease. [Review]. J.Neural Transm.Suppl. Supplementum. 45: 137-141, 1995.

Garcia-Rill, E. The basal ganglia and the locomotor regions. Brain Res. 396: 47-63, 1986.

Georgiou, N., Bradshaw, J. L., Iansek, R., Phillips, J. G., Mattingley, J. B., and Bradshaw, J. A. Reduction in external cues and movement sequencing in Parkinson's disease. J.Neurol.Neurosurg.Psychiatry 57: 368-370, 1994.

Georgiou, N., Iansek, R., Bradshaw, J. L., Phillips, J. G., Mattingley, J. B., and Bradshaw, J. A. An evaluation of the role of internal cues in the pathogenesis of parkinsonian hypokinesia. Brain 116: 1575-1587, 1993.

Georgopoulos, A. P., DeLong, M. R., and Crutcher, M. D. Relations between parameters of step-tracking movements and single cell discharge in the globus pallidus and subthalamic nucleus of the behaving monkey. J.Neurosci. 3: 1586-1598, 1983.

Gerfen, C. R. Synaptic organization of the striatum. J.Electron Microsc.Tech. 10: 265-281, 1988.

Gerfen, C. R. The neostriatal mosaic: multiple levels of compartmental organization. Trends Neurosci. 15: 133-139, 1992.

Gerfen, C. R., Engber, T. M., Mahan, L. C., Susel, Z., Chase, T. N., Monsma, F. J., and Sibley, D. R. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science 250: 1429-1432, 1990.

Gerfen, C. R. and Young, W. S. Distribution of striatonigral and striatopallidal peptidergic neurons in both patch and matrix compartments: an in situ hybridization histochemistry and fluorescent retrograde tracing study. Brain Res. 460: 161-167, 1988.

Gerlach, M. and Riederer, P. F. Time sequences of dopaminergic cell death in Parkinson's disease: indications for neuroprotective studies. Adv Neurol 80: 219-225, 1999.

Gerstein, G.L. and Perkel, D.H. Mutual temporal relationships among neuronal spike trains. Statistical techniques for display and analysis. Biophys J 12: 453-473, 1972.

Gill, S. S. and Heywood, P. Bilateral dorsolateral subthalamotomy for advanced Parkinson's disease. Lancet 350: 1224, 1997.

Glaser, E. M. and Ruchkin, D. S. Principals of neurobiological signal analysis. New York, Academic Press. 1976.

Goldenberg, G. Performance of concurrent non-motor tasks in Parkinson's disease. J.Neurol 237: 191-196, 1990.

Grafton, S. T., Waters, C., Sutton, J., Lew, M. F., and Couldwell, W. Pallidotomy increases activity of motor association cortex in Parkinson's disease: a positron emission tomographic study. Ann.Neurol. 37: 776-783, 1995.

Graham, W. C., Robertson, R. G., Sambrook, M. A., and Crossman, A. R. Injection of excitatory amino acid antagonists into the medial pallidal segment of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated primate reverses motor symptoms of parkinsonism. Life Sci. 47: L91-L97, 1990.

Graybiel, A. M. Neurotransmitters and neuromodulators in the basal ganglia. Trends Neurosci. 13: 244-254, 1990.

Graybiel, A. M., Aosaki, T., Flaherty, A. W., and Kimura, M. The basal ganglia and adaptive motor control. Science 265: 1826-1831, 1994.

Graybiel, A. M. and Ragsdale, C. W., Jr. Histochemically distinct compartments in the striatum of human, monkeys, and cat demonstrated by acetylthiocholinesterase staining. Proc.Natl.Acad.Sci.U.S.A 75: 5723-5726, 1978.

Greenamyre, J. T. Glutamate-dopamine interactions in the basal ganglia: relationship to Parkinson's disease. J.Neural Transm.Gen.Sect. 91: 255-269, 1993.

Greenamyre, J. T. Pharmacological pallidotomy with glutamate antagonists. Ann.Neurol. 39: 557-558, 1996.

Grofova, I., Deniau, J. M., and Kitai, S. T. Morphology of the substantia nigra pars reticulata projection neurons intracellularly labeled with HRP. J.Comp Neurol 208: 352-368, 1982.

Guridi, J., Herrero, M. T., Luquin, M. R., Guillen, J., Ruberg, M., Laguna, J., Vila, M., Javoy-Agid, F., Agid, Y., Hirsch, E., and Obeso, J. A. Subthalamotomy in parkinsonian monkeys. behavioural and biochemical analysis. Brain 119: 1717-1727, 1996.

Guridi, J., Herrero, M. T., Luquin, R., Guillen, J., and Obeso, J. A. Subthalamotomy improves MPTP-induced parkinsonism in monkeys. Stereotact.Funct.Neurosurg. 62: 98-102, 1994.

Hadar, U. and Rose, F. C. Is parkinsonian arm tremor a resting tremor? Eur.Neurol 33: 221-228, 1993.

Hallett, M. and Khoshbin, S. A physiological mechanism of bradykinesia. Brain 103: 301-314, 1980.

Hamada, I. and DeLong, M. R. Excitotoxic acid lesions of the primate subthalamic nucleus result in reduced pallidal neuronal activity during active holding. J.Neurophysiol. 68: 1859-1866, 1992a.

Hamada, I. and DeLong, M. R. Excitotoxic acid lesions of the primate subthalamic nucleus result in transient dyskinesias of the contralateral limbs. J.Neurophysiol. 68: 1850-1858, 1992b.

Hamada, I., DeLong, M. R., and Mano, N. Activity of identified wrist-related pallidal neurons during step and ramp wrist movements in the monkey. J.Neurophysiol. 64: 1892-1906, 1990.

Hammond, C., Rouzaire-Dubois, B., Feger, J., Jackson, A., and Crossman, A. R. Anatomical and electrophysiological studies on the reciprocal projections between the subthalamic nucleus and nucleus tegmenti pedunculopontinus in the rat. Neuroscience 9: 41-52, 1983.

Hassani, O. K. and Feger, J. Effects of intrasubthalamic injection of dopamine receptor agonists on subthalamic neurons in normal and 6-hydroxydopamine-lesioned rats: an electrophysiological and c-Fos study. Neuroscience 92: 533-543, 1999.

Hassani, O. K., Francois, C., Yelnik, J., and Feger, J. Evidence for a dopaminergic innervation of the subthalamic nucleus in the rat. Brain Res. 749: 88-94, 1997.

Hassani, O. K., Mouroux, M., and Feger, J. Increased subthalamic neuronal activity after nigral dopaminergic lesion independent of disinhibition via the globus pallidus. Neuroscience 72: 105-115, 1996.

Hazrati, L. N. and Parent, A. Convergence of subthalamic and striatal efferents at pallidal level in primates: an anterograde double-labeling study with biocytin and PHA-L. Brain Res. 569: 336-340, 1992b.

Hazrati, L. N. and Parent, A. The striatopallidal projection displays a high degree of anatomical specificity in the primate. Brain Res. 592: 213-227, 1992a.

Hedreen, J. C. and DeLong, M. R. Organization of striatopallidal, striatonigral, and nigrostriatal projections in the macaque. J.Comp Neurol. 304: 569-595, 1991.

Hellwig, B., Haussler, S., Lauk, M., Guschlbauer, B., Koster, B,, Kristeva-Feige, R., Timmer, J., and Lucking, C.H. Tremor-correlated cortical activity detected by electroencephalography. Clin Neurophysiol 111: 806-809, 2000.

Henry, B., Crossman, A. R., and Brotchie, J. M. Characterization of enhanced behavioral responses to L-DOPA following repeated administration in the 6-hydroxydopamine-lesioned rat model of Parkinson's disease. Exp.Neurol 151: 334-342, 1998.

Hikosaka, O. and Wurtz, R. H. Visual and oculomotor functions of monkey substantia nigra pars reticulata. III. Memory-contingent visual and saccade responses. J.Neurophysiol. 49: 1268-1284, 1983a.

Hikosaka, O. and Wurtz, R. H. Visual and oculomotor functions of monkey substantia nigra pars reticulata. IV. Relation of substantia nigra to superior colliculus. J.Neurophysiol. 49: 1285-1301, 1983b.

