THE BASAL GANGLIA AS A GATE CONTROL MECHANISM FOR POSTURAL SET

by

ABDEL MAGID OSMAN BAKHEIT

THESIS PRESENTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY TO THE DEPARTMENT OF NEUROLOGY, FACULTY OF MEDICINE, UNIVERSITY OF GLASGOW

(July 1990)

Contents

Dedication

To my parents who withstood sustained hardships so that their children could go to school, although they did not have the opportunity themselves ... who had the foresight to recognise the value of education when their contemporaries did not ... who had the selflessness to sacrifice their own comfort so that their children may have a better chance in life than they themselves had ... to them, in recognition of their huge effort and to express infinite love and gratitude, I dedicate this work.

AMB

Acknowledgement

I would like to record my thanks to many of my medical colleagues and other members of staff at the Institute of Neurological Sciences, Glasgow.

I am particularly most grateful to Professor JA Simpson who conceived the idea of this project, guided and encouraged me throughout the last three years.

Without the continuous and generous support of my supervisor Professor PGE Kennedy this work would have not been possible and I am very grateful to him.

Dr Andrew Weir has kindly allowed me access to the laboratory equipment and introduced me to clinical neurophysiology. My thanks are also due to Dr Stig Hansen and his staff in the department of Medical Physics for writing up the computer programme for my experiments. Dr Gordon Murray, Senior lecturer in Medical Statistics, University of Glasgow, has kindly advised on the statistical analysis of data.

Finally I am also grateful to all patients, their relatives and friends who were keen to participate in this study and eager to help with these experiments.

Summary

Impairment of righting reflexes is one of the cardinal features of basal ganglia disease. Although the precise anatomical organization of these reflexes in man is not fully understood, neurophysiological experiments suggest an important role for the striatum (i.e. caudate nucleus and putamen), pallidum, the supplementary motor area (SMA) and the motor and sensory cortices in righting reactions (see chapter 1-3).

The hypothesis that the present work attempted to test is that the basal ganglia act on the cerebral cortex via dopaminergic pathways to delay the onset of voluntary self-paced movements (which cause perturbation of balance) until the appropriate postural set is adjusted by the SMA and by lower brain stem structures (Simpson, unpublished, 1986, Simpson & Fitch, 1988). This was studied by examining the effects of perturbation of balance on the temporal sequence of activation of postural muscles and its relationship to the Bereitschaftspotential (which probably reflects the functional activity of the SMA as discussed later) in patients with Parkinson's disease (PD).

In this study it was found that the onset of the electromyographic (EMG) activity of postural muscles was significantly later in patients with PD as compared with that of healthy subjects and patients with neurological disorders other than parkinsonism. These findings would be compatible with the hypothesis that failure to establish the SMA controlled postural set allows earlier onset of cortical area 4 activity driven by

volition. Interestingly, the length of delay of EMG activity in these patients was proportional to the severity of PD. This observation is accounted for in this model by a "gating" mechanism. Consequently, gating by the basal ganglia will depend on the degree of perturbation of balance.

List of tables

List of figures

Figure 6/2

Electromyographic activity of "prime mover", tensor fascia lata and tibialis anterior and Bereitschaftspotential and head acceleration in a patient with Parkinson's disease.

CHAPTER ONE

INTRODUCTION

a) Postural reflexes in healthy subjects

b) Disruption of postural mechanisms by disease

c) The basal ganglia as a gate control mechanism for postural set - the hypothesis.

Introduction

a) Postural reflexes in healthy subjects:

The complex mechanism by which man maintains the erect posture against the destabilizing effects of gravity or following perturbation of balance, e.g. caused by a ballistic movement of a body segment, involves a sequence of three related processes, namely:

1. the unconscious assessment of the position of the centre of body mass using a combination of visual, vestibular and somatosensory cues,

2. the integration of this sensory information by a central postural control mechanism, and

3. the co-ordinated activation of limb and trunk musculature to adjust the centre of body mass over the base of support provided by the feet and activation of the neck muscles to position the head in space to maintain gaze fixation in relation to the visual surroundings.

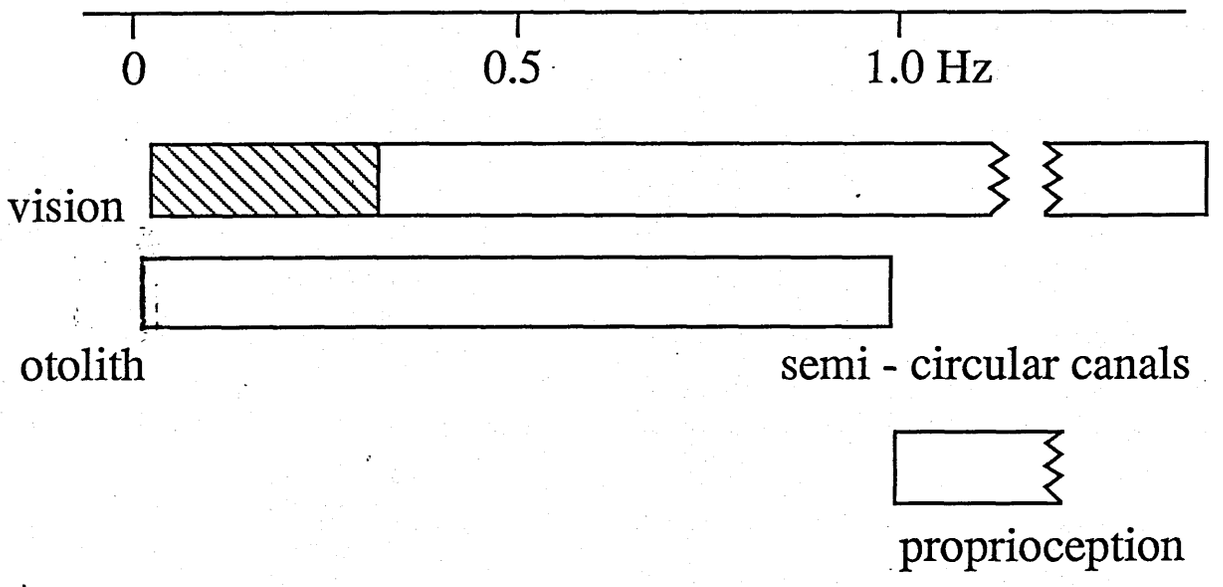
The contribution of visual, vestibular and somatosensory inputs in postural control is confirmed by clinical observations as well as by physiological experiments. Romberg's test, for example, exploits the fact that vision compensates for proprioceptive sensory loss. Vision also compensates for vestibular dysfunction: patients with vestibular

