THE EFFECT OF PALLIDOTOMY ON MOVEMENT IN SEVERE PARKINSON'S DISEASE

A thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

in

The Department of Medicine

University of Adelaide

Adelaide, South Australia

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July 2008

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ABSTRACT

The effects of ablative and non-ablative pallidal surgery in Parkinson's disease (PD) have been the subject of interest for many years. The techniques used have undergone dramatic change over this time. This study examines the effects of pallidal lesions on the clinical signs and the physiology of motor control in PD.

A method for the kinematic analysis of rapid repetitive finger tapping (an "internally generated" movement) and a two stage sequential arm movement made in response to an auditory stimulus (an "externally generated" movement) was devised and validated in control subjects and in patients with PD. Consecutive patients undergoing pallidotomy for severe PD were studied pre-operatively and at 2-4 weeks, 3 months and 6 months post-operatively. In addition to kinematic assessments, clinical assessments of movement were performed using standardised rating scales. The spontaneous blink rate was measured pre- and post-operatively. In some patients, Bereitschaftspotentials (pre-movement cortical potentials) were recorded pre- and post-operatively, as patients performed a self-paced voluntary arm movement. The location of the pallidotomy lesions was established from post-operative CT head scans.

The most dramatic clinical effect of pallidotomy was on drug-induced dyskinesias. Significant clinical improvements were also seen in limb bradykinesia, particularly on the side contralateral to the lesion. Kinematic analysis showed no improvement in rapid finger tapping after pallidotomy. Nor was there any improvement in the spontaneous blink rate or in the early component of the Bereitschaftspotential. However, both the speed and inter-onset latency of the two stage sequential arm movement improved post-operatively.

It is concluded that the improvement in bradykinesia after pallidotomy is not due to an improvement in function of pallido-thalamo-mesial frontal circuits, which are particularly involved in the performance of internally generated movements. Rather, the abolition of pallidal activity by pallidotomy may allow more laterally placed motor circuits greater use of sensory cues to facilitate movement.

Lesions almost always involved the posteroventral portion of the medial segment of the internal pallidum, the conventional site for pallidotomy in PD. However, many lesions also involved the ansa lenticularis, the lateral segment of the internal pallidum and the external pallidum. The potential relevance of these observations on an understanding of the pathogenesis of bradykinesia and dyskinesia in PD is discussed.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Thomas E Kimber

July 2008

ACKNOWLEDGMENTS

I sincerely thank my supervisor, Professor Philip Thompson, for his invaluable support in the performance and analysis of this work. Without his inspiration and academic guidance, this work would not have been possible. Philip first inspired my interest in clinical research and he continues to inspire me as a clinician.

I also thank Professor Brian Brophy, who was the neurosurgeon for all of the patients described in this thesis. He was unfailingly supportive of this work, allowing me access to his patients before, during and after their surgery.

I would also like to acknowledge the patients who participated in this work. I pay tribute to their courage in the face of a debilitating illness. I would also like to acknowledge the kindness of those who acted as control subjects, who also gave generously of their time.

Finally, I would like to thank my wife, Katrina Bochner, who has been unfailingly supportive throughout the long gestation of this thesis.

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AIMS AND GENERAL INTRODUCTION

In recent years there has been a resurgence of interest in the use of stereotaxic pallidotomy for the treatment of advanced Parkinson's disease (PD). Most series agree that the principal motor effects of pallidotomy are improvements in both "off" period bradykinesia and "on" period dyskinesias. However, the mechanisms by which pallidotomy exerts its apparently paradoxical effects on volitional and involuntary movements remain unexplained. Firstly, it is unclear why a lesion of the internal pallidum, which is the major output nucleus of the basal ganglia in the control of volitional movement, should improve, rather than further impair, volitional movement. Secondly, it seems paradoxical that a pallidal lesion should exert opposite effects on volitional and involuntary movements.

The primary aim of this thesis is to elucidate the mechanisms by which pallidotomy exerts its effects on bradykinesia and dyskinesia. Current understanding of the pathophysiology of bradykinesia and dyskinesia is reviewed, along with proposed compensatory mechanisms for the facilitation of volitional movement in PD. A method for the objective measurement of bradykinesia is described and validated in control subjects and PD patients. This method is used to assess volitional upper limb movement in PD patients before and after pallidotomy. This assessment is supplemented by clinical assessments of volitional limb movement, postural instability/gait dysfunction and dyskinesias, using standard rating scales, and by measurement of pre-movement mesial frontal cortex electrical activity pre- and post-operatively. The relative effects of pallidotomy on volitional and automatic movement are compared, using spontaneous blinking as an example of automatic movement. Finally, a method for the measurement of pallidotomy lesion size and location is discussed, as is the issue of the possible impact of lesion site and size on the motor effects of pallidotomy.

CHAPTER 1

Literature Review

1.1 PARKINSON'S DISEASE

1.1.1 Background to the disease

Idiopathic PD is one of the commonest of all neurological disorders and occurs worldwide. The cause is unknown but both genetic and environmental factors are thought to play a role. It generally affects middle-aged and elderly individuals and increases in incidence with advancing age. There is a slight male predominance (Mutch et al., 1986; Schrag et al., 2000). The exact prevalence of PD is difficult to ascertain, as it is likely that many cases go undiagnosed, whereas other individuals may be diagnosed with PD who actually have another condition. Pathological studies suggest that the proportion of individuals diagnosed with PD who actually have another disease at autopsy may be as high as 25% (Hughes et al., 1992). Several epidemiological surveys of the prevalence of PD have been performed. In Aberdeen, Scotland, Mutch et al. (Mutch et al., 1986) found a prevalence of 164.2 per 10^5 population, increasing to a prevalence of 2.7% of men and 2.0% of women aged over 84 years. In other community surveys, the prevalence has been broadly similar: 61 per 10^5 population in Goteborg, Sweden (Broman T. 1963), 78 per 10^5 population in Gippsland, Australia (Jenkins 1966), and 168 per 10^5 population in London, United Kingdom *(*Schrag et al., 2000).

PD imposes significant functional disability. The Aberdeen study (Mutch et al., 1986) found that, while half of patients with PD were independent, 34.7% were considerably disabled and 10.2% were confined to bed or wheelchair. Disabilities experienced by PD patients, especially after having the condition for a number of years,

include cognitive impairment, falls, depression, swallowing difficulties and autonomic dysfunction (Hely et al., 2005). Furthermore, the largest longitudinal study of outcome in PD, the Sydney Multicentre Study of Parkinson's Disease, has shown increased mortality in PD patients after up to 15 years of follow up, compared with the general population (Hely et al., 2005).

The cardinal clinical features of PD are slowness and small amplitude of voluntary movement (bradykinesia), reduction in spontaneous and voluntary movement (akinesia), tremor (predominantly at rest), muscle rigidity and postural instability. A significant and sustained clinical response to levodopa therapy supports the diagnosis. The diagnosis of PD is a clinical one as there is presently no definitive diagnostic test apart from postmortem neuropathological examination (see "Pathology of Parkinson's disease"). In its classical form the diagnosis is relatively straightforward. However, problems in diagnosis frequently arise in those who present an incomplete or atypical syndrome. In particular, 20-25% of cases of PD diagnosed during life have pathological evidence of other "akinetic-rigid" syndromes, the commonest of which are Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy), multiple system atrophy, corticobasal degeneration or arteriosclerotic ("lower body") parkinsonism.

1.1.2 Evolution of disease and the development of motor fluctuations

Early in the course of PD, symptoms are generally mild and may not require treatment. Disease progression is usually very gradual. When treatment is required, levodopa (with a dopa decarboxylase inhibitor) is generally the agent of first choice. More recently, with the realisation that levodopa can promote the development of motor fluctuations, dopamine agonists have emerged as first-line treatment for many patients. Early in the course of the disease, levodopa usually provides an excellent and predictable improvement in symptoms (Marsden and Parkes 1977). At a variable time after the

commencement of levodopa, however, many patients develop fluctuations in their response to levodopa which become increasingly disabling.

The problem of motor fluctuation commonly begins with end-of-dose deterioration: early in the course of levodopa therapy, motor function improves about 30 minutes after the morning dose of levodopa and, as long as levodopa is taken about 4 hourly thereafter, the patient experiences more or less constant benefit during the day (Marsden and Parkes 1977). Later, however, the duration of action of each dose of levodopa begins to shorten such that, between 1 and 3 hours after each dose, the patient becomes significantly parkinsonian again ("wearing off phenomenon" or "end-of-dose deterioration"). With time, the transition from treatment effect ("on" state) to loss of treatment effect ("off" state) becomes more abrupt and less predictable.

At around the same time, dyskinesias frequently develop, particularly when the total daily dose of levodopa is increased to overcome the "wearing off" phenomenon. Dyskinesias usually take the form of choreiform movements of the orofacial muscles, trunk or limbs. Dystonic movements may also occur. In their most severe form, dyskinesias cause significant functional disability and emotional distress. When they first appear, dyskinesias are predictable, usually occurring at the peak of levodopa action, approximately 1-2 hours after each dose ("peak dose" dyskinesias). As the disease advances, the threshold for development of dyskinesias frequently drops so that the plasma levodopa level at which dyskinesias occur approaches that at which relief from Parkinsonian motor symptoms occurs. Clinically, this means that relief of parkinsonian motor symptoms inevitably involves concurrent dyskinesias (Nutt 2000; Obeso et al., 1997). Ultimately, the dyskinesia threshold may fall below the threshold for relief of Parkinsonian motor symptoms. Patients may then develop dyskinesias both at the beginning and end of the dosing interval, as the plasma levodopa level both rises and falls, as well as at peak dose. Such dyskinesias are

called “diphasic dyskinesias”. Dyskinesias that occur during the nadir of plasma levodopa levels (eg. in the early morning) are frequently dystonic in nature (“off dystonia”). In some patients, the motor response to levodopa becomes impossible to predict and the patient oscillates between severe dyskinesias and immobility during the day, apparently without regard to the timing of levodopa dosage. **Figure 1.1** depicts the evolution of dyskinesias at various stages of the disease.

Motor fluctuations and dyskinesias are common and become increasingly common with longer duration of disease and longer treatment duration. Schrag and Quinn (2000) found that, of patients with treatment duration of 6-9 years, 56% and 36% had motor fluctuations and dyskinesias, respectively. In their study, all patients treated for Parkinson’s disease for more than 10 years had both motor fluctuations and dyskinesias. In an 8 year longitudinal study of 34 patients with Parkinson’s disease, McColl et al. (2002) found that 58% of patients developed fluctuations and dyskinesias over a mean follow up period of 35 months. Schrag and Quinn (2000) found that the variables that were most strongly associated with an increased risk of motor fluctuations and dyskinesias were longer disease duration, greater disease severity, longer duration and greater dose of levodopa therapy, shorter interval between onset of symptoms and levodopa therapy and younger age at disease onset. The proposed pathogenesis of motor fluctuations and dyskinesias is discussed in section 1.6 of this chapter.

Figure 1.1 Graphical depiction of the changing motor response to levodopa over time. (figure adapted from Obeso et al, 2004, with modifications).

In early ("mild") disease, the effect of individual doses of levodopa on motor function is relatively subtle in magnitude, long lasting and dyskinesias do not occur.

As the disease advances ("moderate disease"), the difference between motor function in the "off" and "on states is more pronounced and motor function declines towards baseline between doses ("end of dose phenomenon"). Where dyskinesias occur, they tend to correspond to peak plasma levodopa levels.

In advanced disease, the difference between motor function in the "off" and "on" states is even more pronounced and the duration of action of levodopa more shortlived. The "dyskinesia" threshold drops, resulting in so-called "diphasic dyskinesias" ie. dyskinesias occurring both at peak plasma levodopa levels as well as when levels are rising (before motor benefit has occurred) and falling (after motor benefit has occurred).

1.1.3 Pathology of Parkinson's disease

The pathological hallmark of PD is the progressive loss of pigmented neurones in the pars compacta of the substantia nigra, which is seen macroscopically as nigral pallor. This results in a deficiency of dopamine in the main projection area of the substantia nigra compacta, the striatum. This deficiency of striatal dopamine, in turn, is thought to produce the symptoms of PD by disrupting the function of the cortico-striato-pallido-thalamo-cortical motor loop which is critical to the maintenance of normal voluntary movement.

The other pathologic hallmark of PD is the Lewy body. Lewy bodies are eosinophilic cytoplasmic inclusion bodies surrounded by a clear halo and are found within surviving neurones of the substantia nigra compacta. Although a highly sensitive marker for PD, Lewy bodies are not specific to it, being found at autopsy in 5% of brains of unaffected individuals. In PD, Lewy bodies are found in a number of sites within the CNS other than the substantia nigra, including the substantia innominata, the intermediolateral cell column of the spinal cord, the locus coeruleus, the dorsal motor nucleus of the vagus nerve and the cerebral cortex.

1.2 PHYSIOLOGY OF VOLITIONAL LIMB MOVEMENT

1.2.1 Afferent and efferent connections of the globus pallidus: the cortico-striato-pallido-thalamocortical motor loop

1.2.1.1 Corticostriate projections

The final common pathway for the execution of movement is the corticospinal tract which originates in the primary motor area. The primary motor area is subject to a number of influences, both subcortical and cortical. The overall network of neural structures involved in the preparation and execution of volitional movement is known as the "motor circuit" (**figure 1.2**). An understanding of this circuit is critical to an understanding of

pallidal function in human voluntary movement. Knowledge of the human motor circuit is derived in large part from studies on the brains of monkeys, and much of the subsequent discussion refers to such studies.

The basal ganglia are the major subcortical components of the motor circuit and comprise the striatum (composed of the caudate nucleus and putamen), the globus pallidus (external and internal segments), the subthalamic nucleus (STN) and substantia nigra (pars compacta and pars reticulata). The principal receiving nuclei of the basal ganglia are the caudate nucleus and putamen. Nigrostriatal inputs are dopaminergic, while corticostriate inputs are glutamatergic (Somogyi et al., 1981; Flaherty and Graybiel 1994).

Striatal neurons receiving corticostriate projections are arranged in distinct somatotopic and functional groupings (Kunzle, 1975, 1977; Parent 1990). The organisation of neurons according to their somatotopic and functional properties is maintained within the major targets of striatal outflow: the GPi, GPe and SNr (Nauta and Mehler, 1966; Johnson and Rosvold, 1971; Parent 1990), as well as in the STN (Smith et al., 1990; DeLong et al., 1985). On the basis of its afferent inputs from the cerebral cortex, the striatum can be divided functionally into sensorimotor, associative and limbic territories. The sensorimotor cortex projects to the putamen (Kunzle, 1975, 1977). Associative areas of the prefrontal, temporal, parietal and cingulate cortices project mainly to the caudate nucleus (Selemon and Goldman-Rakic, 1985). Limbic and paralimbic cortices, amygdala and hippocampus project to the ventral portion of the striatum, which includes the nucleus accumbens, the deep layers of the olfactory tubercle and the ventral parts of both caudate and putamen (Haber et al., 1990).

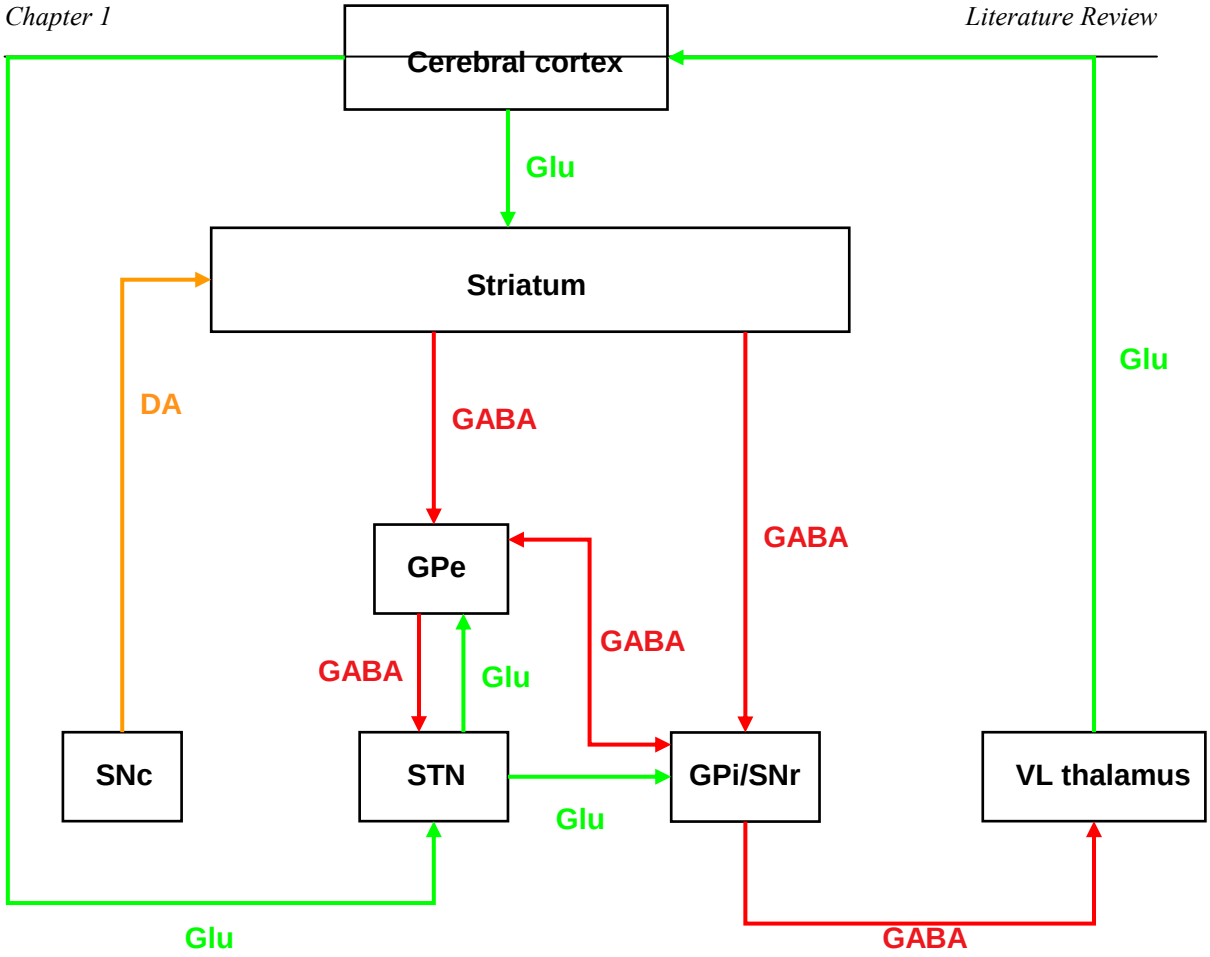


Figure 1.2 Basal ganglia connections subserving motor control in the healthy state.

Excitatory (glutamatergic) pathways are shown in green; inhibitory (GABAergic) pathways are shown in red. Dopaminergic connections from the substantia nigra compacta to the striatum are shown in orange.

(SNc = substantia nigra compacta; GPe = globus pallidus externa; GPi = globus pallidus interna; STN = subthalamic nucleus; SNr = substantia nigra reticulata; GABA = gamma amino butyric acid; Glu = glutamate).

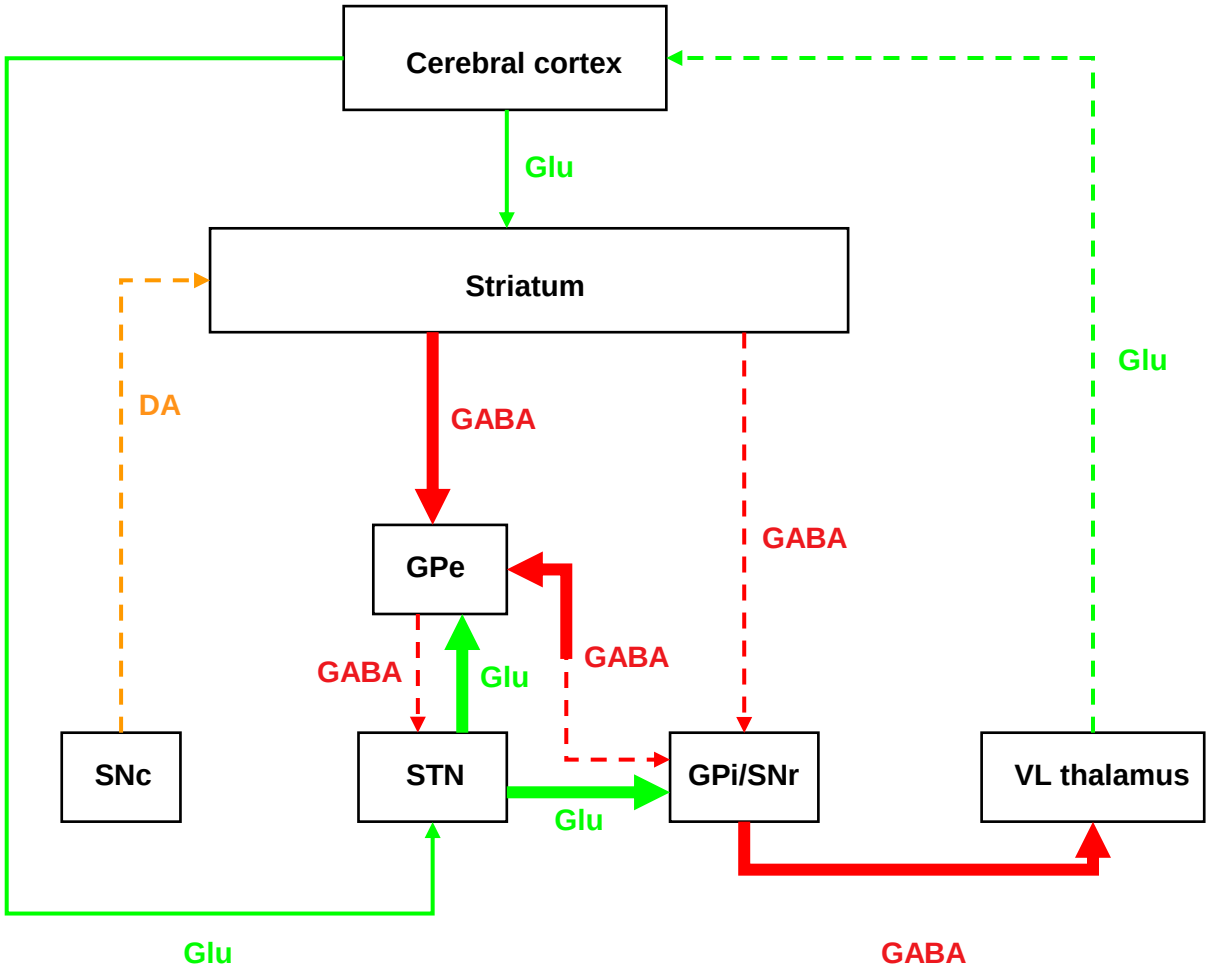


Figure 1.3 Basal ganglia connections subserving motor control in idiopathic Parkinson's disease.

Changes from the normal state, as a result of degeneration of nigrostriatal dopamine terminals (dashed orange line) are shown as follows: dashed lines indicate pathways that are hypoactive compared with normal; solid bold lines indicate pathways that are hyperactive compared with normal. Excitatory (glutamatergic) connections are shown in green; inhibitory (GABAergic) connections are shown in red).

(SNc = substantia nigra compacta; GPe = globus pallidus externa; GPi = globus pallidus interna; STN = subthalamic nucleus; SNr = substantia nigra reticulata; GABA = gamma amino butyric acid; Glu = glutamate).

1.2.1.2 Striatopallidal projections

The principal output nuclei of the basal ganglia are the internal pallidum (GPi) and SNr. The SNr is principally involved in oculomotor (Hikosaka and Wurtz 1983 ref III) and orofacial (DeLong et al., 1983), rather than volitional limb, movements and will be discussed in the following section. The GPi receives direct and indirect projections from the striatum. The direct striatopallidal pathway inhibits activity of GPi neurons by means of the inhibitory neurotransmitter gamma amino butyric acid (GABA), as well as substance P (Penney and Young 1981; Parent 1990). The indirect pathway projects to GPi via the GPe and subthalamic nucleus (STN) (Nauta and Mehler, 1966; Johnson and Rosvold, 1971). Striatal neurons projecting to GPe contain GABA and enkephalin (Parent 1990). Projections from the GPe to the STN are also GABAergic (Parent 1990), whereas the subthalamopallidal pathway is excitatory-glutamatergic (Smith and Parent 1988). Thus, the direct striatopallidal pathway has a net inhibitory effect on the GPi and the indirect striatopallidal pathway has a net excitatory effect on the GPi.

Projections from the various striatal territories retain their functional, as well as somatotopic, segregation within the pallidum. The “limbic” territory of the striatum projects mainly to the ventral pallidum (the portion of the GPe ventral to the intercommissural plane), as well as to the anterior part of GPe and medial GPi (Haber et al., 1990). The “associative” territory of the striatum projects to the dorsal third of GPe and GPi, while the “sensorimotor” territory projects to the ventral two thirds of each pallidal segment (Smith and Parent 1986).

Striatal neurons projecting to the GPi express D1 dopamine receptors (as well as dynorphin and substance P receptors), while striatal neurons projecting to the GPe express D2 dopamine receptors (as well as enkephalin receptors). The effect of dopamine depletion on GPi function in PD is probably mediated by the opposite effects of dopamine on

efferent striatal neurons of the direct and indirect pathways. Dopamine increases activity of striatal neurons that give rise to the direct pathway and decreases activity of striatal neurons that give rise to the indirect pathway (Gerfen et al., 1990) (**figure 1.2**). Thus, dopamine depletion in PD decreases and increases activity in the direct and indirect pathways, respectively, leading to a net increase in neural activity of the GPi (Hutchison et al., 1994; Beric et al., 1996; Vitek et al., 1993) and over-inhibition of thalamocortical neurons (**figure 1.3**).

1.2.1.3 Efferent pallidal projections

Projections from the GPe are mainly directed to the STN, but smaller projections are also directed to the SN and striatum (Parent 1986). Reciprocal connections between the GPe and GPi have been recently discovered (Hazrati et al., 1990), and these will be discussed later in this section. GPi efferent output is GABAergic and predominantly directed to the thalamus (Penney and Young 1981). Pallidothalamic fibres project to different thalamic target areas than nigrothalamic and cerebellothalamic projections (Gerfen 1984). The GPi projects predominantly to the ventral tier thalamic nuclei, centromedian nucleus, lateral habenula and pedunculopontine nucleus (Parent 1986). Within the pallidothalamic projection system, distinct associative/sensorimotor, limbic and reticular (cholinergic) components can be identified. The associative/sensorimotor fibres project to the thalamus and brainstem tegmentum (Parent 1986), whereas limbic fibres from the ventral pallidum project to STN and SN, as well as to the mediodorsal thalamic nucleus, lateral habenula, hypothalamus and amygdala (Haber et al., 1985).

Early studies suggested that outflow from the medial and lateral portions of the GPi was topographically segregated, with the former projecting to the ventral lateral thalamic nucleus, pars oralis (VLo) and the latter to the ventral anterior thalamic nucleus, pars principalis (VApc) (Nauta and Mehler, 1966; Kuo and Carpenter 1973; Kim et al 1976;

DeVito and Anderson 1982). However, subsequent work has shown that neurons within each portion of the GPi send projections to both VA and VL thalamus, as well as limited projections to the centromedian thalamic nucleus and habenula (Parent 1986).

The model of "direct " and "indirect" striatopallidal pathways (**figs 1.2 and 1.3**) has provided a useful starting point from which to discuss the pathophysiology and phenomenology of movement disorders such as PD. However, the model is likely to be a grossly oversimplified account of the factors that modify basal ganglia function in the control of voluntary movement. For example, reciprocal connections have been demonstrated between GPi and GPe (Hazrati et al., 1990). This indicates that a second indirect pathway exists between striatum and GPi, via the GPe, which bypasses the STN. The GPe is known to receive glutamatergic input from the STN, as well as GABergic input from the striatum (Smith and Parent 1988). Thus, it appears that the GPe is not simply a relay nucleus in a unidirectional pathway between the striatum and STN, but that its activity represents a balance between the antagonistic inputs of each. Furthermore, in addition to receiving inputs from the GPe, the STN also receives glutamatergic projections from the cerebral cortex and parafascicular nucleus, and dopaminergic projections from the SNc and ventral tegmental area (Canteras et al., 1990; Mouroux and Féger 1993; Sadikot et al., 1992). As will be discussed later, these additional pathways involving the GPe and STN may play a significant role in the pathophysiology of PD, and may help to explain some of the effects of pallidotomy on motor function.

1.2.1.4 Thalamocortical projections

Projections from the thalamus to limited areas of the cerebral cortex complete the motor circuit. These projections are glutamatergic (Araki and Endo 1976). It is well established that the principal cortical target of pallidothalamic outflow is the SMA, via the VLo thalamic nucleus (Schell and Strick 1984). However, it is now clear that pallido-

thalamocortical outflow is not restricted to the SMA. Studies involving the trans-neuronal transport of viral vectors show that ventral parts of the GPi also project via the VLo to the primary motor cortex and ventral premotor area (Middleton and Strick 1997). Furthermore, pallidothalamic projections to the VApc terminate in areas of the prefrontal cortex, including areas 9 and 46 (Carmel 1970; Middleton and Strick 1997). These findings suggest that the "associative/sensorimotor" component of pallidothalamic outflow is further subdivided on leaving the VL/VA thalamic nuclei, with VL projections terminating in cortical regions subserving motor control and VA projections terminating in more rostral areas involved in cognitive functions, such as working memory (Middleton and Strick 1997).

1.2.2 Anatomy of the pallidum and its efferent pathways

As mentioned above, the GPe is divided functionally into "associative/sensorimotor" and "limbic" divisions. However, the GPe has no anatomical subdivisions. The GPi is divided by the accessory medullary lamina into medial and lateral portions. The medial and lateral portions of the GPi have anatomically distinct efferent pathways (**fig 1.4**). The fibre bundle arising from the lateral segment of the GPi is called the ansa lenticularis. The ansa lenticularis forms a discrete bundle on the ventral surface of the pallidum. This bundle passes ventromedially and rostrally under the posterior limb of the internal capsule, before passing posteriorly to enter Forel's field H. Early descriptions of the ansa lenticularis proposed that it was a three tiered pathway with dorsal, middle and ventral divisions. However, subsequent work (Nauta and Mehler 1966) showed that the dorsal and middle divisions arise from the medial segment of the GPi and from the GPe, respectively, and that only the ventral division contains efferent fibres from the lateral segment of the GPi. The fibre bundle arising from the medial segment of the GPi is called the lenticular fasciculus. It leaves the medial segment of the GPi and initially runs dorsally,

traversing ventral parts of the posterior limb of the internal capsule. The lenticular fasciculus then passes medially and caudally to enter Forel's field H_2, where it merges with the ansa lenticularis and with cerebellothalamic fibres to form the thalamic fasciculus (Forel's field H_1). The pallido-thalamic fibres of the thalamic fasciculus terminate in the ventral anterior (VApc, pars principalis) and ventral lateral (VLo, pars oralis and VLm, pars medialis) thalamic nuclei. Between 10 and 20% of pallidothalamic fibres terminate in the contralateral rather than ipsilateral thalamus (Hazrati and Parent 1991).

Notwithstanding the anatomical segregation of fibres from the medial and lateral portions of the pallidum, labelling studies show that the destination of pallidofugal fibres within the thalamus is more dependent on their functional properties than anatomic origin (see section 1.2.1.4).

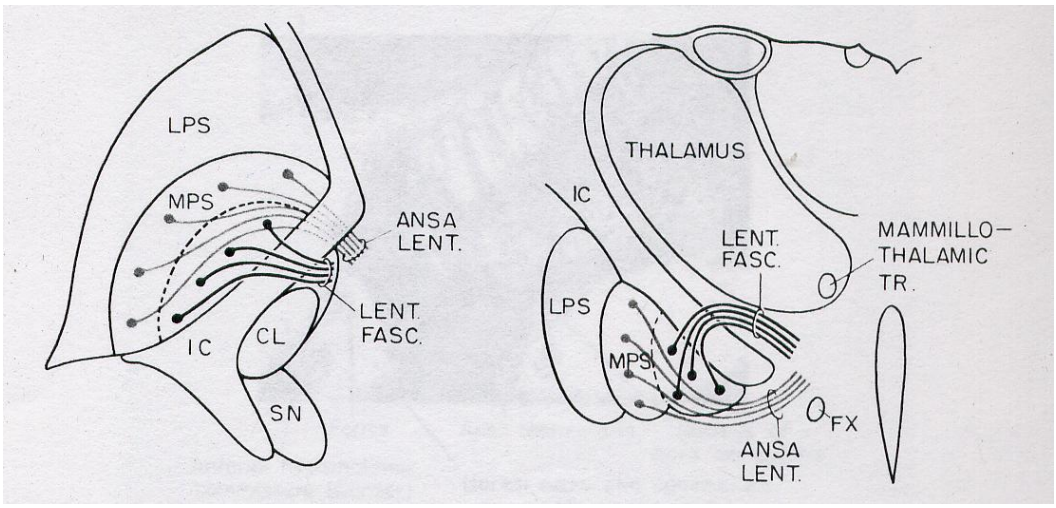


Figure 1.4 Diagrammatic representation of the origin and course of pallidal efferent fibres forming the ansa lenticularis and lenticular fasciculus. From Carpenter and Sutin, *Human Neuroanatomy*, 1983.

[LPS=lateral pallidal segment (GPe), MPS=medial pallidal segment (GPi), IC=internal capsule, CL=subthalamic nucleus,SN=substantia nigra, Ansa Lent=ansa lenticularis, Fx=fornix]

1.2.3 Somatotopic organisation of the sensorimotor pallidum

Early studies of single cell activity in the pallidum of the monkey showed that changes in neural activity were associated with movements of individual body parts performing the task (DeLong 1971). Subsequent studies have shown that the movement parameter most strongly correlated with changes in pallidal neural discharge is direction of movement (Mitchell et al., 1987; Brotchie et al., 1991*a*). The location of neurons within the pallidum that are responsive to somatosensory stimuli and movement has been controversial. In early reports, such neurons were mainly situated in the lateral portions of each pallidal segment throughout its anteroposterior extent (DeLong 1971). Subsequent studies found movement-related neurons in the posterior (Iansek and Porter, 1980) and central (Filion et al., 1988) parts of the pallidum. It has been demonstrated anatomically that striatopallidal fibres from the sensorimotor portion of the striatum terminate in the ventral two thirds of the GPi and GPe (Smith and Parent 1986). Overall, the evidence would suggest that movement-related neurons are distributed widely through both pallidal segments, with the exception of the more dorsal areas (DeLong et al. 1985). Although primarily responsive to ipsilateral limb movements, a minority of pallidal neurons are responsive to movements of the contralateral limbs (DeLong 1971; Filion et al., 1988). This observation is consistent with the anatomical connections that are known to exist between the pallidum and contralateral thalamus (Hazrati and Parent 1991).

Although some early studies failed to find a somatotopic organisation of movement-related neurons in the pallidum (Iansek and Porter 1980), subsequent work showed that sensorimotor neurons are distributed within the pallidum and STN along broadly somatotopic lines. In GPe and GPi, leg movement-related neurons tend to be located centrally in the anteroposterior and dorsoventral dimensions. However, arm movement-related neurons are found throughout the entire anteroposterior extent of both

pallidal segments, especially posteriorly (DeLong et al., 1985). In central parts of the GPe and GPi, arm movement-related neurons tend to be located inferior and lateral to leg movement-related neurons, but this distinction is not absolute (DeLong et al., 1985). As mentioned above, the somatotopic organisation of neurons and fibre projections is consistent within cortex, striatum, pallidum and STN. In other words, cortical neurons subserving arm movements tended to project to "arm" areas of the putamen and thence to "arm" areas of the pallidum and STN (DeLong et al., 1985).

1.2.4 Relation between pallidal discharge and movement

The precise influence of the pallidum and SMA on movement remains the subject of investigation. During a motor task, the activity of most pallidal neurons changes after, rather than before, muscle activation, suggesting that the pallidum does not initiate movement (DeLong and Georgopoulos 1979; Iansek and Porter 1980; Brotchie et al., 1991*b;* Mink and Thach 1991*a*). It has been proposed that the pallidum may receive an "efferent copy" of the signal sent from the motor cortex to the spinal motor neurons and then utilise this information in the planning and preparation of upcoming movements (Marsden 1982). Marsden proposed that the pallidum was involved in the automatic execution of learned motor plans, enabling them to be recalled from "motor memory" when required and then executed automatically (Marsden 1982).

Studies of pallidal neural activity in behaving primates support this hypothesis. In their studies of pallidal neuronal activity in monkeys trained to perform a wrist movement, Brotchie et al. (1991*a*, 1991*b*) found a subset of pallidal neurons whose firing patterns were influenced by the contextual setting of the task being performed. These neurons showed greater change in activity when the task had been learned by the animal, than when the task was novel and unpredictable. A further subset of neurons had a "double bursting" pattern, showing an early rise in discharge rate during the movement followed by a late

increase immediately before the movement finished. This second burst occurred regardless of whether or not the present movement was followed by a second movement. Neurons with a single bursting pattern could be entrained to develop this second burst of activity as the motor task was practised. Two conclusions were drawn from these observations. Firstly, the pallidum is involved in the process by which motor tasks are learned, rather than in the performance of novel, unpredictable tasks. Secondly, the pallidum plays a role in the organisation of sequential movements, by signalling to its major cortical target, the SMA, when the current movement should end and the next one begin. Changes in phasic neural activity in the pallidum may terminate sustained neural activity in the SMA, either terminating movement completely or triggering preparation for the next movement in a sequence.

Mink and Thach (Mink and Thach 1991*b*) examined the effect of chemical inactivation of the pallidum on the performance of visually guided step tracking movements. Pallidal inactivation resulted in the co-contraction of flexor and extensor muscles during movement and, as a result, slowing of movement. Thus, during normal movement, the pallidum may inhibit the activation of antagonist muscles that would otherwise interfere with movement. It is not clear how this proposed role of the pallidum can be reconciled with the knowledge that pallidal discharge more commonly follows than precedes muscle activation.

In summary, the pallidum is a strategic component of the circuitry involved in the learning of complex motor tasks and is particularly responsive to the direction of joint movement. It plays an important role in controlling the temporal characteristics of movement sequences, possibly signalling to the mesial frontal cortex when the present movement should finish so that another can begin. The pallidum may also be involved in

the selection of agonist and/or suppression of antagonist muscle groups for movement, so that a movement may be performed as efficiently as possible.

1.2.5 Role of the supplementary motor area in the control of normal movement

Evidence for the role of the SMA in the control of movement comes both from experimental studies and observation of the clinical effects of SMA lesions. In monkeys, SMA lesions impair performance of bimanual coordination tasks (Brinkman 1984). Humans with bilateral SMA lesions manifest a reduction in spontaneous movement, resembling Parkinsonian akinesia (Forster 1936) and unilateral SMA lesions are also associated with deficits in spontaneous and volitional movements (LaPlane et al., 1977; Dick et al., 1986). Much interest has centred around the role played by the SMA in voluntary movements of various kinds (for example, internally generated as opposed to externally cued movements) and in the timing of SMA activation relative to other cortical areas involved in motor control.

In monkeys, SMA neurons show changes in discharge rate following instructional stimuli which specify the direction of an upcoming limb movement (Alexander and Crutcher 1990; Romo and Schultz 1992, Tanji and Shima 1994), suggesting that the SMA is important in setting the parameters of upcoming movements. In humans, imagination of movement is associated with increased regional cerebral blood flow in the SMA, as measured by positron emission tomography, whereas no such increase is seen in the primary motor or somatosensory cortices (Roland et al 1980, Decety 1988, Rao et al 1993). This observation suggests that the SMA has a role in motor imagery and "intention to act", a hypothesis which is supported by the analysis of movement-related potentials (MRP) preceding both imagined and executed movements (Cunnington et al., 1997).

There is evidence that the SMA is activated in association with internally generated movements. PET studies in humans show greater activation of the SMA in association with

internally generated, compared with externally cued, movements (Dieber et al., 1991). Single cell recordings in monkeys show that the SMA is preferentially active in association with the pre-movement and movement periods of internally generated movements (Mushiake et al., 1991). By contrast, the premotor cortex is active in the pre-movement phase of visually guided movements and the primary motor cortex is active during the pre-movement and movement periods of both types of movement (Mushiake et al., 1991). The significance of these findings is twofold. Firstly, they show that the SMA, like the pallidum, is preferentially involved in movements that have become learned and can thus be performed without recourse to external (eg. visual) cues. Secondly, maximal SMA activity during the pre-movement period, as in pallidal activity, would support its playing a role in the preparation of upcoming movements, rather than in controlling the parameters of movements currently being executed.

Electrophysiological studies in humans also support a role for the SMA in the preparation of movement. One of the best studied cortical correlates of voluntary movement in humans is the Bereitschaftspotential (BP), a progressively increasing negative cortical potential that precedes self-paced voluntary movements (Kornhuber and Deecke 1964, 1965). The BP is divided into two major components. The early component begins between 1 and 2 seconds before movement onset and finishes between 650 and 500 msec before movement onset. The early component of the BP is symmetrically present on both sides of the brain in association with unilateral movement and reaches maximum amplitude at the vertex. The early BP is believed to represent neural processes involved in preparation for movement. The late component begins immediately after the early component and finishes at movement onset. It reaches its maximum amplitude over the hemisphere contralateral to movement and is believed to represent neural changes in the primary cortex associated with movement execution.

The neural origin of the scalp-recorded BP remains a matter of debate (Bötzel and Schulze, 1996). It has been claimed that, as the two SMAs directly face each other and are both activated in association with unilateral movements, their electric fields would cancel each other and therefore be unrecordable from the scalp (Bötzel and Schulze, 1996). It has been suggested that the primary motor cortices are more likely to be the origin of the early BP, and there is some support for this from dipole analysis algorithms (Toro et al., 1993; Botzel et al., 1993). However, several lines of experimental evidence support the SMA as being a major, if not the sole, contributor to the early BP. In patients with unilateral SMA lesions, predominance of the BP at the vertex is lost, suggesting that vertical predominance of the normal BP is due to SMA activity (Deecke et al. 1987). Jahanshahi et al (1995) demonstrated good correlation between MRP amplitude and SMA blood flow in normals and patients with PD. Furthermore, epicortical recordings in humans undergoing operative treatment for epilepsy show a well defined negativity arising from both SMAs and the contralateral primary motor area in the period preceding unilateral movement (Neshige et al., 1988; Ikeda et al., 1992). Although these studies strongly suggest that the SMA and primary motor cortex are involved in generation of the BP, they have not established the precise timing of activation of these two areas relative to one another. However, Lang et al. (1991) used magnetoencephalography in a patient with a unilateral SMA lesion and identified a current dipole source in the intact SMA starting about 1200 milliseconds prior to contralateral thumb movement. This dipole was followed 600 msec later by a dipole which localised to the hand area of the contralateral primary motor cortex.

Thus, there is evidence that the SMA is active in association with internally generated movements and that SMA activation occurs prior to and/or together with activation of the primary motor cortex. There is evidence, in addition, that the SMA is particularly active in association with sequential and simultaneous, compared with simple,

unilateral movements (Benecke et al., 1985). Furthermore, the BP is of greater amplitude, and commences earlier, in association with complex, compared with simple, bimanual sequential finger movements (Cui et al., 2000). Similarly, SMA blood flow is greater during the mental rehearsal and execution of complex sequential finger movements than during simple isometric contractions of individual fingers (Roland et al., 1980). Thus, the SMA appears to be involved in the retrieval of previously learned motor subroutines during the planning and execution phases of complex sequential movements.

1.3. PHYSIOLOGY OF BLINKING AND OCULAR MOTOR CONTROL

1.3.1 The oculomotor circuit

1.3.1.1 Anatomy

As for volitional limb movement, oculomotor control involves the convergence of inputs from several cortical regions on discrete regions of the basal ganglia, whence input is directed to restricted areas of the cortex. For the most part, evidence concerning the influence of the basal ganglia on eye movements is derived from the study of saccadic eye movements in monkeys. However, evidence of anatomical and functional homology between saccadic eye movements and blinking suggests that both types of eye movement may share a common circuitry.