Hoover, J. E. and Strick, P. L. Multiple output channels in the basal ganglia. Science 259: 819-821, 1993.

Hoover, J. E. and Strick, P. L. The organization of cerebellar and basal ganglia outputs to primary motor cortex as revealed by retrograde transneuronal transport of herpes simplex virus type 1. J.Neurosci. 19: 1446-1463, 1999.

Horak, F. B. and Anderson, M. E. Influence of globus pallidus on arm movements in monkeys. I. Effects of kainic acid-induced lesions. J.Neurophysiol. 52: 290-304, 1984.

Horak, F. B., Frank, J., and Nutt, J. Effects of dopamine on postural control in parkinsonian subjects: scaling, set, and tone. J.Neurophysiol. 75: 2380-2396, 1996.

Horak, F. B., Nutt, J. G., and Nashner, L. M. Postural inflexibility in parkinsonian subjects. J.Neurol Sci. 111: 46-58, 1992.

Hornykiewicz, O. and Kish, S. J. Biochemical pathophysiology of Parkinson's disease. Adv Neurol 45: 19-34, 1987.

Horowski, R., Horowski, L., Vogel, S., Poewe, W., and Kielhorn, F. W. An essay on Wilhelm von Humboldt and the shaking palsy: first comprehensive description of Parkinson's disease by a patient. Neurology 45: 565-568, 1995.

Horstink, M. W., Berger, H. J., van Spaendonck, K. P., van den Bercken, J. H., and Cools, A. R. Bimanual simultaneous motor performance and impaired ability to shift attention in Parkinson's disease. J.Neurol.Neurosurg.Psychiatry 53: 685-690, 1990.

Hughes, A. J., Daniel, S. E., Blankson, S., and Lees, A. J. A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol 50: 140-148, 1993.

Hupe, J.M., Chouvet, G., and Bullier, J. Spatial and temporal parameters of cortical inactivation by GABA. J Neurosci Methods 86: 129-143, 1999.

Hurtado, J. M., Gray, C. M., Tamas, L. B., and Sigvardt, K. A. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. Proc.Natl.Acad.Sci.U.S.A 96: 1674-1679, 1999.

Hurtado, J. M., Lachaux, J. P., Beckley, D. J., Gray, C. M., and Sigvardt, K. A. Inter- and intralimb oscillator coupling in parkinsonian tremor. Mov Disord 15: 683-691, 2000.

Hurtig, H. I. Problems with current pharmacologic treatment of Parkinson's disease. [Review]. Exp.Neurol. 144: 10-16, 1997.

Hutchison, W. D., Allan, R. J., Opitz, H., Levy, R., Dostrovsky, J. O., Lang, A. E., and Lozano, A. M. Neurophysiological identification of the subthalamic nucleus in surgery for Parkinson's disease. Ann.Neurol. 44: 622-628, 1998a.

Hutchison, W. D. Microelectrode techniques and findings of globus pallidus. In Krauss, J. K., Grossman, R. G., and Jankovic, J. eds. Pallidal surgery for the treatment of Parkinson's disease and movement disorders. Philadelphia, Lippincott-Raven. 1998b, 135-152.

Hutchison, W. D., Lozano, A. M., Davis, K. D., Saint-Cyr, J. A., Lang, A. E., and Dostrovsky, J. O. Differential neuronal activity in segments of globus pallidus in Parkinson's disease patients. Neuroreport 5: 1533-1537, 1994a.

Hutchison, W. D., Lozano, A. M., Kiss Z.H.T., Davis K.D., Lang, A. E., Tasker, R. R., Dostrovsky, J.O. Tremor-related activity (TRA) in globus pallidus of Parkinson's disease (PD) patients. Soc. Neurosci. Abstr. 20: 783, 1994b.

Hutchison, W. D., Lozano, A. M., Tasker, R. R., Lang, A. E., and Dostrovsky, J. O. Identification and characterization of neurons with tremor-frequency activity in human globus pallidus. Exp.Brain Res. 113: 557-563, 1997.

Ilinsky, I. A., Tourtellotte, W. G., and Kultas-Ilinsky, K. Anatomical distinctions between the two basal ganglia afferent territories in the primate motor thalamus. Stereotact.Funct.Neurosurg. 60: 62-69, 1993.

Inase, M. and Tanji, J. Thalamic distribution of projection neurons to the primary motor cortex relative to afferent terminal fields from the globus pallidus in the macaque monkey. J.Comp.Neurol. 353: 415-426, 1995.

Inglis, W. L. and Winn, P. The pedunculopontine tegmental nucleus: Where the striatum meets the reticular formation. Prog.Neurobiol. 47: 1-29, 1995.

Jaeger, D., Gilman, S., and Aldridge, J. W. Primate basal ganglia activity in a precued reaching task: preparation for movement. Exp.Brain Res. 95: 51-64, 1993.

Jahnsen, H. and Llinas, R. Ionic basis for the electro-responsiveness and oscillatory properties of guinea-pig thalamic neurones in vitro. J.Physiol 349: 227-247, 1984.

Jenkins, I. H., Fernandez, W., Playford, E. D., Lees, A. J., Frackowiak, R. S., Passingham, R. E., and Brooks, D. J. Impaired activation of the supplementary motor area in Parkinson's disease is reversed when akinesia is treated with apomorphine. Ann.Neurol. 32: 749-757, 1992.

Jones, D. L., Phillips, J. G., Bradshaw, J. L., Iansek, R., and Bradshaw, J. A. Impairment in bilateral alternating movements in Parkinson's disease? J.Neurol.Neurosurg.Psychiatry 55: 503-506, 1992.

Kaneoke, Y. and Vitek, J.L. Burst and oscillation as disparate neuronal properties. J.Neurosci.Meth. 68:211-223, 1996.

Karmon, B. and Bergman, H. Detection of neuronal periodic oscillations in the basal ganglia of normal and parkinsonian monkeys. Isr.J.Med.Sci. 29: 570-579, 1993.

Kato, M. and Kimura, M. Effects of reversible blockade of basal ganglia on a voluntary arm movement. J.Neurophysiol. 68: 1516-1534, 1992.

Kawashima, Y., Takahashi, A., Hirato, M., and Ohye, C. Stereotactic Vim-Vo-thalamotomy for choreatic movement disorder. Acta Neurochir.Suppl (Wien.) 52: 103-106, 1991.

Kemp, J. M. and Powell, T. P. The cortico-striate projection in the monkey. Brain 93: 525-546, 1970.

Kilner, J.M., Baker, S.N., Salenius S., Hari, R., and Lemon, R.N. Human cortical muscle coherence is directly related to specific motor parameters. J Neurosci 20: 8838-8845, 2000.

Kimura, M. The role of primate putamen neurons in the association of sensory stimuli with movement. Neurosci.Res. 3: 436-443, 1986.

Kincaid, A. E., Zheng, T., and Wilson, C. J. Connectivity and convergence of single corticostriatal axons. J.Neurosci. 18: 4722-4731, 1998.

Kish, S. J., Shannak, K., and Hornykiewicz, O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. N.Engl.J.Med. 318: 876-880, 1988.

Kita, H., Chang, H. T., and Kitai, S. T. The morphology of intracellularly labeled rat subthalamic neurons: a light microscopic analysis. J.Comp Neurol 215: 245-257, 1983.

Kitai, S. T. and Deniau, J. M. Cortical inputs to the subthalamus: intracellular analysis. Brain Res.Mol.Brain Res. 214: 411-415, 1981.

Kitt, C. A., Cork, L. C., Eidelberg, F., Joh, T. H., and Price, D. L. Injury of nigral neurons exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine: a tyrosine hydroxylase immunocytochemical study in monkey. Neuroscience 17: 1089-1103, 1986.

Klockgether, T. and Turski, L. NMDA antagonists potentiate antiparkinsonian actions of L-dopa in monoamine-depleted rats. Ann Neurol 28: 539-546, 1990.

Klockgether, T. and Turski, L. Toward an understanding of the role of glutamate in experimental parkinsonism: Agonist-sensitive sites in the basal ganglia. Ann.Neurol. 34: 585-593, 1993.