disease can walk when their eyes are open but fall if blindfolded. Furthermore, loss of two of these sensory modalities (in any combination) results in complete failure of postural stabilization.

There is abundance of experimental work which confirms these clinical observations. For example, recently Diener & Dichgans (1988) examined the contribution of visual sensory input to postural stabilization in healthy subjects standing on a platform. Comparison between trials with the eyes open and the eyes closed showed that sudden displacement of the supporting platform caused a 50% increase in postural sway when the subjects were blindfolded. These authors have also evaluated the effect of vestibular dysfunction and the impairment of proprioceptive sense on postural stabilization by changing the head position prior to platform displacement and by ischaemic blocking of 1a afferent fibres at the ankles, respectively. Under both experimental conditions there was a significant body sway with the eyes open and the subjects were unable to stand unsupported when blindfolded. Interestingly, disequilibrium was greatest with slow but not fast platform displacements, suggesting different mechanisms of postural control depending on the velocity of movement causing the perturbation of balance (see below).

While visual, vestibular and somatosensory inputs are complementary to each other in postural stabilization each of these systems operates most efficiently at a given frequency range. This is visually illustrated in figure 1/1 and is confirmed by the following experiments:

Figure 1 /1
Visual illustration of the optimal working frequency range for visual, vestibular and somatosensory inputs. Note the overlap between the various sensory modalities



1. There was no effect of eye closure on displacement of the centre of body mass in subjects standing on a sinusoidally tilting platform when the stimulus frequency was outside the range of 0.03 - 0.3 Hz. However, at this frequency range the displacement was minimal with the eyes open and maximal when the eyes were closed (Diener et al 1982). Vision does not contribute to postural stabilization at velocities less than 0.03 Hz probably because the latter is below the threshold of visual motion perception (Leibowitz et al, 1972).

2. Direct recordings from deafferented human muscle (Poppele & Kennedy, 1974) and also measurements of muscle spindle discharge during movement (Burke 1980) showed that the maximal activity in human muscle spindles resulting from sinusoidally modulated muscle stretch occurs at a frequency between 1 and 2 Hz.

The influx of visual, vestibular and somato-sensory information essential for the control of motor activity is integrated at basal ganglia level (see chapter 3). Depending on stimulus conditions a given "strategy" of postural stabilization is then selected with the net result of bringing the centre of body mass within the area of the base of support. The body is then straightened out with respect to the legs, while gaze fixation is maintained throughout the initial phase by head rotation to compensate for trunk rotations (Allum et al 1988). Three different strategies have been described (Horak & Nashner 1986, Nashner

et al, 1985): an "ankle strategy", a "hip strategy" and a "combined" one. While the ankle strategy is utilized in response to slow perturbations and results in activation of the leg and lower trunk muscles in a distal to proximal sequence, the hip strategy shifts the body mass more quickly by flexing the hip and corrects postural instability caused by high velocity and amplitude perturbations. However, under usual physiological conditions a combination of these two different strategies is used more often.

b) Disruption of postural mechanisms by disease:

Lesions of the basal ganglia, cerebellum and pyramidal tracts, as well as interruption of the peripheral somatosensory pathways may compromise postural stability. However, there are important quantitative and qualitative differences in the postural instability caused by disease of these structures. The physiological mechanisms underlying the impairment of balance in these conditions are also different.

Patients with basal ganglia lesions usually have the most severe postural instability (see chapter 4). Furthermore, in contrast to those with pyramidal tract and cerebellar disease, these patients have no awareness of their postural deficit and make no corrective postural adjustments or attempt to prevent falls. This has been attributed to loss of kinaesthetic self-awareness (Moore, 1987) and faulty processing

of postural reflexes which result from interruption of the striato-pallido- thalamo- cortical pathways (Simpson & Fitch, 1988, Labadie et al, 1989).

On the other hand, conditions which cause damage of the cerebellar afferents, e.g. Friedreich's ataxia, do not interfere with kinaesthetic self-awareness and the resulting postural deficit is usually well-compensated by vision (Diener et al, 1984). Interestingly, disease of the cerebellar hemispheres has no significant effect on postural mechanisms, presumably because the neocerebellum is more important for initiation and control of movement, while the paleocerebellum is concerned with postural reflexes.

The defect leading to impairment of postural reflexes in hemiplegics appears to be in the efferent limb of the postural reflex loop, i.e. the cortico-rubro-spinal tract, as would be expected. This was shown in physiological experiments by demonstrating that the sequence of agonist-antagonist activation of postural muscles in response to perturbation and also the latency and amplitude of muscle activity are quantitatively and qualitatively different in hemiplegics from those of age and sex-matched healthy controls (Di-Fabio, 1987).

c) The basal ganglia as a gate control mechanism for postural set: the hypothesis.