The major striatal input nucleus for oculomotor control is the caudate. It receives projections from the frontal eye fields (FEF), supplementary eye fields (SEF), dorsolateral prefrontal cortex and posterior parietal cortex (Künzle and Akert 1977; Künzle 1978; Selemon and Goldman-Rakic 1985). The caudate projects predominantly to the ventrolateral SNr and has more limited projections to the dorsal third of the GPi (Parent et al., 1984; Smith and Parent 1986). The SNr component of the oculomotor circuit projects to the VAmc (ventralis anterior, pars magnocellularis) and MDmf (medialis dorsalis, pars multiformis) thalamic nuclei, while the GPi component projects to the lateral VApc

(ventralis anterior, pars parvocelluaris) (Carpenter et al., 1976). Each of these thalamic areas projects back to the FEF and SEF (Kievit and Kuypers 1977; Barbas and Mesulam 1981). In addition, collateral branches of the nigrothalamic fibres project to the superior colliculus (Parent et al., 1984b).

1.3.1.2 Neuronal functional specificity within the oculomotor circuit

As for the motor circuit, neurons within the oculomotor circuit show functional specificity for certain types of eye movement. For example, FEF neurons may discharge preferentially in relation to visual fixation, saccadic eye movements or passive visual stimuli (Mohler et al., 1973; Goldberg and Bushnell 1981; Bruce and Goldberg 1985).

This functional specificity has also been demonstrated within the ventrolateral SNr (Hikosaka and Wurtz 1983a, b, c). GABAergic projections from the SNr to the superior colliculus are important for the control of saccadic eye movements (Hikosaka and Wurtz 1985a, b). In addition to its output to the FEF and SEF, other regions of the SNr have been shown to project to areas of the prefrontal cortex involved in working memory (Middleton and Strick 1997). Oculomotor functions for the GPi are surmised, from the knowledge that it receives inputs from the oculomotor territory of the caudate nucleus (Parent et al., 1984), but have not yet been confirmed physiologically.

1.3.2 Neurophysiology of blinking

1.3.2.1 Homology between saccadic eye movements and blinking

The neurophysiology of blinking is less well understood than that of saccadic eye movements. Electromyographically, a blink is characterised by inhibition of tonic levator palpebrae superioris (LPS) activity followed by brief contraction of orbicularis oculi. Blinking is believed to involve the reciprocal innervation of these two antagonist muscles (Schmidtke and Büttner-Ennever 1992). The LPS are supplied by the central caudal nucleus (CCN), an unpaired subgroup of the oculomotor nucleus in the dorsal midbrain

(Warwick 1953). Pre-motor influences on the CCN are thought to include the superior colliculus and posterior commissure nuclei as well as feedback from the LPS (Schmidtke and Büttner-Ennever 1992).

Several lines of evidence suggest that the neural pathways controlling saccadic eye movements and lid control are tightly linked. Firstly, LPS is derived embryologically from superior rectus (Gilbert 1957). Secondly, activity of the lids and globes are tightly coupled during vertical gaze changes (Kennard and Smyth 1963; Becker and Fuchs 1988). Finally, the generation of saccades is facilitated by blinking (Zee et al., 1983). Overall, the evidence points to a coupling of control mechanisms for blinking and saccade generation, especially in the vertical plane, perhaps mediated by shared inputs from the superior colliculus.

1.3.2.2 Central dopaminergic activity and the blink rate

Clinical and experimental evidence shows that the spontaneous blink rate is closely linked with central dopaminergic activity. The blink rate is reduced in akinetic-rigid syndromes, such as idiopathic PD (Hall 1945; Karson 1983), progressive supranuclear palsy (Pfaffenbach et al., 1972) and drug-induced parkinsonism (Karson et al., 1981*a*; Karson 1983). In contrast, dopaminergic drugs increase blink rates in parkinsonian monkeys (Lawrence and Redmond 1991), and some hyperkinetic movement disorders, such as Tourette's syndrome (Cohen et al., 1980) and primary dystonia (Deuschl and Goddemeier 1998) are associated with increased blink rates.

The effect of dopamine on the blink rate may be mediated by its effects on SNr and SC function. Dopamine diminishes net neural activity within the SNr, as it does in the GPi (Gerfen et al., 1990). The superior colliculus receives inhibitory projections from the SNr. Assuming that inputs from the superior colliculus to the CCN are also inhibitory (which has yet to be proven), a transient reduction in SNr-mediated inhibition of superior colliculus would, in turn, inhibit CCN activity, causing a reduction in LPS activity and a

blink. By contrast, dopamine depletion may diminish the blink rate by causing an increase in SNr neural activity, an increase in inhibition of the SC by the SNr and an increase in tonic LPS activity.

1.4. PATHOPHYSIOLOGY OF PARKINSON'S DISEASE

1.4.1 Pallidal dysfunction in Parkinson's disease

1.4.1.1 Pallidal dysfunction in animal models of Parkinson's disease

Evidence of abnormal pallidal neural activity in PD mostly comes from animal models of the disease. The neurotoxin 1-methyl,4-phenyl,1,2,3,6 tetrahydropyridine (MPTP) produces a syndrome in primates which is clinically and pathologically very similar to idiopathic PD (Langston 1987). The firing rates and metabolic activity of GPi and GPe neurons are higher and lower, respectively, in MPTP-treated, compared with healthy, monkeys (Crossman et al., 1985; Mitchell et al., 1986; Miller and DeLong 1987; Filion et al., 1988; DeLong 1990; Filion and Tremblay 1991). GPi neurons in MPTP-treated animals also show an increase in phasic responses to somatosensory stimuli and voluntary movement and a loss of the normal specificity of these responses to specific movement parameters (Filion et al., 1988; Miller and DeLong 1988). As discussed above, the changes in GPi, GPe and STN function that occur in the MPTP model of PD are thought to reflect the differential effect of dopamine depletion on the direct and indirect striatopallidal pathways. The dopamine agonist apomorphine reverses the effect of MPTP on neural activity within the GPi and GPe (Filion et al., 1991).

Increased output from the STN and GPi is believed to play a critical role in the pathogenesis of PD. Excessive inhibition of thalamocortical pathways as a result of inhibitory input from the GPi leads to a breakdown in control of motor subroutines by the SMA and, accordingly, parkinsonism. This hypothesis is supported by the finding that in

monkeys with MPTP-induced parkinsonism, lesions of the STN reduce all the major signs of parkinsonism in the contralateral limbs (Bergman et al., 1990).

1.4.1.2 Pallidal dysfunction in humans with idiopathic Parkinson's disease

Studies of pallidal activity in humans with PD suggest that the MPTP model is an accurate correlate of basal ganglia physiology in idiopathic PD. In humans with PD, neuronal firing rates are higher in the GPi than the GPe (Hutchison et al., 1994; Beric et al., 1996; Vitek et al., 1993). Firing rates of GPi and GPe neurons in PD patients are decreased and increased respectively by the administration of apomorphine (Hutchison et al., 1997). Furthermore, single unit recordings done at the time of pallidotomy in patients with PD indicate that, as in the monkey, GP neurons in humans are somatotopically organised and respond to the direction and amplitude of movements at specific joints (Sterio et al., 1994). Finally, the fact that medial pallidotomy in humans with PD improves the three cardinal elements of parkinsonian motor dysfunction – bradykinesia, tremor and rigidity – provides compelling, if indirect evidence, that overactivity of the GPi underlies the pathophysiology of idiopathic PD.

It is controversial whether neurons with abnormally increased activity are found preferentially within the medial portion of the GPi. This is an important question in so far as it influences the selection of the site within the GPi that is chosen for the surgical treatment of PD. In a study of 6 PD patients, Hutchison et al. (1994) found that neurons with significantly increased firing rates compared with GPe were found predominantly within the medial portion of GPi, whereas the mean firing rate of neurons in the lateral portion of GPi was not significantly different to that of GPe neurons. However, in a subsequent paper, the same authors found that apomorphine significantly decreased neuronal firing rates in both the medial and lateral portions of the GPi in PD patients, suggesting that baseline neural activity is abnormally high in both portions of the GPi in

PD (Hutchison et al., 1997). There is no evidence that striatopallidal projections to the medial and lateral portions of the GPi are differentially affected by dopamine depletion. Hence, it would be expected that both portions of the GPi would exhibit an increase in neural activity in PD. Indirect evidence of abnormally increased neural activity within the lateral GPi in PD is the fact that the signs of Parkinsonism improve after lesions proven at postmortem to be confined to the ansa lenticularis, which arises from the lateral GPi (Beck and Bignami 1968).

1.4.2 Cerebral cortical dysfunction in Parkinson's disease

1.4.2.1 Mesial cortical dysfunction in Parkinson's disease

As with the internal pallidum, activation of the major motor association areas, including the SMA, is depressed in PD. PET imaging studies demonstrate a reduction in activity in both SMAs, prefrontal areas and cingulate cortex during free-selection movements of the arm compared with normal subjects (Playford et al., 1992). As discussed above, these areas are the major cortical targets of GPi outflow. In addition, contralateral putamen, bilateral cerebellum and bilateral thalami, which are activated in normal subjects during free selection movements, are not significantly activated in PD patients (Playford et al., 1992). Impaired activation of SMA during voluntary movements is reversed by administration of apomorphine (Jenkins et al., 1992; Rascol et al., 1992). Therefore, the major physiological correlate of bradykinesia at a mesial frontal level is impaired SMA activity. Furthermore, the correction of impaired GPi, GPe and SMA activation by apomorphine suggests that dopamine depletion is the cause of impaired pallidal and mesial cortical function in PD.

The evidence supporting the SMA as being a major contributor to the readiness potential, or Bereitschaftspotential (BP), has been described above. It is generally agreed that the BP preceding simple, self-willed limb movements is abnormal in PD. Initial reports describing an abnormally small BP in PD (Deecke et al., 1977; Shibasaki et al., 1978) were later questioned on methodological grounds (Barrett et al., 1986). However, subsequent work showed that the early component of the BP is abnormally reduced in amplitude in patients with PD, compared with normal controls (Dick et al., 1989; Jahanshahi et al., 1995). In PD patients, the amplitude of the early component of the BP improves after levodopa (Dick et al., 1987).

The study of movement-related potentials (MRP) preceding complex movements in PD patients provides an insight into the effect of SMA dysfunction on the parameters of complex movements, and the mechanisms in place to compensate for defective SMA function during movement. Cunnington et al. (1995) examined the BP in patients with PD and in control subjects under varying conditions, namely in the presence or absence of spatial and temporal cues and according to whether these cues were predictable or unpredictable. Consistent with previous studies of simple movements, the slope of the early component of the MRP was reduced in PD patients compared with normal subjects. In control subjects, the MRP was present regardless of the presence or absence of external cues, albeit of greater amplitude when cues were absent (ie. indicating greater involvement of the SMA in internally generated movements). In PD patients, however, there was little or no early BP component when movements were made in the presence of external cues dictating the temporal characteristics of the movement to be performed. In other words, when PD patients perform movements for which external cues are available, the SMA appears to be bypassed. What, then, takes its place?

1.4.2.2 Lateral premotor and parietal circuits in Parkinson's disease

PD patients are more reliant than control subjects on external cues to accomplish movement (Flowers 1976; Stern et al., 1983; Brown and Marsden 1988). PD patients appear to use such cues to perform movements, such as gait, that are normally performed "automatically" (Morris et al., 1996).

There is evidence that the increased use of external cues by PD patients compensates for dysfunction of medial motor circuits including the SMA, and is associated with activation of more lateral motor circuits. In PD patients, the decrease in SMA activation during internally-generated finger movements is offset by an increase in activation of lateral premotor and inferolateral parietal cortices (Samuel et al., 1997a). When PD patients are provided with visual cues to facilitate gait, there is an increase in activation of the lateral premotor cortex as compared with normal subjects under the same conditions (Hanakawa et al., 1999). As mentioned above, movement-related electrical activity is diminished over the mesial frontal cortex in PD (Dick et al., 1989) and is reduced further by the provision of external cues to facilitate movement (Cunnington et al., 1995). The reduction in electrical activity over the mesial frontal cortex in PD may be associated with an increase in pre-movement electrical activity over more lateral premotor regions (Cunnington et al., 2000).

The lateral premotor and inferolateral parietal cortices, unlike the SMA, do not receive projections from the GPi (Middleton and Strick 1997). Therefore, increased activation of these areas in PD is likely to be compensatory, rather than a direct result of deficits in pallidocortical circuits. The lateral premotor cortex receives projections from regions of the parietal cortex involved in the integration of somatosensory, visual and limbic inputs (Petrides and Pandya 1984; Cavada and Goldman-Rakic 1989). In monkeys, neurons of the lateral premotor cortex increase their activity in association with movements that are guided by visual cues (Mushiake et al., 1991; Godschalk et al., 1981; Halsband et al.,

1994). Functional imaging studies support a similar role for this area in humans (Roland 1984; Passingham 1988). In summary, these data suggest that the increase in movement-associated activation of the lateral premotor and inferolateral parietal cortices in PD is linked to the increased use of external sensory cues to facilitate movement, to compensate for defective medial motor circuits.

1.5. BRADYKINESIA IN PARKINSON'S DISEASE

1.5.1 Background

In clinical practice, the term "bradykinesia" is used to describe the slowness and small amplitude of voluntary movements in PD. The term "akinesia" refers to a reduction in spontaneous, automatic or associated movement that accompanies voluntary movements, such as blinking or facial expression during conversation and arm swing when walking. Even these fundamental definitions are still debated, in particular the specific aspect of slowing of movement to which each term refers.

A major interest of this study is to understand what physiological aspects of motor performance contribute to what is described, clinically, as bradykinesia, and how these might be altered by pallidal surgery. In this section, I will discuss the range of motor deficits that are subsumed under the term "bradykinesia".

1.5.2 Reduced movement speed in bradykinesia

1.5.2.1 Simple movements

Rapid movements of single joints are significantly slower when performed by patients with PD compared with control subjects (Draper and Johns 1964). In PD, large amplitude ballistic movements are slower than small amplitude movements (Flowers 1975). Hallett and Khoshbin proposed a physiological explanation for this difference (Hallett and Khoshbin 1980). They found that PD patients, like control subjects, performed small amplitude movements using a single triphasic cycle of agonist-antagonist-agonist

muscle activity. By contrast, large amplitude movements required repeated cycles when performed by PD patients. The authors proposed that repeated triphasic cycles are required because PD patients are unable to recruit sufficient muscle activity to complete a large movement in a single cycle. They termed this abnormality an inability to sufficiently "energise" muscles for movement and concluded that the appropriate energising of muscles was a fundamental function of the basal ganglia. Whether a movement is described as large or small amplitude is relative to the joint at which that movement occurs. Berardelli et al. studied 5° and 10° movements of the terminal phalanx of the thumb in PD patients and showed that, as in large amplitude movements of more proximal joints, repeated bursts of activity in flexor pollucis longus were usually required to complete the movements (Berardelli et al., 1984).

Berardelli et al. (1986*a*) also studied the ability of PD patients to increase the size of the initial agonist EMG burst in order to perform movements of increasing amplitude or of the same amplitude made against increasing resistance. They found that PD patients were able to modulate EMG activity in a similar fashion to controls. Furthermore, velocity of movement increased to a similar degree in PD and control subjects when movements of greater amplitude were performed, although absolute velocities remained lower in the PD group. The authors concluded that the initial agonist burst does not saturate in PD patients. Rather, there appears to be a deficit in the ability to match absolute muscle activation to the requirements of the movement being performed. The deficit, therefore, may be "upstream" of motor cortex activation. In planning an upcoming movement, the muscle activation requirements for that movement may be underestimated, leading to an inadequate signal being delivered to the motor cortex.

1.5.2.2 Complex movements

The study of more complex movements in PD arose in part from the finding that a discrepancy exists between clinical ratings of bradykinesia and the abnormalities seen in kinematic analysis of simple movements. In a study of simple wrist movements made by PD patients before and after levodopa administration, Berardelli et al. (1986*a*) found that the degree of improvement in movement speed and agonist EMG size after levodopa was much smaller than the improvement in clinical bradykinesia. In other words, there is clearly more to bradykinesia than simply a reduction in movement speed.

Benecke et al. subsequently confirmed that slowness of movement in PD is more marked for complex movements, such as simultaneous and sequential movements, than simple movements (Benecke et al., 1986*a*; Benecke et al., 1987*a*). The additional slowness in complex movements appeared to arise from two sources. Firstly, the individual component movements of a complex task were slower than when the same movements were performed separately. Secondly, there was an abnormally long delay between the subcomponents of the complex movement (the "inter-onset latency"). Other workers confirmed these findings (Berardelli et al., 1986*b*). When control subjects performed two sequential movements as quickly as possible, the optimum inter-onset latency (IOL) was approximately 230 msec (Benecke et al., 1986*b*). However, in patients with PD, the mean IOL was 400-500 msec (Benecke et al. 1987*a*). Furthermore, it was the length of the IOL in the PD patients, rather than the speed of the movement subcomponents, that correlated best with clinical ratings of bradykinesia (Benecke et al., 1987*a*).

These findings had been foreshadowed by Schwab et al., who found that PD patients had difficulty performing two simultaneous movements and tended to divide the task into its two components and perform them separately (Schwab et al., 1954).

Extending the observation of Berardelli et al (1986*a*) that levodopa produces a greater improvement in clinical akinesia than in the parameters of simple movements, Benecke et al. found that levodopa produced a greater improvement in the performance of complex than simple movements (Benecke et al., 1987*b*). This observation strengthened the evidence that complex movements are a better marker of underlying bradykinesia than simple movements.

In both normal (Benecke et al., 1986*a*) and parkinsonian subjects (Benecke et al., 1987*a*), the two component movements of a sequential movement vary independently of one another. This suggests that the movements are controlled by distinct mechanisms. In the light of their results, Benecke et al. (1987*a*) postulated that complex movements are organised by an executive "motor plan". The motor plan consists of a series of "motor programs", each of which directs the parameters of single subcomponents of the complex movement. According to this hypothesis, prolongation of the IOL between subcomponents of complex movements represents a deficit in switching from one motor program to another in the overall motor plan, because of dysfunction of pallido-thalamocortical inputs to the SMA.

In the performance of any complex motor task, a compromise is struck between speed and accuracy of movement. For example, the optimum IOL in a two-stage sequential upper limb movement performed by control subjects was found by Benecke et al. to be 230 msec (Benecke et al., 1986*b*). This means that, while shorter IOL could be achieved by the subjects, this occurred at the expense of movement accuracy. When PD patients are asked to perform a complex motor task using maximal speed and accuracy, they do so as accurately as control subjects, but are unable to increase movement speed on command (Berardelli et al., 1986*b*). Thus, there appears to be an inflexibility in motor control in PD,

with patients being unable to balance competing kinematic demands on motor performance.

The notion that abnormal switching from one movement to the next underlies the pathophysiology of bradykinesia is consistent with many of the observations on pallidal and mesial frontal cortical function described in sections 1.2.4 and 1.2.5. Changes in pallidal discharge in the monkey are timed to coincide with the end of one movement in a sequence and the beginning of the next (Brotchie et al., 1991*b*). Therefore, increased neural activity in the internal pallidum, as has been documented in the MPTP-monkey (Filion and Tremblay 1991), would be expected to impair the efficient switch from one submovement to the next in a movement sequence. Analysis of movement-related potentials in PD patients performing sequential tasks has shown reduction of the "post-peak slope" following movement (Cunnington et al., 1997). This observation, too, is consistent with there being a defect in PD of the ability to "switch off" SMA function during complex movements, so that one submovement can terminate and the next one begin. Furthermore, the fact that the amplitude of the pre-movement potential is affected by cues that dictate the temporal characteristics of movement is further evidence that the mesial frontal cortex is important in the sequencing of complex movements (Cunnington et al. 1995).

1.5.3 Reduced movement amplitude in bradykinesia

Slowness of movement alone does not explain bradykinesia. Many bedside tests of bradykinesia evaluate different elements of motor dysfunction than reduced movement speed. In perhaps the most commonly used test of bradykinesia - rapid finger opposition on the thumb - the examiner tests the amplitude and rhythm of finger movements, rather than their speed. Typically, movement amplitude progressively declines during this task and the rhythm is irregular. Although such movements are critical for many activities of daily living (eg. handwriting), they have been neglected in previous studies of the kinematics of

movement in PD, in favour of non-repetitive movements of more proximal joints (Benecke et al., 1986, 1987*a*; Berardelli et al., 1986*a*).

It could be argued, however, that small amplitude, repetitive movements of distal joints are equally, if not more, "complex" in neurophysiological terms than more proximal movements. Repetitive finger tapping requires the rapid oscillation between two motor plans at a short inter-onset latency. Therefore, maintenance of regular tapping rhythm would be critically dependent on intact pallidal and SMA function and should deteriorate early in the course of PD when pallidal and SMA function become abnormal. The decline in amplitude of movement during rapid finger tapping may be caused by a failure to "energise" the appropriate muscles to perform the movement (Hallett and Khoshbin, 1980), as discussed above.

1.5.4 Summary

In summary, the term "bradykinesia" in PD encompasses deficits in the speed, amplitude and rhythm of movement. While deficits exist in simple movements, deficits are more marked in complex or repetitive movements, particularly in the ability to switch from one sub-movement to the next in a sequential motor task, and to maintain a consistent amplitude and rhythm in a repetitive motor task.

The ideal test of bradykinesia should therefore measure complex (multi-stage) rather than simple (ballistic) movements. Furthermore, it should measure movements of distal as well as proximal joints. It should include a measurement of the IOL between submovements, as this has been shown to correlate with clinical ratings of bradykinesia. For rapid repetitive movements, the regularity of rhythm should be measured, as well as the degree of amplitude decline during movement repetition.

The experiments in this study were designed to dissect out each component (speed, amplitude, IOL and rhythm) of voluntary movement and observe the effect of intervention

(medication or surgery) on them, as well as which aspects were correlated with any improvement in clinical function. The aims were to better understand the physiological basis of bradykinesia in PD, and the mechanism by which it is altered post-operatively.

1.6 PATHOPHYSIOLOGY OF DRUG-INDUCED DYSKINESIAS IN PARKINSON'S DISEASE

1.6.1 Pathological basis of dyskinesias in idiopathic Parkinson's disease

The pathophysiologic basis of drug-induced dyskinesias remains unclear. It is generally agreed that dyskinesias result both from the underlying disease process and from the peculiar properties of exogenously administered levodopa. Levodopa does not induce dyskinesias in non-parkinsonian individuals, and patients with idiopathic PD who have never been treated with levodopa do not generally develop dyskinesias. The pathological substrate for dyskinesias may be prolonged and massive loss of dopaminergic innervation in the striatum, resulting in hypersensitivity of surviving striatal dopamine receptors (Klawans et al., 1977; Agid et al., 1985). With disease progression, the ability of neurons to store dopamine pre-synaptically diminishes. Therefore, the pulsatile administration of short half-life levodopa preparations may cause dyskinesias by stimulating these hypersensitive receptors (Chase et al., 1996). That pulsatile levodopa administration is in part responsible for dyskinesias is supported by the fact that dyskinesias can be diminished by the continuous administration of levodopa by the intraduodenal or intravenous routes (Mouradian et al., 1988; Sage et al., 1990). The contribution of other neurotransmitter systems (eg. GABA, enkephalin and glutamate) to the pathogenesis of dyskinesias remains speculative (Nutt 1990; Blanchet et al., 1995). The somatic distribution of dyskinesias probably reflects the somatotopic organisation of the underlying striatum from which they arise (Marconi et al., 1994).

1.6.2 Pathophysiology of dyskinesias: animal models

Experimental models of dyskinesia suggest that the GPe is of major importance in the genesis of drug-induced dyskinesias in PD. In MPTP-treated monkeys, drug-induced dyskinesias are associated with a net increase in neuronal firing rate within the GPe (Filion et al., 1991). This is associated with a decrease in firing rate within the GPi, mediated by inhibitory outflow from the GPe to GPi, either directly (Hazrati et al., 1990) or indirectly, via the STN. Choreiform dyskinesias can be induced in healthy monkeys by the injection of the GABA antagonist bicuculline into the GPe, thereby causing a net increase in GPe neural activity (Crossman et al., 1988; Mitchell et al., 1989). Although ablation of the GPe has not been shown to abolish dyskinesias in MPTP-treated monkeys (Blanchet et al., 1994), these data support an important role for the GPe in drug-induced dyskinesias.

Recent work suggests that it is the pattern of neuronal firing within the GPe, rather than the mean firing rate, that is the critical factor in the genesis of dyskinesias. After injection of bicuculline into the GPe, Matsumura et al. (1995) found that 71% of responding GPe neurons increased their activity, in a manner identical to that previously noted in MPTP-treated monkeys with drug-induced dyskinesias (Filion et al., 1991). However, a significant minority of GPe neurons became hypoactive after bicuculline. The response of GPi neurons to bicuculline injection into the GPe was similarly mixed, with the majority becoming hyperactive. However, clusters of GPi neurons were found in which the central neurons were hypoactive. These neurons were surrounded by a rim of hyperactive or unresponsive neurons. The authors postulated that, in these clusters of GPi neurons, the central cells are hypoactive as a result of inhibition by hyperactive GPe cells, while the surrounding GPi cells are hyperactive because of a reduction in inhibitory outflow from GPe cells made hypoactive by monosynaptic lateral inhibition from neighbouring GPe cells. The authors propose that this imbalance of activity between the GPe and GPi is the

neural basis of drug-induced dyskinesias. It is not clear that observations made in the experimental dyskinesia model, in which a GABA antagonist is injected into an intact GPe, can be extrapolated to idiopathic PD. However, if this imbalance between GPi and GPe activity does exist in PD complicated by dyskinesias, it may help explain the paradox by which pallidotomy improves both akinesia and dyskinesia in PD (Obeso et al., 1997).

1.7. PALLIDOTOMY IN THE MANAGEMENT OF PARKINSON'S DISEASE

1.7.1 Historical perspective

In order to understand the resurgence of interest in pallidotomy in the treatment of PD, it is necessary to review the history of surgical treatment for the disease. The initial target for surgery in PD was the pyramidal tract. In the 1930s, Putnam sectioned the pyramidal tracts in the spinal cord (Putnam 1940) and Bucy resected parts of the motor and premotor cortices (Bucy 1942). Although tremor was relieved by these approaches, the incidence of paresis post-operatively mandated a search for other targets. Meyers, in the late 1930s, was the first to target the basal ganglia. He noted improvements in tremor, rigidity and gait, without paresis, in a parkinsonian patient after lesioning the head of the caudate nucleus and anterior limb of the internal capsule (Meyers 1942). He later changed the target to the ansa lenticularis and noted an additional improvement in bradykinesia (Meyers 1942). Fénélon introduced a subfrontal approach to the ansa lenticulotomy in the 1940s (Fénélon and Thiébaut 1950) and this technique was taken up by other workers (Guiot and Brion 1953).

Interest in lesioning the pallidum was stimulated by Cooper, who in 1952 noted improvement in contralateral parkinsonian signs after accidentally ligating the anterior choroidal artery in a patient with post-encephalitic parkinsonism. This prompted Cooper and others to perform other procedures aimed at ablating pallidal function, including

chemopallidotomy and anterior choroidal artery ligation (Cooper 1956; Bravo and Cooper 1959; Narabayahi et al., 1956).

In the early 1950s, Leksell and others began to use the stereotaxic frame of Spiegel and Wycis to perform radiofrequency electrocoagulation of the pallidum. Their initial target was the anterodorsal region. They later moved their target to the posteromedial region because clinical results were better at this target (Svennilson et al., 1960). During the 1950s, pallidotomy was superseded by ventrolateral thalamotomy because of the realisation that the latter produced better relief of tremor (Hassler and Reichert 1954; Cooper and Bravo 1958). After the introduction of levodopa in the late 1960s, surgical treatment of PD was restricted to thalamotomy for severe drug-resistant tremor.

1.7.2 Reasons for the resurgence of pallidotomy in the management of Parkinson's disease

There are several reasons for the resurgence of interest in pallidotomy in recent years. The first was a realisation of the limitations of drug therapy in PD. As mentioned in section 2.2, patients treated with levodopa for more than 5 years commonly develop fluctuations in the motor response to levodopa, including wearing off effects, on-off fluctuations and dyskinesias. A second factor that rekindled interest in pallidotomy was the work of Laitinen et al., who in 1992 reported the results of 54 posteroventral pallidotomies performed on 38 patients with PD, using Leksell's target in the posteromedial pallidum (Laitinen et al., 1992). At a mean follow up period of 28 months, 92% of the patients had complete or almost complete relief of rigidity and hypokinesia and 81% had complete or almost complete relief of tremor. Improvements were also noted in dyskinesia, gait and speech volume. The final reason for the renewal of interest in pallidotomy was that experimental evidence supporting the notion of pallidal overactivity was accumulating in studies of experimental (MPTP) parkinsonism.

1.7.3 Pallidotomy in the modern era: effects on clinical motor dysfunction

Many groups have now reported their experience of the clinical effects of pallidotomy for PD. **Table 1.1** summarises the results of the studies of posteroventral pallidotomy published from 1992 to 2000. Studies omitted from the table include those with very small patient numbers (Sutton et al., 1995), those that are retrospective (Iacono et al., 1995*a*; Iacono et al., 1995*b*), those that included patients with "Parkinson's plus" syndromes as well as those with PD (Iacono et al., 1995*a*), and those that included patients undergoing bilateral as well as unilateral pallidotomies (Scott et al., 1998).

Although the studies listed in table 1.1 vary widely in both operative technique and methods of clinical assessment, there is substantial agreement among them in the nature and magnitude of the clinical effects of pallidotomy.

1.7.3.1 Effects of pallidotomy on “off” state motor function

1.7.3.1.1 Limb bradykinesia/akinesia

With a few exceptions (Uitti et al. 1997; Samuel et al. 1998), studies in which motor function has been assessed in the “off” motor state have usually detected an improvement in “off” state limb bradykinesia/akinesia after pallidotomy (Dogali et al., 1995; Lozano et al., 1995; Baron et al., 1996; Kishore et al., 1997; Fazzini et al., 1997; Lang et al., 1997; Ondo et al., 1998; Shannon et al., 1998; Fine et al., 2000). This improvement is more marked on the contralesional side (Dogali et al., 1995; Lozano et al., 1995; Baron et al., 1996; Kishore et al., 1997; Fazzini et al., 1997; Lang et al., 1997; Shannon et al., 1998; Fine et al., 2000) and is less dramatic than the improvement in dyskinesias on the corresponding side (Lozano et al., 1995; Baron et al., 1996; Kishore et al., 1997; Lang et al., 1997; Samuel et al., 1998; Fine et al., 2000). The duration of the effect of pallidotomy on bradykinesia/akinesia at longer term follow up has varied in various studies. In several studies, the improvement in contralateral bradykinesia persisted

at least 2 years post-operatively (Lang et al., 1997; Fazzini et al., 1997; Fine et al., 2000), while in others, the improvement was no longer significant by this time (Samii et al., 1997; Pal et al., 2000).

Methods used for the measurement of limb bradykinesia/akinesia include the Unified Parkinson's disease rating scale (UPDRS) bradykinesia subscore (Lozano et al., 1995; Lang et al., 1997; Kishore et al., 1997; Samuel et al., 1998; Fine et al., 2000), the Core Assessment Program for Intracerebral Transplantation (CAPIT) score (Langston et al., 1992; Dogali et al., 1995; Fazzini et al., 1997; Baron et al., 1996), the Purdue pegboard score (Tiffin 1941-1948; Uitti et al., 1997; Samii et al., 1999; Pal et al., 2000) or a combination of these methods (Johansson et al., 1997).

The clinical significance of the modest improvement in "off" state bradykinesia/akinesia after pallidotomy is questionable, as the "best off" motor performance post-operatively remains inferior to the "best on" performance, and it has not been possible to significantly reduce levodopa dose post-operatively in any of the studies.

1.7.3.1.2 Tremor

In most studies, contralateral tremor in the "off" state improved significantly at short term follow up (Lozano et al., 1995; Lang et al., 1997; Ondo et al., 1998; Kishore et al., 1997). Studies with longer post-operative follow up show that this improvement is sustained (Samii et al., 1999; Pal et al., 2000; Fine et al., 2000). Studies agree in finding that improvements in ipsilateral "off" state tremor are only seen in the short term (Lang et al., 1997; Samii et al., 1999; Pal et al., 2000; Fine et al., 2000). The method used for the assessment of tremor in all the studies has been the tremor subset of the UPDRS.

1.7.3.1.3 Postural instability/gait dysfunction

Where improvements in "off" state axial motor function occur after pallidotomy, they are short-lived. Several studies have found that postural instability/gait dysfunction

(PIGD) is better at 3-6 months post-operatively, compared with baseline (Dogali et al., 1995; Lozano et al., 1995; Lang et al., 1997; Kishore et al., 1997; Samuel et al., 1998; Ondo et al., 1998). However, in no study has this improvement persisted beyond 12 months post-operatively (Lang et al., 1997; Samuel et al., 1998; Samii et al., 1999; Fine et al., 2000; Pal et al., 2000). Studies with follow up of greater than 2 years show that PIGD is worse at long term follow up than at baseline, indicating that pallidotomy fails to halt the effect of disease progression on PIGD (Pal et al., 2000; Fine et al., 2000).

1.7.3.2 Effects of pallidotomy on "on" state motor function

1.7.3.2.1 Drug-induced dyskinesias

The most marked effect of pallidotomy is on drug-induced dyskinesias. Indeed, in the opinion of some, drug-induced dyskinesias are the major indication for pallidotomy (Olanow 1996). Dyskinesias usually improve bilaterally after pallidotomy, but the improvement is more marked on the contralesional side (Lozano et al., 1995; Baron et al., 1996; Lang et al., 1997; Kishore et al., 1997; Samuel et al., 1998). The improvement in contralateral dyskinesias is sustained at longer term follow up, whereas ipsilateral dyskinesias tend to recur by 2 years post-operatively (Lang et al., 1997; Samii et al., 1999; Pal et al., 1999; Fine et al., 2000).

Various methods for the assessment of dyskinesia severity have been used. These include the Goetz dyskinesia scale (Goetz et al., 1994; Lozano et al., 1995; Lang et al., 1997; Kishore et al., 1997; Samuel et al., 1998; Samii et al., 1999; Pal et al., 2000; Fine et al., 2000), the dyskinesia subset of the UPDRS (Kishore et al., 1997; Samii et al., 1999; Kimber et al., 1999) and the Mayo dyskinesia scale (Uitti et al., 1997).

1.7.3.2.2 Limb bradykinesia/akinesia

With one exception, studies have failed to detect any significant improvement in "on" state limb bradykinesia/akinesia after pallidotomy (Lozano et al., 1995; Lang et al.,

1997; Kishore et al., 1997; Johansson et al., 1997; Samuel et al., 1998; Samii et al., 1999; Pal et al., 2000; Fine et al., 2000). The one exception is the study of Uitti et al. (1997), which found a 17% improvement in "on" state bradykinesia contralateral to the lesion site at 3 months post-operatively. There is some evidence that by 3 years or more post-operatively, "on" state limb bradykinesia is significantly worse than pre-operatively (Fine et al., 2000).

1.7.3.2.3 Tremor

"On" state tremor is not a major contributor to "on" state motor dysfunction. For this reason, it has not been included in the analysis of the motor effects of pallidotomy in many studies. Those studies that have measured "on" state tremor before and after pallidotomy have found no change post-operatively, compared with pre-operatively (Lozano et al., 1995; Kishore et al., 1997; Johansson et al., 1997; Lang et al., 1997; Samuel et al., 1998).

1.7.3.2.4 Postural instability/gait dysfunction

With one exception, no study has detected an improvement in "on" state PIGD after pallidotomy. The exception is the study of Samuel et al. (1998), in which there was a 29% improvement in "on" state PIGD at 3 months post-operatively, compared with baseline. However, this improvement was not significant at 12 months follow up. Recent studies of the long-term effects of pallidotomy indicate that "on" state PIGD begins to significantly deteriorate at 3 years or more post-operatively, compared with baseline (Fine et al., 2000; Pal et al., 2000).

1.7.3.3 Effects of pallidotomy on activities of daily living

Most studies have used the activities of daily living (ADL) subset of the UPDRS and/or the Schwab and England ADL scale to measure the ease with which patients perform ADLs. As might be expected from its effects on "off" motor dysfunction and "on"

dyskinesias, there is a significant early (up to 12 months) improvement in activities of daily living (ADL) scores after pallidotomy, compared with pre-operatively (Lozano et al., 1995; Dogali et al., 1995; Baron et al., 1996; Kishore et al., 1997; Lang et al., 1997; Shannon et al., 1998; Samuel et al., 1998). In some studies, this improvement is seen only in the "off" state (Lozano et al., 1995; Samuel et al., 1998). In others, the improvement occurs in both the "off" and "on" states (Kishore et al., 1997; Lang et al., 1997). To some extent, this discrepancy can be explained by the size of various trials. For example, Lozano et al. (1995) and Lang et al. (1997) are trials from the same group, in which the latter involves a larger number of patients at longer post-operative follow up. The fact that Lang et al. (1997) detected a significant improvement in "on" state ADL performance, while Lozano et al. (1995) did not, is presumably due to the smaller sample size in the earlier study.

Most studies agree in finding that at follow up beyond 12 months, the beneficial effect of pallidotomy on ADL performance disappears and that a progressive deterioration in ADL performance in both "off" and "on" motor states then occurs (Samii et al., 1999; Pal et al., 2000; Fine et al., 2000). Only one study has reported a sustained improvement in ADL score after pallidotomy (Fazzini et al., 1997).

1.7.3.4 Clinical effects of pallidotomy: summary

The main early improvements in motor function occurring after pallidotomy are in drug-induced dykinesias, limb bradykinesia and resting tremor. Improvements in limb bradykinesia and dyskinesia are bilateral, although more significant on the contralesional side. After 12 months or so post-operatively, ipsilateral dyskinesias and, in some studies, contralateral bradykinesia begin to recur. By 2 years post-operatively, only contralateral tremor and dyskinesias are consistently improved compared with baseline values.

1.7.4 Potential mechanisms of improvement in motor function after pallidotomy

The bilateral effects of unilateral pallidotomy are in accord with the observations that 10-20% of pallidal efferents project to the contralateral ventral thalamic nuclei (Hazrati and Parent 1991), and that GPi neurons of MPTP-treated animals respond to movements of both ipsilateral and contralateral limbs (Filion et al., 1988). However, the simultaneous improvements in bradykinesia and dyskinesia after pallidotomy are difficult to explain using the prevailing model of basal ganglia dysfunction in PD.

It seems paradoxical that voluntary movement should improve as a result of a lesion made within an area critical for the maintenance of normal movement. Intuitively, such a lesion would be expected to further disrupt motor control. One way to explain this paradox is by the concept that bradykinesia is the kinematic consequence of GPi overactivity. In other words, if GPi overactivity produces bradykinesia, then diminution of GPi function should restore more normal movement. There is some support for this notion. For example, functional imaging of the brain during arm movements following contralateral pallidotomy in PD has shown a relative increase in cerebral blood flow within the SMA and dorsolateral prefrontal cortex (Ceballos-Baumann et al., 1994; Samuel et al., 1997*b*). This is consistent with a reduction in pallido-thalamocortical inhibitory outflow following pallidotomy. However, it is known that phasic changes in the discharge patterns of GPi neurons herald the switch from one movement task to another in a movement sequence (Brotchie et al. 1991b). Thus, a lesion which reduces pallidal activity without restoring its phasic movement-related activity should not improve the quality of voluntary movement. Marsden and Obeso (1994) have identified this as one of the paradoxes of stereotaxic surgery in PD and postulated that it may be better physiologically "to have no input from a component of a distributed motor system than to have a 'noisy' disturbed input of the sort likely to be present in parkinsonism". If true, this hypothesis requires that the motor system

be capable of triggering and executing movement in the absence of a contribution from the pallidum.

The current model of basal ganglia dysfunction in PD also seems inadequate to explain the abolition of dyskinesias by pallidotomy. According to the model, the inhibition by the GPi of thalamocortical circuits enables both the termination of one movement in a sequence so that the next can begin, and the inhibition of involuntary movements. That the GPi has this role is supported by the observation that lesions of the STN, the major excitatory nucleus of the GPi, cause hemiballismus. Therefore, it would be predicted that a lesion of the GPi (or STN) should increase, rather than reduce involuntary movement. Indeed, exactly this finding has been made in the primate brain, in which chemical inactivation of the globus pallidus results in dystonic posturing of the contralateral arm due to excessive muscle cocontraction (Mink and Thach 1991*c*).

Finally, it is difficult to explain how a lesion of the globus pallidus can both facilitate desired, voluntary movements and reduce involuntary movements. If the internal pallidum is the seat of akinesia, as a result of tonic increase in neural discharge, can it also be the seat of dyskinesia and, if so, by what mechanism?

Several points should be made concerning the mechanisms by which pallidotomy changes motor function in PD. Firstly, it is clear from human pathological studies that the results of a basal ganglia lesion in a healthy brain do not necessarily predict the effects of the same lesion in the PD brain. For example, cases of bilateral globus pallidus lesions due to anoxia of various causes have been described in which no motor deficits were apparent (Laplane et al., 1984; Laplane et al., 1989). Furthermore, in a review of 240 cases with motor or behavioural disorders due to focal basal ganglia lesions, Bhatia and Marsden found 17 cases with isolated lesions of the globus pallidus, of whom parkinsonism occurred in only four and dystonia in seven (Bhatia and Marsden 1994).

Secondly, much remains to be known concerning the neural substrate of drug-induced dyskinesia (section 1.6 of this chapter). The antidyskinetic effect of medial pallidotomy suggests that akinesia and dyskinesia do not simply represent opposite extremes of pallidal dysfunction (namely, tonic increase in GPi neural activity in akinesia and tonic decrease during dyskinesia). Animal models of dyskinesia suggest that populations of inappropriately hypoactive and hyperactive cells within the GPi and GPe are the substrate for dyskinesia. Studies in humans to address this question have produced somewhat conflicting results. One study reported that the transition from akinesia to dyskinesia in humans with PD is associated with a progressive decline in neuronal firing rate to near electrical silence (Papa et al., 1998). However, in patients undergoing pallidotomy for the treatment of idiopathic torsion dystonia (Vitek et al., 1999) and hemiballismus (Suarez et al., 1997), GPi activity is characterised by irregular brief bursts of activity, rather than sustained hypoactivity. Pallidotomy ameliorates torsion dystonia (Vitek et al., 1999) and hemiballismus (Suarez et al., 1997), suggesting that this irregular firing pattern is responsible for dyskinesia in both conditions.

1.7.5 Measurement of lesion location and size

1.7.5.1 Potential effects of lesion location on the results of pallidotomy

It is generally accepted that the optimum site for pallidotomy is the sensorimotor portion of the GPi. Based on anatomical and functional studies in animals, the posterior (Iansek and Porter, 1980) ventral (Smith and Parent 1986) and lateral (DeLong 1971) portions of GPe and GPi have been shown to contain sensorimotor neurons. This is in keeping with the early finding by Leksell that posteroventral pallidotomy produced better results than anterodorsal pallidotomy in PD (Svennilson et al., 1960).

However, the importance of lesion location in determining the effects of pallidotomy in PD is controversial. It is not clear whether extending the lesion outside the

posteroventral GPi affects the motor benefit of pallidotomy, nor is it known whether the location of the lesion within the posteroventral GPi influences the clinical effects of pallidotomy. Using high resolution MRI, Gross et al. (1999) measured lesion location within the anteromedial-posterolateral plane of the posteroventral GPi. They found that centrally placed lesions provided the greatest improvement in contralateral akinesia and postural instability/gait disorder, whereas anteromedially placed lesions had relatively less effect on akinesia but provided greater alleviation of "off" state contralateral rigidity and drug-induced dyskinesias. Lesions of the posterolateral part of the posteroventral GPi were the least efficacious, except for the relief of tremor. In contrast to these findings, other groups have found no relationship between lesion site and clinical outcome (Krauss et al. 1997; Burns et al., 1997). The implication of the findings of Gross et al. (1999) is that different parts of the posteroventral GPi are functionally specific for different aspects of motor dysfunction in PD. For some aspects of motor dysfunction, this concept can be readily accepted. For example, it is known that volitional limb movement is mediated by pallido-thalamocortical outflow (Roland et al., 1980), while muscle tone is mediated by descending pallido-tegmental outflow to the pedunculopontine nucleus (Delwaide et al., 1991). However, it is more difficult to understand how dyskinesia and akinesia, which, kinematically speaking, occupy two ends of a movement continuum, could be controlled by completely separate neuronal populations. This would seem to imply a gain, rather than a loss, of neuronal function in PD, for which there is no experimental evidence. In fact, there is evidence that the reverse applies, with pallidal neurons manifesting a loss of somatotopic specificity in MPTP-treated, compared with normal, monkeys (Filion and Tremblay 1988).