Klockgether, T., Turski, L., Honore, T., Zhang, Z. M., Gash, D. M., Kurlan, R., and Greenamyre, J. T. The AMPA receptor antagonist NBQX has antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys. Ann Neurol 30: 717-723, 1991.

Kojima, J., Yamaji, Y., Matsumura, M., Nambu, A., Inase, M., Tokuno, H., Takada, M., and Imai, H. Excitotoxic lesions of the pedunculopontine tegmental nucleus produce contralateral hemiparkinsonism in the monkey. Neurosci.Lett. 226: 111-114, 1997.

Koller, W., Pahwa, R., Busenbark, K., Hubble, J., Wilkinson, S., Lang, A. E., Sime, E., Lozano, A. M., Hauser, R., Malapira, T., Smith, D., Tarsy, D., Miyawaki, E., Norregaard,

T., and Olanow, C. W. High-Frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Annals of Neurology 42: 292-299, 1997.

Koller, W. C. Levodopa in the treatment of Parkinson's disease. Neurology 55: S2-S7, 2000.

Koller, W. C. and Montgomery, E. B. Issues in the early diagnosis of Parkinson's disease. Neurology 49: S10-S25, 1997.

Kopin, I. J. and Markey, S. P. MPTP toxicity: implications for research in Parkinson's disease. Annu.Rev.Neurosci. 11: 81-96, 1988.

Krack, P., Benazzouz, A., Pollak, P., Limousin, P., Piallat, B., Hoffmann, D., Xie, J., and Benabid, A. L. Treatment of tremor in Parkinson's disease by subthalamic nucleus stimulation. Mov Disord. 13: 907-914, 1998b.

Krack, P., Pollak, P., Limousin, P., Benazzouz, A., and Benabid, A. L. Stimulation of subthalamic nucleus alleviates tremor in Parkinson's disease [letter]. Lancet 350: 1675, 1997.

Krack, P., Pollak, P., Limousin, P., Hoffmann, D., Xie, J., Benazzouz, A., and Benabid, A. L. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 121: 451-457, 1998a.

Kreiss, D. S., Anderson, L. A., and Walters, J. R. Apomorphine and dopamine D(1) receptor agonists increase the firing rates of subthalamic nucleus neurons. Neuroscience 72: 863-876, 1996.

Kreiss, D. S., Mastropietro, C. W., Rawji, S. S., and Walters, J. R. The response of subthalamic nucleus neurons to dopamine receptor stimulation in a rodent model of Parkinson's disease. J.Neurosci. 17: 6807-6819, 1997.

Kultas-Ilinsky, K., Ilinsky, I., Warton, S., and Smith, K. R. Fine structure of nigral and pallidal afferents in the thalamus: an EM autoradiography study in the cat. J.Comp Neurol 216: 390-405, 1983.

Kumar, R., Lozano, A. M., Kim, Y. J., Hutchison, W. D., Sime, E., Halket, E., and Lang, A. E. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. Neurology 51: 850-855, 1998b.

Kumar, R., Lozano, A. M., Montgomery, E., and Lang, A. E. Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease. Mov Disord. 13 Suppl 1:73-82: 73-82, 1998a.

Kumar, R., Lozano, A. M., Sime, E., Halket, E., and Lang, A. E. Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. Neurology 53: 561-566, 1999.

Laitinen, L. V., Bergenheim, A. T., and Hariz, M. I. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. J.Neurosurg. 76: 53-61, 1992a.

Laitinen, L. V., Bergenheim, A. T., and Hariz, M. I. Ventroposterolateral pallidotomy can abolish all parkinsonian symptoms. Stereotact.Funct.Neurosurg. 58: 14-21, 1992b.

Lance, J. W., Schwab, R. S., and Peterson, E. A. Action tremor and cogwheel phenomenon in Parkinson's disease. Brain 86: 95-110, 1963.

Lang, A. E., Lozano, A. M., Montgomery, E., Duff, J., Tasker, R., and Hutchinson, W. Posteroventral medial pallidotomy in advanced Parkinson's disease. N.Engl.J.Med. 337: 1036-1042, 1997.

Lang, A. E. and Lozano, A. M. Parkinson's disease. First of two parts. N.Engl.J.Med. 339: 1044-1053, 1998a.

Lang, A. E. and Lozano, A. M. Parkinson's disease. Second of two parts. N.Engl.J.Med. 339: 1130-1143, 1998b.

Lang, A. E., Duff, J., Saint-Cyr, J. A., Trepanier, L., Gross, R. E., Lombardi, W., Montgomery, E., Hutchinson, W., and Lozano, A. M. Posteroventral medial pallidotomy in Parkinson's disease. J.Neurol 246 Suppl 2: II28-II41, 1999.

Langston, J. W., Forno, L. S., Rebert, C. S., and Irwin, I. Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyrine (MPTP) in the squirrel monkey. Brain Res. 292: 390-394, 1984a.

Langston, J. W., Langston, E. B., and Irwin, I. MPTP-induced parkinsonism in human and non-human primates--clinical and experimental aspects. Acta Neurol Scand.Suppl 100: 49-54, 1984b.

Lavoie, B. and Parent, A. Pedunculopontine nucleus in the squirrel monkey: projections to the basal ganglia as revealed by anterograde tract-tracing methods. J Comp Neurol 344: 210-231, 1994.

Lee, M. S. and Marsden, C. D. Movement disorders following lesions of the thalamus or subthalamic region. [Review]. Mov.Disord. 9: 493-507, 1994.

Lee, R. G. Pathophysiology of rigidity and akinesia in Parkinson's disease. Eur.Neurol 29 Suppl 1: 13-18, 1989.

Lee, R. G. and Stein, R. B. Resetting of tremor by mechanical perturbations: a comparison of essential tremor and parkinsonian tremor. Ann Neurol 10: 523-531, 1981.

Lees, A. J. and Smith, E. Cognitive deficits in the early stages of Parkinson's disease. Brain 106 (Pt 2): 257-270, 1983.

Legendy, C. R. and Salcman, M. Bursts and recurrences of bursts in the spike trains of spontaneously active striate cortex neurons. J.Neurophysiol. 53: 926-939, 1985.

Lemstra, A. W., Verhagen, M. L., Lee, J. I., Dougherty, P. M., and Lenz, F. A. Tremor-frequency (3-6 Hz) activity in the sensorimotor arm representation of the internal segment of the globus pallidus in patients with Parkinson's disease. Neurosci.Lett. 267: 129-132, 1999.

Lenz, F. A., Kwan, H. C., Dostrovsky, J. O., Tasker, R. R., Murphy, J. T., and Lenz, Y. E. Single unit analysis of the human ventral thalamic nuclear group. Activity correlated with movement. Brain 113: 1795-1821, 1990.

Lenz, F. A., Kwan, H. C., Martin, R. L., Tasker, R. R., Dostrovsky, J. O., and Lenz, Y. E. Single unit analysis of the human ventral thalamic nuclear group. Tremor-related activity in functionally identified cells. Brain 117: 531-543, 1994.

Lenz, F. A., Normand, S. L., Kwan, H. C., Andrews, D., Rowland, L. H., Jones, M. W., Seike, M., Lin, Y. C., Tasker, R. R., and Dostrovsky, J. O. Statistical prediction of the optimal site for thalamotomy in parkinsonian tremor. Mov Disord. 10: 318-328, 1995.

Lenz, F. A., Tasker, R. R., Kwan, H. C., Schnider, S., Kwong, R., Murayama, Y., Dostrovsky, J. O., and Murphy, J. T. Single unit analysis of the human ventral thalamic nuclear group: correlation of thalamic "tremor cells" with the 3-6 Hz component of parkinsonian tremor. J.Neurosci. 8: 754-764, 1988a.

Lenz, F. A., Dostrovsky, J. O., Kwan, H. C., Tasker, R. R., Yamashiro, K., and Murphy, J. T. Methods for microstimulation and recording of single neurons and evoked potentials in the human central nervous system. J.Neurosurg. 68: 630-634, 1988b.

Lenz, F. A., Tasker, R. R., Kwan, H. C., Schnider, S., Kwong, R., and Murphy, J. T. Cross-correlation analysis of thalamic neurons and EMG activity in parkinsonian tremor. Appl.Neurophysiol. 48: 305-308, 1985.