There is little doubt that the basal ganglia play a multi-faceted role in the control of voluntary movements because of their anatomical site and abundance of their synaptic connections, but it would appear that a direct influence of these structures on motor function is unlikely since they do not have direct connections with bulbar or spinal motor nuclei (Nauta & Mehler, 1966). Theoretically, however, it is possible that the basal ganglia modulate the cortical output which is essential for the excution of motor activity and / or they regulate the ease with which sensory information gains access to motor areas, i.e. they gate sensory input to the cerebral cortex. The evidence supports both concepts.

Evidence for the first concept was provided by Newton and Price (1975), who found that the simultaneous electrical stimulation of the caudate nucleus and the sensori-motor cortex evoked either inhibition or facilitation (depending on the site of stimulus within the caudate or putamen) of cortically-induced tibialis anterior (TA) responses in the intact cat. Simultaneous stimulation of the globus pallidus and motor cortex increased the tibialis anterior response and had no inhibitory effect. By contrast, stimulation of the same loci in the caudate or globus pallidus alone did not result in TA response. Moreover, similar experiments in the decorticate cat showed deficient inhibitory

influences of the caudate on TA responses which indicates that this structure exerts its inhibitory influences on the motor cortex directly.

Similarly, gating of sensory input by the basal ganglia to the cortex has been established (Schneider et al, 1982). Stimulation of the trigeminal sensory nucleus in the intact animal activates oro-facial sensory afferent fibres and generates short latency field potentials in the trigeminal motor nucleus (TMN). Destructive bilateral striato-pallidal lesions caused a significant decrease in TMN field potentials threshold, i.e. increase in TMN excitability. This facilitatory effect of conduction from the sensory to the motor components of the trigeminal nerve is not due to removal of a direct inhibitory influence of the basal ganglia on TMN, the evidence being that there was no difference in stimulus threshold before and after striato-pallidal lesions when the afferent sensory input from the faces of these animals was blocked with a local anaesthetic (elimination of somatosensory influx should restore excitability to normal if the post-lesion reduced threshold was due to loss of a direct inhibitory influence of the basal ganglia on TMN).

On the other hand, while clinical observations suggest a role for the basal ganglia in postural stabilization in man, experimental evidence is sparse. Furthermore, the physiological significance of the recent findings of an abnormal Bereitschaftspotential in Parkinson's disease (Simpson & Khuraibet, 1987) has not been fully explained. These authors

have demonstrated that the Bereitschaftspotential is short in duration, reduced in amplitude, absent or even has a positive deflection in 96% of patients with idiopathic parkinsonism. Moreover, this study has shown that the fluctuation of symptoms in these patients (whether spontaneous or drug-induced) were associated with changes of the Bereitschaftspotential (BP).

Simpson postulates that the BP (also known as "readiness potential") is an electrocortical response of cortical area 6 and that its fluctuations in Parkinson's disease may be indicative of regulation of the activity of area 6 (the supplementary motor area) by the basal ganglia by a "gating" function of the nigro-striatal-thalamo-cortical projection which postpones transcortical activation of area 4 (the primary motor area) until the postural muscle set is appropriately adjusted by lower level brain stem-putamen-spinal reflex loops (Simpson & Fitch, 1988).

Because impairment of postural reflexes is a consistent finding in basal ganglia disease (Martin, 1967), a link between this impairment of postural mechanisms and the aforementioned abnormality of the Bereitschaftspotential is possible.

The present study extends previous work in this department and attempts to elucidate further the functional relationship between the BP and postural reflexes, by studying patients with idiopathic parkinsonism. It is postulated that the basal ganglia gate sensory information for

postural set to Brodman's area 4 (efferent pathways) with the cortico-rubro-spinal tract acting as an efferent limb for postural righting reflexes. Anatomical, physiological and clinical evidence which supports this hypothesis is presented in the following three chapters.