There is increasing evidence that dyskinesia and akinesia result, not from the activity of separate neuron populations, but from different patterns of aberrant activity of the same population (Levy et al., 1997). Stimulation of the ventral pallidum inhibits

voluntary and involuntary movement in PD, abolishing "on" state dyskinesias, worsening akinesia in the "off" and "on" states, and blocking the effect of levodopa on akinesia (Bejjani et al., 1997; Krack et al., 1998). In contrast, stimulation of the dorsal pallidum has a facilitatory effect on movement, improving akinesia but inducing "off" state dyskinesias (Bejjani et al., 1997; Krack et al., 1998). Rigidity was diminished by stimulation of the ventral pallidum in both studies and by stimulation of both ventral and dorsal pallidum in one (Bejjani et al., 1997). If akinesia and dyskinesia are mediated by different patterns of abnormal firing of the same neuronal population, this may explain the apparent paradox that both akinesia and dyskinesia improve after pallidotomy.

This is not to say that the site and size of pallidal lesions do not affect the results of pallidotomy. If the effects of pallidal stimulation are broadly comparable to those of pallidotomy, the site and size of a pallidal lesion would influence its effect on motor function. According to the stimulation data, a lesion in the posteroventral GPi would be expected to alleviate "on" state dyskinesias. However, according to the same data, a ventral pallidal lesion would be expected to worsen akinesia and diminish the effect of levodopa on akinesia. Although worsening of akinesia has not been reported after pallidotomy, a reduction in motor benefit from levodopa has been noted by several authors (Verhagen et al., 1996; Baron et al., 1997), and an inability to reduce mean levodopa dose despite an improvement in akinesia by almost all. In order to improve akinesia, a lesion would need to encompass the dorsal pallidum, or its efferent output. Therefore, only larger GPi lesions would be expected to improve akinesia as well as dyskinesia. Further evidence that larger pallidal lesions are more effective is the observation that dyskinesias induced during pallidal lesioning correlate with a better post-operative outcome (Merello et al., 1997). Perhaps, extrapolating from the stimulation data (Bejjani et al., 197; Krack et al., 1998), the induction of dyskinesias during lesioning indicates that the dorsal pallidum is being

included in the lesion, thus presaging an improvement in akinesia as well as dyskinesia post-operatively. Variations in lesion size may explain the widely varying magnitudes of improvement in akinesia reported in pallidotomy series [eg. 35% improvement in contralateral limb bradykinesia at 3 months postoperatively in Kishore et al. (1997), compared with 11% in Ondo et al. (1998)].

In summary, the effects of lesion site and size on motor outcome of pallidotomy remain unclear, especially for those lesions not confined within the sensorimotor portion of the GPi (many lesions made without the use of microelectrode recording are probably in this category). Although the same pallidal neuronal population probably mediates akinesia and dyskinesia, different areas of the pallidum may contribute to varying degrees. Thus, variations in lesion location relative to these areas may have a major impact on the motor outcome of pallidotomy.

1.7.5.2 Methods of measuring lesion location and size

There are several methods for determining the location of pallidotomy lesions. These can be divided into methods of pre-operative/intra-operative targeting and methods for the post-operative verification of lesion location.

1.7.5.2.1 Pre-operative and intra-operative targeting

Stereotaxis refers to the 3-dimensional localisation of a target according to the position of that target relative to a reference point. In stereotaxic neurosurgery, the conventional reference point is the convergence of the mid-sagittal (x-axis), mid-commissural (y-axis) and inter-commissural (z-axis) planes. The surgical target can be localised according to coordinates described in human neurosurgical atlases (eg. Schaltenbrand and Bailey, 1959; Schaltenbrand and Wahren, 1977). Because of inter-individual variation in brain size, localisation of the proposed lesion site by means of the neurosurgical atlas is usually supplemented with pre-operative CT and/or MRI scans. The

latter also serve to establish the orientation of the intercommissural plane, which assists in placement of the stereotaxic frame.

Intra-operative localisation is performed by recording electrical activity within the theoretical target and/or by stimulation within the target. Typical patterns of neural firing are described within GPe, GPi, the border zone between GPi/GPe, as well as in white matter ventral to GPi (Lozano et al., 1996). Stimulation can be performed either with a microelectrode/semi-microelectrode (microstimulation) or with the same 1 mm diameter electrode used for lesioning (macrostimulation). It has been demonstrated that, when microelectrode techniques are employed, the lesion site frequently varies significantly from that predicted by pre-operative anatomical localisation (Tsao et al., 1998). However, it has not yet been demonstrated that more accurate lesion location in the posteroventral pallidum equates to better clinical outcome. This depends on the role played by different regions of the internal and external pallidal segments, and their outflow tracts, in the genesis of various aspects of parkinsonian motor dysfunction. This is a controversial issue, as discussed in section 9.1.

1.7.5.2.2 Post-operative measurement of lesion location and size

Post-operative cerebral imaging, by CT or, more commonly, MRI scanning is used to determine lesion location and volume post-operatively. MRI is generally preferred as anatomical resolution is superior to CT and scans are obtained in the sagittal and coronal, as well as axial, planes.

Measurement of lesion volume has been performed using a variety of different formulae, based on assumptions made about lesion shape. In different studies, lesions have been assumed to be spheroidal/ellipsoid (Hariz 1990; Krauss et al., 1997) or cuboidal/cylindrical (Laitinen et al., 1992; Lozano et al., 1996; Kazumata et al., 1991; Junque et al., 1999) in shape, while in many other studies the formulae used to calculate

lesion volume have not been specified. Volumetric MRI, which has been used by several groups, avoids the need to make assumptions about lesion shape (Burns et al., 1997; Samuel et al., 1998; Gross et al., 1999).

Measurement of lesion volume after pallidotomy may be confounded by the inclusion of post-operative oedema in the measurement. This makes it difficult to compare lesion size between different studies. In the immediate post-operative period, the lesion is made up of a core of necrotic tissue surrounded by a rim of oedematous, but viable, tissue. The necrotic core cannot be distinguished from perilesional oedema on CT scans. It is claimed that the two regions can be differentiated on MRI scans by their different signal characteristics on T1 and T2 sequences (Tomlinson et al., 1991; Baron et al., 1996; Krauss et al., 1997; Kazumata et al., 1997).

Studies using early post-operative MRI scans ($\leq$ 1 week post-operatively) have recorded mean lesion volumes, after exclusion of perilesional oedema, of 80-150mm^3 (Lozano et al., 1996), 127mm^3 (Baron et al., 1996), 262.2mm^3 (Krauss et al., 1997) and 262mm^3 (Kazumata et al., 1997). Studies using late (> 3 months post-operatively) CT scans have recorded mean lesion volumes of 67 mm^3 (Hariz 1990), 95mm^3 (Laitinen et al., 1992) and 65.5mm^3 (Johansson et al., 1997), while those using late MRI scans have recorded mean lesion volumes of 22mm^3 (Krauss et al., 1997) and 72.8mm^3 (Johansson et al., 1997). These values would suggest that pallidotomy lesions may diminish in size over time. In the only study to have performed serial imaging of pallidotomy lesions, there was a reduction in mean lesion volume of 92% over time, from 262.2mm^3 one to three days post-operatively to 22mm^3 6 months post-operatively (Krauss et al., 1997). The authors postulated that this represented a reduction in true lesion volume, as they believed they had excluded perilesional oedema from the measurement of early lesion volume. If pallidotomy lesions do shrink over time, the impact of this on motor function is unclear. It is possible

that progressive reduction in lesion size may partly account for the progressive decline in motor benefit that has been reported in several studies after longterm follow up (Lang et al., 1997; Samuel et al., 1998; Samii et al., 1999). However, other factors, such as progression of PD, are also likely to be involved.

Authors	Number of patients	Mean lesion size in mm^3 (range)/ method/ time of assessment	Follow up interval(s) (months)	UPDRS motor score (% improvement)		"Off" bradykinesia score (% improvement)		"On" bradykinesia score (% improvement)		Dyskinesia score (% improvement)			Gait (% improvement)		Operative technique	Comments
				off	*on*	*ipsi*	*contra*	*ipsi*	*contra*	*ipsi*	*contra*	*overall*	*off*	*on*		
Laitinen et al 1992	38	95 (21-160)/ CT/ 3-12/12	2-71 (mean 28)	NA	NA	improved [#]		improved[#]		NSt	NSt	Improved [15*]	improved[◊]		CT/macrostimul-ation	did not use UPDRS or CAPIT rating scales
Dogali et al 1995	18	75 (60-90)/ MRI/ not stated	3, 6, 9, 12	65**	NA	24*	38*	NA	NA	NSt	NSt	NSt	45†	NA	MRI microelectrode recording microstimulation	
Fazzini et al 1997	11		24 (n=11)	66	NA	31*	41*	NA	NA	NSt	abolished at	NSt	NSt	NA		
			36 (n=10)	75	NA	42*	45*	NA	NA	NSt	3 and 4 yrs	NSt	NSt	NA		
			48 (n=5)	NSt	NA	Nst	NSt	NA	NA	NSt		NSt	NSt	NA		
Lozano et al 1995	14		3, 6	30	NS	21[5*]	32[5*]	NS[5*]	NS[5*]	32[9*] (NS)	92[9*]	NA	23[***]	NS	MRI/microelectrode recording	Lang et al. 1997 only improvements sustained at 2 yrs were:
Lang et al 1997	39		3 (n=39)	31	NS	19[5*]	41[5*]	NS[5*]	NS[5*]	42[9*] (Sig)	82[9*]	NA	31[***]	NS	"	"off" c/l bradykinesia,
			6 (n=39)										NS	NS		c/l dyskinesia
			12 (n=27)										NS	NS		(ie. not "off" gait/balance,
			24 (n=11)													"off" ipsi bradykinesia or ipsi
Fine et al 2000	20		mean of 52 (R41-64)	19	nil	NS	18[5*]	NSt	NSt	NS	68[9*]	NA	NS	NSt	"	dyskinesia)

Baron et al 1996	15	127 (65-181)/ MRI/ 1-3/7	3 6 12	25 24 21	NSt 13 NS	moderate imprvmt “	41* (no impr finger dex at 1 year)	NSt NSt NSt	NSt NSt NSt	“unclear” “ “	Abolished in all but 1 case at 1 year[9*]	NSt NSt NSt	“sig impr”*	NS* NS* NS*	MRI or CT/ microelectrode response to limb movement/microstim	improvements in motor UPDRS, dyskinesia and bradykinesia scores sustained to 12 months
Kishore et al 1997	24		3 (n=23) 6 (n=20) 12 (n=11)	36 37 46	NS NS NS	35[5*] 32[5*] NS	43[5*] 43[5*] NSt	NS[5*] NS[5*] NS[5*]	NS[5*] NS[5*] NS[5*]	39[9*11*] 41[9*11*] NSt	78[9*11*] 76[9*11*] NSt	51[11*] 50[11*] 43[11*]	34[6*] 19[6*] NSt	NS NS NSt	CT scan, then targetting by observed responses to macrostimulation “	Samii et al: Recurrence of ipsilat and axial dyskinesias and loss of benefit on “off” state gait and balance by 2
Samii et al 1999	20		24	NA	NA	NA (no imp in PPT)	NA (no imp in PPT)	NA (no imp in PPT)	NA (no imp in PPT)	NS[9*]	83[9*]	NS[11*]	NS	NS		years postop Pal et al: Ipsilateral bradykinesia and axial function
Pal et al 2000	15		36	NA	NA	signif. worse	NS	signif. worse	NS	NS	81[9*]	NS	signif. worse	NS	“	worse than baseline at 3 years postop
Johansson et al 1997	22	65.5 CT) 72.8 (MRI) 4/12	4 12	NA NA	NA NA	NA NA	NA NA	NS[7*] NS[7*]	NS[7*] NS[7*]	33[13*] 33[13*]	33[13*] 33[13*]	NA[13*] NA[13*]	NA[14*] NA[14*]	NS[14*] NS[14*]	CT or MRI, then macrostim around Laitinen’s target	assessments only performed in “on” state
Uitti et al 1997	20		3	20	24	NS[8*]	NS[8*]	NS	17[8*]	NA	NA	34[10*] (p<0.01) but NS[9*]	“improved” (degree of improvement not stated)		MRI followed by microelectrode recording	

Samuel et al 1998	26	145 (±49)/ MRI/ 5-6/12	3 (n=26)	17.8	NS	no change[5*]	NS[5*]	no change[5*]	no change[5*]	45[9*]	67[9*]	NA	7[***] (sig)	29[***] (NS)	CT followed by microelectrode recording	
						NS[5*]		NS[5*]	NS[5*]				NS[***]	NS[***]		
			12 (n=9)	NS	NS	NS	NS[5*]	NS[12*]	NS[12*]	17[9*] (NS)	33[9*] (NS)	NA	4[***]	NS[***]		
Schrag et al 1999	22		3 (n=22)	16	NS	NS	18[5*]	NS[12*]	NS[12*]	39[9*]	67[9*]	48[9*]	4[***]	NS[***]		
			median 14 (n=20)	18	NS		NS[5*]			33[9*]	55[9*]	38[9*]				
Ondo et al 1998	34	22 (0.5-94)/ MRI/ 6/12	3	NA	NA	11[5*]	12[5*]	NA	NA	NA	NA	NA	22[15*]	NA	CT/microelectrode recording/macro-stimulation	Ondo et al: "off" state only; UPDRS motor score not reported; method of gait assessment not described
Lai et al 2000	89		3 (n=89)	35	39	22[5*]	43[5*]	21	54	NA	NA	47[16*]	NSt	NSt		
			12 (n=62)	40	44	28[5*]	47[5*]	35	56	NA	NA	46[16*]	NSt	NSt		
			mean 26.6 (n=41)	34	36	18[5*]	44[5*]	NS	53	NA	NA	36[16*]	NSt	NSt		
Shannon et al 1998	26		1	18	NS	"sig imp" (degree not stated)	26[12*]	NSt	NSt	NA	NA	59[11*]	NS†	NSt	MRI/microelectrode recording/microstimulation	
						NS[12*]										
			6	15	NS		26[12*]	NSt	NSt	NA	NA	59[11*]	NS†	NSt		

Table 1.1 Changes in UPDRS motor score, bradykinesia, dyskinesia and gait in published series (1992-2000) of the clinical effects of pallidotomy.

Values shown are percentage improvements relative to baseline values. Except where otherwise indicated, improvements are statistically significant at the level of significance stipulated in the study. As assessment methods for bradykinesia, dyskinesia and gait vary between the series, the methods employed in the assessment of these clinical features are indicated for each study. Studies written by the same group are listed together. Legend is on page 76.

Legend:

NA: not applicable

NSt: not stated by the authors

NS: not statistically significant

handwriting assessment

◊ walk around 50m circle clockwise, then counterclockwise

† CAPIT walk time (stand, walk 7m, turn, walk 7m and sit)

* CAPIT assessment of voluntary movement (pronation/supination of wrists; hand/arm movement between 2 points; finger dexterity; walk time)

** combined UPDRS motor and ADL score

*** PIGD (postural instability and gait score: items 13- 15 and 27-30 of the UPDRS scale)

4* tapping between 2 points 30cm apart for 10 cycles

5* UPDRS bradykinesia score (items 23-26 of the motor subscore)

6* UPDRS gait score

7* pronation-supination or wrists and Purdue pegboard

8* Purdue pegboard score

9* Goetz dyskinesia scale

10* Mayo dyskinesia scale

11* UPDRS dyskinesia scale

12* sum of UPDRS scores for tremor, rigidity and bradykinesia

13* visual analog scale of dyskinesia severity

14* walk 10m 3 times

15* assessment method not stated

16* percent of waking day spent with dyskinesias

CHAPTER 2

Methods

All experiments performed in the course of this thesis were approved by the Royal Adelaide Hospital Research Ethics Committee, and informed consent was obtained from all subjects.

2.1 Subjects

2.1.1 PD patients

Patients had idiopathic PD according to accepted diagnostic criteria (Calne et al. 1992), namely at least 3 of the following 5 features: (i) rigidity, (ii) bradykinesia, (iii) tremor, (iv) asymmetric onset and slow progression, (v) substantial and sustained response to levodopa at some stage during the illness and (vi) absence of other neurological or systemic disease. Please refer to subsequent chapters for information about numbers and clinical details of patients studied in different experiments.

2.1.2 Control subjects

Normal control subjects were studied in order to validate our technique for measuring the kinematic characteristics of voluntary upper limb movement (Chapter 4, Experiment 1) and to provide control data for comparison of blink rates in PD patients (Chapter 6). Controls were either recruited by advertisement or were spouses of the PD patients. They had no history of neurological disease and were not taking medications that might compromise motor function (eg. neuroleptics, sedatives).

2.2 Clinical assessments

2.2.1 Definition of "off" and "on" states

Assessments in the "off" state were performed in the morning, after overnight withdrawal of anti-parkinsonian medications. Assessments in the "on" state were performed about one hour after the patient took their usual morning dose of levodopa, when the effect of the medication was judged by the patient and doctor to be maximal.

2.2.2 Clinical rating scales

1. Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al., 1987)

This widely-used and well-validated rating scale assesses motor and non-motor symptoms and signs of Parkinson's disease and their effects on activities of daily living. A numerical score is assigned to each component of the scale, with a higher score denoting more severe dysfunction. From the total UPDRS score, the following components were extracted and analysed:

(i) **mentation, behaviour and mood score** (a single score encompassing "off" and "on" states

(ii) **activities of daily living score**

(iii) **motor examination score** (items 18-31) and its 2 subscores

- **a. bradykinesia score** (sum of items 23-26, ie. finger tapping, opening and closing hands, pronation-supination of wrists and leg agility), and
- **b. axial mobility score** (sum of items 27, 29 and 30, ie. arising from chair with arms folded, gait and postural instability)

(iv) **dyskinesia score** (composite score for "off" and "on" states derived from the patient's report of the severity of their dyskinesias and the physician's observations)

(v) **clinical fluctuations score** (composite score for "off" and "on" states. Item 36 ("predictable "off" episodes) was excluded as this is the only item of the UPDRS in which a higher score indicates better motor performance and its inclusion may therefore have provided misleading results)

2. Modified Hoehn and Yahr Stage (Hoehn and Yahr, 1967)

3. Schwab and England Activites of Daily Living Scale (Schwab and England, 1969)

Patients assessed the level and ease and independence with which they performed activities of daily living. We asked patients for a single score which described their usual level of performance, rather than separate scores for "off" and "on" states.

2.3 Timed motor tasks

2.3.1. Purdue Pegboard Test (Tiffin, 1941-8)

Using each hand independently, the patient was allowed one minute to place as many as pegs as possible in the pegboard. Three trials were performed and the mean value for each hand was used in analysis.

2.3.2. Walking time (Langston et al., 1992)

This was the time taken to stand from chair without arms, walk 7m, turn, return to the chair and sit down again. Two trials were performed and the shorter time was used in analysis.

2.4 Kinematic assessment of voluntary upper limb movement

In order to measure the kinematics of voluntary upper limb movement, we chose two different types of movement. The first was repetitive finger tapping on a flat surface. We chose this movement for two main reasons. Firstly, visual assessment of repetitive finger tapping is commonly used in clinical practice as a marker of bradykinesia. Secondly, as patients were provided with a minimum of external cues to facilitate the performance of this movement, we consider it an example of an "internally generated" movement which reflects activity of the striato-pallidal-mesial frontal motor pathways in the relative absence of sensory inputs.

The second type of upper limb movement assessed was a sequential upper limb movement, to pick up an object and then lift it to the nose. Again, this movement was chosen for two main reasons. Firstly, it enables analysis of the individual component movements (sub-movements) in the sequence as well as the interval (inter-onset latency)

between them. As discussed in the introduction, slowing of the sub-movements of a sequential movement and prolongation of the interval between them are known to underly bradykinesia of such movements (Benecke et al. 1987*a*). However, unlike Benecke et al., we chose to examine movement of an unrestrained, rather than restrained, limb. The second reason for choosing this movement is that it was cued both by an auditory stimulus and by the visual cues of the object being picked up and its final destination. Accordingly, we considered this an example of an "externally cued" movement which reflects the influence of sensory inputs on striato-pallidal-mesial frontal motor pathways.

2.4.1. Rapid finger movements

Subjects were seated at a table with the forearm resting unrestrained on the tabletop. A single axis goniometer (Penny and Giles G35, Gwent, UK) was attached across the second metacarpophalangeal joint to record changes in index finger position. The subject was then asked to tap the index finger as quickly and regularly as possible on the table until at least 20 repetitions had been performed. Right and left hands were examined. Off-line analysis of the goniometer tracings of the first 10 taps was performed and the following parameters were measured:

(a) Amplitude of tapping movements

Amplitude was measured from the lowest point of the "trough" preceding each movement (when the index finger struck the table) to the following "peak" (representing the greatest extent of excursion of the finger upwards).

(b) Tapping rhythm and speed

Tapping rhythm and speed were measured from the time intervals, or "tapping intervals", between successive taps in each sequence. Tapping rhythm was measured from the degree of variation among tapping intervals in the sequence of 10 taps. For each subject, a linear regression was fitted to the intervals over time. The degree of variation from this line was measured from the size of the residual mean square error (RMSE), a higher RMSE indicating greater variation from the mean and less regular tapping, and a smaller RMSE indicating less variation from the mean and more regular tapping.

Speed of finger tapping was measured by calculating the mean tapping interval for each subject. A shorter mean interval indicated more rapid tapping and a longer mean interval indicated slower tapping.

2.4.2. Complex upper limb movement ("pick up" task)

Subjects were seated in the same position as for the rapid finger movement task. The thumb and index finger were positioned on either side of a small peg standing upright on the tabletop. A single axis goniometer (Penny and Giles G35, Gwent, UK) was placed over the second MCP joint and a twin axis goniometer (Penny and Giles M180, Gwent, UK) was placed over the elbow joint (the goniometer over the elbow joint measured movements in the flexion/extension axis only). In response to an auditory signal, the subject was instructed to grasp the peg between the thumb and index finger, flex the elbow to lift the peg to the nose and then return the peg to the table. Subjects were instructed to perform the movement as quickly as possible. Both arms were examined in turn. Prior to recording, subjects practised the task until they were proficient at it. Time of onset of movement of the index finger and elbow was measured from the goniometer position traces. The following parameters were measured from at least 10 trials:

(a) Reaction time from the auditory signal to movement onset

(b) Interval between onset of movement at the MCP joint and elbow (inter-onset latency, or IOL) and

(c) Peak angular speed of elbow movement

The mean value of each variable was calculated for each subject.

2.5 Assessment of blink rate

In the PD patients, assessment of blink rate was performed in both the "off" and “on” states. Patients were videotaped while they were talking to the examiner, at rest, and while they performed the tasks of the motor examination subset of the UPDRS. In the control group, subjects were videotaped during a conversation with the examiner. Close up views of the subjects' faces were obtained. Subjects knew that assessments were being made of their speech and motor function, but were not aware that eye blinks were being measured. One minute of each videotape was examined in real time and in slow motion at a quarter of the normal speed. The number of blinks was counted during the course of one minute, which is sufficient time to obtain a representative blink rate (Deuschl and Goddemeier, 1998). A blink was defined as any bilateral movement of the eyelids that resulted in partial or full lid closure. Patients with sustained or forceful lid closure (blepharospasm) were excluded from the study. Blink rate was expressed as blinks per minute.

2.6 Bereitschaftspotentials

Bereitschaftspotentials (BPs) were performed pre- and post-operatively on PD patients undergoing pallidotomy.

2.6.1 Recording of Bereitschaftspotentials

Electroencephalographic (EEG) potentials from 3 scalp electrode positions (C3, Cz, C4) were averaged from 100 self-paced wrist extension movements of the arm contralateral to pallidotomy. EEG potentials were amplified, digitized at a sampling rate of 100 Hz and low-pass filtered at 20Hz. Electromyographic (EMG) signals were obtained by surface electrodes placed over extensor carpi radialis and were low-pass filtered at 3kHz. Recording time was from 2 seconds before to 1 second after movement onset.

2.6.2 Analysis of Bereitschaftspotentials

Analysis was made of the early component of the BP (from 1.5 seconds to 0.5 seconds before movement onset), as this component of the BP is believed to represent neural activity within the mesial frontal cortex during movement preparation. The early component of the BP is said to be symmetrical over both hemispheres. However, the amplitude of the late component of the BP (from 0.5 seconds before movement onset until movement onset) is greater over the hemisphere contralateral to movement. To allow for any effects of laterality on the early component of the BP in our patients, electrode positions C3 and C4 were grouped for analysis according to whether they were ipsilateral or contralateral to the operated (and moving) hand. Separate analyses for then carried out for the following 3 scalp electrode positions:

- Cz
- Ipsilateral to the operated limb
- Contralateral to the operated limb

The pre- and post-operative slopes of the early component of the BP (from 1.5 sec to 0.5 sec prior to movement onset) were compared. BPs were analysed individually and a grand average of the 5 traces was constructed. Comparison of pre- and post-operative results was performed by paired t-tests, with significance set at $p < 0.05$.

2.7 Measurement of pallidal lesion size and location

CT of the brain was performed one day post-operatively in all patients. In 3 of the patients, CT scans were repeated 10 months or more post-operatively, at the time of planning for a second pallidotomy, opposite the first. Horizontal slices through the basal ganglia at intervals of 2mm were obtained. The slice that best demonstrated the maximal antero-posterior dimensions of the third ventricle was chosen as a reference for measurements of lesion site relative to the mid-commissural plane (MCP), inter-commissural plane (ICP) and mid-sagittal plane (MSP). Contiguous CT slices were then magnified and examined to determine the site and dimensions of the pallidal lesion. The following parameters were measured for each lesion:

1) Maximum transverse extent ("width") of the lesion
2) Maximum dorsoventral extent ("length") of the lesion
3) The distance of the centre of the lesion anterior or posterior to the MCP
4) The distance of the centre of the lesion lateral to the MSP
5) The distance of the centre of the lesion below the ICP

Since the horizontal extent of the lesions was consistently greater than their dorsoventral extent, the lesions were assumed to be spheroidal in shape. Lesion volume was calculated using the equation for the volume of a spheroidal object [volume = (4/3) X π X a X b^2, where a is half the longer axis of the spheroid and b is half the shorter axis of the spheroid].

Diagrams of the lesions were superimposed onto coronal and sagittal diagrams of the basal ganglia, obtained from the Schaltenbrand and Wahren neurosurgical atlas (Schaltenbrand and Wahren 1977).

2.8 Surgical procedure

Surgery was performed on the side opposite the worst affected limbs (as judged by dyskinesia severity in most cases) or, in the case of symmetrical disease, on the side opposite the dominant hand. Surgery was performed after overnight withdrawal of medication with the patient in the "off" motor state. Magnetic resonance imaging of the head was performed preoperatively to determine the length of the intercommissural plane. The stereotaxic coordinates of the GPi were computed from a computed tomogram of the brain and head. The initial target was located 2-3 mm below the intercommissural plane, 20-22 mm lateral to the mid-sagittal plane and 3 mm anterior to the mid-commissural plane, as described by Laitinen (Laitinen, 1992). Under local anaesthesia, a 1.8 mm diameter electrode with a 2 mm exposed tip was introduced into this target. Electrical stimulation was performed at low (5 Hz) and high (75-100 Hz) frequencies. The site of the lesion was then established by the motor effects observed during macrostimulation. At this target, evoked motor activity in the contralateral arm was frequently observed at low frequency stimulation. The responses to high frequency stimulation consisted of a variable increase in muscle tone. Visual scintillations indicated that the electrode tip was too caudally placed, in the optic tract, and flexor contraction of the limb indicated proximity to the internal capsule. The first lesion was usually 2 mm below the inter-commissural plane. The electrode was then advanced another 2 mm inferiorly and the same procedure was repeated. If the clinical result was favourable after two lesions, the procedure was terminated at this point. In other cases, the electrode was advanced another 1 mm inferiorly and the above procedure was repeated. Lesions were made at 75-78°C for 60 seconds.

2.9 Statistical analyses

Details of the statistical analyses performed in each part of the thesis are described in the relevant chapter.

CHAPTER 3

CLINICAL RESULTS OF PALLIDOTOMY

3.1 Aims

The aim of this section of the thesis was to measure the effects of pallidotomy on clinical aspects of motor function in the "off" and "on" motor states at both short and longer-term follow up.

3.2 Patients

Twenty eight patients with PD (15 males, 13 females) were studied. Clinical characteristics of the patients at the time of surgery are listed in **table 3.1**. With the exception of one patient, all patients had severe drug-induced dyskinesias that had proved refractory to adjustments in the drug regimen. One patient had had a thalamotomy 25 years previously. None of the other patients had prior neurosurgical procedures.

Variable	Mean ± SD
Age (years)	60.4 ± 8.1
Duration of disease (years)	13.3 ± 6.3
Hoehn and Yahr stage	
off state	3.4 ± 0.7
on state	2.9 ± 0.6
UPDRS motor score	
off state	41.1 ± 13.4
on state	25.0 ± 10.3
Levodopa dose (mg/day)	1143 ± 555

Table 3.1. Characteristics of patients at time of surgery

3.3 Methods

3.3.1 Time of assessments

Patients were assessed in the "off" followed by the "on" state.Assessments were carried out on 3 occasions:

- pre-operatively
- between 3 and 6 months post-operatively and
- 12 months or more post-operatively

All patients were assessed pre-operatively. Twenty-five patients were assessed between 3 and 6 months post-operatively (mean 4.0 ± 1.37 (SD), range 3-7 months). Twenty-six patients were assessed 12 months or more post-operatively (mean 16.1 ± 5.4 (SD), range 12-29 months). Three patients were unavailable for review at 3-6 months post-operatively, but were assessed 12 months post-operatively. Of the 2 patients unavailable for assessment 12 months post-operatively, one had died 4 months post-operatively from unrelated causes, and the other is at 6 months post-operatively at the time of writing.

3.3.2 Methods of assessment

(i) Clinical rating scales

UPDRS, modified Hoehn and Yahr and Schwab and England Activities of Daily Living scores were measured in all patients.

(ii) Timed motor tasks

1. Purdue Pegboard (PPB) Test (Tiffin, 1941-8)

Twenty-three patients performed the pegboard test pre-operatively. Of these, twenty patients performed the test at 3-6 months and 12 months post-operatively.

2. Walking Time

Eight patients performed walking times. Of these, one was not able to perform the task pre-operatively, but could do so post-operatively. This patient had to be excluded from the analysis.

3.3.3 Statistical analysis

Data were analysed by repeated measures analysis of variance (ANOVA). Within-subjects factor was time, with 3 levels (baseline, 3-6 months post-operatively and 12 months or more post-operatively). For many variables, there appeared to be a decline in efficacy between the intermediate and longer term follow up intervals. For these variables, the significance of an early improvement may have been masked by a later deterioration, using the ANOVA with three levels of time. For this reason, a second ANOVA comparing baseline with 3-6 months post-operatively was performed. Between-subjects factors in all analyses were side of operation and gender, and co-variates were patient age and duration of disease. A p-value of < 0.05 was considered to be significant.

3.4 Results

3.4.1 Dyskinesias/other motor fluctuations

The most dramatic improvement was in the severity of dyskinesias. Mean improvement in global dyskinesia score was 59% at 3-6 months post-operatively and 49% at 12 months or more post-operatively ($p < 0.001$) **(figure 3.1)**. Dyskinesias improved most dramatically contralateral to pallidotomy, but there was often a modest improvement in ipsilateral dyskinesias. The slight return to baseline in dyskinesia score at longterm follow up was usually due to a recrudescence of ipsilateral dyskinesias. Improvement in dyskinesia after pallidotomy was not confined to any subtype of dyskinesia, but affected peak-dose and

diphasic dyskinesias, as well as "off" dystonia (eg. early morning dystonia). Unlike dyskinesias, other types of motor fluctuation (eg. predictability, duration and rapidity of onset "off" periods) did not change post-operatively.

3.4.2 Akinesia/bradykinesia

Compared with the improvement in dyskinesias after pallidotomy, improvements in akinesia/bradykinesia were more modest and mainly confined to the "off" state **(figure 3.2)**.

i. Clinical rating scales

There was a 17% improvement in mean "off" state UPDRS motor examination score at 3-6 months post-operatively compared with baseline. At 12 months post-operatively, the improvement in mean "off" state motor examination compared with baseline was 13% ($p < 0.01$). Mean "on" state UPDRS motor examination score did not change significantly post-operatively. At 3-6 months post-operatively, mean Hoehn and Yahr score improved by 15% in the "off" state and 10% in the "on" state, compared with baseline. These improvements had declined somewhat at the time of longterm follow up, but remained statistically significant overall ($p < 0.001$ for the "off" state; $p = 0.023$ for the "on" state).

"Off" state bradykinesia improved on the contralateral, but not ipsilateral, side to pallidotomy **(figure 3.2)**. On the contralateral side, "off" bradykinesia score improved by 18% and 19% at 3-6 months and 12 months post-operatively, respectively ($p=0.001$). On the ipsilateral side, there was no significant improvement in mean "off" bradykinesia score post-operatively. Mean "on" state bradykinesia score did not change significantly on either side after pallidotomy.

There was a 22% improvement in mean "off" state axial mobility score at 3-6 months post-operatively, and this persisted at longterm follow up (p = 0.021). There was no significant improvement in "on" state axial mobility score post-operatively **(figure 3.2)**.

ii. Purdue pegboard test

The mean "off" state PPB score contralateral to pallidotomy improved by 34%, and the mean ipsilateral score improved by 14%, at 3-6 months post-operatively, compared with baseline. At 12 months or greater post-operatively, the magnitude of improvement had diminished to 20% contralaterally and 5% ipsilaterally. Overall improvement in "off" state PPB score was significant on the contralateral, but not the ipsilateral side (contralateral p value = 0.001; ipsilateral p value = 0.05) **(figure 3.3)**.

In the "on" state, the contralateral PPB score improved by 20% and the ipsilateral score by 16% at 3-6 months post-operatively, compared with baseline. As in the "off" state, the magnitude of improvement diminished somewhat at longterm followup, but remained statistically significant on both sides (contralateral p value=0.008; ipsilateral p value=0.021) **(figure 3.2)**.

iii. Walking Time

There was no significant change in mean walking time post-operatively in either the "off" or "on" state. However, this may be due to the relatively small number of patients who performed this test, as axial mobility did improve when judged by the UPDRS score in a larger number of patients. In 6 of the 8 patients who performed "off" state walking times, walking time was improved at 3-6 months post-operatively compared with baseline. Walking time was unchanged at 3-6 months in 1 patient and slightly worse in the other. As for other measures of

"off" state motor function, walking times returned towards pre-operative levels in most patients by longer term follow up.

3.4.3 Activities of daily living

Identical improvements in UPDRS activities of daily living (ADL) scores were seen in the "off" and "on" states post-operatively. Mean UPDRS ADL score improved by 10% at 3-6 months and by 4% at 12 months post-operatively, compared with baseline (p in "off" state = 0.022; p in "on" state = 0.042) **(figure 3.3)**. The mean Schwab and England ADL score, encompassing both "on" and "off" states, improved by 9% at 3-6 months post-operatively, and by 3% at 12 months post-operatively, compared with baseline ($p < 0.001$) **(figure 3.4)**.

3.4.4 Other clinical outcomes

At all pre- and post-operative times, depression was more prevalent in male than female patients ($p=0.025$). There was an increase in mean depression scores in the early post-operative period, but with the inclusion of data at 12 months post-operatively, this was not significant ($p = 0.051$).

There was no significant change in mean levodopa dose post-operatively. Several patients have required the addition of adjunctive dopaminergic therapy to levodopa (eg. COMT inhibitors, dopamine agonists). Seven patients have had a second pallidotomy contralateral to the first. The second pallidotomy was performed a mean of 15.4 months (range 12-25 months) after the first. In six cases, the second operation was performed because of persistent or worsening dyskinesias ipsilateral to the first operation. In the other case, the second operation was performed because of disabling akinesia refractory to medical therapy.

3.4.5 Adverse events

One patient died 4 months post-operatively from a cardiac arrest. An autopsy was not performed. Five patients had dysarthria postoperatively. In four of these patients (3 left-sided lesions, 1 right-sided lesion), the dysarthria was mild. The patient in whom post-operative dysarthria was severe (right-sided lesion) had had a left thalamotomy 25 years earlier. There was one case of post-operative upper motor neuron facial palsy. One patient had scintillations in the contralateral visual field post-operatively, which resolved after several weeks.

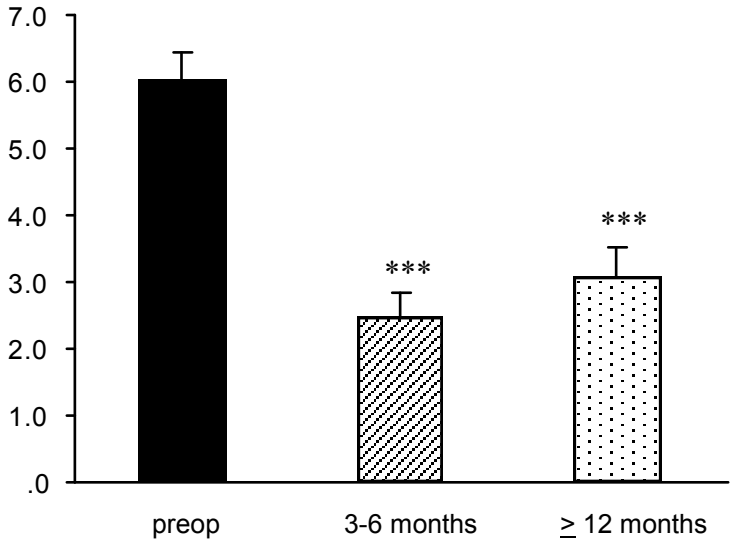


Figure 3.1. Mean UPDRS dyskinesia scores before and after pallidotomy. The dyskinesia score is a global score encompassing both "off" (before levodopa) and "on" (after levodopa) states (*** = $p < 0.001$).

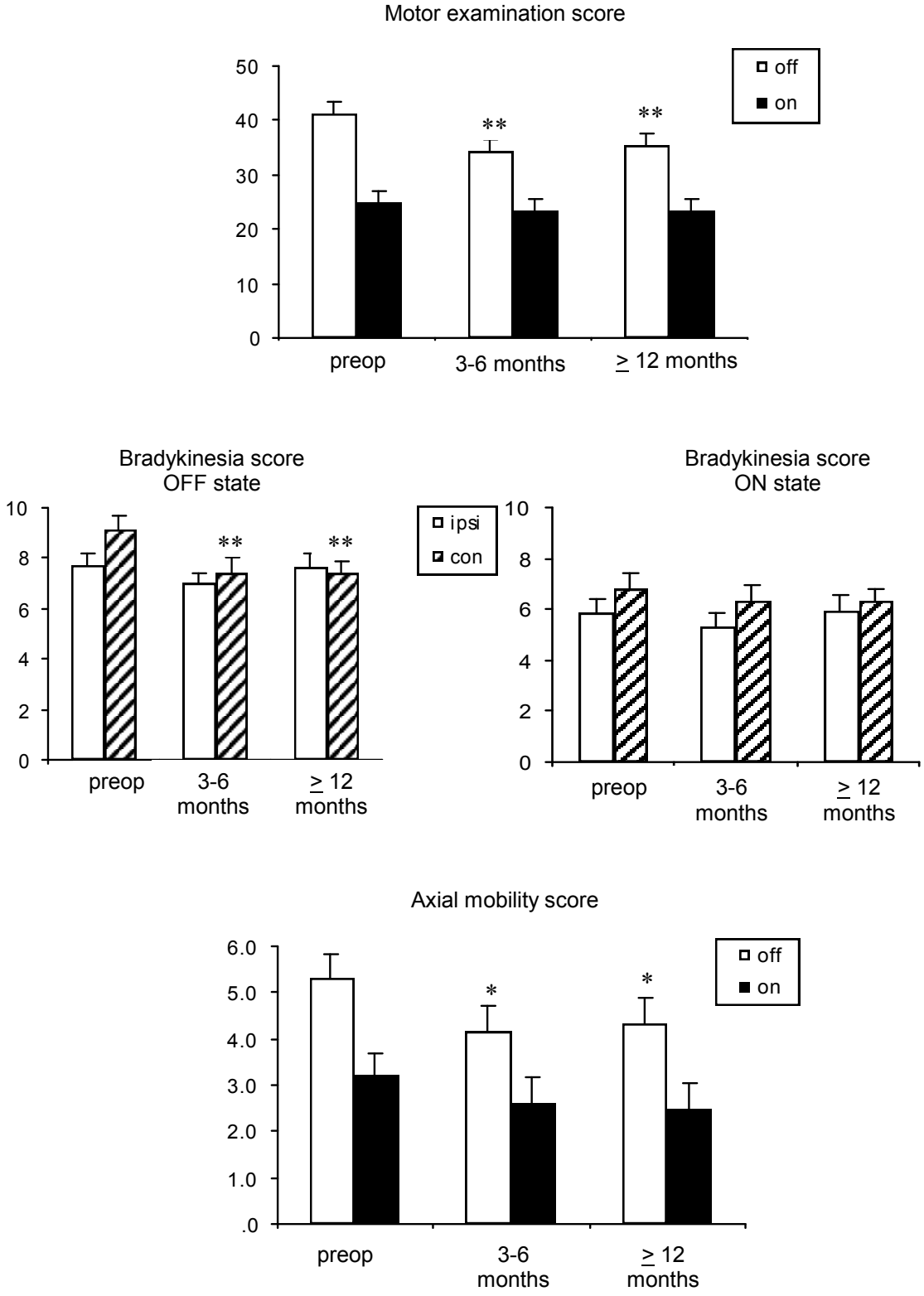


Figure 3.2 Mean UPDRS scores for motor examination, limb bradykinesia and axial mobility before and after pallidotomy ("on" = after levodopa administration; "off" = before levodopa administration; "ipsi" = limbs ipsilateral to pallidotomy; "con" = limbs contralateral to pallidotomy; * = $p < 0.05$; ** = $p < 0.01$).

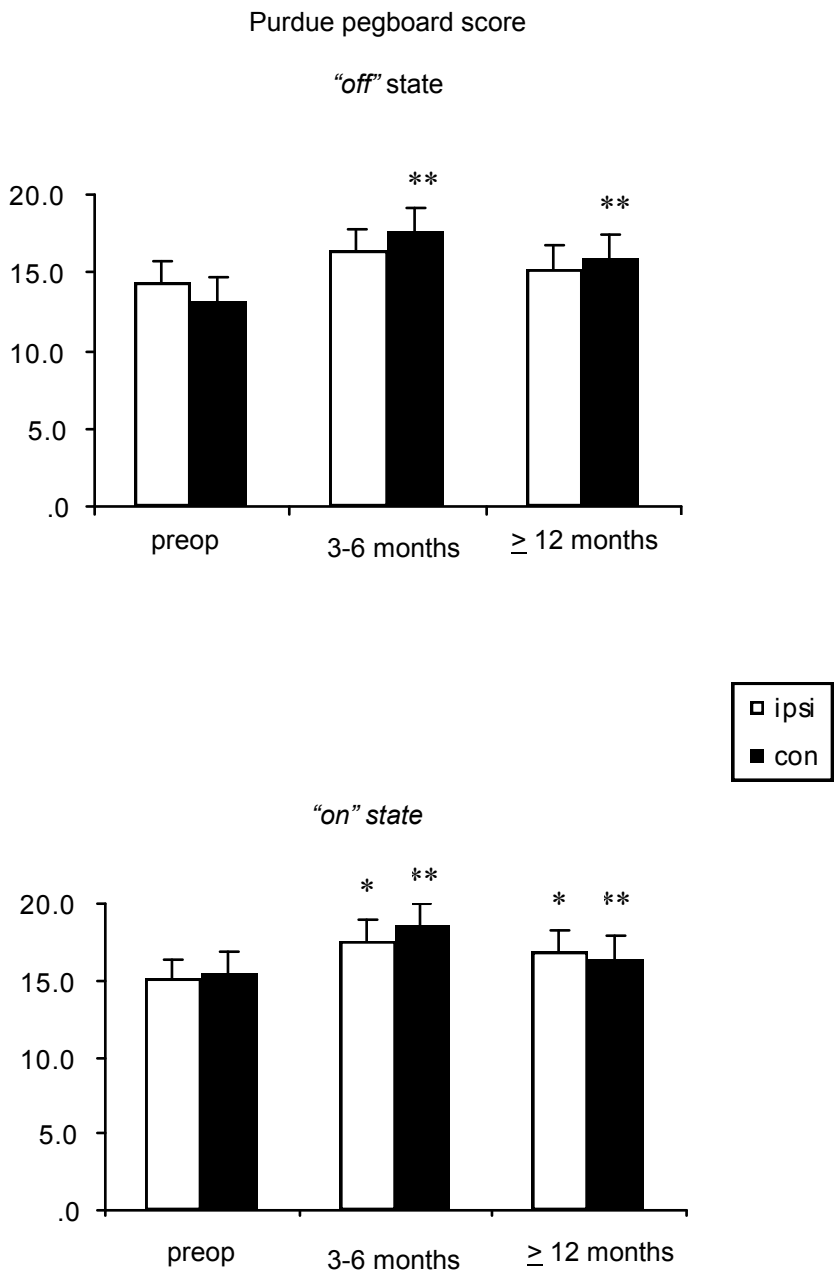


Figure 3.3 Mean Purdue pegboard scores in the "off" and "on" motor states before and after pallidotomy.
("ipsi" = limbs ipsilateral to pallidotomy; "con" = limbs contralateral to pallidotomy; * = $p < 0.05$; ** = $p < 0.01$).