Lenz, F. A., Vitek, J. L., and DeLong, M. R. Role of the thalamus in parkinsonian tremor: evidence from studies in patients and primate models. Stereotact.Funct.Neurosurg. 60: 94-103, 1993.

Lestienne, F. and Caillier, P. Role of the monkey substantia nigra pars reticulata in orienting behaviour and visually triggered arm movements. Neurosci.Lett. 64: 109-115, 1986.

Levy, R., Davis, K. D., Hutchison, W. D., Pahapill, P. A., Lozano, A. M., Tasker, R. R., and Dostrovsky, J. O. Simultaneously recorded neuron pairs in the motor thalamus of patients with Parkinson's disease and essential tremor [abstract]. Soc.Neurosci.Abstr. 25, 1408. 1999.

Levy, R., Hazrati, L. N., Herrero, M. T., Vila, M., Hassani, O. K., Mouroux, M., Ruberg, M., Asensi, H., Agid, Y., Feger, J., Obeso, J. A., Parent, A., and Hirsch, E. C. Re-

evaluation of the functional anatomy of the basal ganglia in normal and Parkinsonian states. Neuroscience 76: 335-343, 1997.

Lilienfeld, D. E. and Perl, D. P. Projected neurodegenerative disease mortality in the United States, 1990-2040. Neuroepidemiology 12: 219-228, 1993.

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Broussolle, E., Perret, J. E., and Benabid, A. L. Bilateral subthalamic nucleus stimulation for severe Parkinson's disease. Mov Disord. 10: 672-674, 1995a.

Limousin, P., Pollak, P., Benazzouz, A., Hoffmann, D., Le Bas, J. F., Broussolle, E., Perret, J. E., and Benabid, A. L. Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 345: 91-95, 1995b.

Limousin, P., Greene, J., Pollak, P., Rothwell, J., Benabid., A. L., and Frackowiak, R. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in parkinson's disease. Annals of Neurology 42: 283-291, 1997.

Limousin, P., Pollak, P., Hoffmann, D., Benazzouz, A., Perret, J.E., and Benabid, A.L. Abnormal involuntary movements induced by subthalamic nucleus stimulation in parkinsonian patients. Mov Disord; 11: 231-235, 1996.

Llinás, R. and Paré, D. Role of intrinsic neuronal oscillations and network ensembles in the genesis of normal and pathological tremors. In Findley, L. J. and Koller, W. C. eds. Handbook of tremor disorders. New York, Marcel Dekker. 1995, 7-36.

Lozano, A. M., Lang, A. E., Galvez-Jimenez, N., Miyasaki, J., Duff, J., Hutchinson, WD, and Dostrovsky, J. O. Effect of GPi pallidotomy on motor function in Parkinson's disease. Lancet 346: 1383-1387, 1995.

Lozano, A., Hutchison, W., Kiss, Z., Tasker, R., Davis, K., and Dostrovsky, J. Methods for microelectrode-guided posteroventral pallidotomy. J Neurosurg 84: 194-202, 1996.

Lozano, A. M., Lang, A. E., and Hutchison, W. D. Pallidotomy for tremor. Mov Disord. 13 Suppl 3:107-10: 107-110, 1998.

Lozano, A.M., Kumar, R., Gross, R.E., Giladi, N., Hutchison, W.D., Dostrovsky, J.O., and Lang, A.E. Globus pallidus internus pallidotomy for generalized dystonia. Mov Disord 12: 865-870, 1997.

Lynd-Balta, E. and Haber, S. N. Primate striatonigral projections: A comparison of the sensorimotor-related striatum and the ventral striatum. J.Comp.Neurol. 345: 562-578, 1994.

Magarinos-Ascone, C.M., Figueiras-Mendez, R., Riva-Meana, C., and Cordoba-Fernandez, A. Subthalamic neuron activity related to tremor and movement in Parkinson's disease. Eur J Neurosci 12: 2597-2607, 2000.

Magill, P. J., Bolam, J. P., and Bevan, M. D. Relationship of activity in the subthalamic nucleus-globus pallidus network to cortical electroencephalogram. J.Neurosci. 20: 820-833, 2000.

Magnin, M., Morel, A., and Jeanmonod, D. Single-unit analysis of the pallidum, thalamus and subthalamic nucleus in parkinsonian patients. Neuroscience 96: 549-564, 2000.

Makela, J.P., Hari, P., Karhu, J., Salmelin, R., and Teravainen, H. Suppression of magnetic mu rhythm during parkinsonian tremor. Brain Res 617: 189-193, 1993.

Malpeli, J.G. Reversible inactivation of subcortical sites by drug injection. J Neurosci Methods 86: 119-128, 1999.

Marsden, C. D. Functions of the basal ganglia. Rinsho Shinkeigaku 22: 1093-1094, 1982.

Marsden, C. D. Motor disorders in basal ganglia disease. Hum.Neurobiol. 2: 245-250, 1984.

Marsden, C. D. and Obeso, J. A. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease [Review]. Brain 117: 877-897, 1994.

Marsden, J.F., Limousin-Dowsey, P., Ashby, P., Pollak, P., Brown, P. Subthalamic nucleus, sensorimotor cortex and muscle interrelationships in Parkinson's disease. Brain 124: 378-388, 2001.

Martin, J.H. and Ghez, C. Pharmacological inactivation in the analysis of the central control of movement. J Neurosci Methods; 86: 145-159, 1999.

Matsumura, M., Kojima, J., Gardiner, T. W., and Hikosaka, O. Visual and oculomotor functions of monkey subthalamic nucleus. J.Neurophysiol. 67: 1615-1632, 1992.

Matsumura, M., Tremblay, L., Richard, H., and Filion, M. Activity of pallidal neurons in the monkey during dyskinesia induced by injection of bicuculline in the external pallidum. Neuroscience 65: 59-70, 1995.

Maurice, N., Deniau, J. M., Glowinski, J., and Thierry, A. M. Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the cortico-nigral circuits. J.Neurosci. 19: 4674-4681, 1999.

Mayeux, R., Marder, K., Cote, L. J., Denaro, J., Hemenegildo, N., Mejia, H., Tang, M. X., Lantigua, R., Wilder, D., Gurland, B., and . The frequency of idiopathic Parkinson's

disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. Am.J.Epidemiol. 142: 820-827, 1995.

Meara, R. J. and Cody, F. W. Relationship between electromyographic activity and clinically assessed rigidity studied at the wrist joint in Parkinson's disease. Brain 115 ( Pt 4): 1167-1180, 1992.

Mehta, A., Thermos, K., and Chesselet, M. F. Increased behavioral response to dopaminergic stimulation of the subthalamic nucleus after nigrostriatal lesions. Synapse 37: 298-307, 2000.

Meibach, R. C. and Katzman, R. Catecholaminergic innervation of the subthalamic nucleus: evidence for a rostral continuation of the A9 (substantia nigra) dopaminergic cell group. Brain Res. 173: 364-368, 1979.

Merello, M., Balej, J., Delfino, M., Cammarota, A., Betti, O., and Leiguarda, R. Apomorphine induces changes in GPi spontaneous outflow in patients with Parkinson's disease. Mov Disord 14: 45-49, 1999.

Merello, M. and Lees, A. J. Beginning-of-dose motor deterioration following the acute administration of levodopa and apomorphine in Parkinson's disease. J.Neurol Neurosurg.Psychiatry 55: 1024-1026, 1992.

Meyers, R. Surgical procedure for postencephalitic tremor, with notes on the physiology of the premotor fibers. Arch of Neurol and Psych 44: 455-459, 1940.

Middleton, F. A. and Strick, P. L. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science 266: 458-461, 1994.

Middleton, F. A. and Strick, P. L. New concepts about the organization of basal ganglia output. Adv Neurol 74: 57-68, 1997.

Miller, W. C. and DeLong, M. R. Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism. In Carpenter, M. B. and Jayaraman, A. eds. The basal ganglia II. Structure and function: current concepts. New York, Plenum. 1987, 415-427.

Mink, J. W. The basal ganglia: focused selection and inhibition of competing motor programs. Prog.Neurobiol. 50: 381-425, 1996.