CHAPTER TWO

THE MORPHOLOGICAL BASIS FOR THE GATE HYPOTHESIS

The morphological basis for the gate hypothesis

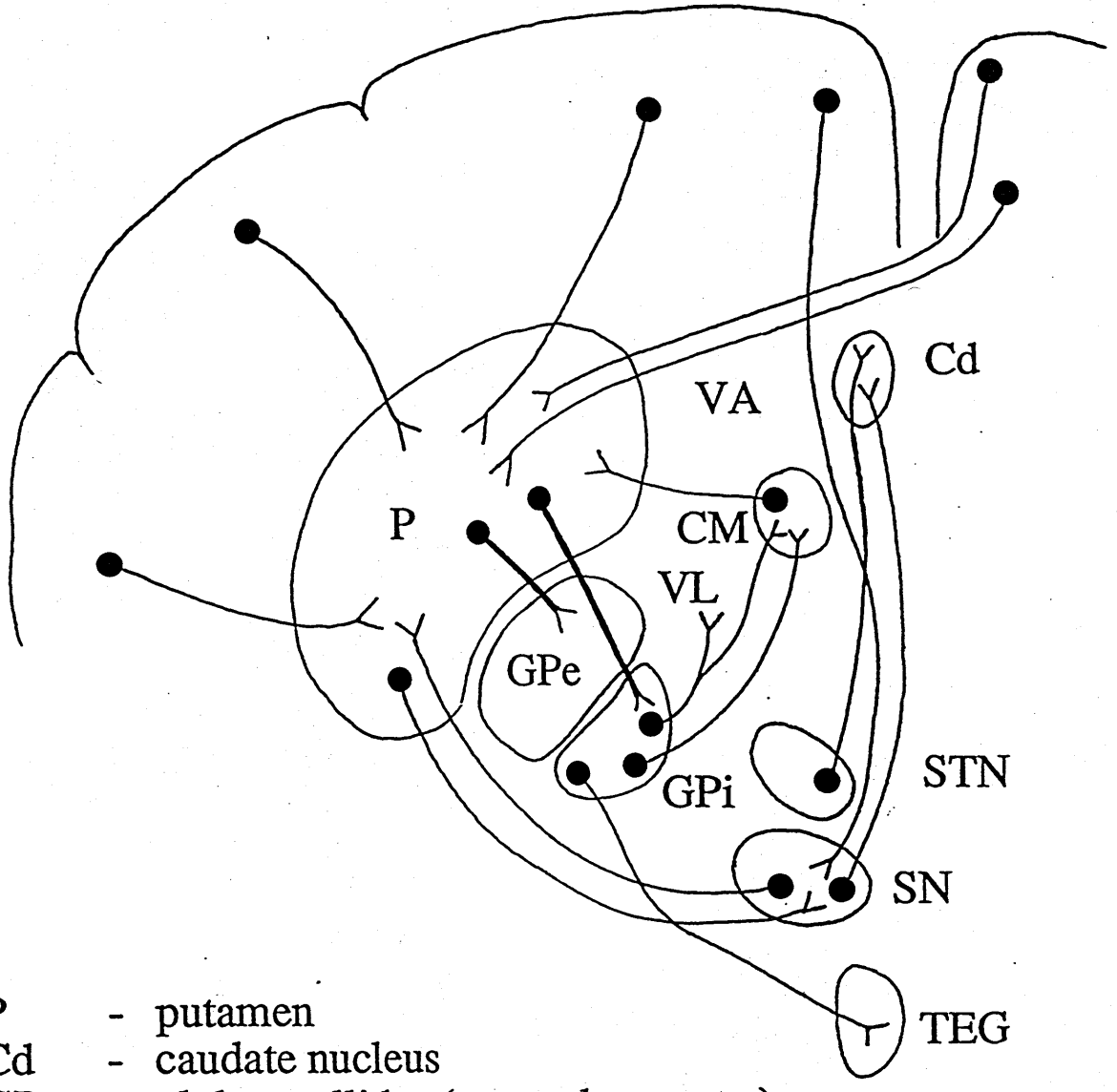
In order to have a role in gating the visual, vestibular and somato-sensory information essential for postural set, the basal ganglia must have the appropriate anatomical connections which link them with both motor and sensory systems and, in addition, they must possess a system of interneurones which enables them to integrate the input from these structures. The evidence presented here and in the following chapter shows that both these criteria are fulfilled.

2/1. Anatomical connections of the basal ganglia:

The fibre connections of the basal ganglia are very extensive and only the major pathways pertinent to this study will be reviewed. A useful generalization is that the caudate nucleus and putamen are the input zone of the basal ganglia, while the pallidum serves as the major output zone. The striatum receives afferent fibres from all parts of the cerebral cortex, the thalamus and some of the brain stem nuclei and project their fibres either directly or indirectly to the same structures (Fig. 2/1, excluding striato-thalamic projections to the cortex). In addition to this reciprocal system of fibre connections, a group of "closed loop" anatomically (and functionally) segregated basal ganglia-thalamo-cortical circuits have recently been described (Alexander et al, 1986). As stated in Chapter 1, the basal ganglia do not have direct connections with the spinal cord.

Figure 2/1

Major fibre connections of the basal ganglia



P - putamen
Cd - caudate nucleus
GPe - globus pallidus (external segment)
GPi - globus pallidus (internal segment)
SN - substantia nigra
STN - subthalamic nucleus
TEG - mid brain tegmentum
VA,VL & CM - ventral anterior, ventral lateral & centromedian nuclei of the thalamus, respectively.

a) Cerebral cortex - basal ganglia pathways:

In most animal species (including man) all parts of the cerebral cortex send efferent fibres to the striatum with the heaviest projections arising from the somato-sensory and motor regions and the least from the visual cortex (Kemp & Powell, 1970). All of these cortical pathways are ipsilateral except those from the somatosensory region which have ipsilateral as well as contralateral projections via the fasciculus subcallosus to the head of the caudate and via the external capsule to the putamen. Fibres to the putamen are much more extensive than those to the caudate (Kunzle, 1975). These fibres project to the supplementary motor area (SMA) via the ventro-lateral thalamic nuclei (Alexander et al, 1986). The SMA has reciprocal connections with the precentral motor cortex and the contralateral SMA (Pandya & Vignolo, 1971). Thus, these fibres form a closed loop - the basal ganglia-thalamo-cortical motor circuit (Alexander et al, 1986).

Direct pathways from the primary and secondary sensori-motor cortex and SMA also descend in the internal capsule and cerebral peduncles to the substantia nigra. In addition, minor cortical fibre connections with the claustrum and subthalamic nucleus have been described but direct cortico-pallidal fibres are not known to exist, nor reciprocal striato-cortical pathways demonstrated. The bulk of basal ganglia pathways to the cerebral cortex originate in the pallidum and project (via the thalamus) mainly to the frontal lobes.

b) Basal ganglia-thalamo-cortical circuits:

Five such pathways have been described (Alexander et al, 1986) and are summarised in table 2/1. The following features are common to all these circuits:

* each circuit receives multiple, partially overlapping cortico-striate inputs which are integrated during their subsequent passage through the pallidum, substantia nigra and thalamus.

* the components of each circuit arise from cortical areas that are functionally related and usually anatomically interconnected.

* the basal ganglia influences through these pathways feedback to restricted portions of the frontal cortex forming a closed loop.