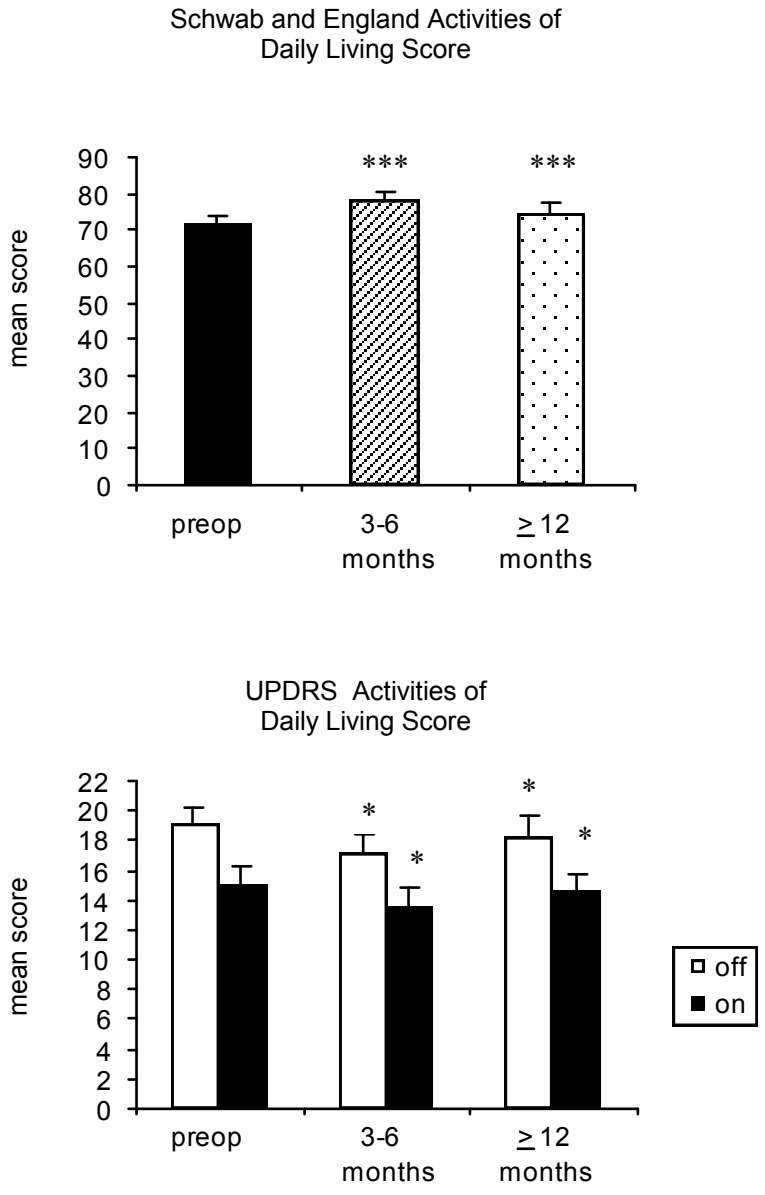


Figure 3.4 Mean UPDRS and Schwab and England activities of daily living scores before and after pallidotomy. Separate UPDRS ADL scores are shown for the "on" and "off" states. The Schwab and England score is a global score encompassing both "on" and "off" states (* = $p<0.05$; *** = $p<0.001$).

3.5 Discussion

3.5.1 Summary of results

We have demonstrated significant improvements in motor function after macrostimulation-guided posteroventral pallidotomy for severe PD. The nature of these improvements is in line with most previous studies of the effects of pallidotomy in PD (Lozano et al., 1995; Dogali et al., 1995; Baron et al., 1996; Fazzini et al., 1997; Lang et al., 1997; Kishore et al., 1997; Samuel et al., 1998; Ondo et al., 1998; Shannon et al., 1998; Samii et al., 1999; Schrag et al., 1999; Lai et al., 2000; Fine et al., 2000; Pal et al., 2000). As in these studies, the most marked clinical improvement post-operatively was in drug-induced dyskinesias. In all cases, there was abolition, or near abolition, of dyskinesias contralateral to the lesion. On the ipsilateral side, dyskinesias were either unchanged or mildly improved. In six of the 28 cases, residual or recurrent ipsilateral dyskinesias were sufficiently severe to justify a second pallidotomy on the other side. Apart from the improvement in dyskinesias, motor function in the "on" motor state was relatively unchanged.

Improvement in "off" state motor function was statistically significant but of lesser magnitude than the improvement in dyskinesias. The biggest "off" state improvements were in contralateral bradykinesia and axial mobility.

3.5.2 Comparison of our results with those of other studies

Different studies have used different methods for measuring dyskinesias. Allowing for these differences, the post-operative improvement in dyskinesias seen in the present study is similar to that reported in other studies with similar follow up times (Lozano et al., 1995; Lang

et al., 1997; Kishore et al., 1997; Samii et al., 1999; Pal et al., 2000; Samuel et al., 1998; Schrag et al., 1999; Shannon et al., 1998; Ondo et al., 1998; Lai et al., 2000).

In contrast to the uniform effect on dyskinesias across most studies, the effects of pallidotomy on "off" state motor dysfunction vary markedly between studies. Of studies that have used the UPDRS and/or PPB scores to measure limb and axial akinesia, some have reported improvements of a similar magnitude to our own (Ondo et al., 1998; Shannon et al., 1998), while others have reported substantially greater (Baron et al., 1996; Dogali et al., 1995; Fazzini et al., 1997; Lozano et al., 1995; Lang et al., 1997; Kishore et al., 1997) or smaller (Uitti et al., 1997; Samuel et al., 1998) improvements than we. The potential reasons for these differences will be discussed in later chapters, but may include differences in lesion size or methods of target localisation.

The results of our study are in keeping with emerging evidence that many of the clinical effects of pallidotomy may decline in magnitude over time. In our study, following an initial improvement, mean "off" state motor scores on the ipsilateral side to pallidotomy and mean "off" state axial mobility scores returned towards baseline by 12 months or more post-operatively. The improvement in mean global dyskinesia score also declined over this time. Again, this was due a recrudescence of dyskinesias on the ipsilateral side to pallidotomy.

The issue of whether the benefit of pallidotomy on "off" state motor dysfunction declines over time is controversial. Two groups, one from Texas (Ondo et al., 1998; Lai et al., 2000) and the other from New York (Dogali et al., 1995; Fazzini et al., 1997) found that the effects of pallidotomy on "off" state bradykinesia did not decline when patients were followed for up to 4 years post-operatively. By contrast, groups from Toronto (Lozano et al., 1995; Lang et al., 1997; Fine et al., 2000), Vancouver (Kishore et al., 1997; Samii et al., 1999; Pal et al.,

2000) and London (Samuel et al., 1998; Schrag et al., 1999) have found, like us, that the effect of pallidotomy on "off" state akinesia/bradykinesia declines over time. By 3 years post-operatively, ipsilateral "off" state akinesia and "off" state gait dysfunction may be worse than baseline (Pal et al., 2000).

The likeliest cause for the decline in effect of pallidotomy over time is disease progression. Pallidotomy is thought to improve akinesia by diminishing excessive inhibitory neural output from the GPi. This effect is more marked on the contralateral side to pallidotomy, presumably because only a minority of pallidal neurons are involved in the control of ipsilateral voluntary movement. It is therefore not surprising that volitional movement would continue to deteriorate on the ipsilateral side post-operatively. The mechanism underlying the decline in contralateral movement after pallidotomy is less clear. GPi neurons and axons should be permanently ablated by thermal injury. However, it is well recognised in other contexts that, following irreversible neural injury, aberrant neural connections can develop. It may be that such connections develop following pallidotomy and have the net effect of increasing inhibitory input to the ventral lateral thalamus and thus worsening contralateral bradykinesia.

CHAPTER 4

ANALYSIS OF THE PHYSIOLOGIOCAL DETERMINANTS OF BRADYKINESIA BY A KINEMATIC ANALYSIS OF VOLUNTARY ARM MOVEMENT: VALIDATION OF METHOD IN PD PATIENTS AND CONTROL SUBJECTS

4.1 Aims

The aim of this section of the thesis was to devise and validate a method for measuring the kinematic characteristics of voluntary upper limb movement in PD patients and controls. Using this method, parameters that differed significantly between control and PD subjects were interpreted to be physiological correlates of bradykinesia. The method could then be used to study the effects of pallidotomy and levodopa therapy on bradykinesia in PD.

4.2 Subjects

The study was conducted in 2 phases. In experiment 1, PD patients in the "off" motor state were compared with normal subjects. In experiment 2, the performance of PD patients before and after levodopa administration was compared.

Experiment 1. PD patients off medication compared with normal controls.

Subjects for experiment 1 comprised 34 patients with idiopathic PD (24 males, 10 females, mean age 63 years ± 9 (SD) and 13 normal controls (6 males, 7 females, mean age 66 years ± 6 (SD)). Clinical characteristics of the PD subjects are shown in table 4.1.

Experiment 2. Comparison of "off" and "on" motor performance in PD patients.

Twenty-five PD patients (16 males, 9 females, mean age 61 years ± 10 (SD)) were studied in experiment 2. Clinical characteristics of these patients are shown in **table 4.2**. Patients in the two experiments did not differ significantly in disease severity and duration or in any other clinical characteristics.

	Mean (SD)
Hoehn and Yahr score OFF state (range 0-5)	2.9 (1.0) Distribution: score 1-1.5 = 5 subjects score 2-2.5 = 10 subjects score 3 = 8 subjects score 4 = 11 subjects score 5 = 0 subjects
UPDRS motor score OFF state (range 0-108)	32.5 (15.5)
Schwab and England ADL score (range 0-100)	77.9 (14.7)
Duration of disease (years)	9.6 (5.7)

Table 4.1 Characteristics of the PD patients (n = 34) in experiment 1.

	Mean (SD)
Hoehn and Yahr score OFF state (range 0-5)	3.0 (0.9) Distribution: score 1-1.5 = 3 subjects score 2-2.5 = 8 subjects score 3 = 4 subjects score 4 = 10 subjects score 5 = 0 subjects
UPDRS motor score OFF state (range 0-108)	33.2 (15.7)
Schwab and England ADL score (range 0-100)	76.2 (15.2)
Duration of disease (years)	10.0 (6.1)

Table 4.2 Characteristics of the PD patients (n=25) in experiment 2.

4.3. Methods

4.3.1 Clinical and kinematic assessments

Clinical assessments and kinematic assessments of upper limb movement were performed as described in Chapter 2. The author performed all the clinical assessments and measurements of upper limb movement. For each patient, clinical assessment was performed before assessment of upper limb movement, to avoid the risk of biasing the clinical assessments by knowledge of kinematic results.***4.3.2 Experiment format***

Experiment 1. PD patients off medication compared with normal controls

In this experiment, voluntary upper limb movement of PD patients in the "off" motor state (n=34) was compared with that of normal subjects (n=13).

Experiment 2. Comparison of "off" and "on" motor performance in PD patients

In this experiment, voluntary upper limb movement was compared in 25 of the PD patients "off" and "on" levodopa therapy. "Off" and "on" assessments in each subject were always performed on the same morning.

4.3.3 Statistical analysis

Experiment 1 data were analysed by multivariate analysis of variance (MANOVA) for all kinematic variables of interest. For comparison of normal subjects with PD patients, the between-subjects factor in the analysis was presence or absence of PD. A second MANOVA was then performed on the data of the PD patients alone in order to investigate the effects of disease severity on the kinematic variables. For this analysis, the between-subjects factor was the Hoehn and Yahr score. Covariates in all analyses were patient gender, age, side tested (ie. right or left, dominant or non-dominant hand), duration of disease and Schwab and England activities of daily living score. Experiment 2 data were

analysed by repeated measures analysis of variance for the within-subjects factor of time (before or after levodopa), using the same covariates as for Experiment 1.

Significance level was set at less than 0.05 in all analyses.

4.4. Results

4.4.1 Experiment 1. PD patients in "off" state compared with normal controls

Results are summarised in **table 4.3**.

i. Rapid finger movements

Mean amplitude of index finger movements was 11.8° (SE 0.9) in the PD patients and 17.0° (SE 1.8) in the normal subjects, representing a 31% reduction in tapping amplitude in PD patients compared to normal subjects (p=0.008) (**figs 4.1, 4.2**). Among PD patients, mean tapping amplitude was significantly lower in those with more severe, compared with milder, disease (p<0.001) (**fig 4.2**).

Mean tapping interval during the tapping sequence was 19% longer in the PD patients (254 msec, SE 14.0) than the normal controls (214 msec, SE 6.8) (p=0.03). Amongst PD patients, tapping interval did not correlate with disease severity (p=0.636).

Rhythm of finger tapping was significantly impaired in PD patients, as a group, compared with normal controls (p<0.001). However, as for tapping speed, no significant correlation was detected between tapping rhythm and disease severity in the PD patients (p=0.26).

(ii) Sequential upper limb movement ("pick up" task)

Significant differences between the PD patients, in the OFF state, and the normal controls were seen in all parameters of the "pick up" task (**figs 4.3, 4.4**). Mean reaction time was 106% longer in the PD patients (350 msec, SE 27.4) than the normal subjects (170 msec, SE 10.8) (p=0.003). Mean inter-onset latency between index finger and elbow movement was 96% longer in the PD patients (583 msec, SE 36.0) than the normal

subjects (298 msec, SE 21.3) ($p<0.001$). Mean peak elbow speed was 37% slower in the PD patients (112°/sec, SE 7.2) than the normal subjects (179°/sec, SE 9.8) ($p<0.001$).

Task	Variable	Normal subjects	PD patients	PD patients compared with normal subjects (p value)	Effect of disease severity in PD patients (p value)
Rapid finger movements	Mean tapping amplitude (◦±SE)	17.0 (±1.8)	11.8 (±0.9)	0.008	<0.001
	Mean tapping interval (ms±SE)	214 (±6.8)	254 (±14.0)	0.03	0.636
"Pick up" task	Auditory reaction time (ms±SE)	170 (10.8)	350 (27.4)	0.003	0.003
	Inter-onset latency (ms±SE)	298 (21.3)	583 (36.0)	<0.001	<0.001
	Peak elbow speed (◦/sec±SE)	179 (9.8)	112 (7.2)	<0.001	<0.001

Table 4.3 Results of experiment 1, comparing PD patients in the "off" motor state (n=34) with normal subjects (n=13) in performance of the rapid finger tapping and "pick-up" tasks. Significance levels in column 5 refer to comparisons between normal subjects and PD patients. Significance levels in column 6 refer to analysis of disease severity in PD patients, using Hoehn and Yahr score as a "between-subjects" factor in analysis.

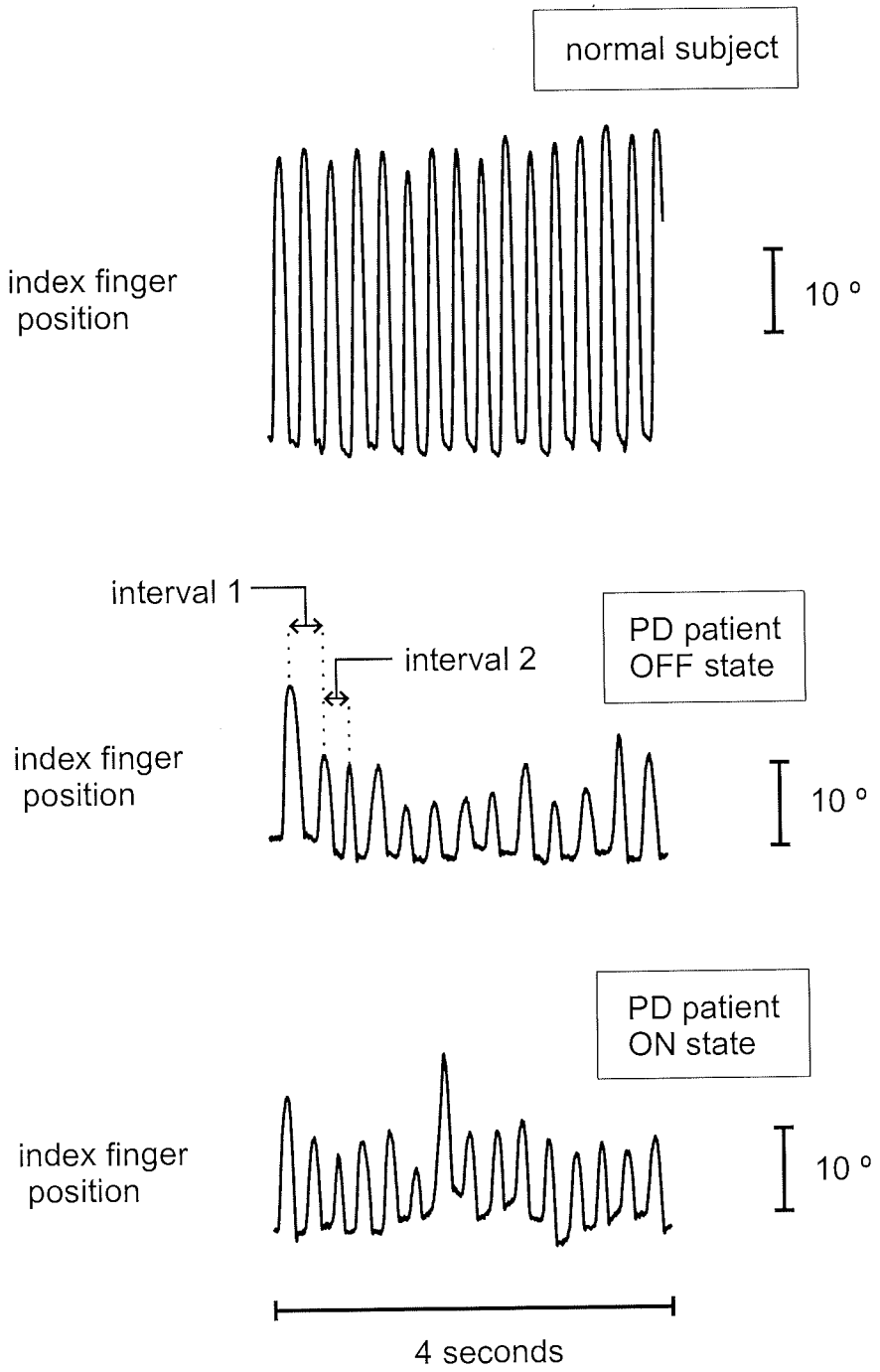


Figure 4.1 Position traces of the index finger during a tapping movement performed by a normal subject (upper panel), a patient with Parkinson's disease in the "off" motor state (middle panel) and by the same patient in the "on" motor state (lower panel). The position traces were derived from a goniometer placed across the second metacarpo-phalangeal joint while tappinf the index finger on a table top. The amplitude of each tap was measured from each trough to the following peak. The tapping interval was measured from peak to peak (interval 1 and 2). Note that in the parkinsonian patient, rhythm is slightly irregular and mean tapping amplitude is lower than in the normal subject. Note also that mean tapping amplitude increases after levodopa in the parkinsonian patient.

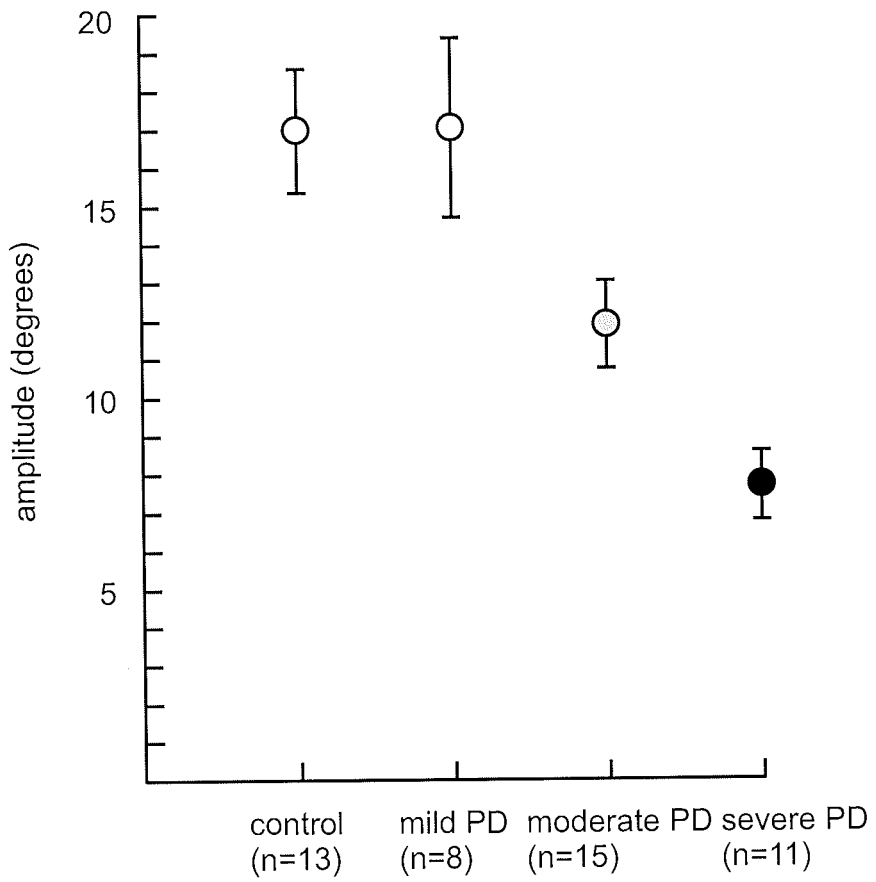


Figure 4.2 Mean (±SE) amplitude of repetitive tapping movements of the index finger in normal subjects and in patients with PD of varying degrees of severity. For each subject, the mean of 10 successive amplitudes was recorded and used in the analysis. PD patients were assessed afterovernight withdrawal of anti-parkinsonian medications. Severity of PD was rated by the modified Hoehn and Yahr score (score 1-2=mild, score 2.5-3=moderate, score 4=severe. No patient had a score of 5). Mean tapping amplitude was significantly smaller in PD patients than in controls ($p<0.01$) and declined significantly with advancing disease ($p<0.001$).

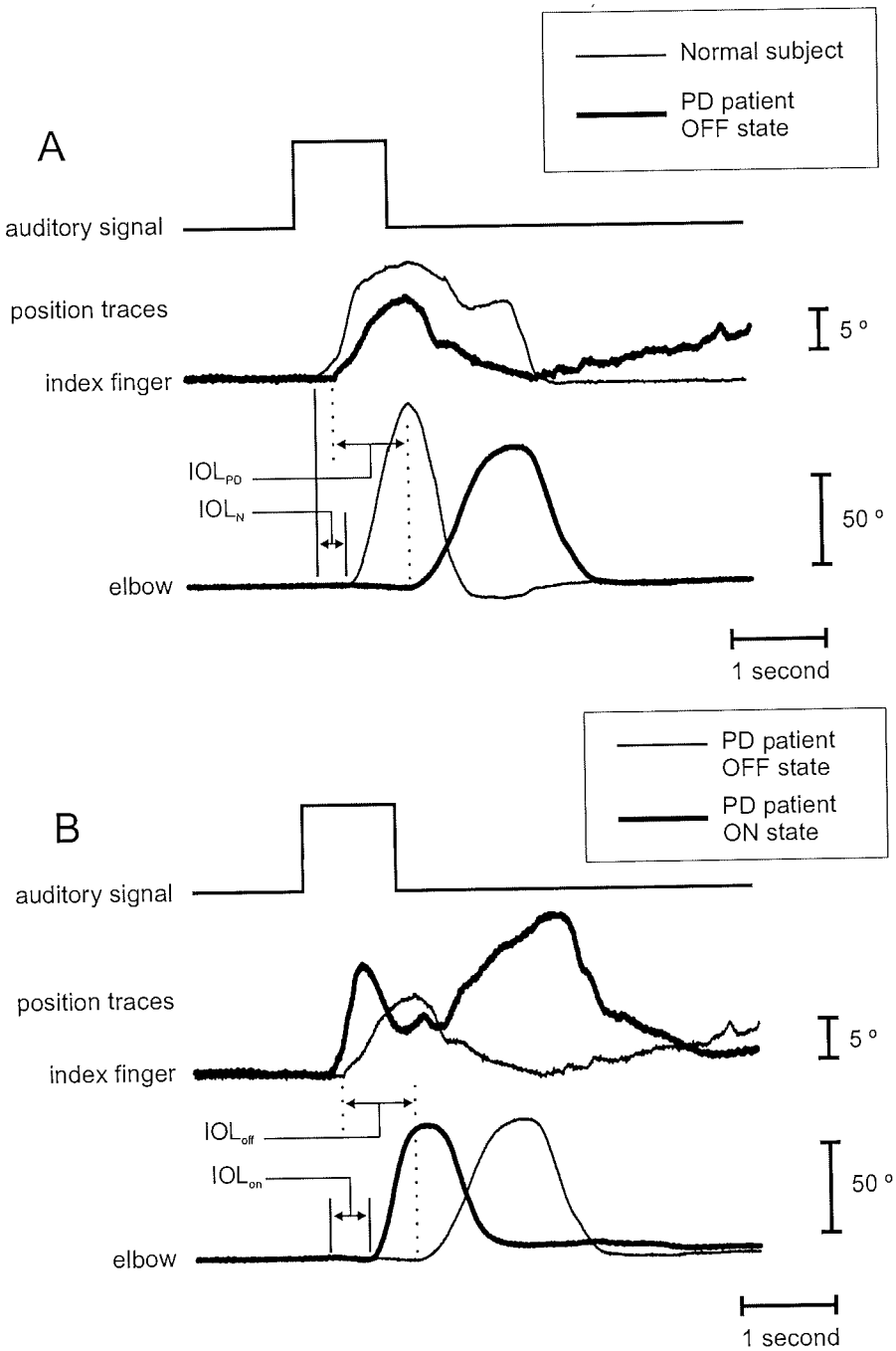


Figure 4.3 Position traces of movement at the second metacarpophalangeal and elbow joints from a table top, lifted it towards their nose and returned the peg to the table (the pick-up task). Single trials are shown in response to an auditory cue. In **A** the position traces from a patient with Parkinson's disease in the "off" motor state (Hoehn and Yahr score 2) are superimposed on those from a control subject. In **B** the position traces of the patient after levodopa ("on" state) are superimposed on those of the same patient before levodopa ("off" state).

In **A**, note that the interval between activation of the finger and elbow movement (inter-onset latency,or IOL) is longer in the patient (IOL_{PD}=769ms) compared with the control subject (IOL_N=273ms),and that peak elbow speed is slower in the parkinsonian patient (67°/sec) than in the control subject (128°/sec). In **B**, note that in the parkinsonian patient, IOL decreases from 769ms in the "off" state to 405ms in the "on" state, and peak elbow speed increaes from 67°/sec in the "off" state to 121°/sec in the "on" state.

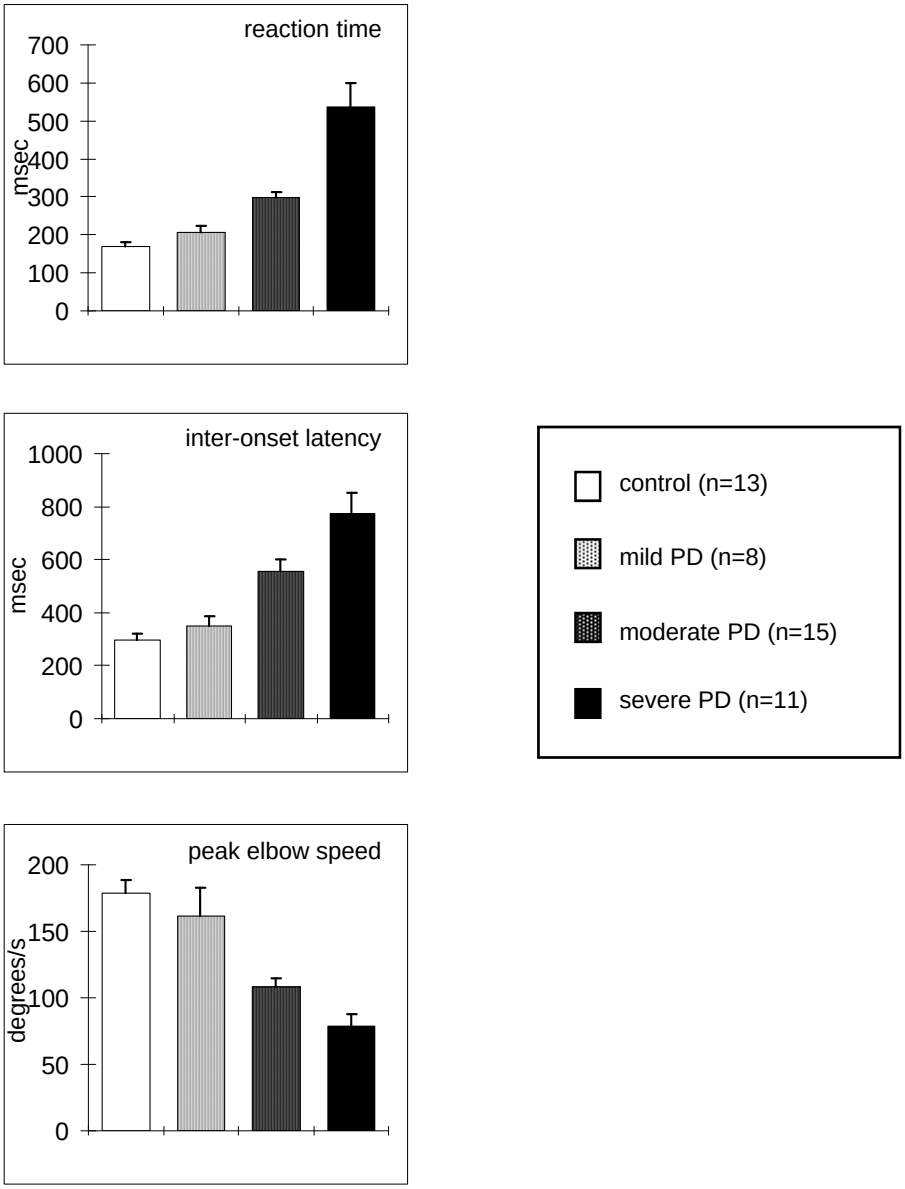


Figure 4.4 Mean (±SE) reaction time, inter-onset latency (IOL) and peak elbow speed during the "pick-up task " in control subjects and in patients with PD of varying degrees of severity. For each subject, the mean of 10 successive trials was recorded and used in the analysis. PD patients were assessed after overnight withdrawal of anti-parkinsonian medications. Among the PD group, there was a significant increase in reaction time ($p=0.003$) and IOL ($p<0.001$) and reduction in elbow speed ($p<0.001$) in patients with more severe, compared with milder, disease.

Among the PD group, there was a significant increase in reaction time ($p=0.003$) and IOL ($p<0.001$) and reduction in elbow speed ($p<0.001$) in patients with more severe, compared with milder, disease. (**fig 4.4**). Reaction time and IOL also showed a significant correlation with age, with older patients manifesting longer reaction times ($p=0.007$) and IOL ($p=0.029$) than younger patients. The effect of age was independent of disease duration.

The Schwab and England activities of daily living score showed an inverse correlation with the duration of the IOL ($p<0.01$), indicating that PD patients with longer IOL during sequential movement performed worse in activities of daily living.

4.4.2 Experiment 2. Comparison between "off" and "on" motor performance in PD patients

Results are summarised in **table 4.4**.

i. Rapid finger movements

The only parameter of rapid finger tapping to improve after levodopa was tapping amplitude (**fig 4.1)**. Mean finger tapping amplitude improved by 20% after levodopa, from 12.0° (SE 0.9) to 14.4° (SE 1.2) ($p=0.025$). There was no change in mean tapping interval after levodopa or rhythm after levodopa.

ii. Sequential upper limb movement ("pick up" task)

In contrast to the lack of effect of levodopa on rapid finger movements, there were significant improvements in all 3 parameters of the "pick up" task after levodopa (**figs 4.3, 4.5**). Mean reaction time decreased by 22% from 405 msec (SE 34.3) to 317 msec (SE 20.7) ($p=0.042$), mean IOL decreased by 17% from 622 msec (SE 43.1) to 514 msec (SE 34.9) ($p=0.047$) and mean peak elbow speed increased by 18% from 99°/sec (SE 6.1) to 117°/sec (SE 4.8) ($p=0.001$).

Task	Variable	"Off" state	"On" state	p value
Rapid finger movements	Mean tapping amplitude (° ± SE)	12.0 (± 0.9)	14.4 (± 1.2)	0.025
	Mean tapping interval (msec ± SE)	270 (± 18.3)	258 (± 10.3)	0.539
"Pick up" task	Auditory reaction time (msec ± SE)	405 (34.3)	317 (20.7)	0.042
	Inter-onset latency (msec ± SE)	622 (43.1)	514 (34.9)	0.047
	Peak elbow speed (°/sec ± SE)	99 (6.1)	117 (4.8)	0.001

Table 4.4 Results of experiment 2, comparing PD patients (n=25) before ("off") and approximately one hour after ("on") levodopa.

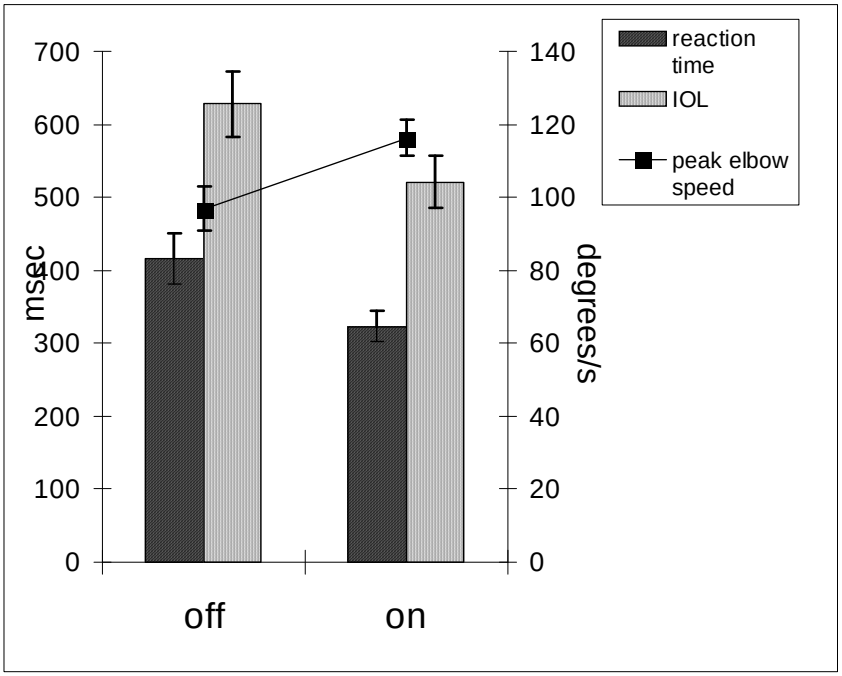


Figure 4.5 Reaction time, inter-onset latency (IOL) and peak elbow speed during the "pick up task" in PD patents before ("off) and after ("on") levodopa administration. Results are mean values ± SEM. Mean reaction time decreased by 22% after levodopa, compared with baseline ($p<0.05$), mean IOL decreased by 17% after levodopa, compared with baseline ($p<0.05$) and mean peak elbow speed increased by 18% after levodopa, compared with baseline ($p<0.01$).

4.5. Discussion

We have described a method for the assessment of volitional upper limb movement in PD. The "pick up "task is a modification of the method devised by Benecke et al. (1986, 1987*a*, 1987*b*) – that is, a two-stage sequential movement of both distal and proximal joints. However, unlike in Benecke's model, in the "pick up" task, the limb is unrestrained. The finger tapping task incorporates the measurement of movement amplitude, speed and rhythm in a repetitive motor task of a distal joint.

Finger tapping task

The importance of measuring distal limb movements in PD is that such movements are important for many activities of daily life, such as writing and dressing. However, much of the early work on the measurement of volitional movement in PD focussed on proximal, large amplitude movements. The reasons for this may be traced back to the work of Flowers et al. (1975,1976), who found that slowness of movement in PD was greater for large than small amplitude movements. Hallett and Khoshbin (1980) proposed that the relative preservation of speed of small amplitude movements was explained by their being executed by a single triphasic EMG burst, rather than the multiple bursts required for large amplitude movements.

We found that finger tapping amplitude, speed and rhythm were all significantly impaired in PD patients compared with normal subjects. A motor task such as writing requires the harmonious, rhythmic and fractionated activation of muscles controlling the digits. The present study suggests that deficits in the rhythm and amplitude, as well as speed, of fractionated finger movements contribute to bradykinesia during such tasks. The decline in tapping amplitude with more advanced disease, when speed and rhythm were relatively preserved, may indicate that movement amplitude is more sensitive to disease progression than speed and rhythm. A disproportionate decline in amplitude, compared

with speed and rhythm, may have occurred because of the manner in which the task was explained to the patients. Patients were asked to tap the finger "as quickly and as regularly as possible", with no instruction being given as to amplitude. In their attempts to maximise speed and rhythm of movement, patients may have sacrificed movement amplitude. If so, the effect of this sacrifice was more marked in patients with more advanced disease.

The neurophysiological basis for reduced amplitude of finger tapping is not clear. It may be caused by a "failure to energise" the muscles that perform this movement, as suggested by Hallett and Khoshbin (Hallett and Khoshbin, 1980). If so, this "energy failure" would presumably be associated with defective output from the primary motor cortex. However, movement-associated activation of the primary motor cortex has been found to be either normal (Playford et al., 1992; Rascol et al., 1994) or increased (Haslinger et al., 2001) in PD patients. Another explanation for diminished amplitude of finger tapping in PD is that movement excursion may be inhibited by agonist muscle rigidity, despite normal, or possibly increased, primary motor cortical output to those muscles.

Impaired speed and rhythm of rapid finger movements in the PD patients in our study may be explained by dysfunction of pallido-mesial frontal connections. It has been shown that, in monkeys performing a learned motor task, the transition from one movement to the next is preceded by a change in the pattern of firing of GPi neurons (Brotchie et al., 1991*b*). Brotchie et al. postulated that the role of the GPi was to send a "stop" signal to the SMA, to signal that the current movement (or "motor plan") should end and the next one begin (Brotchie et al., 1991*b*). In performing a fractionated motor task such as finger tapping, the individual must alternate rapidly between sequential motor plans. This sort of task would be critically dependent on the integrity of pallido-mesial frontal connections and would deteriorate with dysfunction of these connections, leading to

deterioration in both speed and rhythm of movement. As previously discussed, there is considerable evidence that neural activity in the GPi and SMA is abnormal in experimental and idiopathic PD (Filion and Tremblay, 1991; Sterio et al., 1994; Playford et al., 1992; Rascol et al., 1994; Haslinger et al., 2001).

"Pick up" task

In the "pick up" task, we found, like Benecke et al., (Benecke et al., 1987*a*) that movement speed and IOL were abnormal in the PD patients in the "off" state (Benecke et al., 1987*a*). However, unlike Benecke et al., who found that only IOL correlated with clinical bradykinesia (Benecke et al., 1987*a*), we found that auditory reaction time, IOL and elbow speed all correlated with clinical markers of disease severity. As for the speed and rhythm of finger tapping, the IOL of a sequential movement reflects the integrity of pallido-mesial frontal connections. Kinematically speaking, the IOL represents the period during which one "motor plan" is switched to another. This is a process managed by the SMA under pallidal influence (Brotchie et al. 1991*b*). With disease progression in PD, SMA function would deteriorate and the duration of the IOL increase. In the present study, there was an inverse correlation between ADL performance, on the Schwab and England Scale, and duration of the IOL. This suggests that the IOL during complex movements is functionally significant for the performance of everyday activities.

Elbow flexion in the "pick up" task is a ballistic component of a sequential movement. In normal subjects, control of the speed of ballistic movements involves a number of different cortical and subcortical regions, including the posterior pallidum, primary sensorimotor cortex and mesial cerebellum (Turner et al., 1998). It is tempting to attribute the deficit in peak elbow speed in the PD patients in our study, and the deterioration in elbow speed with advancing disease, to pallidal dysfunction. However, the role of different movement-associated cerebral regions in the control in movement speed

has not been compared in PD patients and control subjects. Furthermore, the improvement in movement speed after procedures that reduce or ablate pallidal function (eg. pallidotomy, pallidal and STN stimulation) runs counter to such an interpretation. The role of increased muscle rigidity in causing a reduction in speed of ballistic movements is not clear. It has been postulated that the increase in primary motor cortex activation that has been detected in some studies of PD (Haslinger et al., 2001) results from defective cortico-cortical inhibition of the primary motor cortex (Ridding et al., 1995). It has been postulated that increased primary motor cortex excitability in PD may be the neural substrate of rigidity (Haslinger et al., 1995), but this remains unproven.

Comparison of the finger tapping and "pick up" tasks

An important difference between the rapid finger tapping and "pick up" tasks must be borne in mind when evaluating the effect of disease severity on their performance. The two tasks differ in the extent to which they can utilise external cues. The finger tapping task is a self-paced movement in which subjects tap the finger as quickly and regularly as possible. Each subject must formulate a technique that meets the dual demands of speed and regularity of rhythm. No external cues are provided to facilitate this movement, making it "internally generated". The "pick up" task, on the other hand, incorporates both auditory and visual cues. It is believed that internally generated movements are more dependent than externally cued movements on pallido-mesial frontal activity (Mushiake et al., 1990). PD patients perform motor tasks better when external cues are provided (Georgiou et al., 1999; Martin et al., 1994). In performing complex movements, PD patients show increased activation of lateral premotor and parietal cortices, compared with normal subjects (Samuel et al., 1997*a*; Hanakawa et al., 1999). This activation is believed to represent increased utilisation of sensory inputs during movement, in order to

compensate for defective activation of pallido-mesial frontal circuits (Samuel et al., 1997*a*).

Effects of levodopa on task performance

All three parameters of the "pick up" task improved after levodopa. Of the parameters of rapid finger movement, tapping amplitude improved after levodopa, but tapping speed and rhythm did not improve. As discussed above, it is believed that impaired performance of complex movements in PD is caused by defective function of mesial frontal cortical regions, but that this is partially compensated by increased activation of more lateral cortical areas associated with the utilisation of sensory inputs (Samuel et al., 1997*a*). It is well established that, in PD patients, movement-associated mesial frontal cortical activity improves after dopaminergic drug therapy (Jenkins et al., 1992; Rascol et al., 1992; Haslinger et al., 2001). Furthermore, dopaminergic drugs decrease neural firing within the GPi in PD patients (Hutchison et al., 1997), suggesting that the mechanism of improved frontal mesial cortical activation after dopaminergic therapy is by a reduction in pallidal inhibition of the SMA.

In a study of event-related functional MRI during a self-selected, externally triggered ballistic arm movement in PD patients, activation of the SMA increased after levodopa, while that of the primary motor, lateral premotor and superior parietal cortices decreased (Haslinger et al., 2001). However, cortical activation patterns remained abnormal in PD patients after levodopa administration, compared with control subjects (Haslinger et al., 2001). In other words, levodopa partially reverses movement-associated mesial frontal hypoactivity and compensatory lateral premotor/parietal/primary motor hyperactivity in PD. The results of the present study are broadly in line with these findings. The finger tapping task is different to the motor task used in the Haslinger study, being a repetitive, distal, small amplitude movement, rather than a single, ballistic, proximal movement as in

the Haslinger study. The lack of improvement in tapping speed and rhythm after levodopa administration indicates that, although SMA function improves after levodopa, the degree of improvement is inadequate to improve the temporal characteristics of this complex movement. By contrast, IOL did improve after levodopa. This may indicate that the "pick up" task makes fewer kinematic demands on the SMA, as it involves a single switch from one motor plan to another, rather than multiple such switches, as in finger tapping. Alternatively, IOL may improve because the availability of external cues in the "pick up" task helps compensate for persistent, albeit improved, SMA dysfunction after levodopa administration.