Mink, J. W. and Thach, W. T. Preferential relation of pallidal neurons to ballistic movements. Brain Res. 417: 393-398, 1987.

Mink, J. W. and Thach, W. T. Basal ganglia motor control. I. Nonexclusive relation of pallidal discharge to five movement modes. J.Neurophysiol. 65: 273-300, 1991a.

Mink, J. W. and Thach, W. T. Basal ganglia motor control. II. Late pallidal timing relative to movement onset and inconsistent pallidal coding of movement parameters. J.Neurophysiol. 65: 301-329, 1991b.

Mink, J. W. and Thach, W. T. Basal ganglia motor control. III. Pallidal ablation: normal reaction time, muscle cocontraction, and slow movement. J.Neurophysiol. 65: 330-351, 1991c.

Mitchell, I. J., Boyce, S., Sambrook, M. A., and Crossman, A. R. A 2-deoxyglucose study of the effects of dopamine agonists on the parkinsonian primate brain. Implications for the neural mechanisms that mediate dopamine agonist-induced dyskinesia. Brain 115 ( Pt 3): 809-824, 1992.

Mitchell, I. J., Clarke, C. E., Boyce, S., Robertson, R. G., Peggs, D., Sambrook, M. A., and Crossman, A. R. Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine. Neuroscience 32: 213-226, 1989.

Mitchell, S. J., Richardson, R. T., Baker, F. H., and DeLong, M. R. The primate globus pallidus: neuronal activity related to direction of movement. Exp.Brain Res. 68: 491-505, 1987.

Monakow, K. H., Akert, K., and Kunzle, H. Projections of the precentral motor cortex and other cortical areas of the frontal lobe to the subthalamic nucleus in the monkey. Exp.Brain Res. 33: 395-403, 1978.

Moore, G. P., Segundo, J. P., Perkel, D. H., and Levitan, H. Statistical signs of synaptic interaction in neurons. Biophys.J. 10: 876-900, 1970.

Mora, F., Mogenson, G. J., and Rolls, E. T. Activity of neurons in the region of the substantia nigra during feeding in the monkey. Brain Res. 133: 267-276, 1977.

Mouroux, M., Hassani, O. K., and Feger, J. Electrophysiological study of the excitatory parafascicular projection to the subthalamic nucleus and evidence for ipsi- and contralateral controls. Neuroscience 67: 399-407, 1995.

Mouroux, M., Hassani, O. K., and Feger, J. Electrophysiological and Fos immunohistochemical evidence for the excitatory nature of the parafascicular projection to the globus pallidus. Neuroscience 81: 387-397, 1997.

Murer, M. G., Ferrario, J., Delfino, M., Dziewczapolski, G., Gershanik, O. S., and Raisman-Vozari, R. Increased [125I]sulpiride binding in the subthalamic nucleus of rats with nigrostriatal lesions. Neuroreport 10: 1501-1505, 1999.

Murthy, V.N. and Fetz, E.E. Oscillatory activity in sensorimotor cortex of awake monkeys: synchronization of local field potentials and relation to behavior. J Neurophysiol 76: 3949-3967, 1996a.

Murthy, V.N. and Fetz EE. Synchronization of neurons during local field potential oscillations in sensorimotor cortex of awake monkeys. J Neurophysiol 76: 3968-3982, 1996b.

Mushiake, H. and Strick, P. L. Pallidal neuron activity during sequential arm movements. J.Neurophysiol. 74: 2754-2758, 1995.

Muthane, U.B., Varma, R.M., Sundarajan, P., Hegde, T., Jayakumar, P.N., and Shankar, S.K. Percutaneous trans-Foramen Ovale approach to subthalamic nucleus (Varma's technique): A shorter and economical technique in the surgical management of Parkinson's disease. [Abstract]. Mov Disord 13 Suppl 2: 71, 1998.

Myers, R.D. Injection of solutions into cerebral tissue: relation between volume and diffusion. Physiol Behav 1: 171-174, 1966.

Nambu, A., Takada, M., Inase, M., and Tokuno, H. Dual somatotopical representations in the primate subthalamic nucleus: evidence for ordered but reversed body-map transformations from the primary motor cortex and the supplementary motor area. J.Neurosci. 16: 2671-2683, 1996.

Nambu, A., Tokuno, H., Hamada, I., Kita, H., Imanishi, M., Akazawa, T., Ikeuchi, Y., and Hasegawa, N. Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. J Neurophysiol 84: 289-300, 2000.

Narabayashi, H. Procaine blocking of the globus pallidus for the treatment of rigidity and tremor of Parkinsonism. Psych.Neurol.Jap. 50: 471-495, 1954.

Neufeld, M.Y., Blumen, S., Aitkin, I., Parmet, Y., and Korczyn, A.D. EEG frequency analysis in demented and nondemented parkinsonian patients. Dementia 5: 23-28, 1994.

Ni, Z., Bouali-Benazzouz, R., Gao, D., Benabid, A.L., and Benazzouz, A. Changes in the firing pattern of globus pallidus neurons after the degeneration of nigrostriatal pathway are mediated by the subthalamic nucleus in the rat. Eur J Neurosci 12: 4338-4344, 2000.

Nicola, S. M., Surmeier, J., and Malenka, R. C. Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. Annu.Rev.Neurosci. 23: 185-215, 2000.

Nini, A., Feingold, A., Slovin, H., and Bergman, H. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. J.Neurophysiol. 74: 1800-1805, 1995.

Nishimura, Y., Takada, M., and Mizuno, N. Topographic distribution and collateral projections of the two major populations of nigrothalamic neurons. A retrograde labeling study in the rat. Neurosci.Res. 28: 1-9, 1997.

Nishino, H., Ono, T., Sasaki, K., Fukuda, M., and Muramoto, K. Caudate unit activity during operant feeding behavior in monkeys and modulation by cooling prefrontal cortex. Behav.Brain Res. 11: 21-33, 1984.

O'Suilleabhain, P. E. and Matsumoto, J. Y. Time-frequency analysis of tremors. Brain 121: 2127-2134, 1998.

Obeso, J. A., Alavarz, L. M., Macias, R., Guridi, J., Teijeiro, J., and Juncos, J. L. Lesions of the subthalamic nucleus (STN) in Parkinson's disease (PD). Neurology 48 (Suppl 3): A138-A138, 1997a.

Obeso, J. A., Rodriguez-Oroz, M. C., Chana, P., Lera, G., Rodriguez, M., and Olanow, C. W. The evolution and origin of motor complications in Parkinson's disease. Neurology 55: S13-S20, 2000.

Obeso, J. A., Rodriguez, M. C., and DeLong, M. R. Basal ganglia pathophysiology. A critical review. Adv Neurol 74: 3-18, 1997b.

Oertel, W.H., Nitsch, C., and Mugnaini, E. Immunocytochemical demonstration of the GABA-ergic neurons in rat globus pallidus and nucleus entopeduncularis and their GABA-ergic innervation. Adv Neurol 40: 91-98, 1984.

Oguztoreli, M. N. and Stein, R. B. The effects of multiple reflex pathways on the oscillations in neuro-muscular systems. J.Math.Biol. 3: 87-101, 1976.

Oguztoreli, M. N. and Stein, R. B. Interactions between centrally and peripherally generated neuromuscular oscillations. J.Math.Biol. 7: 1-30, 1979.

Ohye, C., Hirato, M., Takahashi, A., Watanabe, K., and Murata, H. Physiological study of the pallidal neurons in Parkinson's disease. In Ohye, C., Kimura, M., and Mckenzie, J. S. eds. The basal ganglia V. New York, Plenum Press. 1996, 317-324.

Olney, J. W., Price, M. T., Labruyere, J., Salles, K. S., Frierdich, G., Mueller, M., and Silverman, E. Anti-parkinsonian agents are phencyclidine agonists and N-methyl-aspartate antagonists. Eur.J.Pharmacol. 142: 319-320, 1987.

Orieux, G., Francois, C., Feger, J., Yelnik, J., Vila, M., Ruberg, M., Agid, Y., and Hirsch, E. C. Metabolic activity of excitatory parafascicular and pedunculopontine inputs to the subthalamic nucleus in a rat model of Parkinson's disease. Neuroscience 97: 79-88, 2000.