The motor circuit, i.e. the striato-pallido-thalamo-cortical fibre connection, is of particular interest to us in this study. The origins of these fibres in the basal ganglia are the lateral part of the putamen, the ventral part of the external segment of the globus pallidus and the caudal part of the substantia nigra pars reticulata. Using retrograde transport of wheat germ agglutinin conjugated with horseradish peroxidase, Schell and Strick (1984) traced these fibres to pars oralis of nucleus ventralis lateralis. These fibres terminate in the supplementary motor area. By contrast, fibres from cerebellar nuclei

Table 2/1

Basal ganglia-thalamo-cortical circuits.

Circuit	Source of fibres	Integration at level of: Striatum	Pallidum/Nigra	Thalamus	Termination
Motor circuit	area 3, 1, 2 area 4 arcuate premotor & SMA.	lateral part of putamen	ventral ⅔ of GPe & caudal part of SNr	VLN	SMA
Oculo-motor	frontal eye fields, prefrontal cortex (area 9 & 10), posterior parietal cortex	central part of caudate	caudal & rostro-medial GPi, ventro-lateral SNr	medial nuclei	frontal eye fields
dorso-lateral pre-frontal	area 9 & 10, posterior parietal & arcuate pre-motor areas	head of caudate	dorso-medial GPi & rostral SNr	ventral anterior & dorso-medial	dorso-medial pre-frontal cortex
Lateral orbito-frontal	lateral orbito-frontal cortex & auditory & visual association areas	ventro-medial part of caudate	GPi & rostral SNr	as above	lateral orbito-frontal cortex
Anterior cingulate	anterior cingulate gyrus, hippo-campus, entorhinal cortex, superior & inferior temporal gyrus	ventral striatum	ventral part of pallidum & SNr	as above	anterior cingulate area

Abbreviations: SMA = supplementary motor area, VLN = ventro-lateral thalamic nuclei, GPi & GPe = internal & external segments of globus pallidus, SNr = substantia nigra pars reticulata

project via nucleus ventralis posterior of the thalamus to the arcuate premotor area, cortical area 1, 2 and 3 and the motor cortex proper.

c) Basal ganglia interconnections and links with brain stem structures:

The different grey matter masses which collectively constitute the basal ganglia are connected to each other and also to other brain stem nuclei (Figure 2/1).

While all but a few afferent striatal fibres terminate in the globus pallidus, the sources of the fibre input to the striatum are diverse. The largest afferent mesencephalic pathway to the caudate nucleus arises in the pars compacta of the substantia nigra (Szabo, 1980). The latter structure receives fibres mainly from the striatum and frontal lobes. The nigral-caudate pathway is predominantly ipsilateral with only 5% of fibres crossing to the opposite side (Parent et al, 1983). Other fibre inputs to the striatum include: the subthalamic nucleus projection to the caudate (Jayaraman, 1985), the substantia innominata-to-caudate and the amygdalo-striate fibres (Arikuni & Kubota, 1984).

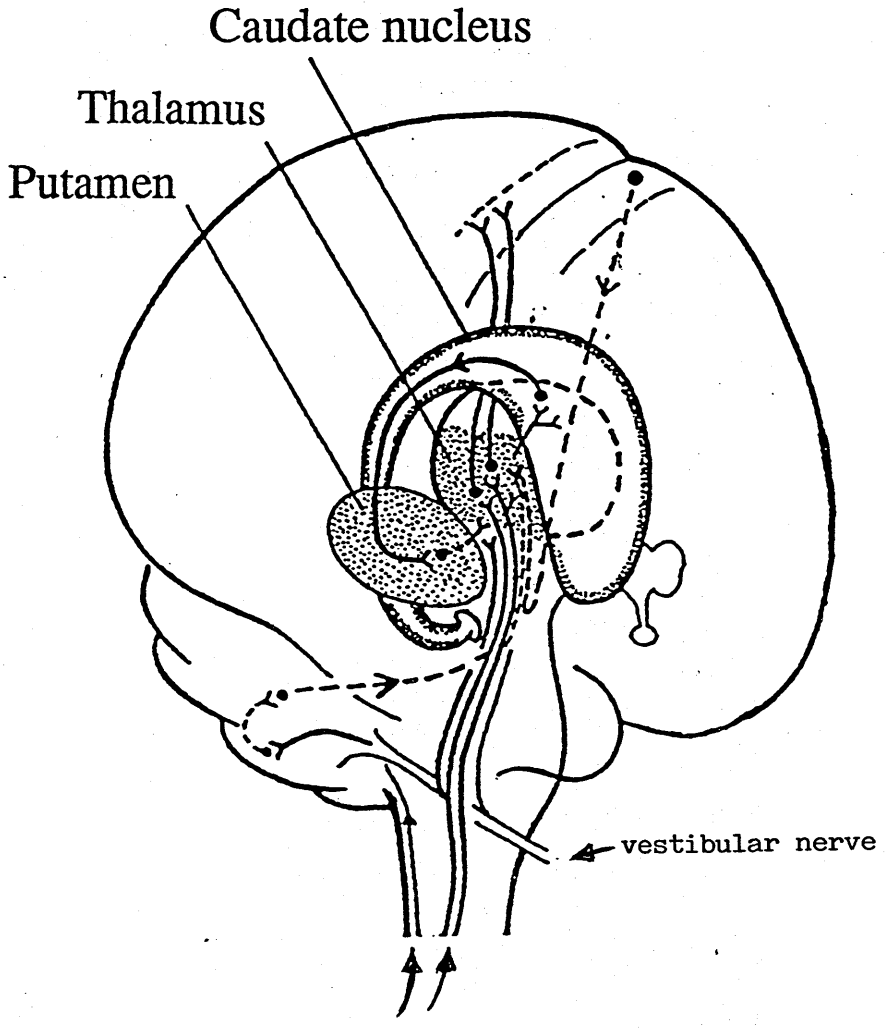
The vast majority of pallidal efferent fibres project to the thalamus (see below). Fibres from the pallidum to the red nucleus, mesencephalic reticular formation, inferior olive and hypothalamus are few in number (Brodal, 1969), but may be very important for control of righting reflexes.

d) Thalamic pathways:

The role played by the thalamus in motor function is unique. While it serves as a relay station for all sensory input which is essential for motor control, it also receives and integrates inputs from the cortical motor areas, basal ganglia and cerebellum.