In our study, elbow flexion was the parameter that showed the greatest degree of improvement after levodopa administration. It is well established that the speed of ballistic movements, whether performed singly or as part of a sequential movement, improves after levodopa administration (Benecke et al., 1997*b*). As discussed above, the mechanism by which this occurs is not known. Studies in control subjects suggest that the speed of ballistic movements is controlled by the pallidum and primary sensorimotor cortex. In PD patients, these regions show changes in neural activity following dopaminergic therapy (Haslinger et al., 2001; Hutchison et al., 1997).

CHAPTER 5

The effects of pallidotomy on objective measures of bradykinesia in Parkinson's disease

5.1 Aims

In this section of the thesis, the method described in chapter 4 was used to measure the kinematics of upper limb movement in patients with advanced PD before and after pallidotomy. The aims were to investigate the effects of pallidotomy on quantitative measures of voluntary movement in PD, and to examine the relation of any kinematic changes to clinical rating scores of motor function and the mechanisms of bradykinesia.

5.2 Patients

Seventeen PD patients (10 males, 7 females) aged 45 to 75 years (mean age 61 years) underwent unilateral pallidotomy (**table 5.1**). Lesions were left sided in 11 cases and right sided in 6. Two patients had undergone contralateral pallidotomy approximately one year previously and the remaining 15 had no prior neurosurgical procedures. The clinical characteristics of the patients are summarized in **table 5.1**.

	Mean ± SD
Age (years)	61.4 ± 8.6
Duration of disease (years)	12.9 ± 4.9 (range 7-25)
Hoehn and Yahr Score in off state	3.4 ± 0.6
UPDRS motor score in off state	38.1 ± 15.1
Schwab and England ADL score (%)	71.9 ± 11.2

Table 5.1 Characteristics of patients at time of surgery. All patients exhibited significant motor fluctuations on conventional drug therapy, including dyskinesias, wearing off effects and unpredictable "off" periods.

5.3 Methods

5.3.1 Clinical assessment

Patients were assessed preoperatively, then at 2-4 weeks (14 subjects), 3 months (15 subjects) and 6 months (12 subjects) postoperatively using the clinical rating scales described in Chapter 2.

5.3.2 Assessment of upper limb movement

Studies of upper limb function (Purdue pegboard test, rapid finger tapping and "pick up" task) were conducted as described in Chapter 4. Studies were conducted in the "off" motor state.

5.3.3 Statistical analysis

Each variable was analysed separately and in turn. A repeated measures analysis of variance was used for the within-subject factor of time of measurement (preoperatively and on 3 occasions postoperatively). Separate analyses were performed for the sides ipsilateral and contralateral to surgery. As there were missing data for some subjects at certain time points post-operatively, an unbalanced repeated measures analysis of variance was used (program 5V of the BMDP statistical software package Ed. W Dixon 1993 UCLA Press).

Inspection of the pooled data of finger tapping amplitude and interval indicated that a linear relationship existed between these variables and time during the tapping sequence. For this reason, a model of linear regression was applied to these data. A p value less than 0.01 was considered significant in all analyses in order to take account of the multiple comparisons performed.

5.4 Results

5.4.1 Clinical assessment

Results obtained from the various clinical rating scales and levodopa dose pre-operatively, at 2-4 weeks, 3 months and 6 months post-operatively are shown in **table 5.2**. There were maximal improvements of 25-30% in the mean "off" state total UPDRS score ($p<0.001$) and the mean "off" motor score at 3 months ($p<0.01$) compared with preoperative values. Mean bradykinesia score did not change on the side ipsilateral to surgery. On the side contralateral to surgery, the mean bradykinesia score improved by 22% at 3 months compared with preoperative values ($p<0.01$). The total dyskinesia score improved by 58% at 6 months postoperatively ($p<0.001$). The latter result represented a mean improvement of around 90% in contralateral dyskinesias and 30% in ipsilateral dyskinesias. Scores for mentation, behaviour and mood and clinical fluctuations did not change post-operatively. Both ADL performance in the "off" state, measured by the UPDRS scale ($p<0.01$), and the patient-rated ADL performance, measured by the Schwab and England scale ($p<0.0001$) improved significantly post-operatively. The Schwab and England scale represents a global assessment of ADL performance in both "on" and "off" states and was also influenced by the reduction in dyskinesias, and therefore showed a greater degree of improvement than the UPDRS "off" score. The mean "off" state Hoehn and Yahr score improved from 3.4 pre-operatively to 2.8 at 3 and 6 months post-operatively ($p<0.0001$).

The improvements in total UPDRS, motor, bradykinesia and ADL scores began to decline at the 6 months follow up. The improvements in dyskinesia, Hoehn and Yahr and Schwab and England scores remained stable at the 6 months assessment.

Variable	Score range	Baseline (n=17)	2-4 weeks (n=14)	3 months (n=15)	6 months (n=12)	p value
UPDRS scores:						
Total score	0-178	67.4±4.5	49.9±4.7	53.5±4.9	59.3±5.2	<0.001
Cognition	0-16	2.8±0.6	3.4±0.6	3.3±0.6	3.8±0.7	0.29
ADL	0-52	18.4±1.2	16.0±1.2	16.5±1.2	19.0±1.3	<0.01
Motor	0-108	38.1±2.6	30.5±2.7	29.5±2.8	33.9±3.0	<0.01
Ipsilateral bradykinesia	0-16	7.0±0.7	7.3±0.7	6.4±0.7	7.1±0.8	0.324
Contralateral bradykinesia	0-16	8.1±0.7	6.1±0.7	6.3±0.7	7.1±0.8	<0.01
Dyskinesias	0-13	5.7±0. 5	2.3±0.5	2.3±0.5	2.4±0.5	<0.0001
Clinical fluctuations	0-6	2.5±0.3	2.0±0.3	1.9±0.4	2.2±0.4	0.25
Other scores:						
Ipsilateral pegboard	0-25	16.4±1.5	18.5±1.4	17.4±1.3	15.2±2.4	0.326
Contralateral pegboard	0-25	14.8±1.6	17.5±1.5	18.3±1.7	14.9±2.2	0.102
Hoehn and Yahr	0-5	3.4±0.1	2.8±0.1	2.7±0.1	2.8±0.2	<0.0001
Schwab and England (%)	0-100	71.9±2.4	81.1±2.5	81.8±2.5	78.8±2.8	<0.0001
Levodopa dose (mg/day)		1041±106	1081±119	1067±127	1097±117	>0.01

Table 5.2 Results (means±SE) of clinical rating scales, Purdue pegboard tests and levodopa doses at baseline and at 2-4 weeks, 3 months and 6 months postoperatively. Results are. With the exception of the Schwab and England Scale, higher scores on the rating scales indicate more severe dysfunction.

5.4.2 Upper limb movement

i. Global arm function

Slight improvements in mean pegboard scores were seen on both sides postoperatively. However, these changes were not statistically significant on either side (**table 5.2**).

ii. Rapid finger movements

An example of the index finger position trace during rapid finger movements from a normal subject and a patient with PD (pre- and postoperatively) is shown in **figure 5.1**. In the patient group, tapping amplitude progressively declined during the course of the task. When all assessment times (pre- and postoperatively) were pooled and analysed together for each side, there was a significant decline in finger tapping amplitude during the task on both sides (**figure 5.2**). On the side ipsilateral to pallidotomy, there was a 27% decline in mean tapping amplitude from tap 1 to tap 10 in the sequence ($p<0.01$) and on the contralateral side, there was a 24% decline over this time ($p<0.01$). The tapping amplitude was greater on both sides at all three postoperative assessment times than preoperatively. However, when each assessment time was considered independently, this trend was not significant on either side after pallidotomy (**figure 5.2**).

At each assessment time, mean tapping interval shortened bilaterally during the sequence so that patients tended to tap the index finger more rapidly at the end of the task than at the beginning (**figure 5.3**). When all assessment times (pre- and post-operative) were pooled and analysed together for each side, the shortening of mean tapping interval was significant on the contralateral ($p<0.01$) but not the ipsilateral ($p=0.04$) side to the pallidotomy. On the contralateral side, mean tapping interval was shorter at all postoperative assessment times compared with preoperatively but this was not statistically significant (**figure 5.3**).

Analysis of the degree of variation in tapping interval at each assessment time did not detect any change in postoperative tapping rhythm compared with preoperatively ($p>0.01$).

iii. Sequential upper limb movement ("pick up" task)

Inter-onset latency (IOL) during the "pick up" task improved significantly on the side ipsilateral to pallidotomy (**figures 5.4 and 5.5**). On this side, the improvement in mean IOL was maximal 3 months after pallidotomy, with a 36% reduction compared with preoperative values ($p<0.001$). At 6 months post pallidotomy, the 21% improvement compared with preoperative values in mean IOL on the ipsilateral side was no longer significant ($p=0.05$). There was no significant change in auditory reaction time or peak elbow speed on the side ipsilateral to surgery (**figure 5.5**).

On the side contralateral to surgery, both IOL and peak elbow speed significantly improved postoperatively. Improvement in mean IOL was maximal 3 months after pallidotomy with a 32% reduction compared with preoperative values ($p<0.001$) (**figure 5.5**). At 6 months, the improvement in mean IOL on the contralateral side had fallen to 23% compared with preoperative values and was no longer significant ($p=0.05$). Mean peak elbow speed contralateral to the side of surgery increased by 29% compared with preoperative values ($p<0.001$) at 3 months (**figure 5.5**). At 6 months, the increase in mean peak elbow speed had fallen to 19% compared with preoperative values and was no longer significant ($p=0.05$). There was no significant change postoperatively in auditory reaction time for the arm contralateral to surgery (**figure 5.5**).

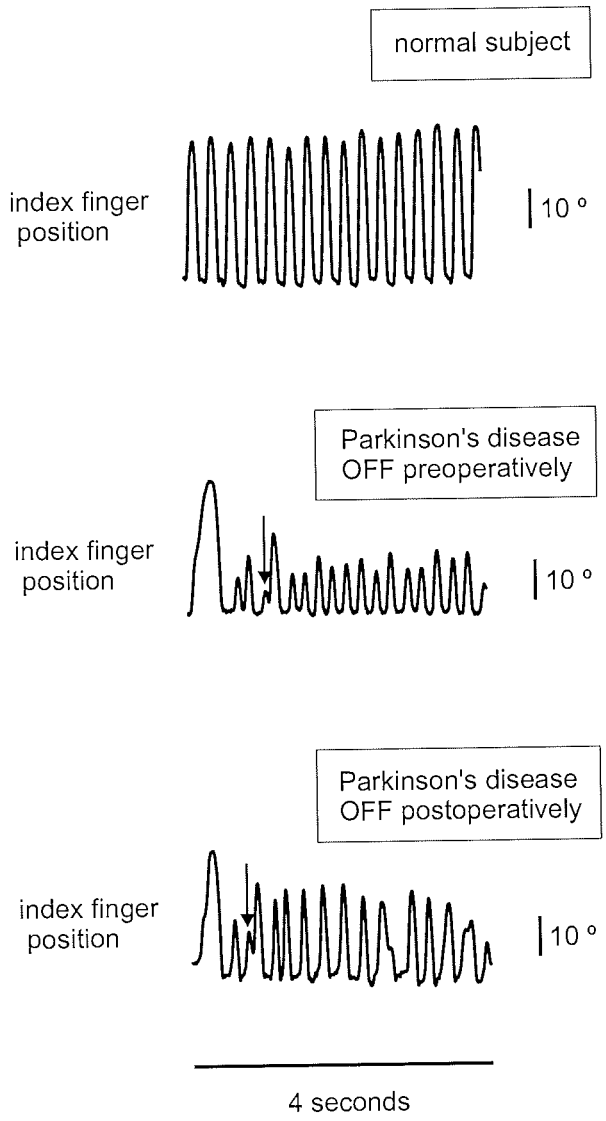


Figure 5.1

Position traces of the index finger during a tapping movement. The position traces were derived from a goniometer placed across the second metacarpophalangeal joint while tapping the index finger on a table top. The amplitude of each tap was measured from each trough to the following peak. The tapping interval was measured from peak to peak. Movement of the parkinsonian patient (lower panels) is smaller in amplitude than the normal subject (upper panel). Post-operatively (lower panel), there is some improvement in movement amplitude. Note that as part of a concerted effort by the parkinsonian patient to maintain a large amplitude movement, the first tap is much larger than those that follow. Note also that in the parkinsonian patient, rhythm is irregular and interrupted by lower amplitude taps (arrows).

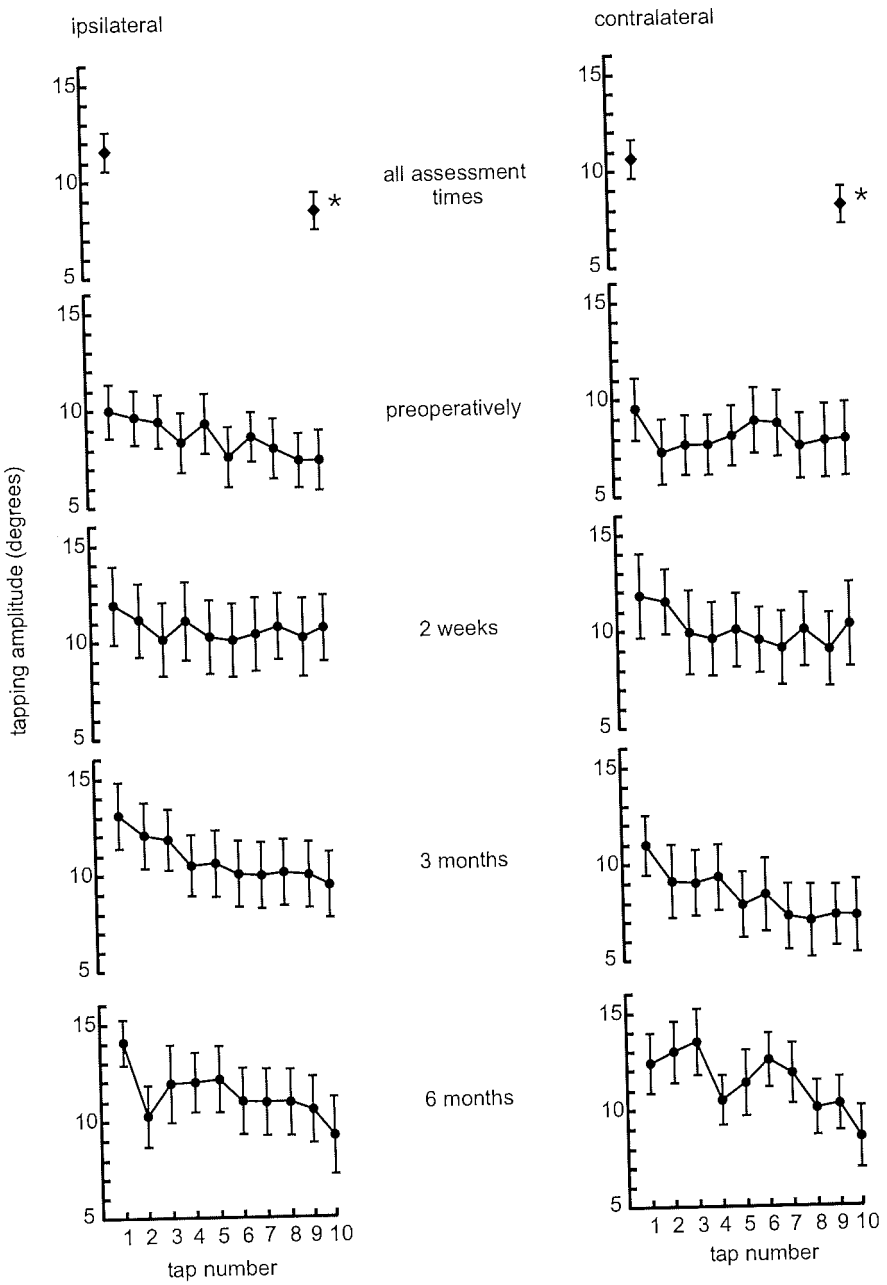


Figure 5.2

Mean (±SE) amplitude of repetitive tapping movements of the index finger, ipsilateral and contralateral to pallidotomy. The bilateral increase in mean tapping amplitude after pallidotomy was not statistically significant. At all four assessment times, there was a progressive decline in amplitude during the task. After pooling the results from the four assessment times (top panel), this decline in amplitude was significant bilaterally (* $p<0.01$).

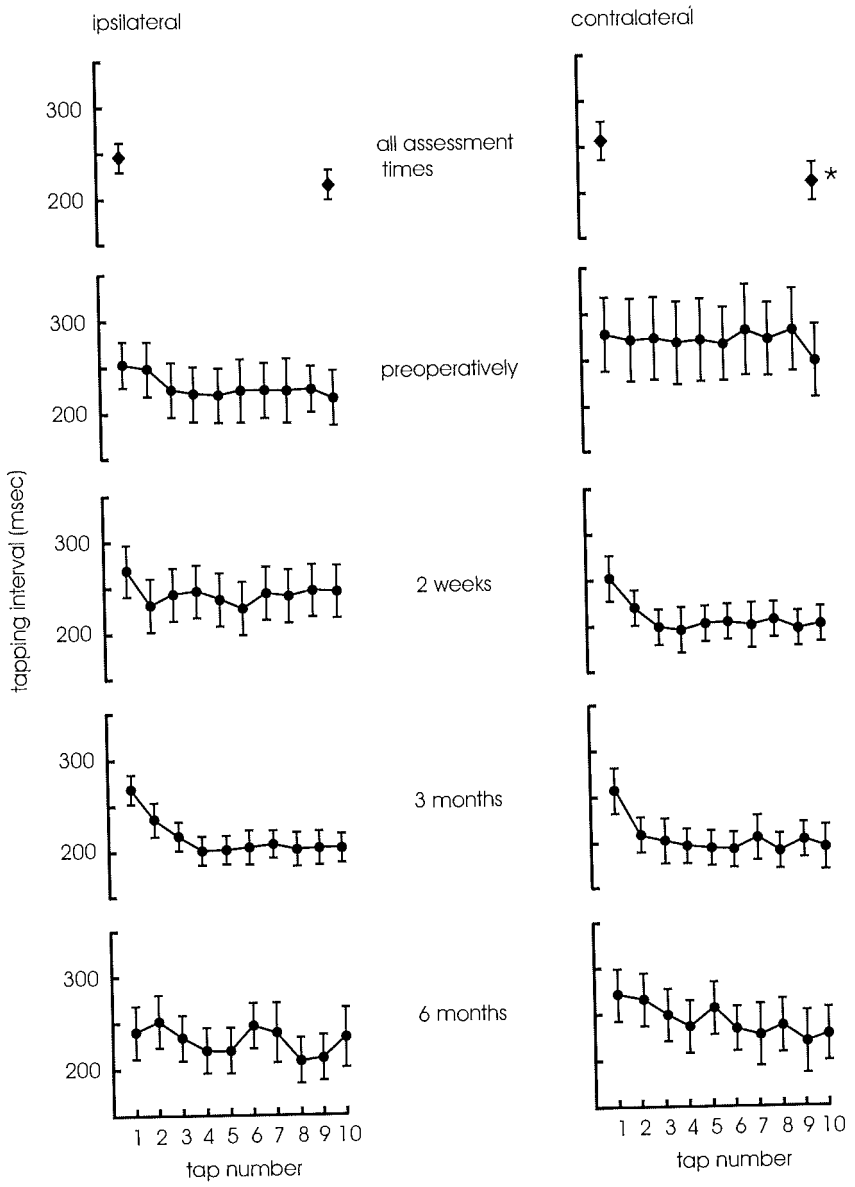


Figure 5.3

Mean (±SE) tapping intervals during repetitive finger tapping, showing the results for sides ipsilateral and contralateral to pallidotomy. On the contralateral side, there was a reduction in mean tapping interval at all assessment times post-operatively compared with pre-operatively, but this was not statistically significant ($p>0.01$). On both sides and at all assessment times, the mean tapping interval declined from the first to the final tap in the sequence. Although this decline was not statistically significant for any single assessment time, when results of all assessment times were pooled and analysed together (top panel), this decline was significant contralaterally (* $p<0.01$), but not ipsilaterally ($p=0.04$) to pallidotomy.

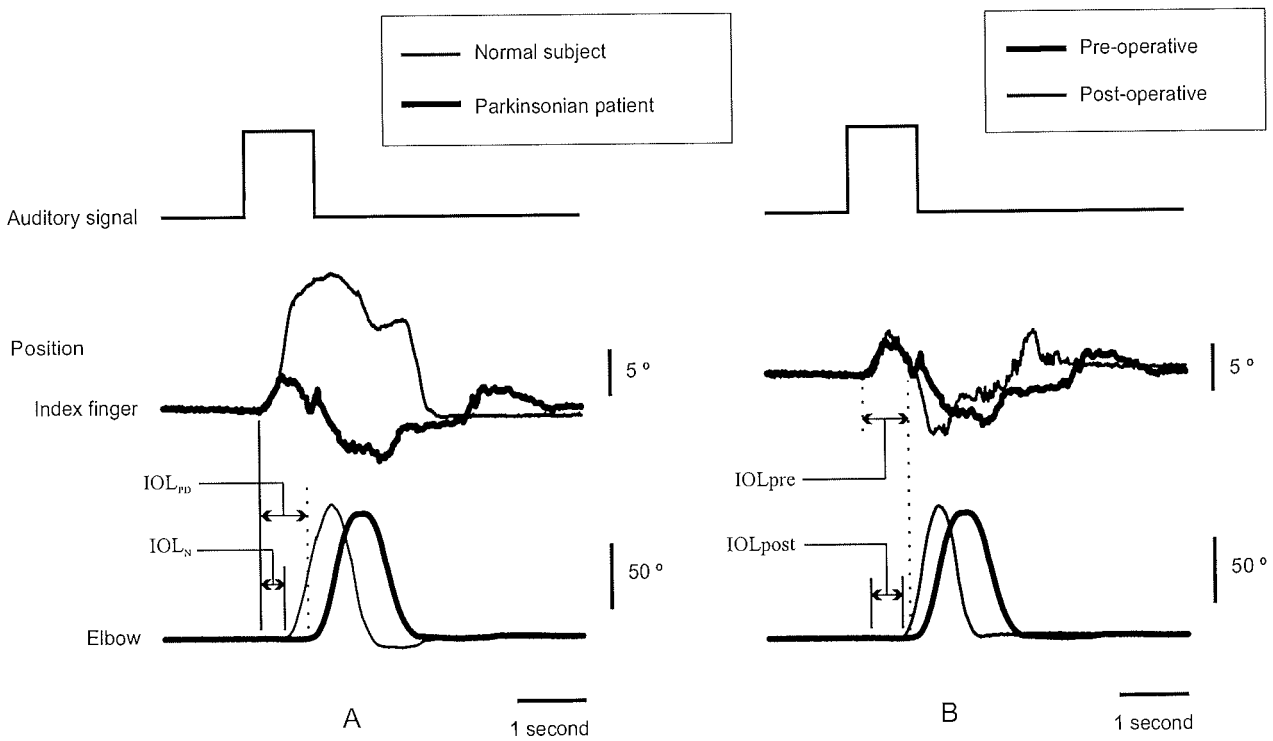


Figure 5.4

Position traces of movement at the second metacarpophalangeal and elbow joints while subjects picked a peg from a table top, lifted it towards their nose and returned the peg to the table (the "pick up" task). Single trials are shown in response to an auditory cue. In the left panel (A), the position traces from a patient with Parkinson's disease are superimposed on those from a control subject. The reaction times are comparable, but the amplitude of finger movement is smaller and the interval between activation of the finger and elbow movement, the "interonset latency" is longer in the patient (IOL_{PD} = 747ms) compared with the normal subject (IOL_{N} = 273ms). Preoperative peak elbow velocity is also slightly lower in the parkinsonian patient (119°/sec) compared with the normal subject (128°/sec).

In the right panel (B), the post-operative performance of the same parkinsonian patient 3 months after pallidotomy, using the hand contralateral to pallidotomy, is superimposed on the pre-operative traces. Post-operatively, the interonset latency (IOL_{post}) shortens to 402 ms and the peak elbow velocity increases to 166°/sec.

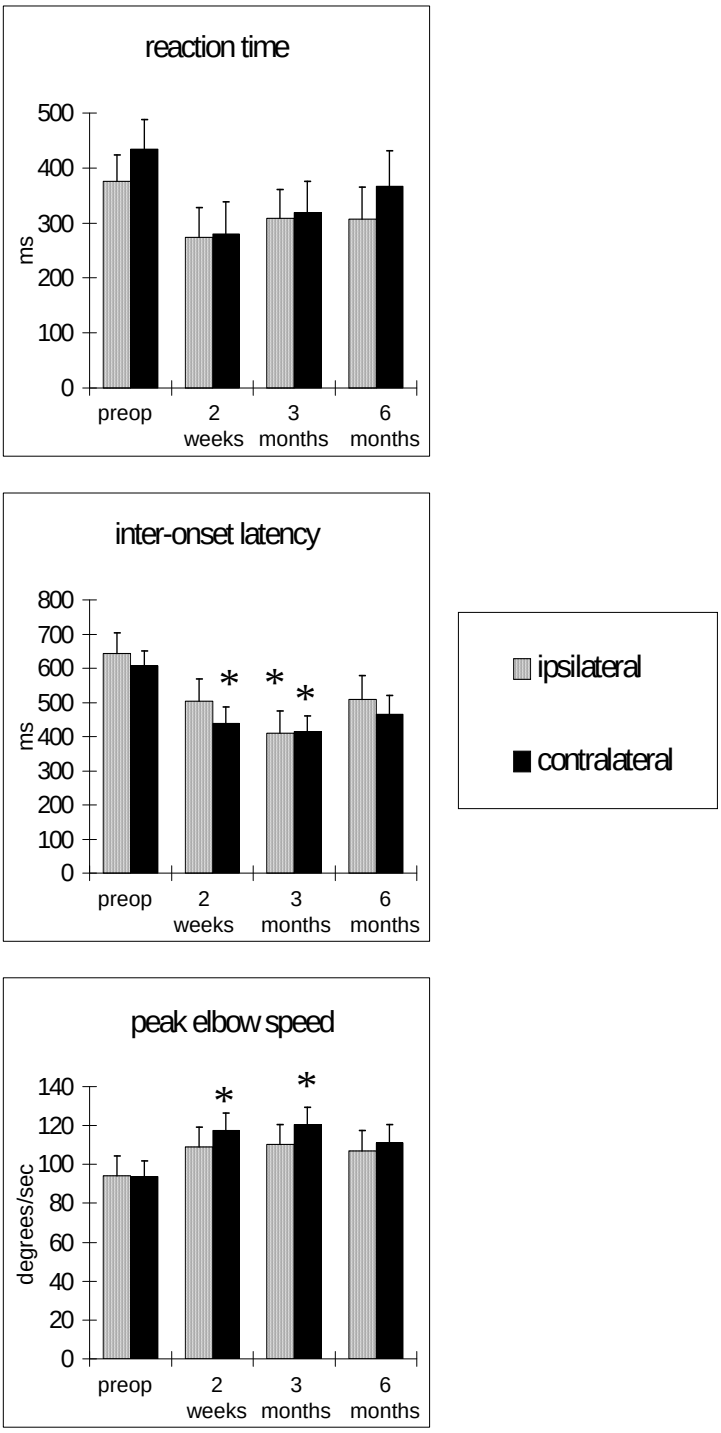


Figure 5.5 Summary of ipsilateral and contralateral auditory reaction time, inter-onset latency and peak elbow speed for ipsilateral and contralateral limbs (relative to the side of pallidotomy) during the "pick up" task. Results are means ± SE. Post-operative values which differ significantly ($p<0.01$) from pre-operative values are denoted by an asterisk.

Five of the patients who exhibited the most marked clinical improvement after pallidotomy also showed the most dramatic changes in movement kinematics. However, there was no clear relationship between the degree of clinical improvement in bradykinesia (measured by the change in UPDRS motor score) and IOL and velocity of movement during the "pick up" task for the overall group (linear regression R^2 0.22, F-value 0.34, p=0.57).

5.5 Discussion

5.5.1 Effects of pallidotomy on clinical assessments of motor performance

This study has demonstrated a number of changes in both clinical assessments and objective kinematic analyses of motor function after posteroventral pallidotomy in advanced Parkinson's disease. In keeping with results from other series, the most dramatic effect of pallidotomy was a reduction in drug-induced dyskinesias in the "on" motor state. In addition, "off" motor function, of which bradykinesia is a major feature, also improved. The total UPDRS, motor subset and clinical bradykinesia scores when "off" fell by 20-25%, comparable to the changes reported in clinical rating scales in other studies of pallidotomy in PD (Lozano et al., 1995; Baron et al., 1996; Kishore et al., 1997; Lang et al., 1997; Samuel et al., 1998). Overall ADL performance as judged by the Schwab and England scale improved significantly, but unlike other series, the post-operative improvement in ADL UPDRS "off" scores was not significant, suggesting the major functional effects of the operation were related to the reduction in "on" dyskinesias.

5.5.2 Effects of pallidotomy on quantitative assessments of movement performance

The main interest of the present findings lies in the kinematic assessment of upper limb movement as this provides an insight into the mechanism of changes in "off" period bradykinesia after pallidotomy. When "off", a bilateral improvement of around 35% in IOL during sequential arm movement was evident at 3 months post-operatively, corresponding

to the 23% improvement in the "off" period UPDRS motor score. The bilateral effect on the quality of movement mirrors the bilateral reduction in dyskinesias after unilateral pallidotomy (Lozano et al., 1995; Lang et al., 1997). These bilateral effects are in accord with the observations that 10-20% of pallidal efferent fibres project to the contralateral ventral thalamic nuclei (Hazrati and Parent, 1991), and that neurons of the GPi in monkeys rendered parkinsonian by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exhibit responsiveness to both ipsilateral and contralateral limbs (Filion et al., 1988).

The magnitude of change in IOL at 3 months was almost identical on the two sides, yet clinical ratings of bradykinesia and the speed of elbow movement improved only on the contralateral side after pallidotomy. This suggests the reduction in IOL and increased movement speed may have combined to effect the improvement in bradykinesia on the contralateral side, even though movement speed does not correlate closely with clinical assessments of bradykinesia in Parkinson's disease (Benecke et al., 1987).

5.5.3 Mechanisms of improvement in bradykinesia after pallidotomy

Clinical ratings of bradykinesia and akinesia correlate more with the degree of prolongation of the IOL than the speed of individual movements suggesting that prolongation of the IOL may account for much of the slowness of complex movements in PD (Benecke et al., 1987). The shortening of the IOL, increased speed of movement, and greater facility of movement after pallidotomy shown in the present results are consistent with this concept.

The IOL is derived from the time taken to link a series of individual movements into a complex sequence. This is believed to be a function of the SMA (Benecke et al., 1987). Single cell recordings in monkeys (Mushiake et al., 1991) and cerebral blood flow studies in humans (Dieber et al., 1991; Samuel et al., 1997a) reveal involvement of the globus pallidus, SMA and dorsolateral prefrontal area in the performance of internally

generated complex movements. In the monkey, phasic discharges in GPi neurons herald the switch from one movement task to another in a movement sequence, and it has been suggested this pallidal activity is conveyed to the SMA to halt one movement and start another (Brotchie et al., 1991).

Increased spontaneous tonic discharge and augmented phasic responses to limb perturbation in GPi neurons are found in MPTP-induced parkinsonism in monkeys (Filion and Tremblay, 1991), and in patients with PD undergoing pallidotomy (Sterio et al., 1994; Lozano et al., 1996). This pattern can be reversed by apomorphine (Hutchison et al., 1997), reinforcing the notion that the abnormal pallidal neuronal activity of parkinsonism is a consequence of dopamine deficiency.

Altered patterns of GPi discharge in patients with PD are accompanied by abnormal activation of a number of brain regions, including the SMA. Cerebral blood flow studies show impaired activation of the putamen, anterior cingulate, SMA and dorsolateral prefrontal cortex during performance of complex movements (Playford et al., 1992; Haslinger et al., 2001). Reduced activation of the SMA is partly reversed by apomorphine (Jenkins et al., 1992) and levodopa (Rascol et al., 1994; Haslinger et al., 2001). PET studies in PD patients have demonstrated an increase in pallidothalamic and pontine activity and a reduction in activity in premotor and posterior parietal cortical regions (Eidelberg et al., 1994; Lozza et al., 2004). This abnormal pattern of regional metabolic activity in PD has been termed the "Parkinson's disease-related covariance pattern".

Functional imaging of the brain after pallidotomy in PD has shown a relative increase in cerebral blood flow (Ceballos-Baumann et al., 1994; Grafton et al., 1995; Samuel et al., 1997b) and metabolism (Eidelberg et al., 1996) in a number of areas, including the SMA (Ceballos-Baumann et al., 1994; Grafton et al., 1995; Samuel et al., 1997b) and dorsolateral prefrontal cortex (Ceballos-Baumann et al., 1994; Samuel et al.,

1997b; Eidelberg et al., 1996), and a reduction in thalamic metabolism (Eidelberg et al., 1996). These findings suggest that pallidotomy may improve motor control by reducing inhibitory pallido-thalamic outflow and thereby improving activation of motor cortical areas.

The present results also demonstrate that pallidotomy improves "off" motor performance in PD at least in the short term. However, it is surprising that a lesion of the abnormal pallidum should restore motor performance (Marsden and Obeso, 1994). Partial ablation of the overactive pallidum would be expected to reduce pallidal inhibitory outflow to the ventral thalamus and increase thalamo-cortical excitatory activity, but is unlikely to restore phasic pallidal activity. Accordingly, the pallidal lesion would not be expected to restore phasic pallido-thalamic modulation of SMA activity. Since functional imaging suggests there is an increase in prefrontal motor cortex activity after pallidotomy, this change and any improvement in facility of movement must occur by mechanisms other than restoration of pallidal communication with motor cortical areas. The increase in prefrontal motor cortex activity after pallidotomy may represent the substitution of tonic cortical inhibition by tonic disinhibition. Alternatively, it may present the increased use of auditory, visual, attentional and somatosensory signals, which can act as alternative cues to trigger the execution of movement. The use of such cues in facilitating movement is well recognised in PD (for example, paradoxical hyperkinesia). This mechanism may also contribute to the relative increase in cerebral blood flow in lateral premotor and inferolateral parietal regions in Parkinsonian patients performing a complex finger keypad task (Samuel et al., 1997*a*). Indeed, those authors concluded that PD patients "switch from the use of striato-mesial frontal to parieto-lateral premotor circuits in order to facilitate performance of complex finger movements" (Samuel et al., 1997*a*). We suggest that this phenomenon may be one explanation for the improvement in sequential movement after

pallidotomy in PD. Various external cues may gain greater access to motor areas once the aberrant pallidal outflow is reduced or eliminated, or they may be used more effectively in the absence of the abnormal pallidal signals.

Recent PET studies tend to support this hypothesis. A number of interventions that improve bradykinesia, including subthalamotomy (Trošt et al., 2003), STN stimulation (Asanuma et al., 2006), levodopa infusion (Asanuma et al., 2006) and, most recently, subthalamic gene therapy (Feigin et al., 2007) have been shown to increase lateral premotor and posterior parietal activity. Increased activity in these regions would be consistent with an increased role for sensory cues in the execution of movement, following pallidotomy.

Accordingly, improvement in "off" motor performance after pallidotomy does not occur by restoring normal function within subcortical-cortical connections. Rather, by reducing abnormal pallidal activity, pallidotomy may allow alternative motor strategies to influence the cortical control of movement. There is some support for this hypothesis from functional imaging studies after pallidotomy. Increases in movement-associated regional cerebral blood flow or cortical metabolism after pallidotomy are consistent with the restoration of pallidocortical communication (Ceballos-Baumann et al., 1994; Grafton et al., 1995; Samuel et al., 1997*b*). However, in several of these studies the alterations in cortical function were also evident in the lateral premotor cortex (Ceballos-Baumann et al., 1994; Grafton et al., 1995), parietal association cortex (Ceballos-Baumann et al., 1994) and visual association areas (Samuel et al., 1997*b*), which do not receive direct inputs from the globus pallidus. Similar changes were present in one study performed at rest (Eidelberg et al., 1996). One explanation for these findings may be the greater utilization of auditory, visual and somatosensory inputs to the lateral premotor areas to facilitate movement after pallidotomy (Goldberg et al., 1985).

5.5.4 The effects of pallidotomy on different movements

In contrast to the complex arm movements, there was no change in the speed or rhythm of finger tapping movements after pallidotomy and the subtle improvement in repetitive finger tapping amplitude did not reach statistical significance. A comparatively weak effect of pallidotomy on finger tapping compared with other arm movements (Lang et al., 1997) and loss of improvement in finger dexterity 1 year post-operatively (Baron et al., 1996) have been noted previously in clinical studies.

The apparent difference in the effect of pallidotomy on these two movements is of interest and may provide further insight into the effects of pallidotomy on Parkinsonian movement. It is necessary first to consider the different qualities of these two motor tasks. The "pick up" task consists of two discrete movements, involving anatomically separate parts of the limb, linked together as a "complex" movement and triggered by external sensory cues. In contrast, finger tapping involves fractionated finger movement alone, the maintenance of which is largely an internal process without external cues. Therefore it could be argued that finger tapping is more critically dependent on normal pallidal-SMA function than the complex arm movement. Indeed, decay in the amplitude of repetitive finger tapping is a robust clinical sign of bradykinesia in PD. In performing the "pick up" task after pallidotomy, compensation for absent pallidal function may be achieved by using the auditory, somatosensory and visual cues inherent to that task. Such cues may also improve movement performance in the absence of abnormal pallidal output. The finger tapping task, however, does not use external cues and is more reliant on internal cues and intact basal ganglia function to maintain the rhythm and amplitude of movement. It would be of interest to examine whether finger tapping, which does not normally involve external factors, could be influenced by an external cue (eg. a metronome) to improve performance, and whether this effect would be greater after pallidotomy.

CHAPTER 6

EFFECT OF PALLIDOTOMY ON THE SPONTANEOUS BLINK RATE IN PARKINSON'S DISEASE

6.1 Aims

The aim of this section of the thesis was to examine the effect of pallidotomy on a spontaneous motor activity, the neural control of which occurs at a largely subcortical level. This would enable a comparison to be made of the effects of pallidotomy on spontaneous and volitional movements.

6.2 Methods

The study was performed in two parts. In the first part, blink rates were compared in patients with advanced PD and in control subjects, and the response of the blink rate to levodopa in the PD patients was measured. In the second part of the study, the BR was measured in a group of patients with advanced PD before and after pallidotomy.

6.2.1 Experiment 1. Comparison of blink rates in PD patients and control subjects, and response of the blink rate to levodopa in PD patients.

6.2.1.1 Subjects

Twenty-five patients with PD comprising 14 males and 11 females, aged from 42 to 73 years (mean 61+3.5 (SD) years) with mean disease duration of 13.3 years (SD 5.5, range 6-30) were examined. All had advanced disease with disabling drug-induced dyskinesias, mostly of the limbs and axial muscles. Mean "off" state UPDRS motor score was 41.2 (SD 14.0) and mean "off" state Hoehn and Yahr score was 3.5 (SD 0.7).

Sixteen control subjects were examined. Mean age of the control subjects was significantly less than that of the PD patients (34 years, range 18-50 years). However, a

previous study of 156 normal subjects showed no correlation of blink rate with age (Deuschl and Goddemeier, 1998).

6.2.1.2 Assessment of blink rate

The method of measurement of blink rate is described in Chapter 2. In PD patients, measurements were performed in the “off” and “on” states. The "off" state blink rate in the PD patients is also referred to in this chapter as the baseline blink rate.

6.2.1.3 Definition of low and high baseline blink rates

PD patients with blink rates of less than 15/minute in the "off" state were defined as having low baseline blink rates (LBR). Those with "off" state blink rates of greater than 15/minute were defined as having high baseline blink rates (HBR). There were two reasons for choosing this value. Firstly, in a recent study of 51 patients with moderate to severe PD, the mean blink rate was 5.8/minute (SD 5.3) (Deuschl and Goddemeier, 1998). A blink rate of 15/minute is approximately 2 standard deviations above this mean, indicating that a blink rate higher than 15/minute is significantly greater than the norm for PD patients. Furthermore, when we reviewed the data obtained from the PD patients in our study, there was a clear demarcation in "off" state blink rate at around 15/minute (see Results), with PD patients in general manifesting blink rates either well below or well above this value.

6.2.1.4 Statistical analysis

Baseline blink rates of the control and PD groups were compared by single factor analysis of variance (ANOVA), with the single factor being blink rate and the between-subjects factor being group. The effect of levodopa on blink rates in the two PD groups was analysed by repeated measures ANOVA, with the within-subjects factor being motor state ("off" or "on" state) and the between-subjects factor being group (low or high baseline blink rate).

6.2.2 Experiment 2. Effect of pallidotomy on the "off" state blink rate in PD patients

6.2.2.1 Subjects

Fourteen patients with advanced PD were assessed before and after unilateral pallidotomy. Patients comprised 6 males and 8 females with a mean age of 60.9 years (SD 8.7 years). Patients who had blepharospasm as a complication of their anti-parkinsonian drug therapy were excluded from the study. The indication for surgery in all cases was severe drug-induced dyskinesias.

6.2.2.2 Assessment of blink rate

Blink rate was measured as in Part 1 of the study. Measurements were made pre-operatively and at a variable time post-operatively (mean 4.9 months; range 3 days to 24 months). Assessments were performed in the "off" and "on" states.

6.2.2.3 Clinical assessment

The UPDRS was performed in the "off" and "on" states. From the total UPDRS score, the motor examination score (items 18 to 31), bradykinesia score (items 23 to 26) and dyskinesia score (items 32 to 35) were extracted and analysed. The Purdue pegboard test (Tiffin, 1948) was conducted as a test of global upper limb function.

6.2.2.4 Statistical analysis

Pre- and post-operative data, and "off" and "on" data, were compared by means of paired t-tests.

6.3 Results

6.3.1 Experiment 1. Comparison of blink rates in PD patients and control subjects, and response of the blink rate to levodopa in PD patients.

6.3.1.1 Baseline blink rates

The mean (+SD) blink rate in the control group was 27.1+10.1. The mean (+SD) "off" state blink rate in the PD patients, when the latter were considered as a single group, was 20.3+24.1. This difference was not significant (p=0.29). However, in the "off" state, the PD blink rate fell into two discrete groups, one with a low blink rate (mean 5.1/minute, median rate 3/minute; SD 4.6) in 17 patients, and one with a high blink rate (mean 52.8/minute, median rate 53/minute; SD 13.2) in 8 patients. The difference in blink rate between the three groups (control, LBR PD and HBR PD) was highly significant (p<0.001). Baseline blink rates of the two PD groups are shown, together with control subject blink rates, in **fig 6.1**.

6.3.1.2 Effect of levodopa on blink rate in the PD patients

In the LBR group, mean blink rate increased from 5.1/minute before levodopa to 14.2/minute after levodopa (median rate 11.0/minute; SD 11.1) (p=0.001) (**fig 6.2a**). In the HBR group, mean blink rate decreased from 52.8/minute before levodopa to 36.6/minute after levodopa (median rate 35/minute; SD 9.3) (p=0.004) (**fig 6.2b**). The difference in levodopa effect between the two groups was statistically significant ("group by motor state" interaction: p<0.001).

6.3.2 Experiment 2. Effect of pallidotomy on the "off" state blink rate in PD patients

6.3.2.1 Blink rate

The mean blink rate was significantly higher in the "on" than the "off" state before and after pallidotomy. Pre-operatively, mean blink rate in the "off" state was 5.1/minute (SD 4.9) and increased to 15.4 (SD 11.4) after levodopa (p=0.002). Post-operatively, mean blink rate in the "off" state was 6.0/minute (SD 7.3) and increased to 13.1 (SD 9.3) after levodopa (p=0.005). Results for individual patients before and after levodopa are shown in **fig 6.3.**

There was no significant change in blink rate after pallidotomy, either in the "off" or "on" states. In the "off" state, mean blink rate was 6.0/minute (SD 7.3) post-operatively, as compared with 5.1/minute (SD 4.9) pre-operatively (p=0.565). In the "on" state, mean blink rate post-operatively was 13.1/minute (SD 9.3), as compared with 15.4 (SD 11.4) pre-operatively (p=0.337). Results for individual patients in the "off" state pre- and post-operatively are shown in **fig 6.4**.