Pahapill, P. A., Levy, R., Dostrovsky, J. O., Davis, K. D., Rezai, A. R., Tasker, R. R., and Lozano, A. M. Tremor arrest with thalamic microinjections of muscimol in patients with essential tremor. Ann Neurol 46: 249-252, 1999.

Pahapill, P. A. and Lozano, A. M. The pedunculopontine nucleus and Parkinson's disease. Brain 123 ( Pt 9): 1767-1783, 2000.

Paladini, C. A., Celada, P., and Tepper, J. M. Striatal, pallidal, and pars reticulata evoked inhibition of nigrostriatal dopaminergic neurons is mediated by GABA(A) receptors in vivo. Neuroscience 89: 799-812, 1999.

Palmer, S. S. and Hutton, J. T. Postural finger tremor exhibited by Parkinson patients and age-matched subjects. Mov.Disord. 10: 658-663, 1995.

Papa, S. M., Desimone, R., Fiorani, M., and Oldfield, E. H. Internal globus pallidus discharge is nearly suppressed during levodopa- induced dyskinesias. Ann Neurol 46: 732-738, 1999.

Parent, A. Extrinsic connections of the basal ganglia. Trends Neurosci. 13: 254-258, 1990.

Parent, A. Carpenters human neuroanatomy. Baltimore, Williams & Wilkins. 1996, 795-863.

Parent, A., Charara, A., and Pinault, D. Single striatofugal axons arborizing in both pallidal segments and in the substantia nigra in primates. Brain Res. 698: 280-284, 1995.

Parent, A. and Hazrati, L. N. Anatomical aspects of information processing in primate basal ganglia. Trends Neurosci. 16: 111-116, 1993.

Parent, A. and Hazrati, L. N. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia- thalamo-cortical loop. Brain Res.Brain Res.Rev. 20: 91-127, 1995b.

Parent, A. and Hazrati, L. N. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res.Brain Res.Rev. 20: 128-154, 1995a.

Parent, A., Mackey, A., Smith, Y., and Boucher, R. The output organization of the substantia nigra in primate as revealed by a retrograde double labeling method. Brain Res.Bull. 10: 529-537, 1983.

Parent, A., Sato, F., Wu, Y., Gauthier, J., Levesque, M., and Parent, M. Organization of the basal ganglia: the importance of axonal collateralization. Trends Neurosci. 23: S20-S27, 2000.

Paré, D., Curro'Dossi, R., and Steriade, M. Neuronal basis of the parkinsonian resting tremor: A hypothesis and its implications for treatment. Neuroscience 35: 217-226, 1990.

Parker, F., Tzourio, N., Blond, S., Petit, H., and Mazoyer, B. Evidence for a common network of brain structures involved in parkinsonian tremor and voluntary repetitive movement. Brain Res 584: 11-17, 1992.

Parrent, A. G., Tasker, R. R., and Dostrovsky, J. O. Tremor reduction by microinjection of lidocaine during stereotactic surgery. Acta Neurochir Suppl (Wien) 58:45-7: 45-47, 1993.

Penn, R. D., Kroin, J. S., Reinkensmeyer, A., and Corcos, D. M. Injection of GABA-agonist into globus pallidus in patient with Parkinson's disease. Lancet 351: 340-341, 1998.

Percheron, G. and Filion, M. Parallel processing in the basal ganglia: up to a point [letter; comment]. Trends Neurosci. 14: 55-59, 1991.

Percheron, G., Francois, C., Talbi, B., Yelnik, J., and Fenelon, G. The primate motor thalamus. Brain Res.Brain Res.Rev. 22: 93-181, 1996.

Percheron, G., Yelnik, J., and Francois, C. A Golgi analysis of the primate globus pallidus. III. Spatial organization of the striato-pallidal complex. J.Comp Neurol 227: 214-227, 1984.

Perkel, D.H., Gerstein, G.L., and Moore, G.P. Neuronal spike trains and stochastic point processes. II. Simultaneous spike trains. Biophys J 7: 419-440, 1967.

Pfann, K. D., Penn, R. D., Shannon, K. M., and Corcos, D. M. Pallidotomy and bradykinesia: implications for basal ganglia function. Neurology 51: 796-803, 1998.

Pfurtscheller, G. Central beta rhythm during sensorimotor activities in man. Electroencephalogr Clin Neurophysiol 51: 253-264, 1981.

Pfurtscheller, G., Stancak, A., Jr., and Neuper, C. Post-movement beta synchronization. A correlate of an idling motor area? Electroencephalogr Clin Neurophysiol 98: 281-293, 1996.

Pfurtscheller, G. and Lopes, da Silva F.H. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol 110: 1842-1857, 1999.

Pillon, B., Dubois, B., Cusimano, G., Bonnet, A. M., Lhermitte, F., and Agid, Y. Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J.Neurol Neurosurg.Psychiatry 52: 201-206, 1989.

Playford, E. D., Jenkins, I. H., Passingham, R. E., Nutt, J., Frackowiak, R. S., and Brooks, D. J. Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. Ann Neurol 32: 151-161, 1992.

Plenz, D. and Kital, S. T. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. Nature 400: 677-682, 1999.

Poewe, W. H. and Wenning, G. K. The natural history of Parkinson's disease. Ann Neurol 44: S1-S9, 1998.

Pollak, P., Benabid, A. L., Gross, C., Gao, D. M., Laurent, A., Benazzouz, A., Hoffmann, D., Gentil, M., and Perret, J. [Effects of the stimulation of the subthalamic nucleus in Parkinson disease]. Rev.Neurol (Paris) 149: 175-176, 1993.

Pollak, P., Benabid., A. L., Limousin, P., Benazzouz, A., Hoffman, D., Le Bas, J.-F., and Perret, J. Subthalamic nucleus stimulation alleviates akinesia and rigidity in parkinsonian patients. Adv.Neurol. 69: 591-594, 1996.

Prochazka, A., Bennett, D. J., Stephens, M. J., Patrick, S. K., Sears-Duru, R., Roberts, T., and Jhamandas, J. H. Measurement of rigidity in Parkinson's disease. Mov Disord. 12: 24-32, 1997.

Rack, P. M. Stretch reflexes and parkinsonian tremor. Acta Neurochir.Suppl (Wien.) 39: 51-53, 1987.

Rack, P. M. and Ross, H. F. The role of reflexes in the resting tremor of Parkinson's disease. Brain 109 ( Pt 1): 115-141, 1986.

Raethjen, J., Lindemann, M., Schmaljohann, H., Wenzelburger, R., Pfister, G., and Deuschl, G. Multiple oscillators are causing parkinsonian and essential tremor. Mov Disord 15: 84-94, 2000.

Raeva, S. N. Unit activity of the human thalamus during voluntary movements. Stereotact.Funct.Neurosurg. 54-55:154-8: 154-158, 1990.

Raeva, S. N., Vainberg, N. A., and Dubynin, V. A. Spontaneous activity of individual neurons in the human ventrolateral thalamus during changes in the functional state of the brain. Neurosci.Behav.Physiol 28: 513-520, 1998.

Rafols, J. A. and Fox, C. A. The neurons in the primate subthalamic nucleus: a Golgi and electron microscopic study. J.Comp Neurol 168: 75-111, 1976.

Rascol, O., Brefel-Courbon, C., Descombes, S., and Montastruc, J. L. Clinical pharmacology of levodopa-induced dyskinesia in parkinsonian patients. Adv Neurol 80: 485-490, 1999.

Raz, A., Feingold, A., Zelanskaya, V., Vaadia, E., and Bergman, H. Neuronal synchronization of tonically active neurons in the striatum of normal and parkinsonian primates. J.Neurophysiol. 76: 2083-2088, 1996.

Raz, A., Frechter-Mazar, V., Feingold, A., Abeles, M., Vaadia, E., and Bergman, H. Activity of pallidal and striatal tonically active neurons is correlated in mptp-treated monkeys but not in normal monkeys. J.Neurosci. 21: RC128, 2001.

Raz, A., Vaadia, E., and Bergman, H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1, 2,3,6-tetrahydropyridine vervet model of parkinsonism. J.Neurosci. 20: 8559-8571, 2000.