Of the five nuclear groups of the thalamus only two are directly involved in the motor circuitry. These are the posterior ventral and lateral ventral nuclei (lateral nuclear group) and the dorsomedial and centromedian nuclei (medial group). Somatic sensory fibres, i.e. spinothalamic and trigeminothalamic pathways as well as proprioceptive fibres, relay through the posterior ventral nucleus while the lateral ventral nucleus receives fibres from the cerebellum, red nucleus and pallidum. Pathways from both nuclei project somatotopically to the primary sensory and motor cortex. It has been shown that the cells forming the vestibulo-spinal tracts receive labyrinthine and also somatosensory fibre projections, a finding which indicates vestibular-somatosensory integration at the level of the vestibular nuclei (Rubin et al 1978). The bulk of proprioceptive pathways then ascends to the posterior ventral nucleus of the thalamus via the medial lemniscus, while some fibres pass to the cerebellum. Fibres from both these sources are integrated at basal ganglia level (figure 2/2). On the other hand, the nuclei of the medial group receive afferents from basal ganglia structures and also from other thalamic nuclei and project their

Figure 2/2



Proprioceptive pathways

(From Simpson & Fitch, 1988)

efferent fibres to the neostriatum and prefrontal cortex (for a more complete review of thalamic pathways see Everett, 1971) .

2/2. Interneuronal systems of the basal ganglia:

The caudate nucleus and putamen (the neostriatum) are telencephalic structures similar in their fine structure and phylogenetic development.They contain two different populations of neurones: small polymorphous cells which constitute about 95% of all striatal neurones and a small group (5%) of large multipolar cells with long axons (Crosby et al, 1962).

The small polymorphous neurones are covered with 7-8 spines and receive extensive incoming afferents from the cerebral cortex, thalamus and midbrain forming dense axonal plexuses (Kemp & Powell, 1971). Fibres from these axonal plexuses cross the dendrites of other cells thus insuring convergence (and integration) of information from all these structures. These cells project upon the efferent striatal neurones which send their fibres to the pallidum and substantia nigra (Preston et al, 1980). The small striatal cells are, therefore, interneurones.

On the other hand, the large multipolar striatal neurones are cell bodies of efferent striato-pallidal and striato-nigral fibres. In aldehyde preparations all the striatal neurones have the morphological

features of inhibitory neurones, i.e. symmetrical axonal thickening and flattened vesicles in the presynaptic knob (Gray, 1969, Kemp & Powell,1971). In this respect both types of striatal neurones are morphologically similar to Purkinje cells of the cerebellum (Uchizono, 1975). Further elaboration on the complex internal organization of the striatum was provided by Graybiel and collaborators (Graybiel & Ragsdale,1978, Graybiel et al, 1986). Using immunohistochemical methods these authors have demonstrated two neuronal systems in the caudate and putamen: a population of dark staining cells which they named "matrix" and a group of less intensely staining neurones - striatal patches or striosomes. These two neuronal populations differ in their content of neurotransmitters, fibre connections and presumably also in their functions. While the striatal matrix receives its input through the cortico-striatal pathways and projects its output to the pallidum and substantia nigra pars reticulata, the striosomes connect the limbic system to substantia nigra pars compacta (Gerfen, 1984).

The pallidum is phylogenetically older than and morphologically different from the neostriatum. In contrast to the latter, the pallidum contains a relatively small amount of interneurones. Electron microscopy has demonstrated that fibres from many striatal cells converge upon a single pallidal neurone (Carpenter, 1986). Interestingly, the lateral pallidal segment is more cellular than the medial and projects to the ventro-lateral nucleus of the thalamus (and the cerebral cortex). By

contrast, the medial pallidal segment sends its fibres to the subthalamic nucleus.

2/3. Concluding remarks on the morphological basis of the gate hypothesis:

The fibre connections within the basal ganglia and between the basal ganglia and other parts of the motor system have been discussed. The interneuronal systems of the neostriatum which form the morphological basis of sensory integration at basal ganglia level have also been presented. This is an oversimplified account of an increasingly complicated system. The core structures of this system are the caudate nucleus and putamen, which receive their major inputs from the association cortical areas and the primary sensory and motor cortex, respectively as well as from the substantia nigra pars compacta. The fibre output of the caudate and putamen is predominantly to the globus pallidus which, in turn, projects to the supplementary motor area via the ventrolateral thalamic nucleus. Gate control of the primary motor area may occur at the basal ganglia interneurones or at the SMA, or both.

Visual, vestibular and somatosensory fibres also ascend to the same motor areas, which have strong anatomical links with area 4, i.e. the motor cortex proper. The latter, therefore, is the major descending

motor outflow of the basal ganglia with respect to intended movement as distinct from righting and postural reflexes.

This brief anatomical review shows that the basal ganglia can influence motor behaviour through an efferent system of striato-pallido-thalamo-cortical connections and an efferent projection involving the cortico-rubro-spinal tract.

CHAPTER THREE

PHYSIOLOGICAL EVIDENCE OF CENTRAL INTEGRATION OF POSTURAL MECHANISMS

Physiological evidence of central integration of postural mechanisms

Measurements of regional cerebral blood flow during ballistic voluntary movements of one arm (which caused perturbation of balance) have shown a selective increase of blood flow in the supplementary motor area (SMA), premotor area, striatum, putamen, thalamus and contralateral motor hand area only (Roland et al, 1982). This observation suggests that the organization of this function is restricted to the above-mentioned areas, a finding which is consistent with the neuro-anatomical data presented earlier.