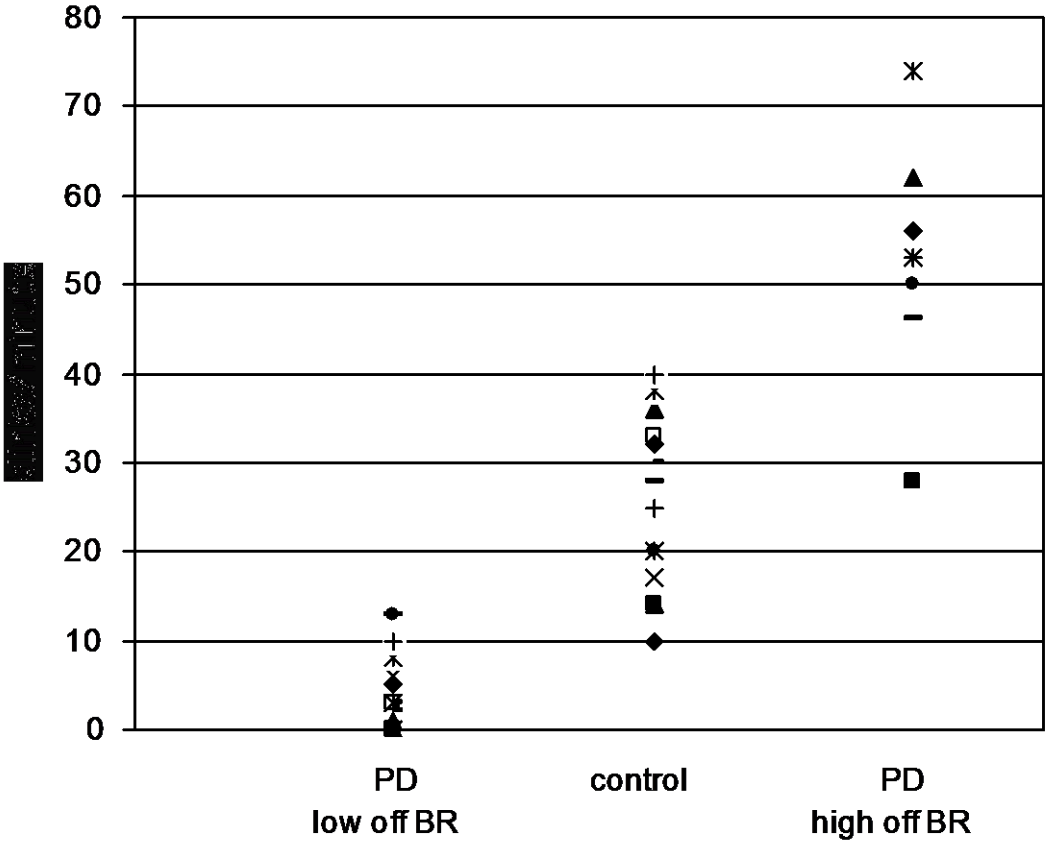


Figure 6.1

Baseline blink rates (BR) in PD patients with low and high "off" state blink rates, and in control subjects. The difference in mean blink rate between the three groups was statistically significant ($p<0.001$).

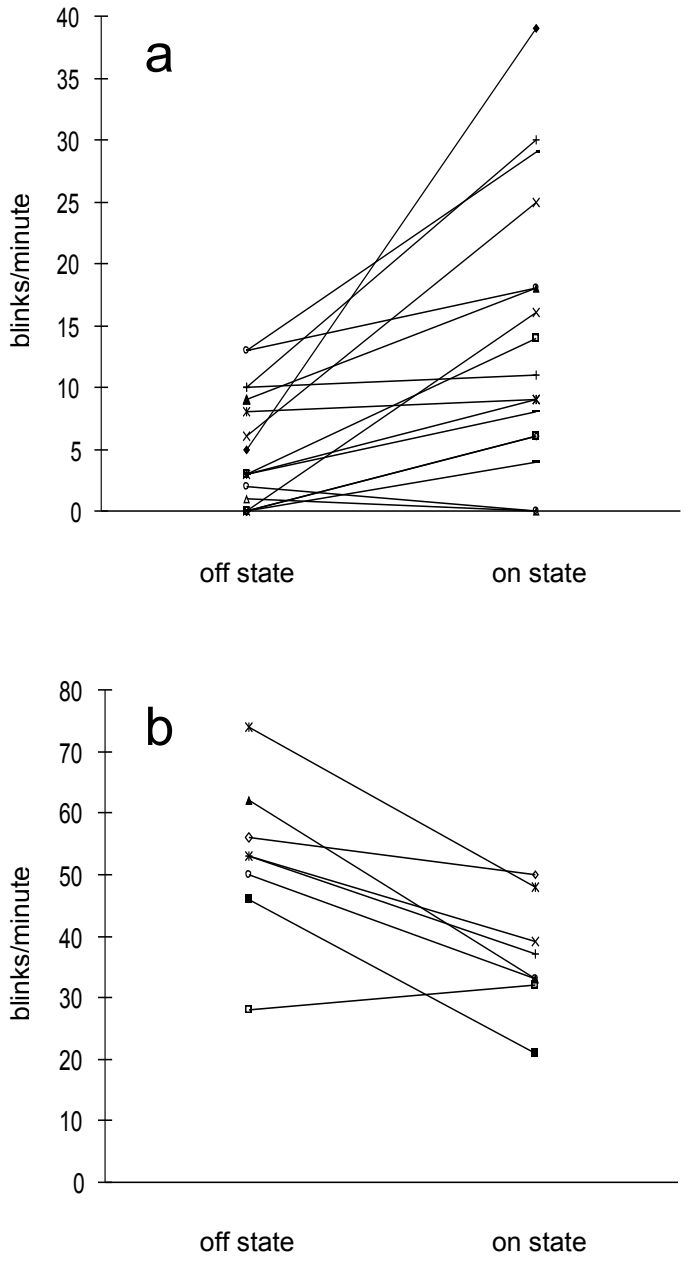


Figure 6.2

Blink rates before ("off" state) and after ("on" state) levodopa in patients with low (**a**) and high (**b**) baseline blink rates. Note that blink rate increases after levodopa in group **a** ($p=0.001$) and decreases after levodopa in group **b** ($p=0.004$). Difference between groups **a** and **b** in response to levodopa was statistically significant ($p<0.001$).

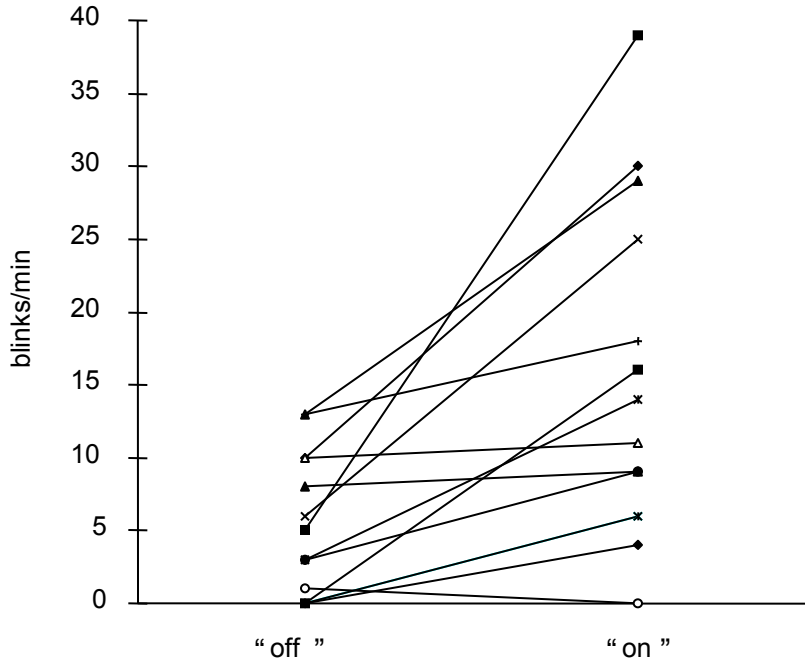


Figure 6.3

Spontaneous blink rate in PD patients pre-operatively, showing results after overnight withdrawal of anti-parkinsonian drug therapy ("off") and one hour after levodopa ("on").

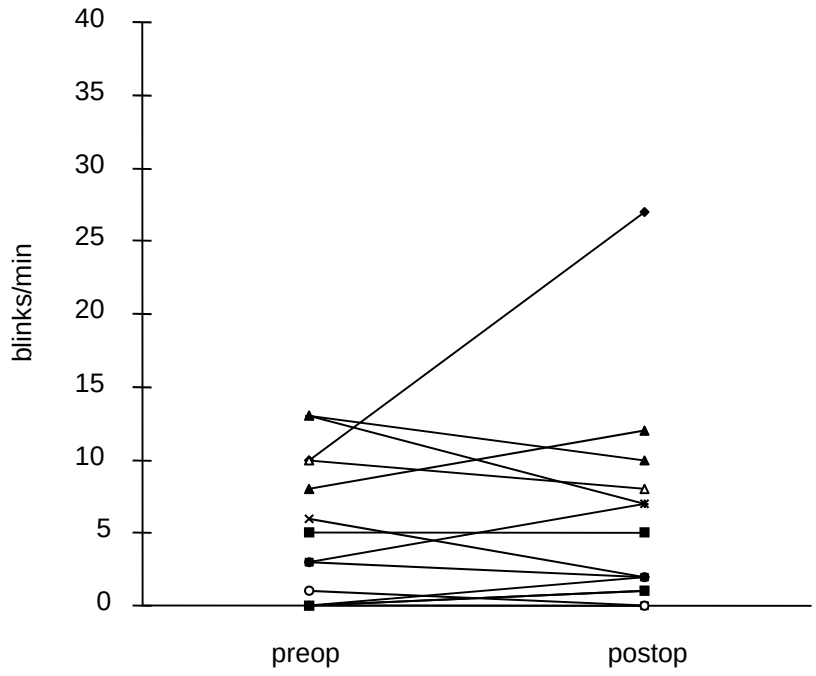


Figure 6.4

Spontaneous blink rate in PD patients after overnight withdrawal of anti-parkinsonian drug therapy (“off” state), before and after pallidotomy.

6.3.2.2 Clinical assessment

Mean "off" motor examination, bradykinesia and Purdue pegboard scores, and mean global dyskinesia score, all improved post-operatively, compared with pre-operatively. Results are shown in **fig 6.5.**

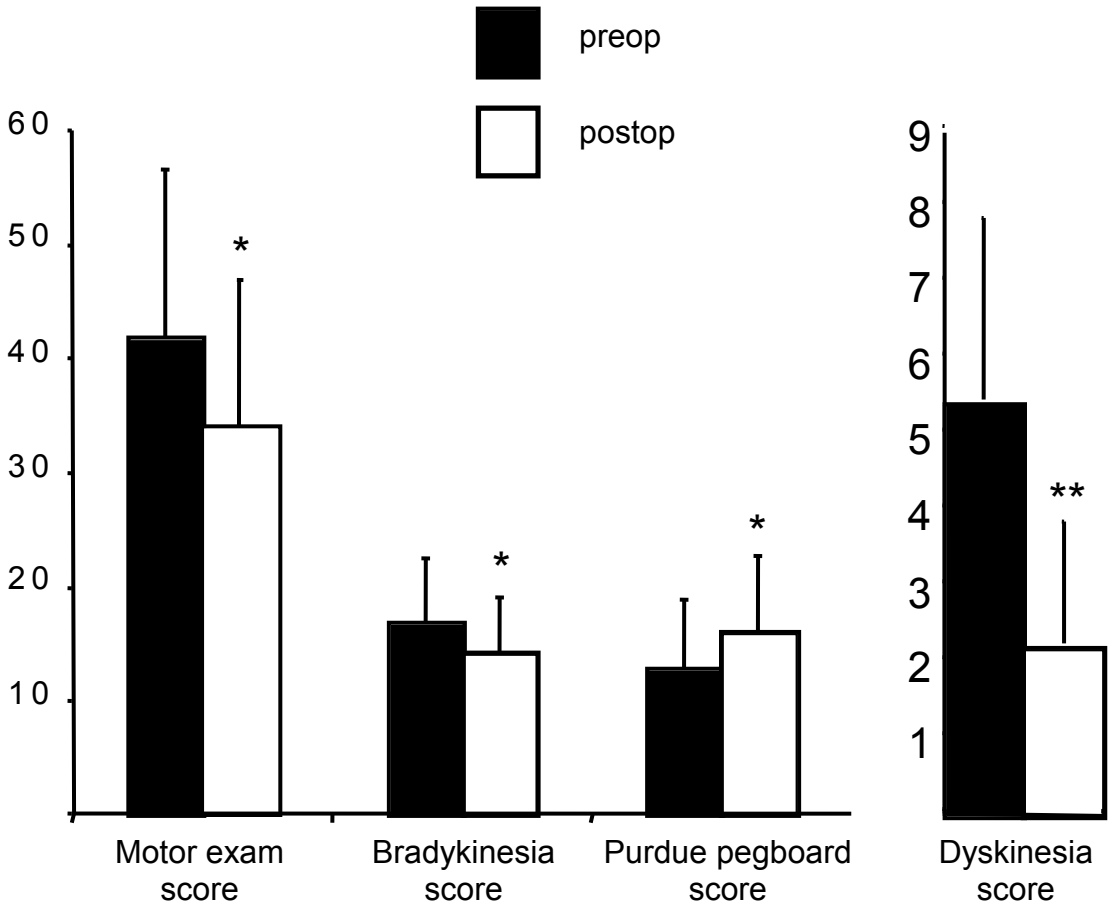


Figure 6.5 Mean UPDRS motor examination, bradykinesia and dyskinesia scores, and mean Purdue pegboard scores pre- and post-operatively (+SD). Results apply to the "off" motor state, apart from dyskinesia score, which is a global score encompassing "off" and "on" states (*=$p<0.01$; **=$p<0.001$).

6.4. Discussion

6.4.1 Experiment 1. Blink rates in patients with advanced PD and their response to levodopa

The study of spontaneous blink rates in patients with advanced fluctuating PD has identified two different patterns of blinking. The first group exhibits the "typical" parkinsonian blink pattern with an abnormally low blink rate in the "off" state, which increases significantly after levodopa. The second group exhibits an atypical blink pattern for PD – an abnormally high blink rate in the "off" state, which decreases significantly after levodopa. The pathogenesis of increased "off" state blinking in these patients is not clear. Patients with increased blink rates did not differ from those with lower blink rates in any clinical respect. There were no clear differences between the 2 groups in the type of motor fluctuations, levodopa dose, use of other antiparkinsonian drugs, age, duration of disease or severity of disease. Therefore, the phenomenon of abnormally increased "off" state blink rate in PD patients appears to be a form of levodopa-responsive "off" dystonia.

The neural control of blinking is incompletely understood, but probably involves a number of converging inputs to the central caudal nucleus (CCN), a subgroup of the oculomotor nuclear complex which innervates the levator palpebrae superioris muscles (Schmidtke and Büttner-Ennever, 1992). Reduced blinking in PD may be caused by hyperactivity of the substantia nigra pars reticulata (SNr), which projects to the superior colliculus, one of the premotor influences on CCN function. The increase in BR following levodopa administration that occurs in most PD patients may be mediated by reduced neural firing in the SNr after levodopa, as occurs in the GPi after dopaminergic therapy (Hutchison et al., 1997). Considerable speculation surrounds the pathophysiology of the levodopa-induced

dyskinesias and their predilection for certain anatomical locations (Marconi et al., 1994). Increased "off" state blinking in PD may be caused by loss of dopaminergic innervation in parts of the striatum with connections to the SNr and superior colliculus.

Excessive blinking shares similarities with akathisia and blepharospasm, which are both well recognised forms of drug-induced dyskinesia in idiopathic PD (Marconi et al., 1994; Lang and Johnson 1987; Poewe et al., 1988). As none of our patients had trunkal or limb akathisia, it seems unlikely that increased blinking in these patients is a form of "ocular" akathisia. We excluded patients who had clinically obvious blepharospasm – that is, visible contraction of the orbicularis oculi - in association with blinking. However, increased blinking may precede blepharospasm in patients with cranial dystonia and blepharospasm (Elston et al., 1989). Without electrophysiological correlation of levator and orbicularis oculi muscle activity, we cannot be certain that none of the PD patients with high “off” state blink rates did not have blepharospasm.

6.4.2 Experiment 2. The effect of pallidotomy on the blink rate in advanced PD

The PD patients in Study 2 all had the more typical Parkinsonian blink rate pattern ie. a low baseline blink rate which increased significantly after levodopa. Post-operatively, the blink rate response to levodopa was maintained. In contrast to the improvement in dyskinesias and limb bradykinesia after pallidotomy, there was no significant change in blink rate post-operatively, compared with pre-operatively.

There are several possible explanations for the failure of improvement in blink rate after pallidotomy, despite an improvement in voluntary limb movement. These will be discussed in turn.

i. Basal ganglia influences on blinking and volitional movement are anatomically distinct

The neural influences on voluntary limb and automatic eyelid movement may be segregated anatomically, so that a lesion in a region critical to the former may not affect the latter. In other words, spontaneous blinking may be dependent on SNr activity with little or no input from the GPi. Accordingly, a lesion of the GPi in a PD patient may reduce inhibition of thalamo-mesial frontal circuits, thereby improving volitional limb movement, but have no effect on circuits controlling spontaneous blinking. However, the connections of the GPi and SNr within oculomotor circuits suggest that the GPi may be involved in the control of eye movements. Both the dorsomedial GPi and the ventrolateral SNr receive oculomotor projections from the frontal eye fields via the caudate nucleus (Parent et al., 1994; Szabo 1970). There is evidence that these projections are utilised by the SNr for the generation of visually-guided and memory-contingent saccades (Hikosaka and Wurtz 1983*b*). It is not known whether the GPi is also involved in the generation of saccades. However, both the GPe and STN house neurons that demonstrate saccade-related activity (Hikosaka et al., 1993). Given that it receives oculomotor projections from the caudate, it is possible that the dorsomedial GPi also contains saccade-related neurons. As has been mentioned above, the premotor control of spontaneous blinking is less well characterised than that of saccadic eye movements. However, there is evidence of anatomical and functional homology between the neural circuits controlling blinking and saccade generation. Firstly, the superior colliculus – the major target of SNr outflow – is the major output nucleus for both blinking and saccade generation. Secondly, saccadic eye movements are facilitated by blinking (Zee et al., 1983), indicating that inhibition of LPS activity by the superior colliculus may facilitate activation of the pontine burst cells that generate saccades.

If it is accepted that the dorsomedial GPi may be involved in oculomotor control, it does not necessarily follow that a lesion aimed at the posteroventral GPi will lesion oculomotor pallidal neurons. However, post-operative imaging in the patients in this study confirmed that the dorsomedial GPi was frequently involved by the lesions.

A final issue of possible relevance to the effect of pallidotomy on the blink rate is that the GPe and, to a lesser extent, the GPi send GABA-ergic projections to the SNr (Smith and Bolam, 1989). Therefore, a lesion involving the GPi in a PD patient may further disinhibit SNr activity, leading to further suppression of the blink rate. However, it may be that in late stage PD, the SNr is already maximally hyperactive as a result of increased glutamatergic inputs from the STN and reduced GABA-ergic inputs from the GPe. If so, a lesion of the GPi would not significantly alter SNr activity.

ii. Extra-pallidal influences on volitional versus automatic movements

Another explanation for the different effects of pallidotomy on blinking and volitional limb movements is that blinking may be more dependent than volitional limb movement on intact basal ganglia function. Whether GPi/SNr function is rendered abnormal by disease, as in PD, or iatrogenically, as after pallidotomy, a reduction in blink rate may be the common outcome. In contrast, compensatory mechanisms may exist for the maintenance of voluntary limb movement in the setting of abnormal or absent pallidal function. This compensation may involve increased use of sensory cues to facilitate movement. In PD, increased use of sensory cues appears to manifest as increased activation of lateral premotor and inferolateral parietal cortices (Samuel et al., 1997*a*; Cunnington et al., 2000), where sensory inputs of many modalities are integrated (Petrides and Pandya, 1984; Cavada and Goldman-Rakic 1989). Pallidotomy increases metabolic activity in the lateral premotor cortex and sensory association

areas, which do not receive pallido-thalamic afferents, as well as in the SMA and dorsolateral prefrontal cortices, which do (Ceballos-Baumann et al., 1994; Eidelberg et al., 1996). This suggests that the effects of pallidotomy on motor function may be mediated, at least in part, by an increased use of compensatory lateral motor circuits. This hypothesis is supported by the observation that the improvement in limb bradykinesia after pallidotomy is associated with an improvement in the kinematics of externally-cued, but not internally-generated, upper limb movements (Kimber et al., 1999).

Therefore, blinking and volitional limb movements may differ in their response to pallidotomy, not because they are controlled by anatomically separate basal ganglia regions, but because compensatory strategies to optimise movement in the absence of pallidal function can be employed for volitional, but not automatic, motor behaviours.

CHAPTER 7

EFFECT OF PALLIDOTOMY ON THE BEREITSCHAFTSPOTENTIAL IN PD

7.1 Aims

The Bereitschaftspotential (BP) is believed to be generated by the supplementary motor area (SMA) and primary motor cortex, and is thought to reflect neural activity within these areas prior to volitional movement (Ikeda et al., 1992). The early component of the BP is reduced in PD. The aim of this section of the thesis was to measure the effect of pallidotomy on the BP in patients undergoing pallidotomy for severe PD, in order to better understand the effect of pallidotomy on pre-movement cortical activity.

7.2 Subjects

Patient details are summarised in table 6.1. Five patients (4M, 1F) with severe PD underwent pallidotomy. Mean patient age was 67.4 years (range 51-77). Mean duration of disease was 20.4 years (range 15-27). Lesions were right-sided in 4 cases and left-sided in one case.

7.3 Methods

BPs were obtained after overnight withdrawal of anti-parkinsonian medications. Baseline recordings were made 4 or 5 days preoperatively and postoperative recordings were made at times varying from 2 days to 3 months post-operatively (**table 7.1**). The method used for the recording and analysis of BPs is described in Chapter 2.

Patient number	**1**	**2**	**3**	**4**	**5**
Gender	M	M	F	M	M
Age (years)	68	74	77	67	51
Duration of PD (years)	15	23	27	21	16
Side of lesion	L	R	R	R	R

Table 7.1 Characteristics of the patients at the time of pallidotomy.

7.4 Results

Of the three scalp electrode positions, mean slope of the early BP was greatest in Cz both pre- and post-operatively (**table 7.2**). This is consistent with previous work showing that early BP amplitude is greatest over the vertex (Tamas and Shibasaki, 1985). With the exception of one patient, early component BP slope decreased in all patients post-operatively in all 3 EEG locations (**table 7.2**). This decline was statistically significant in the EEG location ipsilateral to the operated limb ($p = 0.045$), and just failed to reach statistical significance in Cz ($p = 0.068$). In the ipsilateral EEG position, the mean decline in early slope post-operatively, compared with baseline, was 42%. In Cz, the mean decline in early slope post-operatively, compared with baseline, was 27%.

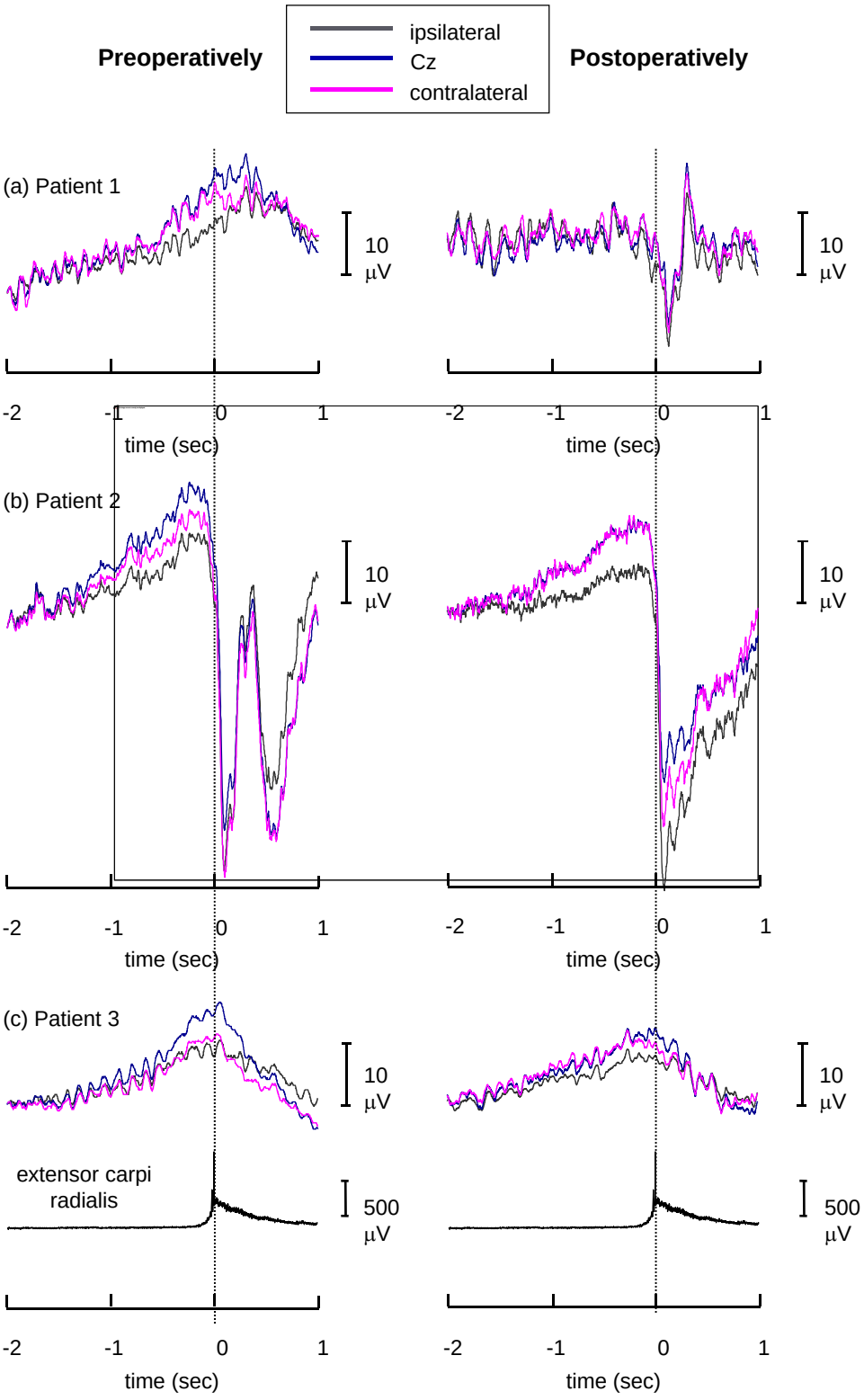
The individual BP traces for each patient, as well as the grand average, are shown in **figure 7.1.**

7.5 Discussion

The present study suggests that the slope of the early component of the BP does not improve - and may, in fact, decline - after pallidotomy. Probably because of the small number of patients in the study, it was only possible to demonstrate a statistically significant decline in early component slope in the EEG position ipsilateral to limb movement. This was the electrode position where baseline early component slopes were lowest in all 5 patients and showed least inter-individual variation. Ipsilateral to limb movement, only one of the five patients (patient 1) did not show a decrease in early component slope post-operatively. This patient showed a 12% increase in early BP slope. Another group has made the observation that the early component of the BP does not improve after pallidotomy for PD (Limousin et al., 1999).

Patient	Early BP slope (μV/s)					
	Ipsilateral		**Cz**		**Contralateral**	
	pre	*post*	*pre*	*post*	*pre*	*post*
1	2.40	2.68	2.66	3.6	3.03	3.20
2	4.83	3.99	7.08	5.5	5.15	6.04
3	2.06	0.045	4.03	1.42	2.58	-0.66
4	2.53	0.56	4.8	1.85	4.11	1.20
5	6.33	4.49	12.01	9.3	10.5	8.84
Grand average	3.63	2.35	6.1	4.3	5.08	3.72

Table 7.2 Early slope of the Bereitschaftspotential before and after pallidotomy in 3 scalp electrode locations (Cz, and over the motor cortices ipsilateral and contralateral to the moving limb).


Preoperatively
ipsilateral
Cz
contralateral
Postoperatively
(a) Patient 1
10 μV
-2
-1
0
1
time (sec)
(b) Patient 2
(c) Patient 3
extensor carpi radialis
500 μV

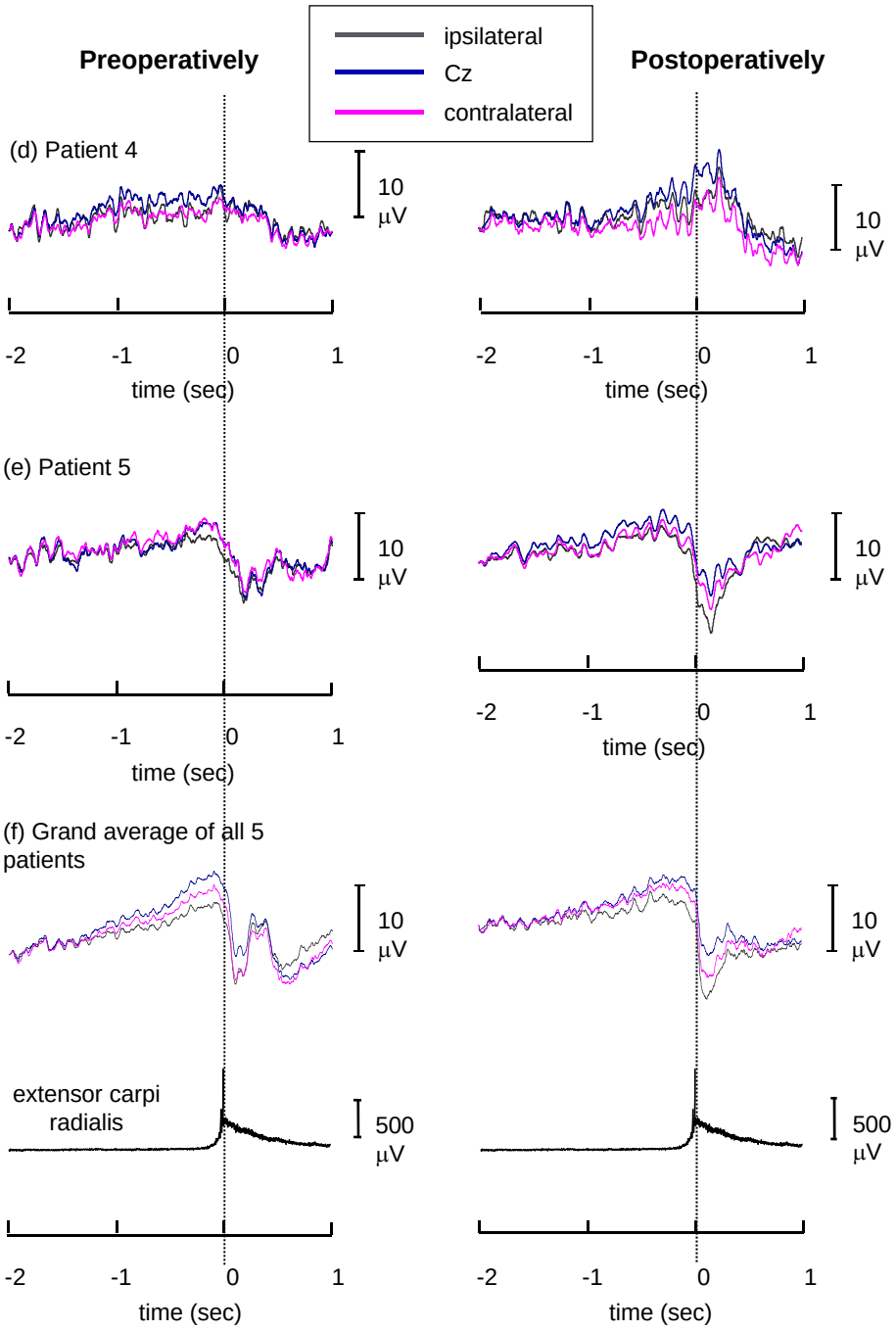


Fig 7.1
Bereitschaftspotentials (BPs) of 5 patients before and after pallidotomy (traces a-e). Also shown is the grand average of the 5 BPs (trace f). EEG traces were obtained from scalp electrode positions C3, Cz and C4. EEG recording was triggered by activation of the extensor carpi radialis muscle contralateral to pallidotomy. Recording time was from 2 seconds prior to movement until 1 second after movement. For BP analysis, electrode positions C3 and C4 were grouped according to whether they were ipsilateral or contralateral to movement.

The reduction in slope of the early component of the BP in PD patients, compared with normal controls, is believed to reflect defective SMA activity as a result of excessive pallido-thalamocortical inhibition (Cunnington et al., 1995). Accordingly, our results suggest that SMA function in the pre-movement phase of voluntary movement does not improve after pallidotomy. These results contrast with those of several other studies that have demonstrated, using positron emission tomography, an increase in movement-associated blood flow in the SMA after pallidotomy for PD (Ceballos-Baumann et al., 1994; Grafton et al., 1995; Samuel et al., 1997a). This improvement in SMA blood flow after pallidotomy has been interpreted as indicating a restoration of more normal communication between the GPi, which is hyperactive in PD, and the mesial frontal cortex. A possible explanation for the discrepancy between the results of BP and PET studies is that the two techniques measure different aspects of cortical function. The BP measures cortical electrical activity around the time of movement with a high degree of temporal accuracy, but lacks spatial sensitivity. By contrast, PET measures cortical blood flow (and, by extrapolation, neural activity) with good spatial sensitivity, but lacks temporal sensitivity to particular phases of movement. Therefore, the increase in SMA blood flow seen after pallidotomy in PET studies may not necessarily represent an improvement in SMA neural activity during movement preparation. Rather, it may simply reflect the abolition of tonic pallidal inhibition of the mesial frontal cortex by pallidotomy.

How, then, can we explain a decline (or, at least, failure of improvement) in slope of the early BP with an improvement in akinesia/bradykinesia? Reduction in early BP slope after pallidotomy may indicate that cortical areas outside the pallido-thalamo-mesial cortical loop, which do not contribute to the BP, play a greater role in movement preparation after pallidotomy than before it. PD patients rely more than control subjects on external cues to

facilitate movement. Studies using both PET and movement-related cortical potentials suggest that the cortical correlate of this increased reliance on external cues is increased activation of cortical regions outside the mesial frontal cortex (Samuel et al., 1997b, Hanakawa et al., 1999; Cunnington et al., 2000). These regions include the inferolateral and lateral premotor cortices, which are involved in the integration of sensory stimuli into motor processing. There is evidence that, following pallidotomy, externally cued movements improve more than internally cued movements (Kimber et al., 1999). Furthermore, pallidotomy is associated with an improvement in movement-associated blood flow within lateral premotor (Ceballos-Baumann et al., 1994; Grafton et al., 1995), parietal association (Ceballos-Baumann et al., 1994) and visual association cortices (Samuel et al., 1997*a*), as well as within the SMA. These observations suggest that, following pallidotomy, there is a switch from the "medial motor system", which includes the SMA and governs internally generated movements, to the "lateral motor system", which uses sensory inputs to facilitate externally cued movements. Reduction in slope of the early component of the BP after pallidotomy would be consistent with this hypothesis, as it has been shown that the slope of the early component of the BP declines when external cues are provided (Cunnington et al., 1995). Although no overt external cues were provided in our experiments, it is possible that, after the abolition of pallidal function by pallidotomy, patients began to utilise external sensory inputs (eg visual attention on the upper limb) to a greater degree.

An alternative explanation for our failure to detect an improvement in early BP slope after pallidotomy must be considered. It is possible that the motor task employed in our study was not ideally suited to analysis of the early BP. We used a simple task, namely repeated dorsiflexion of the wrist. A number of studies have shown that the SMA is more closely

involved with complex, rather than simple movements (Roland et al., 1980; Mushiake et al., 1991; Dieber et al., 1991). Furthermore, Benecke et al. (1985) showed that early BP amplitude is greater with complex than with simple movements. It is possible that, had we employed a more complex task, we may have seen an improvement in early BP slope after pallidotomy. However, we think this is unlikely, as a number of authors have found that simple, internally cued movements, such as the one in our study, are adequate to demonstrate abnormalities of the early component of the BP in PD (Dick et al., 1989; Jahanshahi et al. 1995).

A previous study of movement-related cortical potentials in PD patients before and after pallidotomy has shown an increase in the slope of the late component for movements made by the contralesional hand, without significant change in the early slope (Limousin et al., 1999). The authors interpreted this as suggesting that the later stages of movement preparation improve after pallidotomy, but that earlier preparatory processes do not improve. They proposed that the SMA, with the premotor cortex and motor cortex, contributes to neural activity immediately preceding movement, while earlier phases of movement preparation are the domain of the pre-SMA and dorsolateral prefrontal cortex. Hence, in their view, an increase in late BP slope after pallidotomy would be consistent with an improvement in SMA (as well as primary motor area) function. However, it is not clear that an increase in late BP slope in fact represents a change towards normality. Several studies have shown that the late component of the BP is larger in PD patients than in control subjects (Dick et al., 1989; Harasko-van der Meer et al., 1996). This may reflect increased activation of other cortical regions to compensate for reduced SMA activity (Dick et al., 1989). Thus, increased late BP slope after pallidotomy may represent an increased reliance on such compensatory activity because of ablation of the pallido-mesial frontal connection post-operatively. The precise

origins of the various components of the BP remain to some extent speculative. Thus, conclusions concerning the mechanisms of changes in BP components after pallidotomy must be made cautiously. However, the principal finding of our study is in agreement with that of Limousin et al. (1999) in suggesting that neural activity in cortical regions responsible for the early preparatory phase of volitional movement does not improve after pallidotomy.

In summary, this study shows that there is a decline in slope of the early BP after pallidotomy for severe PD. This finding raises doubt as to whether SMA function in the preparatory phases of movement improves after pallidotomy for PD. We propose that the decline in early BP slope after pallidotomy may be due to a greater use post-operatively of lateral motor circuits which receive sensory inputs and which do not contribute to the early BP.

CHAPTER 8

EFFECT OF PALLIDOTOMY LESION LOCATION ON CLINICAL OUTCOME IN PARKINSON'S DISEASE

8.1 Aims

The aims of this section of the thesis were:

i. to devise a method for the measurement of lesion size and location following posteroventral pallidotomy in PD and

ii. use this method to better understand the influence of lesion size and location on clinical results of pallidotomy

8.2 Methods

Sixteen subjects (10 males, 6 females) aged 45-72 years (mean age 60.6 years) underwent unilateral pallidotomy. All patients had advanced PD with severe drug-induced dyskinesias that could not be managed adequately medically.

Details of the surgical procedure, method for determination of lesion size and location and assessment of motor function are described in Chapter 2. The first assessment of motor function was made several days pre-operatively and the second three months post-operatively.

Statistical analysis of the movement parameters was performed by repeated measures analysis of variance (ANOVA). A p-value of <0.05 was considered significant in all analyses.

8.3 Results

8.3.1 Lesion location and size

Lesion parameters derived from CT scans performed on the first post-operative day are shown in **table 8.1**. Lesions are shown diagrammatically in **figures 8.1** and **8.2**, superimposed on the representative sagittal and coronal sections from the Schaltenbrand and Wahren atlas. Lesion centres ranged from 0 to 7.5mm anterior to the mid-commissural plane (MCP) (mean

3.0), 17.5 to 25mm lateral to the mid-sagittal plane (MSP) (mean 22.3) and 0 to 5mm below the inter-commissural plane (ICP) (mean 2.1). Lesion width in the axial plane ranged from 7.5 to 12.5mm (mean 10.3). Lesion length in the dorsoventral plane ranged from 4 to 12mm (mean 7.1). Lesion volume ranged from 74 to 942mm^3 (mean 300).

Figure 8.1 shows that lesions almost always encompassed the posteroventral aspect of the medial portion of the GPi. Almost all lesions were sufficiently ventral in location to involve in addition the ansa lenticularis, in its passage ventral to the lateral and medial portions of the GPi. The more lateral of the lesions also frequently involved the lateral portion of GPi and GPe. **Figure 8.1** shows that the GPi and GPe extend progressively more posteriorly with increasing laterality from the midline, such that by 22mm lateral to the MSP and 3mm anterior to the MCP (the mean location of the centre of our lesions), central parts of the lesions would have involved the lateral GPi/ansa more than the medial GPi. Indeed, the area common to all lesions of the 13 represented in **figure 8.1c** lies within the lateral GPi, in the vicinity of the exit zone of the ansa lenticularis. Similarly, in **figure 8.2d**, which represents 7 of the 16 lesions in coronal section 4mm anterior to the MCP, only the most medial lesion would have involved the medial GPi. The region common to all 7 lesions in **figure 8.2d** spans the ventral GPe and lateral ansa lenticularis. Although early perilesional oedema probably involved the optic tract in several cases (**figure 8.1c**), central parts of the lesions, which include the core of coagulative necrosis, spared the optic tracts in all cases. One of the more medially situated lesions, the centre of which was located 17.5mm lateral to the MSP (**figure 8.1a**), extended medially to involve the posterior limb of the internal capsule. However, this was not associated with any detectable clinical deficit.

Patient number	Distance of centre of lesion anterior to MCP (mm)	Distance of centre of lesion lateral to MSP (mm)	Distance of centre of lesion below ICP (mm)	Maximum width of lesion (mm)	Maximum length of lesion (mm)	Lesion volume (mm^3)
1	1.1	23.75	5	7.5	6	141
2	5	22.5	1	10	8	335
3	7.5	22.5	3	10	6	189
4	3.85	22.5	2	12	7	308
5	1	24.2	2	8.8	4	74
6	3.3	25	2	11.25	4	94
7	1.1	22.5	2	15	7	385
8	4.4	22	2	8.8	8	295
9	4.4	22.5	4	10	7	257
10	1.25	20	2	8.8	4	74
11	3.75	20	4	7.7	6	145
12	3.75	17.5	0	10	9	424
13	3.3	24	3	11	9	467
14	2.5	25	2	10	6	188
15	0	21.25	0	11.25	9	477
16	2	22.5	0	12.5	12	942
Mean	3.0	22.3	2.1	10.3	7	299.7

Table 8.1 Lesion dimensions Day 1 post-operatively (MCP = mid-commissural plane; MSP = mid-sagittal plane; ICP = inter-commissural plane).

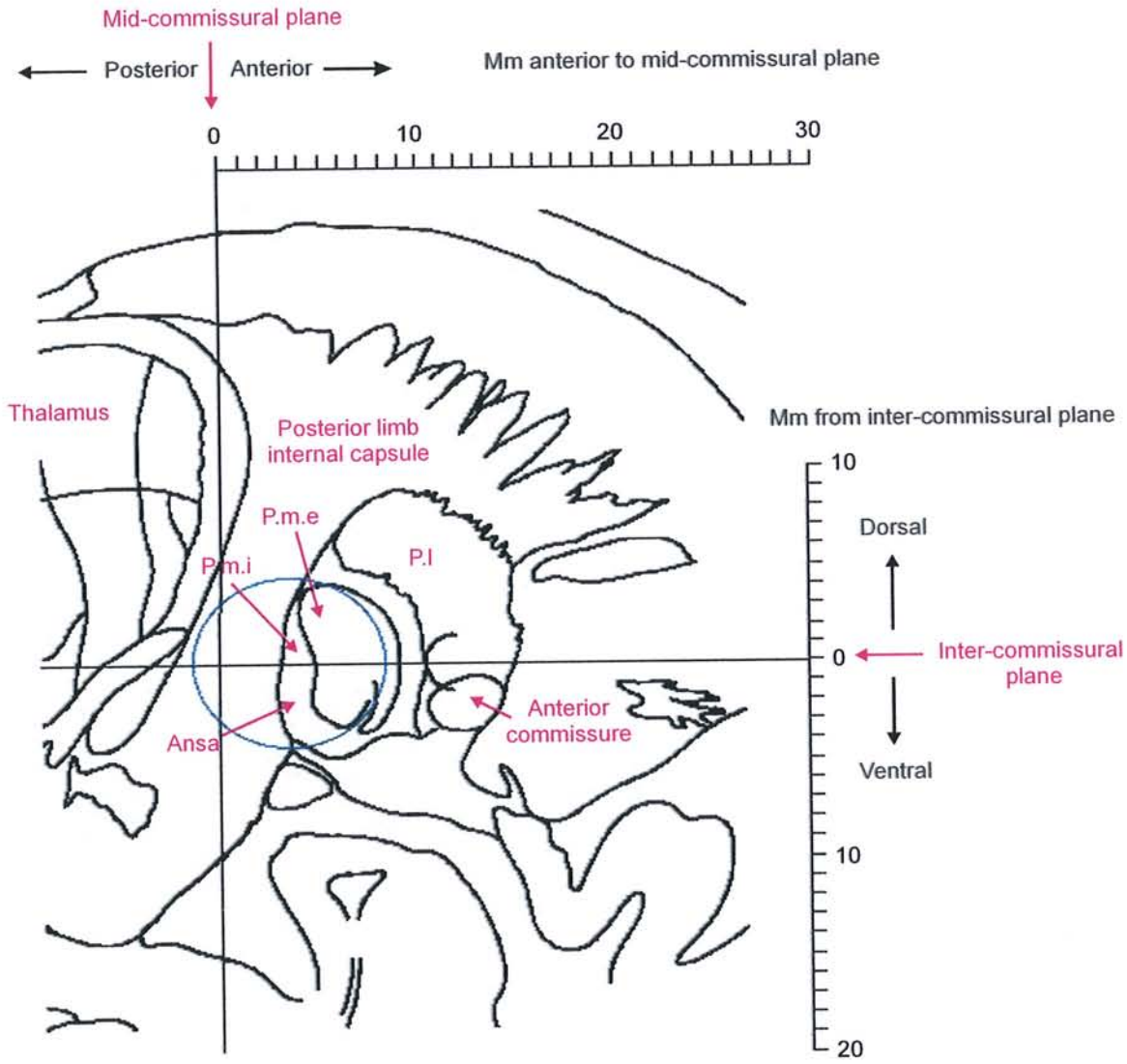


Fig 8.1a Sagittal section from the Schaltenbrand and Wahren atlas showing the anteroposterior and dorsoventral extent of one lesion (shown in blue), the centre of which was situated approximately 17mm lateral to the mid-sagittal plane.