Reardon, K. A., Shiff, M., and Kempster, P. A. Evolution of motor fluctuations in Parkinson's disease: a longitudinal study over 6 years. Mov Disord 14: 605-611, 1999.

Robertson, R. G., Farmery, S. M., Sambrook, M. A., and Crossman, A. R. Dyskinesia in the primate following injection of an excitatory amino acid antagonist into the medial segment of the globus pallidus. Brain Res. 476: 317-322, 1989.

Robledo, P. and Feger, J. Excitatory influence of rat subthalamic nucleus to substantia nigra pars reticulata and the pallidal complex: electrophysiological data. Brain Res. 518: 47-54, 1990.

Rodriguez, M. C., Guridi, O. J., Alvarez, L., Mewes, K., Macias, R., Vitek, J., DeLong, M. R., and Obeso, J. A. The subthalamic nucleus and tremor in Parkinson's disease. Mov Disord. 13 Suppl 3:111-8, 1998.

Rosenberg, J. R., Amjad, A. M., Breeze, P., Brillinger, D. R., and Halliday, D. M. The Fourier approach to the identification of functional coupling between neuronal spike trains. Prog.Biophys.Mol.Biol. 53: 1-31, 1989.

Rothwell, J. C. Physiology and anatomy of possible oscillators in the central nervous system. Mov Disord 13 Suppl 3: 24-28, 1998.

Rouiller, E. M., Liang, F., Babalian, A., Moret, V., and Wiesendanger, M. Cerebellothalamocortical and pallidothalamocortical projections to the primary and supplementary motor cortical areas: a multiple tracing study in macaque monkeys. J.Comp Neurol 345: 185-213, 1994.

Rouzaire-Dubois, B., Hammond, C., Hamon, B., and Feger, J. Pharmacological blockade of the globus palidus-induced inhibitory response of subthalamic cells in the rat. Brain Res. 200: 321-329, 1980.

Rouzaire-Dubois, B. and Scarnati, E. Bilateral corticosubthalamic nucleus projections: an electrophysiological study in rats with chronic cerebral lesions. Neuroscience 15: 69-79, 1985.

Rouzaire-Dubois, B. and Scarnati, E. Pharmacological study of the cortical-induced excitation of subthalamic nucleus neurons in the rat: evidence for amino acids as putative neurotransmitters. Neuroscience 21: 429-440, 1987.

Ruskin, D. N., Bergstrom, D. A., and Walters, J. R. Multisecond oscillations in firing rate in the globus pallidus: synergistic modulation by D1 and D2 dopamine receptors [In Process Citation]. J.Pharmacol.Exp.Ther. 290: 1493-1501, 1999.

Ryan, L. J. and Clark, K. B. The role of the subthalamic nucleus in the response of globus pallidus neurons to stimulation of the prelimbic and agranular frontal cortices in rats. Exp.Brain Res. 86: 641-651, 1991.

Ryan, L. J., Sanders, D. J., and Clark, K. B. Auto- and cross-correlation analysis of subthalamic nucleus neuronal activity in neostriatal- and globus pallidal-lesioned rats. Brain Res. 583: 253-261, 1992.

Sadikot, A. F., Parent, A., and Francois, C. The centre median and parafascicular thalamic nuclei project respectively to the sensorimotor and associative-limbic striatal territories in the squirrel monkey. Brain Res. 510: 161-165, 1990.

Sadikot, A. F., Parent, A., and Francois, C. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections. J.Comp Neurol 315: 137-159, 1992a.

Sadikot, A. F., Parent, A., Smith, Y., and Bolam, J. P. Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity. J.Comp Neurol 320: 228-242, 1992b.

Salenius, S., Portin, K., Kajola, M., Salmelin, R., and Hari, R. Cortical control of human motoneuron firing during isometric contraction. J Neurophysiol 77: 3401-3405, 1997.

Salmelin, R. and Hari, R. Spatiotemporal characteristics of sensorimotor neuromagnetic rhythms related to thumb movement. Neuroscience 60: 537-550, 1994.

Salmelin, R., Hamalainen, M., Kajola, M., and Hari, R. Functional segregation of movement-related rhythmic activity in the human brain. Neuroimage 2: 237-243, 1995.

Samuel, M., Ceballos-Baumann, A. O., Turjanski, N., Boecker, H., Gorospe, A., Linazasoro, G., Holmes, A. P., DeLong, M. R., Vitek, J. L., Thomas, D. G., Quinn, N. P., Obeso, J. A., and Brooks, D. J. Pallidotomy in Parkinson's disease increases supplementary motor area and prefrontal activation during performance of volitional movements an H2(15)O PET study. Brain 120: 1301-1313, 1997.

Sandkuhler, J., Maisch, B., and Zimmermann, M. The use of local anaesthetic microinjections to identify central pathways: a quantitative evaluation of the time course and extent of the neuronal block. Exp Brain Res 68: 168-178, 1987.

Sato, F., Parent, M., Levesque, M., and Parent, A. Axonal branching pattern of neurons of the subthalamic nucleus in primates. J Comp Neurol 424: 142-152, 2000.

Sato, F., Lavallee, P., Levesque, M., and Parent, A. Single-axon tracing study of neurons of the external segment of the globus pallidus in primate. J Comp Neurol 417: 17-31, 2000.

Schaltenbrand, G. and Wahren, W. Atlas for stereotaxy of the human brain. Stuttgart, 1977.

Scholz, E. and Bacher, M. Problems in the measurement of parkinsonian tremor. In: Handbook of tremor disorders (Findley LJ, Koller WC, eds), pp 293-311. New York: Marcel Dekker Inc., 1995.

Schultz, W. Activity of pars reticulata neurons of monkey substantia nigra in relation to motor, sensory, and complex events. J.Neurophysiol. 55: 660-677, 1986b.

Schultz, W. Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. J.Neurophysiol. 56: 1439-1461, 1986a.

Schultz, W., Studer, A., Romo, R., Sundstrom, E., Jonsson, G., and Scarnati, E. Deficits in reaction times and movement times as correlates of hypokinesia in monkeys with MPTP-induced striatal dopamine depletion. J.Neurophysiol. 61: 651-668, 1989.

Schwab R.S., Chafetz M.E., and Wang, B. Control of two simultaneous voluntary motor acts in normals and in parkinsonism. Arch of Neurol and Psych 72: 591-598, 1954.

Schwab R.S. and Cobb, S. Simultaneous electromyograms and electroencephalograms in paralysis agitans. J.Neurophysiol. 2: 36-41, 1939.

Shahani, B. T. and Young, R. R. Physiological and pharmacological aids in the differential diagnosis of tremor. J.Neurol Neurosurg.Psychiatry 39: 772-783, 1976.

Sheridan, M. R., Flowers, K. A., and Hurrell, J. Programming and execution of movement in Parkinson's disease. Brain 110 ( Pt 5): 1247-1271, 1987.

Shink, E., Bevan, M. D., Bolam, J. P., and Smith, Y. The subthalamic nucleus and the external pallidum: two tightly interconnected structures that control the output of the basal ganglia in the monkey. Neuroscience 73: 335-357, 1996.

Smith, Y., Bennett, B. D., Bolam, J. P., Parent, A., and Sadikot, A. F. Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. J.Comp Neurol 344: 1-19, 1994a.

Smith, Y., Bevan, M. D., Shink, E., and Bolam, J. P. Microcircuitry of the direct and indirect pathways of the basal ganglia. Neuroscience 86: 353-387, 1998.

Smith, Y. and Bolam, J. P. The output neurones and the dopaminergic neurones of the substantia nigra receive a GABA-containing input from the globus pallidus in the rat. J.Comp Neurol 296: 47-64, 1990.

Smith, Y., Hazrati, L. N., and Parent, A. Efferent projections of the subthalamic nucleus in the squirrel monkey as studied by the PHA-L anterograde tracing method. J.Comp Neurol 294: 306-323, 1990.

Smith, Y. and Parent, A. Neurons of the subthalamic nucleus in primates display glutamate but not GABA immunoreactivity. Brain Res. 453: 353-356, 1988.

Smith, Y., Wichmann, T., and DeLong, M. R. Synaptic innervation of neurones in the internal pallidal segment by the subthalamic nucleus and the external pallidum in monkeys. J.Comp Neurol. 343: 297-318, 1994b.