Physiological experiments are also in keeping with these findings and some of the evidence is reviewed in this section.

Role of the supplementary motor cortex in postural control:

Recordings with chronically implanted electrodes in the conscious monkey have shown that as many as 80% of the neuronal pool in the SMA are active during the performance of a motor task (Brinkman & Porter, 1979). Typically, the activity of most of these neurones precedes the onset of movement. This phenomenon undoubtedly reflects some of the various functions ascribed to the SMA, e.g. programming of movements (Tanji et al, 1980), control of muscle tone (Bowsher, 1979) and somatosensory integration. The latter function has been suggested because of the

abundant fibre connections from the precentral motor cortex and the somatosensory areas which converge upon the SMA and also because animals (Goldman & Rosvold, 1970) and humans (Damasio & Van Hoesen, 1980) with discrete SMA lesions develop neglect of the limbs contralateral to the lesion.

In primates pyramidal tract fibres arise from the SMA as well as from area 4, i.e. the primary motor cortex. Pathways originating in the SMA clearly have a function distinct from those fibres arising in area 4. This is suggested by the different threshold for stimulation of the SMA and the primary motor cortex and also by the qualitatively different responses to the same stimulus intensity. Experiments in monkeys have demonstrated that the threshold for SMA stimulation is greater than that of area 4 (Brodal, 1969, Wiesendanger et al, 1973). On the other hand, electrical stimulation of SMA neurones evokes sustained tonic contractions of postural muscles as compared with the discrete movements produced by stimulation of primary motor cortex neurones (see below). In the following paragraphs we will review evidence to show the involvement of SMA in postural control.

Postural muscle activity always precedes the electromyographic (EMG) activity in the prime mover, indicating that it is preprogrammed and not the result of a sensory input initiated by the muscular activity of the prime mover (Belen'kii et al, 1967). In animal experiments surface and

intracortical stimulation of the primate SMA resulted in tonic contractions predominantly of proximal muscles and these responses outlasted the stimulus duration by up to 30 seconds (Wiesendanger et al, 1973). These movements are in sharp contrast with the discrete responses evoked by stimulation of area 4. These observations strongly indicate a role for SMA in the postural stabilization which is an integral component that precedes a voluntary movement.

However, a more direct evidence for the contribution of the SMA in postural control was provided by Tanji and coworkers (1980). In this study single unit discharges from SMA and EMG activity in shoulder and paravertebral muscles in monkeys trained to push or pull a metal rod were recorded simultaneously. Two specific groups of SMA neurones were demonstrated: one which discharged 140 ms following the instruction to push or pull (i.e. well before the onset of movement) and a smaller group of cells (5%) which responded with postural adjustments. The activity of the latter group of neurones correlated with that of the paravertebral muscles but not with the instruction-triggered movements.

Involvement of the SMA in postural control is also evident from the fact that diverse motor and sensory pathways which subserve postural mechanisms converge upon this structure and also from its role in the maintenance of tone of the antigravity muscles. The SMA receives somatosensory feedback directly via afferent fibres [which could be stimulated via peripheral receptors (Brinkman & Porter, 1979)] and

projects directly to the spinal motoneurones (Palmer et al, 1981). Its connection via the motor and sensory cortex to the striatum (motor circuit) has been mentioned earlier. The role of this structure in the control of muscle tone is also clear from ablation experiments. Ablation of the SMA in animals results in spasticity without muscle weakness whereas extirpation of area 4 leads to the opposite. This observation indicates that the SMA exerts tonic inhibitory influence on antigravity muscle tone and also explains the phenomenon of spastic hemiparesis with capsular strokes in man (Bowsher, 1979).

The motor cortex and postural mechanisms:

Discharge in postcentral (sensory) and precentral motor neurones is also known to precede that which initiates the cortico-spinal tract volley associated with a motor act. In experiments in which monkeys were trained to grasp and position a movable handle in the correct place, Evarts (1973) distinguished three groups of cortical neurones in the motor hand area according to their response latency in relation to this task. These are neurones in the postcentral cortex with a latency of 10 ms, precentral pyramidal tract cells (identified by their response to antidromic stimulation in the medullary pyramid) and precentral non-pyramidal tract neurones. The latter two groups of neurones had a latency of 24 and 14 ms, respectively. The corresponding muscle activity was a triphasic response occuring with a latency of 12, 30-40 and 80 ms. The first EMG response is almost certainly mediated by a monosynaptic

muscle stretch reflex since its latency is so brief as to preclude a role for the cerebral cortex. Evarts found that the second EMG response, i.e. the 30-40 ms response, was affected by learning and was also task-dependent. He argued that this short latency response (which is under volitional control) indicates that some cortical neurones function as a transcortical servo-loop. However, another explanation would be that the discharge of these cells is associated with postural set which typically precedes voluntary movements. In this respect the experiments of Hammond (1955) in man are more revealing.

Hammond's experimental paradigm was similar to the one described above except for one detail: he instructed the subjects either to resist or let go when the handle was forcibly removed by the experimenter. He found that the pattern of EMG activity was similar to that recorded in the monkey and occurred with latencies of 18, 40-50 and 100 ms. Interestingly, in "let go" experiments the 40-50 ms response was, as a rule, absent but it was invariably present when the same subjects were instructed to resist the sudden pull of the handle. Clearly, the perturbation of balance in the latter situation increases the requirements for postural adjustments. The presence of the 40-50 ms response under these circumstances and its absence in experiments which caused little or no perturbation of balance (as in the "let go" paradigm), therefore, appears to indicate that this response is related to postural stabilization.