(P.m.i=medial portion of internal pallidum; P.m.e=lateral portion of internal pallidum; P.l=external pallidum; ansa=ansa lenticularis; II=optic tract)

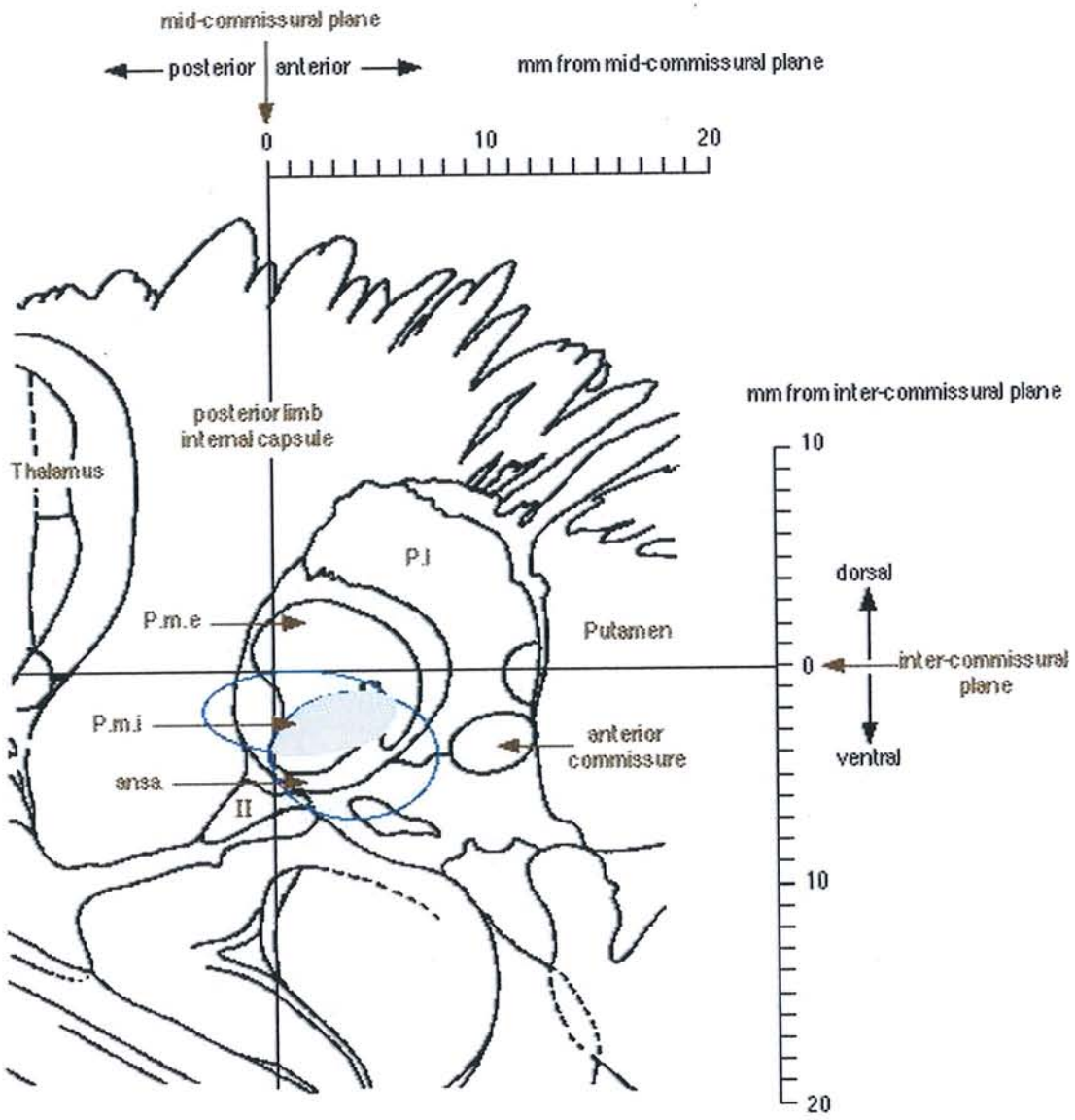


Fig 8.1b Sagittal section from the Schaltenbrand and Wahren atlas showing the anteroposterior and dorsoventral extent of 2 lesions (shown in blue), the centres of which were situated approximately 20mm lateral to the mid-sagittal plane. The area common to both lesions is shaded in grey.

(P.m.i=medial portion of internal pallidum; P.m.e=lateral portion of internal pallidum; P.l=external pallidum; ansa=ansa lenticularis; II=optic tract).

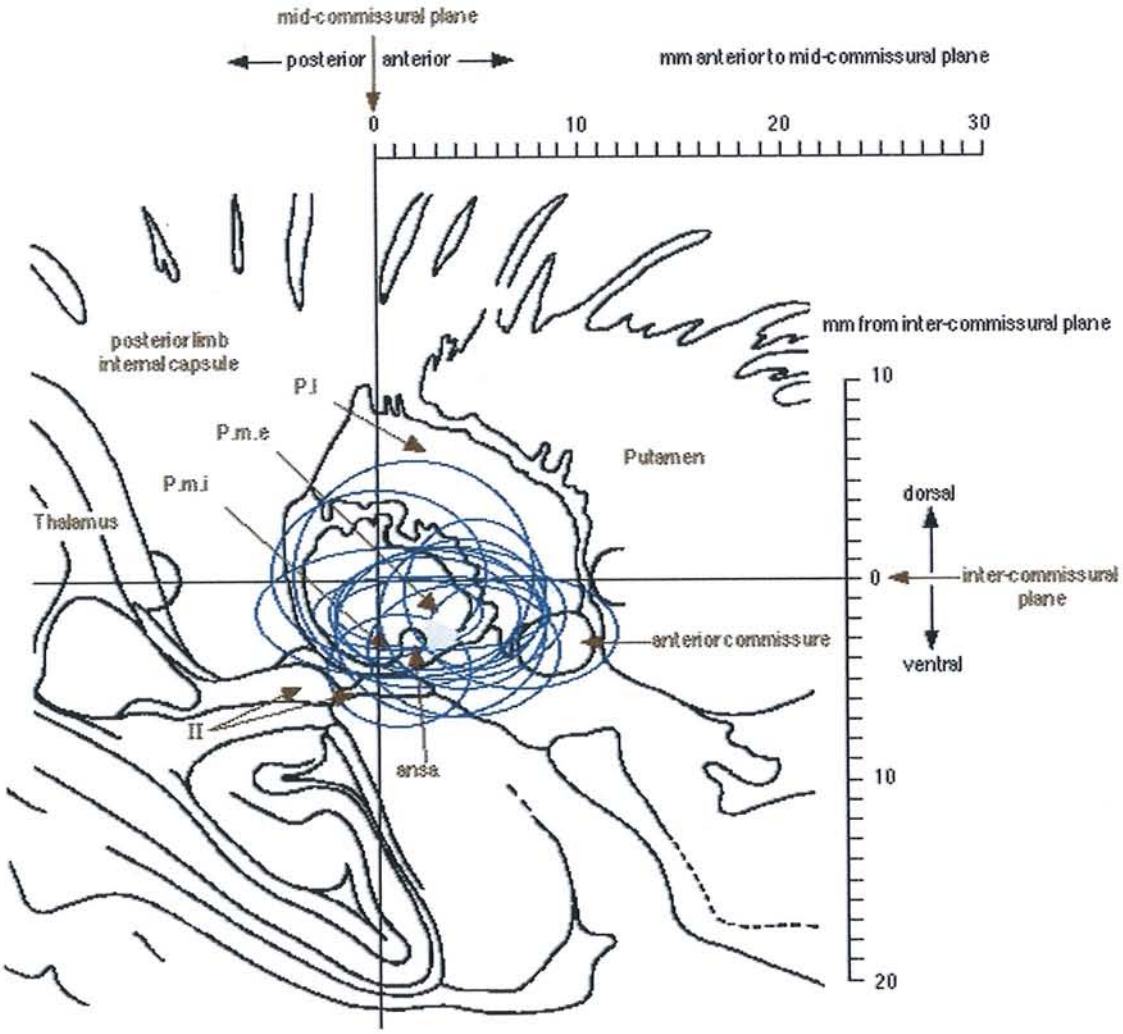


Fig 8.1c Sagittal section from the Schaltenbrand and Wahren atlas showing the anteroposteriorband dorsoventral extent of 13 lesions (shown in blue), the centres of which were located approximately 22mm lateral to the mid-sagittal plane. The area common to all 13 lesions is shaded in grey.

(P.m.i=medial portion of internal pallidum; P.m.l= lateral portion of internal pallidum; P.l=external pallidum; ansa=ansa lenticularis; II=optic tract)

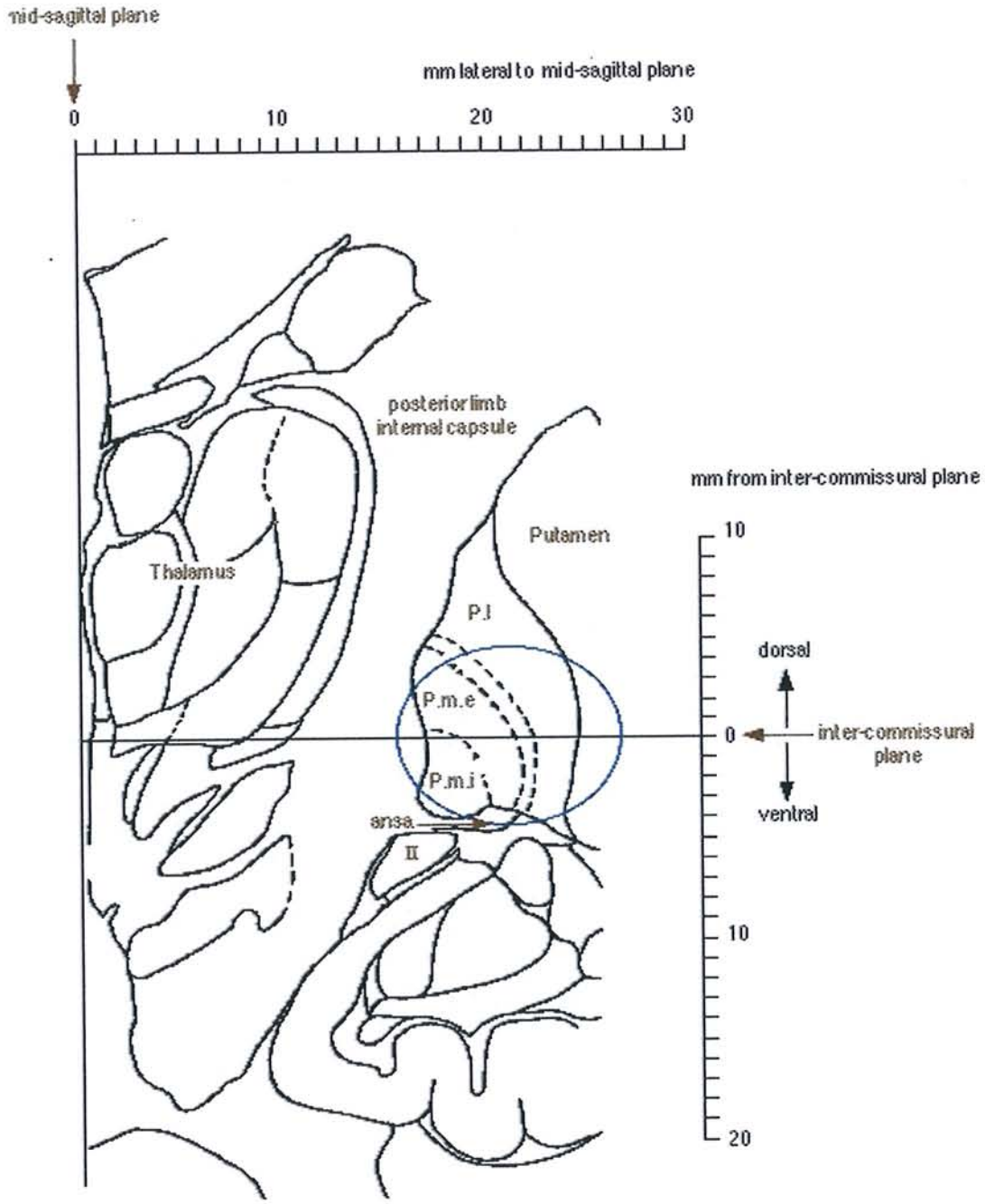


Fig 8.2a Coronal section from the Schaltenbrand and Wahren atlas showing the mediolateral and dorsoventral extent of one lesion (shown in blue), the centre of whichwas situated approximately 1.5cm posterior to the mid-commissural plane.

(P.m.i = medial portion of internal pallidum; P.m.e = lateral portion of internal pallidum; P.l = external pallidum; ansa = ansa lenticularis; II = optic tract)

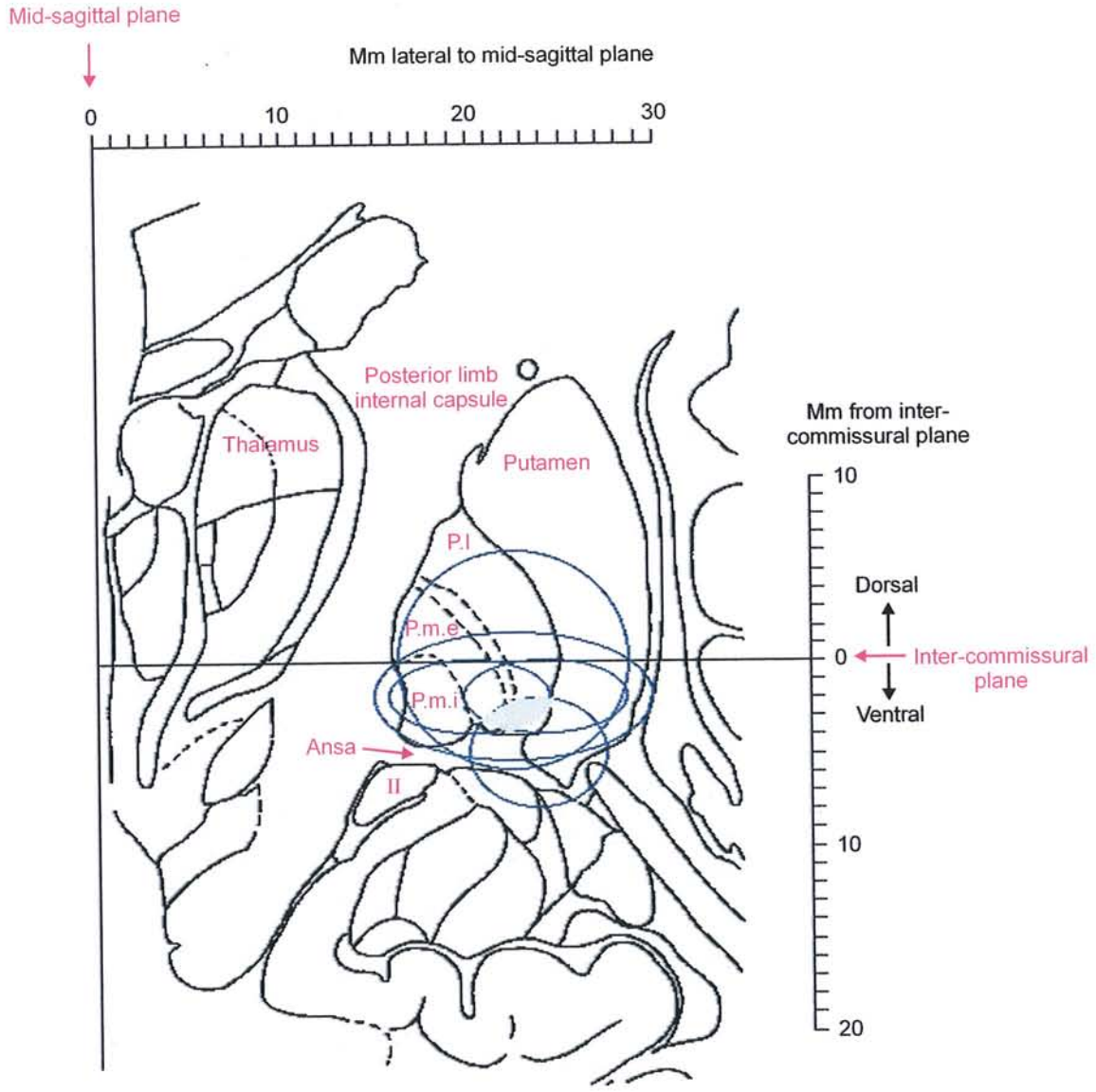


Fig 8.2b Coronal section from the Schaltenbrand and Wahren atlas showing the mediolateral and dorsoventral extent of 5 lesions (shown in blue), the centres of which were situated approximately 2mm anterior to the mid-commissural plane. The area common to all 5 lesions is shown in grey.

(P.m.i=medial portion of internal pallidum; P.m.e=lateral portion of internal pallidum; P.l=external pallidum; ansa=ansa lenticularis; II=optic tract)

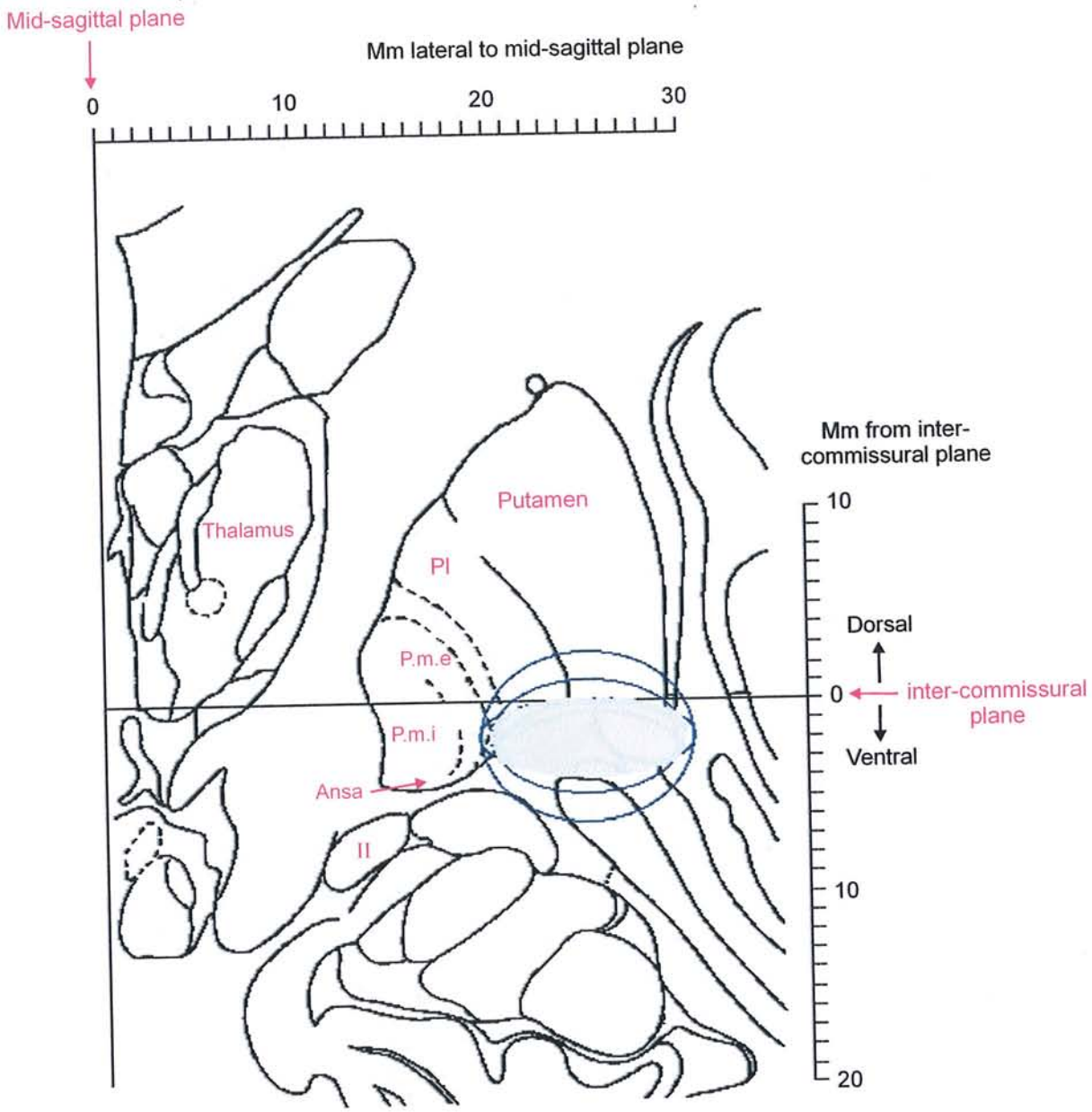


Fig 8.2c Coronal section from the Schaltenbrand and Wahren atlas showing the mediolateral and dorsoventral extent of 3 lesions (shown in blue), the centres of which were situated approximately 3mm anterior to the mid-commissural plane. The area common to all 3 lesions is shown in grey.

(P.m.i=medial portion of internal pallidum; P.m.e=lateral portion of internal pallidum; P.l=external pallidum; ansa=ansa lenticularis; II=optic tract)

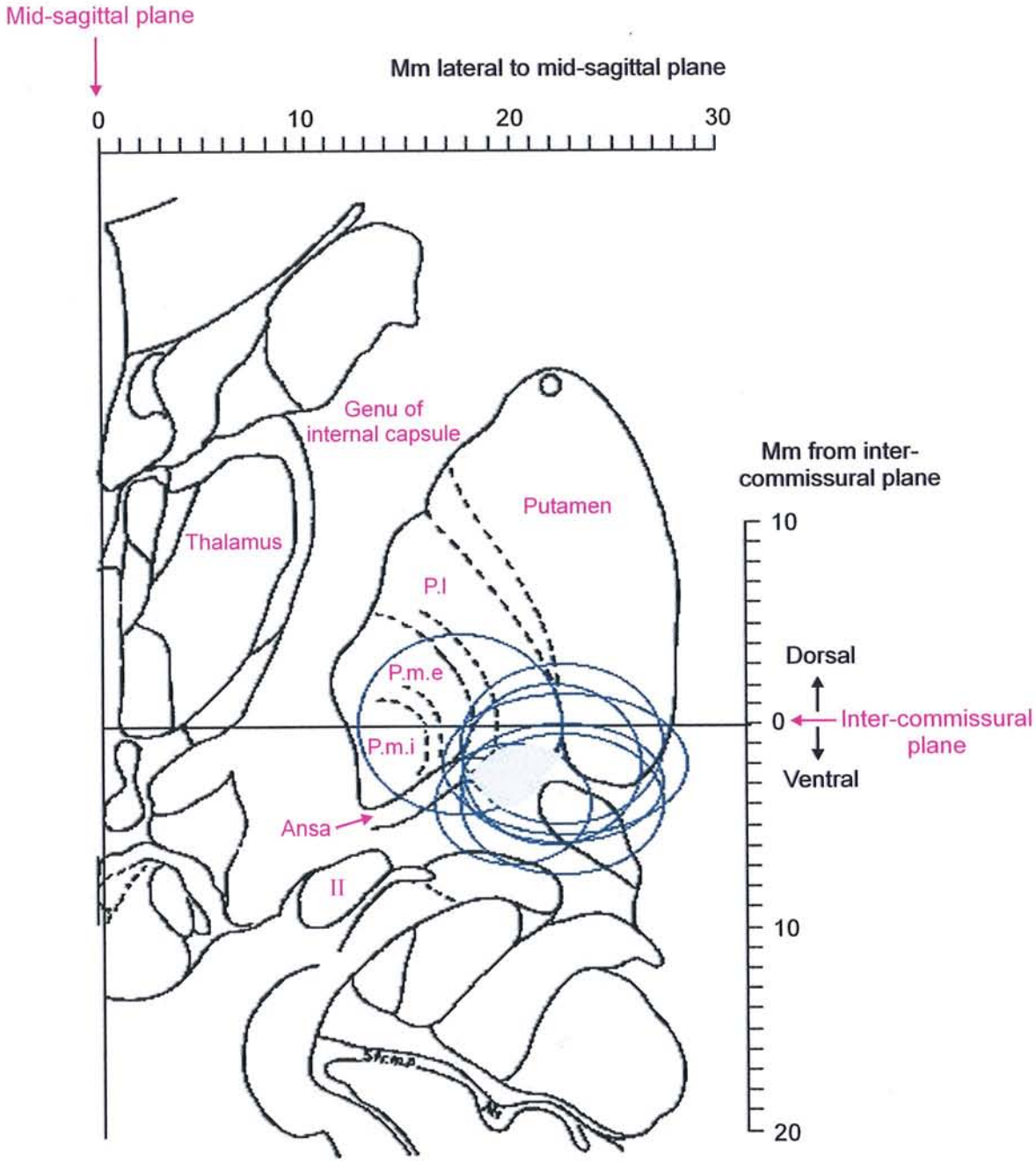


Fig 8.2d Coronal section from the Schaltenbrand and Wahren atlas showing the mediolateral and dorsoventral extent of 7 lesions (shown in blue), the centres of which were situated approximately 4 mm anterior to the mid-commissural plane. The area common to all 7 lesions is shown in grey.

(P.m.i=medial portion of internal pallidum; P.m.e=lateral portion of internal pallidum; P.l=external pallidum; ansa=ansa lenticularis; II=optic tract)

In the 3 patients who had late as well as early post-operative CT scans, lesion parameters were compared between the two scans (**table 8.2**). Measurements of lesion centres relative to the three reference planes were highly consistent between the two scans. The most consistent measurement between the 2 scans was distance from the MCP in the antero-posterior plane. This varied by less than 1mm between the 2 scans in all three cases. Differences of 1mm or less were seen in other measurements, with the exception of laterality from the MSP (3.75mm difference in patient 1 and 1.5mm difference in patient 13) and distance below ICP (2mm difference in patient 12). There was a marked difference between early and late scans in lesion volume, which diminished by a mean of 90% (range 83%-96%) at the time of the second scan, compared with the first.

Lesion parameter	Patient 1		Patient 12		Patient 13	
	Early CT	*Late CT*	*Early CT*	*Late CT*	*Early CT*	*Late CT*
Distance of centre of lesion anterior to MCP (mm)	1.1	1.25	3.75	4.4	3.3	3.75
Distance of centre of lesion lateral to MSP (mm)	23.75	20	17.5	17.6	24	22.5
Distance of centre of lesion below ICP (mm)	5	4	0	2	3	3
Maximum width of lesion (mm)	7.5	2.5	10	4.4	11	5
Maximum length of lesion (mm)	6	2	9	4	9	6
Lesion volume (mm^3)	141	5.2	424	36.9	467	78.5

Table 8.2 Lesion parameters in 3 patients in whom CT scans were performed both day 1 post-operatively and 10 months or more post-operatively (MCP = mid-commissural plane; MSP = mid-sagittal plane; ICP = inter-commissural plane).

8.3.2 Motor function

The effect of pallidotomy on voluntary upper limb movement and dyskinesias in these patients was reported and discussed in detail in our earlier paper (Kimber et al., 1999), so is summarised here in brief.

i. Voluntary limb movement

On the contralesional side at 3 months post-operatively, mean inter-onset latency decreased by 32% and mean peak elbow speed increased by 26% compared with pre-operative values (P values for both results < 0.01) (**figure 8.3**). Mean contralateral bradykinesia score, using the UPDRS, fell from 7.9 pre-operatively (SE 0.8) to 6.4 at 3 months post-operatively (SE 0.5) (p=0.05) (**figure 8.3**).

ii. Drug-induced dyskinesias

Mean dyskinesia score fell from 5.8 (SE 0.5) pre-operatively to 2.4 (SE 0.4) at 3 months post-operatively (p<0.001) (**figure 8.3**).

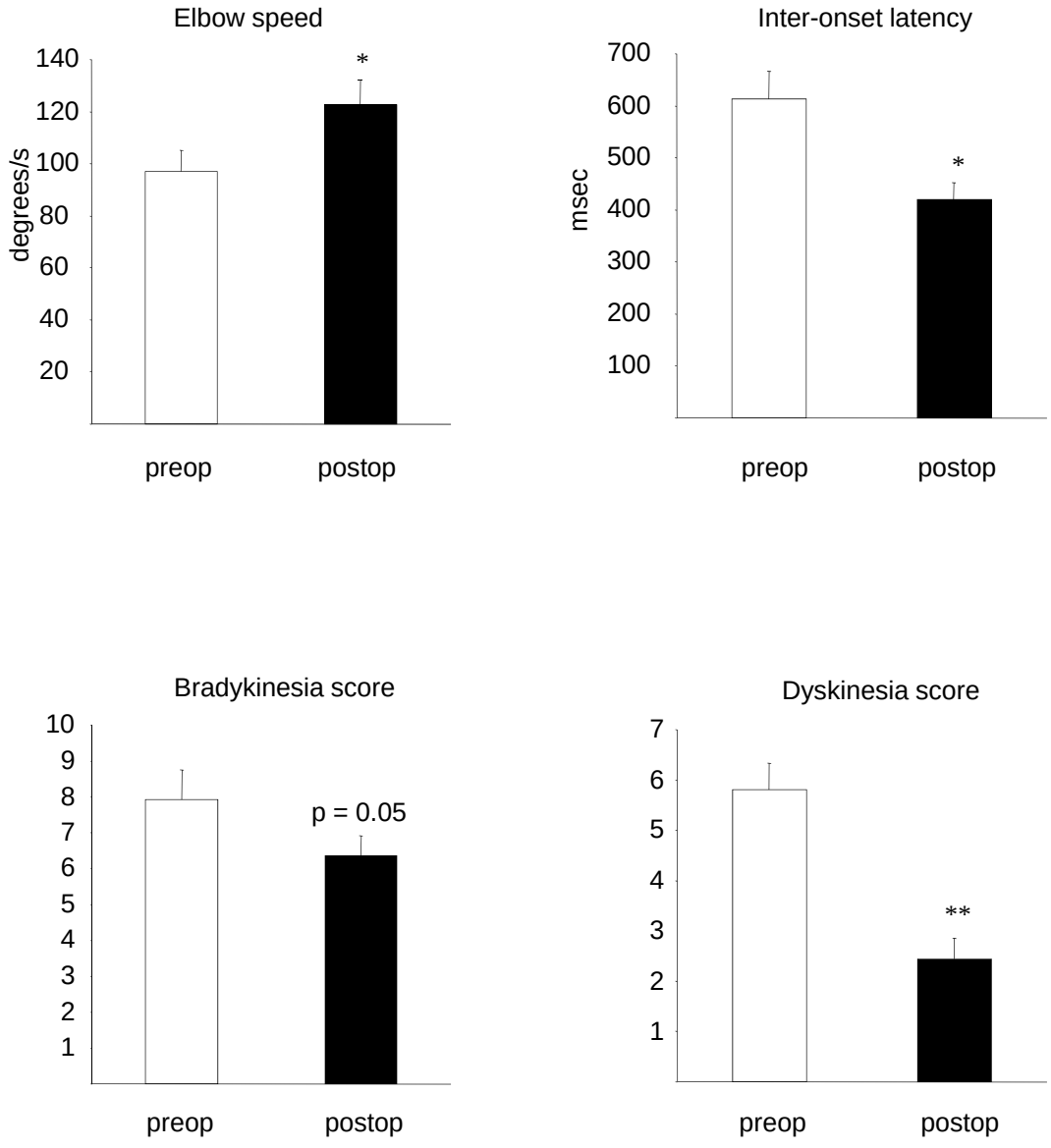


Fig 8.3 Motor function of the arm contralateral to pallidotomy pre- and post-operatively (elbow speed and inter-onset latency during the "pick-up" task and UPDRS bradykinesia and dyskinesia scores (*=$p<0.05$; **=$p<0.01$).

8.4 Discussion

8.4.1 Lesion volume in this study as compared with others

Lesion sizes in different studies are not always comparable. This is because different imaging methods are used, measurements are made at different times post-operatively – thus incorporating variable amounts of perilesional oedema – and because different assumptions are made about lesion morphology. The 3 cases in our study who had late as well as early post-operative CT scans confirm that early CT scans markedly overestimate true lesion volume by including perilesional oedema. It is claimed that early MRI scanning can differentiate perilesional oedema from the necrotic core of the lesion by their different signal characteristics on T1 and T2 sequences (Baron et al., 1996; Krauss et al., 1997). However, there is no direct comparison of radiological and pathological measurements of lesion size to confirm this. Furthermore, it is not always clear which studies using early post-operative MRI to measure lesion volume have excluded perilesional oedema from their calculations, and which have not. There are no previous studies in which lesion volume was measured from early post-operative CT scans with which to compare the size of our lesions. Studies using MRI performed in the first post-operative week have recorded mean lesion volumes of 262.2mm^3 (range 65-576), (Krauss et al., 1997), 80-150mm^3 (Lozano et al., 1996) and 127mm^3 (range 65-181) (Baron et al., 1996), compared with 300mm^3 (range 74-942) in our study. However, the other studies excluded the rim of presumed perilesional oedema from the measurement of lesion volume. Several studies have used late (> 3 months post-operatively) CT scans to measure lesion volume, and these have recorded mean volumes of 95mm^3 (Laitinen et al., 1992), 65.5mm^3 (Johansson et al., 1997) and 67 mm^3 (Hariz 1990). Studies using late MRI scans have recorded mean lesion volumes of 22mm^3 (Krauss et al., 1997) and

72.8mm^3 (Johansson et al., 1997). These values compare with a mean late lesion volume of 40.2mm^3 (range 5.2-78.5) in the 3 patients who underwent late CT scans in our study. We conclude that early and late lesion volumes in the present study varied widely between patients, but were broadly similar to those of previous studies.

The issue of reduction in lesion volume over time is controversial. The only other studies to have described sequential imaging of pallidotomy lesions, both using MRI, are Krauss et al. (1997) and Tomlinson et al. (1991). Krauss et al. (1997) reported a reduction in mean lesion volume of 92% over time, from 262.2mm^3 one to three days post-operatively to 22mm^3 6 months post-operatively. The authors postulated that this represented a reduction in true lesion volume, as they believed they had excluded perilesional oedema from early measurements of lesion volume. However, the reduction in lesion volume reported by Krauss et al. is very similar to the 90% reduction in mean lesion volume between early and late CT scans in the 3 patients in our study. This suggests that perilesional oedema may have been included in measurements of early lesion volume in their study.

If, as has been claimed (Krauss et al., 1997; Tomlinson et al., 1991), pallidotomy lesions due shrink over time, the impact of this on motor function is unclear. It is possible that progressive reduction in lesion size may partly account for the progressive decline in motor benefit that has been reported in several studies of the longterm effects of pallidotomy (Lang et al., 1997; Samuel et al., 1998; Samii et al., 1999). However, other factors, such as progression of PD, are also likely to be involved.

8.4.2 The impact of lesion location on the clinical effects of pallidotomy

The lesions in this study almost always encompassed the posteroventral portion of the medial segment of the GPi, the conventional site for pallidotomy (Baron et al., 1996; Lang et al., 1997). However, many lesions extended ventral and lateral to this region and involved the

ansa lenticularis, lateral GPi and GPe. Furthermore, comparison of early and late post-operative CT scans suggests that some of the involvement of medial GPi one day post-operatively was probably due to perilesional oedema. After resolution of this oedema, the lesions were not only much smaller, but in many cases may not have included the medial GPi at all. Despite this, the motor effects of pallidotomy in this series are remarkably similar to those of other series in which lesions were confined to the posteroventral GPi (Baron et al., 1996). The possible explanations for our findings will be addressed in turn.

8.4.2.1 GPi lesions outside the posteroventral portion are effective in the treatment of "off" state akinesia

There is considerable historical evidence that lesions of the lateral GPi and its output pathway, the ansa lenticularis, can be effective in the treatment of parkinsonian motor dysfunction. In the earliest studies of pallidotomy for the relief of Parkinsonism, the surgical target frequently included the ansa lenticularis as well as the pallidum itself. Pallido-ansotomy for PD led to improvements in tremor, rigidity and akinesia (Meyers 1942; Fénélon and Thiébaut 1950; Spiegel et al., 1958). With the advent of stereotactic surgical techniques, it became possible to lesion selectively certain regions of the pallidum, and it was reported by Svennilson et al. (1960) that lesions of the posteroventral portion of the GPi produced better clinical results than those of the anterodorsal portion (Svennilson et al., 1960). Therefore, the posteroventral pallidum became the preferred target for pallidotomy.

After interest in pallidotomy was rekindled by the work of Laitinen et al. (1992), the posteroventral portion remained the recommended site for lesioning (Lozano et al., 1997). However, the evidence that lesions of the posteroventral GPi are more efficacious than lesions of other parts of the GPi is debatable. Firstly, Svennilson et al. were working in the pre-levodopa era, when drug-induced dyskinesias were unheard of. However, dyskinesias are the

primary indication for pallidotomy in the modern era. Secondly, the primacy of the posteroventral GPi as the preferred surgical target for the relief of "off" state motor dysfunction is based in part on the fact that it houses movement-related neurons. However, such neurons are found elsewhere in the pallidum as well. Various studies have found movement-related neurons within posterior (Iansek and Porter, 1980), lateral (DeLong 1971) and central parts of the both pallidal segments (Filion et al., 1988). Overall, the evidence would suggest that movement-related neurons are distributed widely through both pallidal segments, with the exception of the more dorsal areas, without a preference for the posteroventral GPi (DeLong et al. 1985).

Furthermore, abnormally functioning neurons are not confined to the posteroventral GPi in PD. The characteristics of pallidal neuronal activity in experimental and idiopathic PD are well established. Firing rates of GPi and GPe neurons are higher and lower, respectively, in MPTP-treated, compared with healthy, monkeys (Filion et al., 1988; Filion and Tremblay 1991). In MPTP-treated monkeys, the dopamine agonist apomorphine decreases the firing rate of GPi neurons and increases the firing rate of GPe neurons (Filion et al., 1991). Furthermore, movement-related GPi neurons of MPTP-treated monkeys show a loss of their normal specificity for movements of single joints, and instead respond to movements of several joints (Filion et al., 1988). There is evidence that similar patterns of pallidal function occur in humans with idiopathic PD (Sterio et al., 1994; Hutchison et al., 1994; Beric et al., 1996), and that these firing patterns, too, are responsive to apomorphine (Hutchison et al., 1997).

It is not clear, however, that pallidal neurons with abnormally increased activity in PD are confined to the medial portion of the GPi. In a study of 6 PD patients, Hutchison et al. (1994) found that neurons with significantly increased firing rates compared with GPe were

found predominantly within the medial portion of GPi, whereas the mean firing rate of neurons in the lateral portion of GPi was not significantly different to that of GPe neurons. However, in a subsequent paper, the same authors found that apomorphine significantly decreased neuronal firing rates in both the medial and lateral portions of the GPi in PD patients, suggesting that baseline neural activity is abnormally high in both portions of the GPi in PD (Hutchison et al., 1997). Secondly, if, as is generally accepted, increased neural activity within the GPi is a consequence of nigrostriatal dopamine depletion, it is difficult to explain how the medial and lateral portions of the GPi could be differentially affected by this. Neurons forming the direct pathway from striatum to GPi contain the inhibitory neurotransmitter GABA, as well as substance P (Graybiel 1986). Therefore, increased striatopallidal outflow in PD should diminish inhibitory outflow to the entire GPi. The division of the GPi into medial and lateral portions is based on anatomical rather than physiological grounds, as the pallido-fugal pathways from each portion (the ansa lenticularis and fasciculus lenticularis, respectively) are anatomically separate (Nauta and Mehler, 1966). Finally, if heightened neural activity were confined to the medial portion of the GPi in PD, how could one explain the improvement in Parkinsonism resulting from lesions pathologically proven to be confined to the ansa lenticularis, which arises from its lateral portion (Beck and Bignami, 1968)?

In summary, there is considerable evidence to support the claim that lesions of the GPi outside its posteroventral portion are effective for the relief of "off" state motor dysfunction in PD.

8.4.2.2 Lesions of the GPe and of the GPi outside the posteroventral portion are effective for the treatment of drug-induced dyskinesias

Like those examining akinesia, studies that have examined the neural correlates of drug-induced dyskinesia have mostly used animal models. These models have either used dopaminergic drugs to induce dyskinesias in MPTP-treated monkeys (Filion et al., 1991), or have injected GABA antagonists into the GPe in order to induce GPi hypoactivity via a reduction in subthalamopallidal outflow (Crossman et al., 1988; Mitchell et al., 1989). In neither model has a preponderance of abnormally functioning neurons in the posteroventral GPi been described.

The situation may be different in idiopathic than in experimental PD. Results from studies of GPi stimulation suggest that relief of "on" state dyskinesias is best obtained by stimulation in the most ventral part of the GPi (Bejjani et al., 1997; Krack et al., 1998). By contrast, dyskinesias were exacerbated by stimulation of more dorsal parts of the pallidum. It is not clear that the results of stimulation studies are applicable to lesion studies, as stimulation of more dorsal contacts within the GPi may affect GPe function, with secondary and as yet uncertain effects on GPi function. However, there is some evidence that the location of the pallidotomy lesion within the posteroventral GPi influences clinical results. Gross et al. (1999) found significant variations in the effect of pallidotomy on dyskinesia, akinesia, rigidity and postural instability/gait disturbance according to lesion location along the anteromedial to posterolateral plane within the posteroventral GPi. Such regional specialisation of the GPi is easier to understand for some motor functions than for others. For example, it is known that volitional limb movement is mediated by pallido-thalamocortical outflow (Roland et al., 1980), while muscle tone and axial mobility are mediated by descending pallido-tegmental outflow to the pedunculopontine nucleus (Delwaide et al., 1991). However, it is more difficult

to understand how dyskinesia and akinesia which, in kinematic terms, occupy two ends of a movement continuum, could be controlled by completely separate neuronal populations. This would seem to imply a gain, rather than a loss, of neuronal function in PD, for which there is no experimental evidence. In fact, there is evidence that the reverse applies, with pallidal neurons manifesting a loss of somatotopic specificity in MPTP-treated monkeys (Filion and Tremblay 1988). It is likely that dyskinesia and akinesia are the result, not of the activity of separate neuron populations, but of different patterns of activity of the same population (Obeso et al. 1997; Levy et al. 1997). In keeping with this notion, several other studies have found no relationship between lesion site within the GPi and clinical outcome (Krauss et al. 1997; Burns et al., 1997).