Smith, Y., Parent, A., Seguela, P., and Descarries, L. Distribution of GABA-immunoreactive neurons in the basal ganglia of the squirrel monkey (Saimiri sciureus). J Comp Neurol 259: 50-64, 1987.

Stebbins, G. T., Goetz, C. G., Lang, A. E., and Cubo, E. Factor analysis of the motor section of the unified Parkinson's disease rating scale during the off-state. Mov Disord 14: 585-589, 1999.

Stefani, A., Stanzione, P., Bassi, A., Mazzone, P., Vangelista, T., and Bernardi, G. Effects of increasing doses of apomorphine during stereotaxic neurosurgery in Parkinson's disease: clinical score and internal globus pallidus activity. J.Neural Transm. 104: 895-904, 1997.

Steininger, T. L., Wainer, B. H., and Rye, D. B. Ultrastructural study of cholinergic and noncholinergic neurons in the pars compacta of the rat pedunculopontine tegmental nucleus. J.Comp Neurol 382: 285-301, 1997.

Stelmach, G. E., Teasdale, N., Phillips, J., and Worringham, C. J. Force production characteristics in Parkinson's disease. Exp.Brain Res. 76: 165-172, 1989.

Stelmach, G. E. and Worringham, C. J. The control of bimanual aiming movements in Parkinson's disease. J.Neurol.Neurosurg.Psychiatry 51: 223-231, 1988.

Sterio, D., Beric, A., Dogali, M., Fazzini, E., Alfaro, G., and Devinsky, O. Neurophysiological properties of pallidal neurons in Parkinson's disease. Ann Neurol 35: 586-591, 1994.

Stiles, R. N. and Pozos, R. S. A mechanical-reflex oscillator hypothesis for parkinsonian hand tremor. J.Appl.Physiol 40: 990-998, 1976.

Sutton, J. P., Couldwell, W., Lew, M. F., Mallory, L., Grafton, S., DeGiorgio, C., Welsh, M., Apuzzo, M. L., Ahmadi, J., and Waters, C. H. Ventroposterior medial pallidotomy in patients with advanced Parkinson's disease. Neurosurgery 36: 1112-1116, 1995.

Svennilson, E., Torvit, A., Lorno, R., and Leksell, L. Treatment of Parkinsonism by stereotactic thermolesions in the pallidal region. Acta Psychiat.Neurol.Scand. 35: 358-377, 1960.

Szabo, J. The efferent projections of the putamen in the monkey. Exp.Neurol 19: 463-476, 1967.

Taha, J. M., Favre, J., Baumann, T. K., and Burchiel, K. J. Tremor control after pallidotomy in patients with Parkinson's disease: correlation with microrecording findings. J.Neurosurg. 86: 642-647, 1997.

Tanner, C. M. Epidemiology of Parkinson's disease. Neurol Clin 10: 317-329, 1992.

Teravainen, H. and Calne, D. B. Assessment of hypokinesia in Parkinsonism. J.Neural Transm. 51: 149-159, 1981.

Tremblay, L. and Filion, M. Responses of pallidal neurons to striatal stimulation in intact waking monkeys. Brain Res. 498: 1-16, 1989.

Tremblay, L., Filion, M., and Bedard, P. J. Responses of pallidal neurons to striatal stimulation in monkeys with MPTP-induced parkinsonism. Brain Res. 498: 17-33, 1989.

Tresilian, J. R., Stelmach, G. E., and Adler, C. H. Stability of reach-to-grasp movement patterns in Parkinson's disease. Brain 120 ( Pt 11): 2093-2111, 1997.

Van Der Kooy, D. and Hattori, T. Single subthalamic nucleus neurons project to both the globus pallidus and substantia nigra in rat. J.Comp Neurol 192: 751-768, 1980.

Vingerhoets, F. J., Schulzer, M., Calne, D. B., and Snow, B. J. Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion? Ann Neurol 41: 58-64, 1997.

Vitek, J., Kaneoke, Y., Turner, R., Baron, M., Bakay, R., and DeLong, M. R. Neuronal activity in the internal (GPi) and external (GPe) segments of the globus pallidus (GP) of parkinsonian patients is similar to that in the MPTP-treated primate model of parkinsonism [abstract]. Soc.Neurosci.Abstr. 19, 1584. 1993.

Vitek, J. L., Ashe, J., DeLong, M. R., and Alexander, G. E. Physiologic properties and somatotopic organization of the primate motor thalamus. J.Neurophysiol. 71: 1498-1513, 1994.

Vitek, J.L., Chockkan, V., Zhang, J.Y., Kaneoke, Y., Evatt, M., DeLong, M.R., Triche, S., Mewes, K., Hashimoto, T., and Bakay, R.A. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 46: 22-35, 1999.

Vitek, J. L. and Bakay, R. A. The role of pallidotomy in Parkinson's disease and dystonia. Curr.Opin.Neurol 10: 332-339, 1997.

Vitek, J. L. and Giroux, M. Physiology of hypokinetic and hyperkinetic movement disorders: model for dyskinesia. Ann Neurol 47: S131-S140, 2000.

Volkmann, J., Joliot, M., Mogilner, A., Ioannides, A. A., Lado, F., Fazzini, E., Ribary, U., and Llinas, R. Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography. Neurology 46: 1359-1370, 1996.

Volkmann, J. Oscillations of the human sensorimotor system as revealed by magnetoencephalography. Mov Disord 13 Suppl 3: 73-76, 1998.

Wichmann, T., Baron, M. S., and DeLong, M. R. Local inactivation of the sensorimotor territories of the internal segment of the globus pallidus and the subthalamic nucleus alleviates parkinsonian motor signs in MPTP treated monkeys. In Percheron, G. ed. The basal ganglia IV. New York, Plenum Press. 1994c, 357-363.

Wichmann, T., Bergman, H., and DeLong, M. R. The primate subthalamic nucleus. I. Functional properties in intact animals. J.Neurophysiol. 72: 494-506, 1994a.

Wichmann, T., Bergman, H., and DeLong, M. R. The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. J.Neurophysiol. 72: 521-530, 1994b.

Wichmann, T., Bergman, H., Starr, P. A., Subramanian, T., Watts, R. L., and DeLong, M. R. Comparison of MPTP-induced changes in spontaneous neuronal discharge in the internal pallidal segment and in the substantia nigra pars reticulata in primates. Exp.Brain Res. 125: 397-409, 1999.

Wichmann, T. and DeLong, M. R. Functional and pathophysiological models of the basal ganglia. Curr.Opin.Neurobiol. 6: 751-758, 1996.

Wichmann, T., Kliem, M. A., and DeLong, M. R. Antiparkinsonian and behavioral effects of inactivation of the substantia nigra pars reticulata in hemiparkinsonian primates. Exp.Neurol 167: 410-424, 2001.

Yelnik, J., Francois, C., Percheron, G., and Heyner, S. Golgi study of the primate substantia nigra. I. Quantitative morphology and typology of nigral neurons. J.Comp Neurol 265: 455-472, 1987.

Yelnik, J. and Percheron, G. Subthalamic neurons in primates: a quantitative and comparative analysis. Neuroscience 4: 1717-1743, 1979.

Yoshida, M. Electrophysiological characterization of human subcortical structures by frequency spectrum analysis of neural noise (field potential) obtained during stereotactic surgery. Preliminary presentation of frequency power spectrum of various subcortical structures. Stereotact.Funct.Neurosurg. 52: 157-163, 1989.

Yoshida, S., Nambu, A., and Jinnai, K. The distribution of the globus pallidus neurons with input from various cortical areas in the monkeys. Brain Res. 611: 170-174, 1993.

Zigmond, M. J., Abercrombie, E. D., Berger, T. W., Grace, A. A., and Stricker, E. M. Compensations after lesions of central dopaminergic neurons: some clinical and basic implications. Trends Neurosci. 13: 290-296, 1990.

Zirh, T. A., Lenz, F. A., Reich, S. G., and Dougherty, P. M. Patterns of bursting occurring in thalamic cells during parkinsonian tremor. Neuroscience 83: 107-121, 1998.