What effect might lesioning the GPe, as occurred in many cases, have had on our clinical results? The role of the GPe in Parkinsonian motor dysfunction, such as akinesia and dyskinesia, is being reevaluated. According to the model of basal ganglia circuitry proposed by Albin et al. (Albin et al., 1989), pathological hyperactivity of the STN in PD, which is believed to cause akinesia, is a direct effect of pathological hypoactivity of the GPe. However, recent studies of the biological activity of GPe neurons in control and Parkinsonian subjects have called this model into question. Herrero et al. (Herrero et al., 1996) found that levels of mRNA encoding glutamic acid decarboxylase (GAD_{67}), the synthetic enzyme for GABA, were not significantly different in the GPe of monkeys and humans with PD as compared with their normal counterparts. This contrasted with the situation in GPi and SNr, where levels of GAD_{67} mRNA were significantly higher in Parkinsonian than control subjects. Similar results were obtained when cytochrome oxidase activity was used as a marker of metabolic activity (Vila et al., 1996). If metabolic activity of the GPe is unchanged in PD, how can one explain the reduction in GPe neuronal firing rate that has been repeatedly demonstrated in

experimental and idiopathic PD (Filion and Tremblay 1991; Hutchison et al., 1994)? Neurophysiological studies of the GPe in MPTP-treated monkeys show that, although net firing rate is diminished compared with normal animals, there is an increase in so-called "burst firing activity" (Filion and Tremblay 1991). This pattern of firing may actually increase GABA release to the STN, as has been demonstrated in other neurotransmitter systems (Gonon 1988).

A recently proposed model of basal ganglia function has the GPe and STN, via their reciprocal connections, varying their activity according to the demands of normal movement. In PD, the GPe is able to maintain relatively normal metabolic activity by balancing competing inhibitory inputs from the striatum and excitatory inputs from STN. According to this model, the STN becomes hyperactive in PD, not because of reduced GABAergic input from GPe, but because of disruption of putative inputs to the STN from SNc, parafascicular nucleus and/or cerebral cortex, as a result of nigrostriatal dopamine depletion (Chesselet and Delfs 1996; Levy et al., 1997; Obeso et al., 1997). According to the model, lesioning the GPe would have little or no effect on akinesia.

However, recent work suggests that the GPe is of major importance in the genesis of drug-induced dyskinesias. GPe neurons of MPTP-treated monkeys increase their firing rate in association with dyskinesias induced by dopaminergic drugs (Filion et al., 1991). This is associated with a decrease in firing rate within the GPi, presumably mediated by inhibitory outflow from the GPe to GPi, either directly (Hazrati et al., 1990) or indirectly, via the STN. It is known that choreiform dyskinesias can be induced in healthy monkeys by the injection of the GABA antagonist bicuculline into the GPe (Crossman et al., 1988; Mitchell et al., 1989). Studies of 2-deoxyglucose uptake suggest that these dyskinesias are mediated by inhibition of subthalamopallidal and pallidothalamic pathways (Crossman et al., 1988; Mitchell et al.,

1989). Data such as this suggested that the GPe played an important role in drug-induced dyskinesias, but this was tempered by the finding that ablation of the GPe in dyskinetic MPTP-treated monkeys did not have any anti-dyskinetic effect (Blanchet et al., 1994). More recently, however, Matsumura et al. (1995) measured the firing rates of GPe and GPi neurons in healthy monkeys before and after injection of bicuculline into the GPe. The majority (71%) of responding GPe neurons increased their activity following bicuculline injection, in a manner identical to that previously noted in MPTP-treated monkeys in whom dyskinesias were induced by dopaminergic drugs (Filion et al., 1991). This strongly suggests that GPe hyperactivity is a driving force for drug-induced dyskinesias in PD. However, within the GPe, a significant minority of cells became hypoactive after bicuculline. Furthermore, only a minority (41%) of GPi neurons decreased their activity in response to bicuculline injection into the GPe, with the majority becoming hyperactive. This suggests that it may be the pattern of neural firing, rather than the net firing rate, that is the critical factor in driving drug-induced dyskinesias. In support of this notion, the authors found clusters of GPi neurons in which the central neurons were hypoactive, and were surrounded by a rim of hyperactive or unresponsive neurons. The authors postulate that, in these clusters of GPi neurons, the central cells are hypoactive as a result of inhibition by hyperactive GPe cells, while the surrounding GPi cells are hyperactive because of a reduction in inhibitory outflow from GPe cells made hypoactive by monosynaptic lateral inhibition within the GPe. The authors propose that it is this imbalance of activity within the GPe and GPi, rather than a net reduction in GPi activity, that is the neural basis of drug-induced dyskinesias. This may help explain the paradox by which pallidotomy, by abolishing this unbalanced GPi neural activity, can relieve dyskinesias as well as improve akinesia (Obeso et al., 1997).

8.5 Conclusions

The present study does not help clarify the issue of whether either method of intra-operative targeting - by microelectrode recording or macrostimulation – is superior to the other, either in terms of efficacy or safety. However, our study does demonstrate that, although precise lesioning within the posteroventral GPi may not be as reliably achieved with macrostimulation guidance, this need not occur at the cost of reduced clinical efficacy. Significant improvements in akinesia and dyskinesia occurred despite lesions being made in structures ventral and lateral to the posteroventral GPi.

Our results invite several possible interpretations. On the one hand, they can be interpreted as supporting the primacy of the posteroventral GPi as the preferred site for pallidotomy lesions. In other words, as long as the posteroventral GPi is included in the lesion, as it was in most cases, then lesioning adjacent parts of the pallidum or its efferent pathways will not necessarily diminish the clinical effect. However, relative sparing of the medial GPi on late post-operative CT scans performed on several of our cases suggest that the early involvement of the GPi in many of our lesions was probably due to perilesional oedema, rather than coagulative necrosis. This invites an alternative interpretation of our results – namely, that including the posteroventral GPi in lesions is not critical for clinical efficacy, and that comparable results can be obtained by including lateral GPi, ansa lenticularis and/or GPe in the lesion. As has been discussed, several levels of scientific evidence support this interpretation of our results.

According to this interpretation, the critical requirement for an effective GPi lesion in PD is that it should significantly diminish GPi output. Akinesia and dyskinesia are seen to represent the results of different types of aberrant activity of the same pallidal neuron population. Thus, relief of akinesia and dyskinesia may simply require the ablation of a critical

number of such neurons, irrespective of where in the GPi they reside. Clearly, other factors, such as lesion size, patient age and duration of disease may also influence results of lesioning, but this remains largely unproven. Recent evidence on neural activity within the GPe in experimental PD suggests than lesioning the GPe may not exacerbate akinesia, as would be predicted from the conventional model of basal ganglia function, and may aid in the relief of dyskinesias.

CHAPTER 8

EFFECT OF PALLIDOTOMY LESION LOCATION ON CLINICAL OUTCOME IN PARKINSON'S DISEASE

8.1 Aims

The aims of this section of the thesis were:

i. to devise a method for the measurement of lesion size and location following posteroventral pallidotomy in PD and

ii. use this method to better understand the influence of lesion size and location on clinical results of pallidotomy

8.2 Methods

Sixteen subjects (10 males, 6 females) aged 45-72 years (mean age 60.6 years) underwent unilateral pallidotomy. All patients had advanced PD with severe drug-induced dyskinesias that could not be managed adequately medically.

Details of the surgical procedure, method for determination of lesion size and location and assessment of motor function are described in Chapter 2. The first assessment of motor function was made several days pre-operatively and the second three months post-operatively.

Statistical analysis of the movement parameters was performed by repeated measures analysis of variance (ANOVA). A p-value of <0.05 was considered significant in all analyses.

8.3 Results

8.3.1 Lesion location and size

Lesion parameters derived from CT scans performed on the first post-operative day are shown in **table 8.1**. Lesions are shown diagrammatically in **figures 8.1** and **8.2**, superimposed on the representative sagittal and coronal sections from the Schaltenbrand and Wahren atlas. Lesion centres ranged from 0 to 7.5mm anterior to the mid-commissural plane (MCP) (mean

3.0), 17.5 to 25mm lateral to the mid-sagittal plane (MSP) (mean 22.3) and 0 to 5mm below the inter-commissural plane (ICP) (mean 2.1). Lesion width in the axial plane ranged from 7.5 to 12.5mm (mean 10.3). Lesion length in the dorsoventral plane ranged from 4 to 12mm (mean 7.1). Lesion volume ranged from 74 to 942mm^3 (mean 300).

Figure 8.1 shows that lesions almost always encompassed the posteroventral aspect of the medial portion of the GPi. Almost all lesions were sufficiently ventral in location to involve in addition the ansa lenticularis, in its passage ventral to the lateral and medial portions of the GPi. The more lateral of the lesions also frequently involved the lateral portion of GPi and GPe. **Figure 8.1** shows that the GPi and GPe extend progressively more posteriorly with increasing laterality from the midline, such that by 22mm lateral to the MSP and 3mm anterior to the MCP (the mean location of the centre of our lesions), central parts of the lesions would have involved the lateral GPi/ansa more than the medial GPi. Indeed, the area common to all lesions of the 13 represented in **figure 8.1c** lies within the lateral GPi, in the vicinity of the exit zone of the ansa lenticularis. Similarly, in **figure 8.2d**, which represents 7 of the 16 lesions in coronal section 4mm anterior to the MCP, only the most medial lesion would have involved the medial GPi. The region common to all 7 lesions in **figure 8.2d** spans the ventral GPe and lateral ansa lenticularis. Although early perilesional oedema probably involved the optic tract in several cases (**figure 8.1c**), central parts of the lesions, which include the core of coagulative necrosis, spared the optic tracts in all cases. One of the more medially situated lesions, the centre of which was located 17.5mm lateral to the MSP (**figure 8.1a**), extended medially to involve the posterior limb of the internal capsule. However, this was not associated with any detectable clinical deficit.

Table 8.1

fig 8.1a

fig 8.1b

fig 8.1c

fig 8.2a

fig 8.2b

fig 8.2c

fig 8.2d

In the 3 patients who had late as well as early post-operative CT scans, lesion parameters were compared between the two scans (**table 8.2**). Measurements of lesion centres relative to the three reference planes were highly consistent between the two scans. The most consistent measurement between the 2 scans was distance from the MCP in the antero-posterior plane. This varied by less than 1mm between the 2 scans in all three cases. Differences of 1mm or less were seen in other measurements, with the exception of laterality from the MSP (3.75mm difference in patient 1 and 1.5mm difference in patient 13) and distance below ICP (2mm difference in patient 12). There was a marked difference between early and late scans in lesion volume, which diminished by a mean of 90% (range 83%-96%) at the time of the second scan, compared with the first.

Table 8.2

8.3.2 Motor function

The effect of pallidotomy on voluntary upper limb movement and dyskinesias in these patients was reported and discussed in detail in our earlier paper (Kimber et al., 1999), so is summarised here in brief.

i. Voluntary limb movement

On the contralesional side at 3 months post-operatively, mean inter-onset latency decreased by 32% and mean peak elbow speed increased by 26% compared with pre-operative values (P values for both results < 0.01) (**figure 8.3**). Mean contralateral bradykinesia score, using the UPDRS, fell from 7.9 pre-operatively (SE 0.8) to 6.4 at 3 months post-operatively (SE 0.5) (p=0.05) (**figure 8.3**).

ii. Drug-induced dyskinesias

Mean dyskinesia score fell from 5.8 (SE 0.5) pre-operatively to 2.4 (SE 0.4) at 3 months post-operatively (p<0.001) (**figure 8.3**).

fig 8.3

8.4 Discussion

8.4.1 Lesion volume in this study as compared with others

Lesion sizes in different studies are not always comparable. This is because different imaging methods are used, measurements are made at different times post-operatively – thus incorporating variable amounts of perilesional oedema – and because different assumptions are made about lesion morphology. The 3 cases in our study who had late as well as early post-operative CT scans confirm that early CT scans markedly overestimate true lesion volume by including perilesional oedema. It is claimed that early MRI scanning can differentiate perilesional oedema from the necrotic core of the lesion by their different signal characteristics on T1 and T2 sequences (Baron et al., 1996; Krauss et al., 1997). However, there is no direct comparison of radiological and pathological measurements of lesion size to confirm this. Furthermore, it is not always clear which studies using early post-operative MRI to measure lesion volume have excluded perilesional oedema from their calculations, and which have not. There are no previous studies in which lesion volume was measured from early post-operative CT scans with which to compare the size of our lesions. Studies using MRI performed in the first post-operative week have recorded mean lesion volumes of 262.2mm^3 (range 65-576), (Krauss et al., 1997), 80-150mm^3 (Lozano et al., 1996) and 127mm^3 (range 65-181) (Baron et al., 1996), compared with 300mm^3 (range 74-942) in our study. However, the other studies excluded the rim of presumed perilesional oedema from the measurement of lesion volume. Several studies have used late (> 3 months post-operatively) CT scans to measure lesion volume, and these have recorded mean volumes of 95mm^3 (Laitinen et al., 1992), 65.5mm^3 (Johansson et al., 1997) and 67 mm^3 (Hariz 1990). Studies using late MRI scans have recorded mean lesion volumes of 22mm^3 (Krauss et al., 1997) and

72.8mm^3 (Johansson et al., 1997). These values compare with a mean late lesion volume of 40.2mm^3 (range 5.2-78.5) in the 3 patients who underwent late CT scans in our study. We conclude that early and late lesion volumes in the present study varied widely between patients, but were broadly similar to those of previous studies.

The issue of reduction in lesion volume over time is controversial. The only other studies to have described sequential imaging of pallidotomy lesions, both using MRI, are Krauss et al. (1997) and Tomlinson et al. (1991). Krauss et al. (1997) reported a reduction in mean lesion volume of 92% over time, from 262.2mm^3 one to three days post-operatively to 22mm^3 6 months post-operatively. The authors postulated that this represented a reduction in true lesion volume, as they believed they had excluded perilesional oedema from early measurements of lesion volume. However, the reduction in lesion volume reported by Krauss et al. is very similar to the 90% reduction in mean lesion volume between early and late CT scans in the 3 patients in our study. This suggests that perilesional oedema may have been included in measurements of early lesion volume in their study.

If, as has been claimed (Krauss et al., 1997; Tomlinson et al., 1991), pallidotomy lesions due shrink over time, the impact of this on motor function is unclear. It is possible that progressive reduction in lesion size may partly account for the progressive decline in motor benefit that has been reported in several studies of the longterm effects of pallidotomy (Lang et al., 1997; Samuel et al., 1998; Samii et al., 1999). However, other factors, such as progression of PD, are also likely to be involved.

8.4.2 The impact of lesion location on the clinical effects of pallidotomy

The lesions in this study almost always encompassed the posteroventral portion of the medial segment of the GPi, the conventional site for pallidotomy (Baron et al., 1996; Lang et al., 1997). However, many lesions extended ventral and lateral to this region and involved the

ansa lenticularis, lateral GPi and GPe. Furthermore, comparison of early and late post-operative CT scans suggests that some of the involvement of medial GPi one day post-operatively was probably due to perilesional oedema. After resolution of this oedema, the lesions were not only much smaller, but in many cases may not have included the medial GPi at all. Despite this, the motor effects of pallidotomy in this series are remarkably similar to those of other series in which lesions were confined to the posteroventral GPi (Baron et al., 1996). The possible explanations for our findings will be addressed in turn.

8.4.2.1 GPi lesions outside the posteroventral portion are effective in the treatment of "off" state akinesia

There is considerable historical evidence that lesions of the lateral GPi and its output pathway, the ansa lenticularis, can be effective in the treatment of parkinsonian motor dysfunction. In the earliest studies of pallidotomy for the relief of Parkinsonism, the surgical target frequently included the ansa lenticularis as well as the pallidum itself. Pallido-ansotomy for PD led to improvements in tremor, rigidity and akinesia (Meyers 1942; Fénélon and Thiébaut 1950; Spiegel et al., 1958). With the advent of stereotactic surgical techniques, it became possible to lesion selectively certain regions of the pallidum, and it was reported by Svennilson et al. (1960) that lesions of the posteroventral portion of the GPi produced better clinical results than those of the anterodorsal portion (Svennilson et al., 1960). Therefore, the posteroventral pallidum became the preferred target for pallidotomy.

After interest in pallidotomy was rekindled by the work of Laitinen et al. (1992), the posteroventral portion remained the recommended site for lesioning (Lozano et al., 1997). However, the evidence that lesions of the posteroventral GPi are more efficacious than lesions of other parts of the GPi is debatable. Firstly, Svennilson et al. were working in the pre-levodopa era, when drug-induced dyskinesias were unheard of. However, dyskinesias are the

primary indication for pallidotomy in the modern era. Secondly, the primacy of the posteroventral GPi as the preferred surgical target for the relief of "off" state motor dysfunction is based in part on the fact that it houses movement-related neurons. However, such neurons are found elsewhere in the pallidum as well. Various studies have found movement-related neurons within posterior (Iansek and Porter, 1980), lateral (DeLong 1971) and central parts of the both pallidal segments (Filion et al., 1988). Overall, the evidence would suggest that movement-related neurons are distributed widely through both pallidal segments, with the exception of the more dorsal areas, without a preference for the posteroventral GPi (DeLong et al. 1985).

Furthermore, abnormally functioning neurons are not confined to the posteroventral GPi in PD. The characteristics of pallidal neuronal activity in experimental and idiopathic PD are well established. Firing rates of GPi and GPe neurons are higher and lower, respectively, in MPTP-treated, compared with healthy, monkeys (Filion et al., 1988; Filion and Tremblay 1991). In MPTP-treated monkeys, the dopamine agonist apomorphine decreases the firing rate of GPi neurons and increases the firing rate of GPe neurons (Filion et al., 1991). Furthermore, movement-related GPi neurons of MPTP-treated monkeys show a loss of their normal specificity for movements of single joints, and instead respond to movements of several joints (Filion et al., 1988). There is evidence that similar patterns of pallidal function occur in humans with idiopathic PD (Sterio et al., 1994; Hutchison et al., 1994; Beric et al., 1996), and that these firing patterns, too, are responsive to apomorphine (Hutchison et al., 1997).

It is not clear, however, that pallidal neurons with abnormally increased activity in PD are confined to the medial portion of the GPi. In a study of 6 PD patients, Hutchison et al. (1994) found that neurons with significantly increased firing rates compared with GPe were

found predominantly within the medial portion of GPi, whereas the mean firing rate of neurons in the lateral portion of GPi was not significantly different to that of GPe neurons. However, in a subsequent paper, the same authors found that apomorphine significantly decreased neuronal firing rates in both the medial and lateral portions of the GPi in PD patients, suggesting that baseline neural activity is abnormally high in both portions of the GPi in PD (Hutchison et al., 1997). Secondly, if, as is generally accepted, increased neural activity within the GPi is a consequence of nigrostriatal dopamine depletion, it is difficult to explain how the medial and lateral portions of the GPi could be differentially affected by this. Neurons forming the direct pathway from striatum to GPi contain the inhibitory neurotransmitter GABA, as well as substance P (Graybiel 1986). Therefore, increased striatopallidal outflow in PD should diminish inhibitory outflow to the entire GPi. The division of the GPi into medial and lateral portions is based on anatomical rather than physiological grounds, as the pallido-fugal pathways from each portion (the ansa lenticularis and fasciculus lenticularis, respectively) are anatomically separate (Nauta and Mehler, 1966). Finally, if heightened neural activity were confined to the medial portion of the GPi in PD, how could one explain the improvement in Parkinsonism resulting from lesions pathologically proven to be confined to the ansa lenticularis, which arises from its lateral portion (Beck and Bignami, 1968)?

In summary, there is considerable evidence to support the claim that lesions of the GPi outside its posteroventral portion are effective for the relief of "off" state motor dysfunction in PD.

8.4.2.2 Lesions of the GPe and of the GPi outside the posteroventral portion are effective for the treatment of drug-induced dyskinesias

Like those examining akinesia, studies that have examined the neural correlates of drug-induced dyskinesia have mostly used animal models. These models have either used dopaminergic drugs to induce dyskinesias in MPTP-treated monkeys (Filion et al., 1991), or have injected GABA antagonists into the GPe in order to induce GPi hypoactivity via a reduction in subthalamopallidal outflow (Crossman et al., 1988; Mitchell et al., 1989). In neither model has a preponderance of abnormally functioning neurons in the posteroventral GPi been described.

The situation may be different in idiopathic than in experimental PD. Results from studies of GPi stimulation suggest that relief of "on" state dyskinesias is best obtained by stimulation in the most ventral part of the GPi (Bejjani et al., 1997; Krack et al., 1998). By contrast, dyskinesias were exacerbated by stimulation of more dorsal parts of the pallidum. It is not clear that the results of stimulation studies are applicable to lesion studies, as stimulation of more dorsal contacts within the GPi may affect GPe function, with secondary and as yet uncertain effects on GPi function. However, there is some evidence that the location of the pallidotomy lesion within the posteroventral GPi influences clinical results. Gross et al. (1999) found significant variations in the effect of pallidotomy on dyskinesia, akinesia, rigidity and postural instability/gait disturbance according to lesion location along the anteromedial to posterolateral plane within the posteroventral GPi. Such regional specialisation of the GPi is easier to understand for some motor functions than for others. For example, it is known that volitional limb movement is mediated by pallido-thalamocortical outflow (Roland et al., 1980), while muscle tone and axial mobility are mediated by descending pallido-tegmental outflow to the pedunculopontine nucleus (Delwaide et al., 1991). However, it is more difficult

to understand how dyskinesia and akinesia which, in kinematic terms, occupy two ends of a movement continuum, could be controlled by completely separate neuronal populations. This would seem to imply a gain, rather than a loss, of neuronal function in PD, for which there is no experimental evidence. In fact, there is evidence that the reverse applies, with pallidal neurons manifesting a loss of somatotopic specificity in MPTP-treated monkeys (Filion and Tremblay 1988). It is likely that dyskinesia and akinesia are the result, not of the activity of separate neuron populations, but of different patterns of activity of the same population (Obeso et al. 1997; Levy et al. 1997). In keeping with this notion, several other studies have found no relationship between lesion site within the GPi and clinical outcome (Krauss et al. 1997; Burns et al., 1997).

What effect might lesioning the GPe, as occurred in many cases, have had on our clinical results? The role of the GPe in Parkinsonian motor dysfunction, such as akinesia and dyskinesia, is being reevaluated. According to the model of basal ganglia circuitry proposed by Albin et al. (Albin et al., 1989), pathological hyperactivity of the STN in PD, which is believed to cause akinesia, is a direct effect of pathological hypoactivity of the GPe. However, recent studies of the biological activity of GPe neurons in control and Parkinsonian subjects have called this model into question. Herrero et al. (Herrero et al., 1996) found that levels of mRNA encoding glutamic acid decarboxylase (GAD_{67}), the synthetic enzyme for GABA, were not significantly different in the GPe of monkeys and humans with PD as compared with their normal counterparts. This contrasted with the situation in GPi and SNr, where levels of GAD_{67} mRNA were significantly higher in Parkinsonian than control subjects. Similar results were obtained when cytochrome oxidase activity was used as a marker of metabolic activity (Vila et al., 1996). If metabolic activity of the GPe is unchanged in PD, how can one explain the reduction in GPe neuronal firing rate that has been repeatedly demonstrated in

experimental and idiopathic PD (Filion and Tremblay 1991; Hutchison et al., 1994)? Neurophysiological studies of the GPe in MPTP-treated monkeys show that, although net firing rate is diminished compared with normal animals, there is an increase in so-called "burst firing activity" (Filion and Tremblay 1991). This pattern of firing may actually increase GABA release to the STN, as has been demonstrated in other neurotransmitter systems (Gonon 1988).

A recently proposed model of basal ganglia function has the GPe and STN, via their reciprocal connections, varying their activity according to the demands of normal movement. In PD, the GPe is able to maintain relatively normal metabolic activity by balancing competing inhibitory inputs from the striatum and excitatory inputs from STN. According to this model, the STN becomes hyperactive in PD, not because of reduced GABAergic input from GPe, but because of disruption of putative inputs to the STN from SNc, parafascicular nucleus and/or cerebral cortex, as a result of nigrostriatal dopamine depletion (Chesselet and Delfs 1996; Levy et al., 1997; Obeso et al., 1997). According to the model, lesioning the GPe would have little or no effect on akinesia.

However, recent work suggests that the GPe is of major importance in the genesis of drug-induced dyskinesias. GPe neurons of MPTP-treated monkeys increase their firing rate in association with dyskinesias induced by dopaminergic drugs (Filion et al., 1991). This is associated with a decrease in firing rate within the GPi, presumably mediated by inhibitory outflow from the GPe to GPi, either directly (Hazrati et al., 1990) or indirectly, via the STN. It is known that choreiform dyskinesias can be induced in healthy monkeys by the injection of the GABA antagonist bicuculline into the GPe (Crossman et al., 1988; Mitchell et al., 1989). Studies of 2-deoxyglucose uptake suggest that these dyskinesias are mediated by inhibition of subthalamopallidal and pallidothalamic pathways (Crossman et al., 1988; Mitchell et al.,

1989). Data such as this suggested that the GPe played an important role in drug-induced dyskinesias, but this was tempered by the finding that ablation of the GPe in dyskinetic MPTP-treated monkeys did not have any anti-dyskinetic effect (Blanchet et al., 1994). More recently, however, Matsumura et al. (1995) measured the firing rates of GPe and GPi neurons in healthy monkeys before and after injection of bicuculline into the GPe. The majority (71%) of responding GPe neurons increased their activity following bicuculline injection, in a manner identical to that previously noted in MPTP-treated monkeys in whom dyskinesias were induced by dopaminergic drugs (Filion et al., 1991). This strongly suggests that GPe hyperactivity is a driving force for drug-induced dyskinesias in PD. However, within the GPe, a significant minority of cells became hypoactive after bicuculline. Furthermore, only a minority (41%) of GPi neurons decreased their activity in response to bicuculline injection into the GPe, with the majority becoming hyperactive. This suggests that it may be the pattern of neural firing, rather than the net firing rate, that is the critical factor in driving drug-induced dyskinesias. In support of this notion, the authors found clusters of GPi neurons in which the central neurons were hypoactive, and were surrounded by a rim of hyperactive or unresponsive neurons. The authors postulate that, in these clusters of GPi neurons, the central cells are hypoactive as a result of inhibition by hyperactive GPe cells, while the surrounding GPi cells are hyperactive because of a reduction in inhibitory outflow from GPe cells made hypoactive by monosynaptic lateral inhibition within the GPe. The authors propose that it is this imbalance of activity within the GPe and GPi, rather than a net reduction in GPi activity, that is the neural basis of drug-induced dyskinesias. This may help explain the paradox by which pallidotomy, by abolishing this unbalanced GPi neural activity, can relieve dyskinesias as well as improve akinesia (Obeso et al., 1997).

8.5 Conclusions

The present study does not help clarify the issue of whether either method of intra-operative targeting - by microelectrode recording or macrostimulation – is superior to the other, either in terms of efficacy or safety. However, our study does demonstrate that, although precise lesioning within the posteroventral GPi may not be as reliably achieved with macrostimulation guidance, this need not occur at the cost of reduced clinical efficacy. Significant improvements in akinesia and dyskinesia occurred despite lesions being made in structures ventral and lateral to the posteroventral GPi.

Our results invite several possible interpretations. On the one hand, they can be interpreted as supporting the primacy of the posteroventral GPi as the preferred site for pallidotomy lesions. In other words, as long as the posteroventral GPi is included in the lesion, as it was in most cases, then lesioning adjacent parts of the pallidum or its efferent pathways will not necessarily diminish the clinical effect. However, relative sparing of the medial GPi on late post-operative CT scans performed on several of our cases suggest that the early involvement of the GPi in many of our lesions was probably due to perilesional oedema, rather than coagulative necrosis. This invites an alternative interpretation of our results – namely, that including the posteroventral GPi in lesions is not critical for clinical efficacy, and that comparable results can be obtained by including lateral GPi, ansa lenticularis and/or GPe in the lesion. As has been discussed, several levels of scientific evidence support this interpretation of our results.

According to this interpretation, the critical requirement for an effective GPi lesion in PD is that it should significantly diminish GPi output. Akinesia and dyskinesia are seen to represent the results of different types of aberrant activity of the same pallidal neuron population. Thus, relief of akinesia and dyskinesia may simply require the ablation of a critical

number of such neurons, irrespective of where in the GPi they reside. Clearly, other factors, such as lesion size, patient age and duration of disease may also influence results of lesioning, but this remains largely unproven. Recent evidence on neural activity within the GPe in experimental PD suggests than lesioning the GPe may not exacerbate akinesia, as would be predicted from the conventional model of basal ganglia function, and may aid in the relief of dyskinesias.

CHAPTER 9

CONCLUDING REMARKS

The central aim of this thesis has been to better understand the mechanism by which pallidotomy influences the control of voluntary movement in PD. The paradox of improved motor function after pallidotomy is two-fold. Firstly, it is difficult to conceive how a procedure that destroys a critical output nucleus of the basal ganglia could improve volitional movement. Secondly, it is not clear how pallidal lesioning could simultaneously improve both hypokinetic (akinesia/bradykinesia) and hyperkinetic (drug-induced dyskinesia) aspects of Parkinsonian motor dysfunction.

The experiments described in this thesis have provided valuable insights into both these questions.

Improvement in akinesia/bradykinesia after pallidotomy for PD

Some early reports suggested that the improvement in akinesia/bradykinesia after pallidotomy occurs because of a restoration of normal signalling between the GPi and SMA. However, this idea presupposes that abnormal GPi function in PD is simply a matter of "too much" neuronal function, which can be returned towards normal by partial ablation of the GPi. However, abnormal GPi neuronal activity in PD is both qualitative and quantitative in nature. Disinhibition of the GPi as a result of striatal dopamine depletion causes a net increase in mean firing rate of GPi neurons. This is associated with a loss of the normal phasic modulations in GPi activity that govern the initiation and termination of movements by the SMA. Ablation of the GPi might diminish net neural firing rate, but would not restore – and,

indeed, may damage further – these phasic variations in GPi activity. The disruption of GPi neural firing patterns becomes even more complex when drug-induced dyskinesias alternate with akinesia. Here, rapid oscillations between neural hypoactivity and hyperactivity within the GPi are seen.

Our results suggest that the improvement in volitional movement after pallidotomy does not result from improved signalling between the GPi and mesial frontal cortex. Rather, volitional movement appears to improve by means of a shift in motor control away from the "medial motor system", which includes the GPi, VL thalamus and SMA, to a more laterally placed cortical network. This network, which includes the lateral premotor and inferior parietal cortices, is believed to govern the integration of somatosensory and visual inputs into motor control. The lateral premotor system is hyperactive in PD as a result of increased reliance on sensory cues for the execution of movement. Pallidotomy, by abolishing excessive inhibition of the SMA, may allow sensory inputs greater access to premotor/supramotor cortical areas, thus facilitating movement. A number of lines of evidence in our work support this concept. Firstly, our analysis of the kinematics of voluntary upper limb movement showed that the performance of externally cued movements improved after pallidotomy, while internally generated finger movements did not. Secondly, the early component of the Bereitschaftspotential, which is believed to reflect neural activity within the mesial frontal cortex ahead of internally generated movements, did not improve after pallidotomy. As for the kinematic experiment, the failure of the early BP to improve may also represent a greater use of external cues to facilitate movement post-operatively. Previous work has shown that when external cues are provided to PD patients, the amplitude of the movement-related potential measured over the vertex declines, and that this is offset by an increased amplitude over more

lateral cortical areas. Similarly, recent PET studies have demonstrated an increase in activity of posterior parietal cortical regions after interventions such as levodopa infusion, subthalamotomy and STN stimulation that, like pallidotomy, improve bradykinesia. Increased activity in posterior parietal regions would support a greater role for sensory cues in the execution of movement.

Our observations on the effect of pallidotomy on spontaneous blinking provide further evidence that basal ganglia function does not improve after pallidotomy. Spontaneous blinking is an automatic movement that is controlled at a mainly subcortical level by a neural network that includes the SNr/GPi complex. The SNr has reciprocal connections with the GPi and, like the GPi, exhibits an increase in neural activity in PD. If pallidotomy caused a partial normalisation of neural activity within the SNr/GPi, one would expect to see an increase in blink rate post-operatively. However, no such improvement occurred.

Improvement in both akinesia and drug-induced dyskinesias after pallidotomy for PD

The second paradox of the effect of pallidotomy on motor function in PD is the simultaneous improvement of both hypo- and hyperkinetic aspects of motor dysfunction. Our results do not resolve this paradox, but highlight several possible explanations. Dyskinesias and akinesia may represent the kinematic consequences of two different types of aberrant pallidal neural activity. Neurophysiological studies in Parkinsonian animals and humans show that akinesia is associated with a tonic increase in GPi neural activity. This pattern of activity is the dominant pattern early in the course of the disease, before the development of motor fluctuations. Dyskinesias, on the other hand, are associated with rapid variations in neural activity from marked hypoactivity to marked hyperactivity. It can be seen that pallidotomy would abolish both forms of abnormal activity. Akinesia would improve because sensory cues

are allowed greater access to medial premotor areas formerly under tonic pallidal inhibition. Dyskinesias would improve because the chaotic GPi neural activity that drove them has been abolished.

An alternative explanation for the improvement in dyskinesias after pallidotomy is that lesioning the GPe, as occurred in many of our cases, may improve dyskinesias. Experimental models of dyskinesias suggest that the GPe plays an important role in the control of dyskinesias. It is possible that some of the improvement in dyskinesias in our study was due to inclusion of the GPe in the lesion, while improvement in akinesia was mediated by lesioning the GPi. However, this hypothesis would not explain the improvement in both akinesia and dyskinesias seen in other studies in which post-operative imaging confirmed that lesions involved the GPi alone.

The impact of surgical technique and lesion location on the clinical results of pallidotomy

The best surgical technique for pallidotomy would provide the best clinical results with the least morbidity. The two main methods of intraoperative lesion localisation are by microelectrode recording/stimulation and by macrostimulation. This thesis was not designed to compare the two techniques and thus does not resolve the question of which, if either, is superior. However, it does confirm that good clinical results, with negligible morbidity, can be obtained using macrostimulation following radiological targeting. The implications of this are significant. Microelectrode guided pallidotomy requires substantially more time, neurophysiological monitoring and expense than macrostimulation guided pallidotomy. Patients, who undergo surgery awake and in the “off” motor state, are likely to tolerate macrostimulation guided pallidotomy better because the procedure is shorter.

The significance of pallidotomy lesion location on clinical results is another controversial issue. There is little doubt that targeting by means of microelectrode techniques provides more accurate placement of lesions. Microelectrode recording enables the operator to verify placement of the electrode within the GPi and avoid neighbouring areas in which lesions might be ineffective or even harmful. Using post-operative CT scans, we confirmed that, while lesions made under macrostimulation guidance consistently involved the medial portion of the GPi, many lesions also involved the lateral portion of the GPi or the GPe. This observation, taken in association with our clinical results, can be interpreted in a number of different ways. Firstly, it may be that other regions of the GPi, in addition to the posteroventral medial GPi, play an important role in causing motor dysfunction in PD. Thus, the critical issue in pallidotomy may be that net GPi output is diminished, not the exact location of the lesion itself. However, as the medial GPi was consistently lesioned in our patients, the opposite view can also be taken. In other words, the critical pallidal region in pallidotomy may be the posteroventral medial GPi. As long as this region is included in the lesion, it does not matter clinically if other regions are also lesioned as "innocent bystanders". We favour the first interpretation for a number of reasons. Firstly, abnormally functioning neurons are not confined to the posteroventral medial GPi in animals with experimental PD, but are widely distributed through both portions of the GPi. Secondly, the division of the GPi into medial and lateral portions is an anatomical concept, based on their discrete input and output pathways. However, the two portions of the GPi share common connections with the striatum, STN and GPe and should respond in similar ways to changes in activity of these connections as a result of dopamine depletion in PD. Thirdly, the ansa lenticularis takes its origin from the lateral portion of the GPi, and ansa lenticulotomy improves akinesia/bradykinesia in PD.

In contrast to the potential role for the GPe in the genesis of dyskinesias, our results suggest that the GPe does not play a critical role in generating akinesia in PD. Our study showed that the GPe can be included in pallidal lesions without compromising the effect of surgery on akinesia. This finding challenges the traditional model of basal ganglia function, in which the GPe is seen as an important conduit between the striatum and STN. According to this model, hypofunction of the GPe as a result of dopamine depletion in PD leads to hyperfunction of its target, the STN. Lesioning the GPe should exacerbate akinesia by further disinhibiting the STN and GPi. Several lines of evidence now cast doubt on this concept. It has been shown that, although net neural activity in the GPe is decreased in PD compared with control animals, metabolic activity within the GPe does not significantly differ between the two groups (Herrero et al., 1996; Vila et al., 1996). In PD, there is an increase in so-called "burst firing activity" within the GPe (Filion and Tremblay 1991). This pattern of firing may actually increase GABA release to the STN, as has been demonstrated in other neurotransmitter systems (Gonon 1988). Thus, a revised model of basal ganglia function has the GPe and STN, via their reciprocal connections, varying their activity according to the demands of normal movement. In PD, the GPe is able to maintain relatively normal metabolic activity by balancing competing inhibitory inputs from the striatum and excitatory inputs from STN. According to this model, the STN becomes hyperactive in PD, not because of reduced GABAergic input from GPe, but because of disruption of inputs to the STN from SNc, parafascicular nucleus and/or cerebral cortex (Chesselet and Delfs 1996; Levy et al., 1997; Obeso et al., 1997). According to the model, lesioning the GPe would have little or no effect on akinesia, as we found in our study. In summary, our results tend to support an important role for the GPe in the genesis of dyskinesias, but not for akinesia/bradykinesia. At the very

least, they suggest that including the GPe in the pallidal lesion dos not compromise the beneficial effect of pallidotomy on either akinesia or dyskinesias.

Many studies of pallidotomy in PD, particularly those in which microelectrode targeting has been used, emphasise the importance of making lesions within the posteroventral medial GPi. Indeed, one study has found that the degree of improvement in dyskinesias, akinesia, rigidity and axial motor dysfunction varies according to the location of the lesion along the anteromedial to posterolateral plane *within* the posteroventral GPi (Gross et al., 1999). The implication of this finding is that, not only is the posteroventral GPi critical for the control of motor function, but different regions of it are specialised for different aspects of motor control. However, this view of GPi function is not supported by other experimental evidence we have quoted, including the fact that abnormally functioning neurons are widely distributed throughout the GPi in PD, and that dyskinesia and akinesia have been shown to represent the consequences of different patterns of dysfunction of the same neuron population.

Our results support a somewhat "reductionist" view of the importance of precise lesion placement in pallidotomy. We propose that the critical issue in pallidotomy lesion placement is that GPi output be significantly diminished, so as to diminish activity of the medial motor system in favour of the lateral motor system. Total ablation of the GPi may be more reliably achieved using microelectrode guidance, but clinically useful improvements in akinesia and dyskinesia can be achieved by partial ablation of the GPi using macrostimulation-guided pallidotomy. Furthermore, inclusion of the GPe within the lesion does not appear to compromise the beneficial effects of pallidotomy on akinesia. The GPe appears to play a relatively small role in the genesis of STN hyperfunction and, therefore, in the pathogenesis of akinesia. However, experimental models of drug-induced dyskinesias suggest that the GPe

may play a role in the pathogenesis of dyskinesias. If so, inclusion of the GPe in pallidotomy lesions may be therapeutically useful.

The influence of pallidotomy lesion size on the duration of the clinical effects of pallidotomy

Like other studies before it, our study is too small to make conclusions on the influence of lesion size on clinical outcome. We can, however, make several observations on this topic. Firstly, although statistically significant, the improvements in akinesia in our study were maximal at 3 months post-operatively, and were returning towards baseline values at 6 months post-operatively. This observation has been made by another group that has, over the course of 3 papers, reported longterm follow up of PD patients following macrostimulation-guided pallidotomy (Kishore et al., 1997; Samii et al., 1999; Pal et al., 2000). In this group's series, the beneficial effects of pallidotomy on akinesia/bradykinesia were negligible by 12 months' follow up. In contrast, several groups using microelectrode techniques have reported more durable effects on akinesia/bradykinesia (Fazzini et al., 1997; Lang et al., 1997; Fine et al., 2000; Lai et al., 2000). It is tempting to conclude that microelectrode-guided pallidotomy produces more long lasting effects than macrostimulation-guided pallidotomy on akinesia/bradykinesia. The mechanism for this difference may be that, using microelectrode recording and stimulation, the operator can be more confident of being in the GPi and of avoiding other eloquent areas, such as the optic tract. Thus, he or she could make larger GPi lesions with more long lasting effects on akinesia/bradykinesia. Is this hypothesis supported by observations on relative lesion sizes in macrostimulation versus microelectrode-guided pallidotomy? In our study, mean lesion volume at the time of late post-operative CT scanning was 40.2mm^3. This compares with lesion volumes of 95mm^3 (Laitinen et al., 1992) and

65.5mm^3 (Johansson et al., 1997) in two previous studies in which late post-operative CT scans were used to measure lesion volume following macrostimulation-guided pallidotomy, and with 22mm^3 (Krauss et al., 1997) in a study in which late post-operative MRI was used to measure lesion volume following microelectrode-guided pallidotomy. Many other studies have used early post-operative MRI to measure lesion volume, either before or after subtracting presumed perilesional oedema. Such studies are not directly comparable with ours, as it is not possible to differentiate lesion from perilesional oedema using CT.

In summary, the data do not support the contention that the use of microelectrode techniques during pallidotomy leads to the formation of larger pallidal lesions. It remains unclear whether lesions strategically placed in certain parts of the pallidum may lead to more long lasting effects on akinesia/bradykinesia. There is an emerging consensus that, whatever the surgical technique used, the effects of pallidotomy on akinesia/bradykinesia and on axial motor dysfunction are temporary, while the effects on drug-induced dyskinesias persist. However, there appears to be a difference between surgical techniques in the longevity of the effects on akinesia/bradykinesia. Studies using microelectrode techniques have shown that benefits on akinesia/bradykinesia can persist to between 2 and 4 years, while studies, like ours, in which macrostimulation-guidance was used, show the effects on akinesia/bradykinesia wearing off by 12 months post-operatively, and being non-significant thereafter. Some aspects of "off" motor dysfunction, such as ipsilateral bradykinesia and postural instability/gait dysfunction are in fact worse than baseline by 2 years follow up. As improvement in akinesia after pallidotomy appears to rely on adequate ablation of the GPi, this suggests that ablation of the GPi is more complete following microelectrode-guided pallidotomy. As microelectrode-guided lesions appear to be no larger in general from lesions made using macrostimulation

techniques, the difference presumably lies in the precision with which lesions can be placed within the GPi using microelectrode recording. Lesioning regions outside the GPi may not mitigate against a favourable clinical outcome, as we have argued above, but optimal results appear to require adequate reduction in GPi output, however that is achieved.

Final conclusions on the role of pallidotomy in the management of Parkinson's disease

The major aim of this thesis has been to elucidate the mechanism by which pallidotomy improves volitional movement in PD. However, the results of the clinical part of this thesis, taken in association with the results of other series, enable us to make several conclusions concerning the role of pallidotomy in the management of PD. Firstly, the beneficial effect of pallidotomy on drug-induced dyskinesias is greater and more long lasting than that on akinesia/bradykinesia. Secondly, when akinesia/bradykinesia improves following pallidotomy, it does not usually improve sufficiently to allow a reduction in dopaminergic drug therapy. Thirdly, the improvements in quality of life and activities of daily living that occur after pallidotomy are mostly attributable to the effects on "on" state motor dysfunction (ie. dyskinesias), rather than on "off" motor dysfunction. For these reasons, we do not believe that pallidotomy should be used primarily for the treatment of akinesia and bradykinesia, especially where they remain drug responsive. Rather, the main role of pallidotomy in the management of Parkinson's disease is in the palliation of disabling drug-induced dyskinesias. Any additional benefit of pallidotomy on akinesia/bradykinesia is welcome, but should not constitute the primary indication for the procedure. When dyskinesias have been alleviated by pallidotomy, symptoms of akinesia/bradykinesia can then be managed by continuation of dopaminergic drug therapy, often at higher doses than could be tolerated pre-operatively. Pallidotomy is an ablative procedure that is irreversible and does not prevent underlying disease progression.

Therefore, while it is an extremely useful palliative procedure in certain patients with advanced disease, it is one of several different surgical approaches that should be considered in patients in whom medication alone is providing inadequate symptom control.

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REPRINTS OF PUBLISHED PAPERS

ASSOCIATED WITH THIS THESIS

T. E. Kimber, C. S. Tsai, J. Semmler, B. P. Brophy and P. D. Thompson (1999)
Voluntary movement after pallidotomy in severe Parkinson's disease.
Brain, v. 122 (5), pp.895-906, May 1999

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Movement Disorders, v. 15 (5), pp.982-985, September 2000