The integrative role of the putamen in postural reflexes:

In an attempt to clarify the influence of the putamen on motor activity and also to determine whether somatosensory inputs to this structure are specific enough to be used by the basal ganglia in motor control, Crutcher and DeLong (1984) studied the relationship of putamenal neurones discharge during voluntary movements and also in response to passive rotation of joints in the awake monkey. In this study it was found that neurones related to different body parts are functionally segregated. The most effective stimulus which evoked responses in most of these neurones was passive rotation of joints. Moreover, sensory driving for each cluster of neurones was very specific: each group of neurones was activated in response to rotation of a single joint, often in one direction only. Interestingly, the clustering of putamenal neurones with similar functional properties which was demonstrated in this study is in good agreement with the mosaic structure of the striatum discussed earlier (chapter 2).

The findings of Crutcher and DeLong contrast sharply with an earlier report (Sedgwick & Williams, 1967). The latter investigators have found that striatal neurones responded to polysensory stimuli in anaesthetized animals. This discrepancy could be explained by the different methods employed by these authors. It is known that labile and polysensory responses occur in the anaesthetized monkey, although these responses

are always specific and fixed to a small receptive field in the awake animal (Lemon & Porter, 1967).

A similar conclusion on the role of the putamen in postural reflexes was reached by Liles (1985), who confirmed that in a population of putamenal neurones, which increase their discharge in relation to movement, 44% of cells responded to proprioceptive stimuli.
Similarly, it has been shown that caudate neurones increase their discharge during the maintenance of postures (Buser et al, 1974).

The globus pallidus and posture:

The same pattern of functional organization as in the putamen was also found in the globus pallidus and subthalamic nucleus (DeLong 1973, DeLong & Georgopoulos, 1979). Interestingly, cells of the globus pallidus associated with a particular movement are tonically active and increase their discharge rate prior to the onset of movement, indicating that the pallidum influences cortically-induced responses. This pattern of neuronal discharge is also exhibited in putamenal and pallidal neurones associated with postural set. Experiments using a chair-tilt paradigm in which the monkey was required to make postural adjustments to actively maintain a restricted head position have shown that there was an increase in the firing rate of a specific group of pallidal and putamenal neurones which corresponded to the activity of postural muscles (Anderson, 1977).

Specific cell groups in the ventral posterior and ventral lateral thalamic nuclei were also shown to discharge in response to a stimulus in advance of cortical neurones. In addition, each group of cells was specifically related to a given movement (MacPherson et al, 1980).

In summary, the evidence reviewed here shows that the neuronal response latencies to perturbation in all parts of the motor circuit have a close temporal relationship to postural set. It is also clear that the specificity of the somatosensory input and motor activity in the motor circuit is maintained throughout the system despite the anatomical convergence of these pathways and the cross modality linkage in these neurones.

"Gating" of postural responses by the basal ganglia:

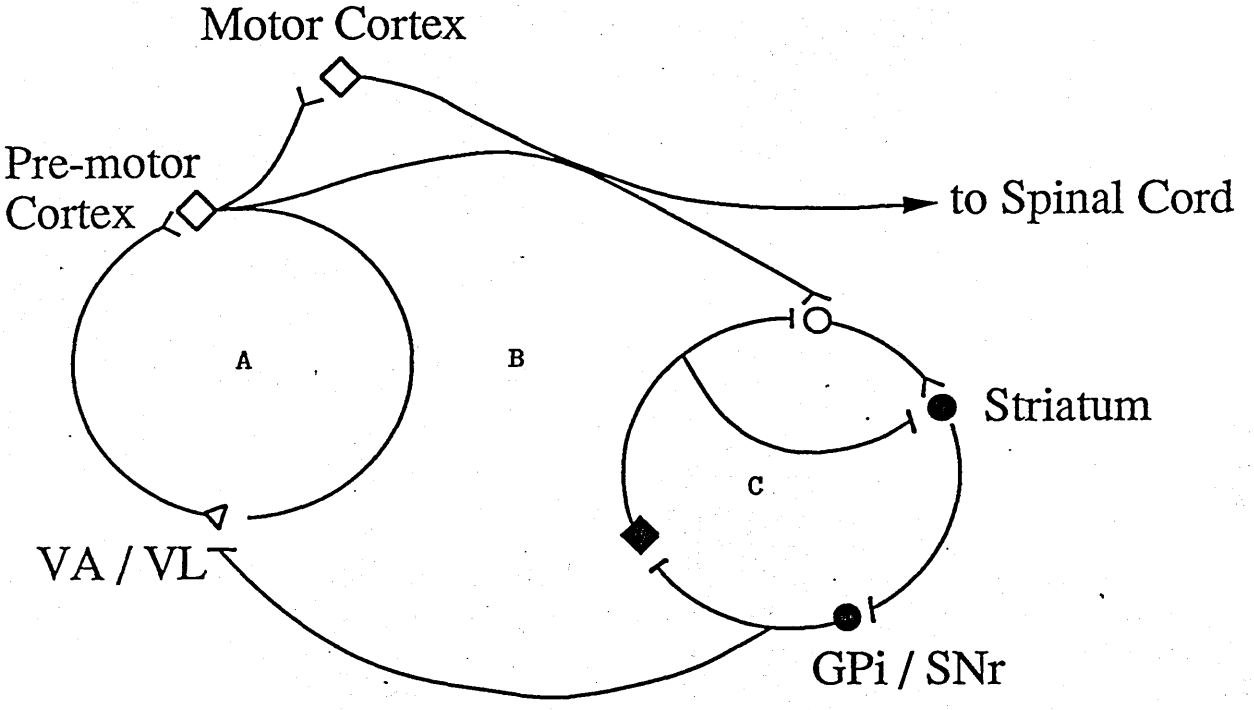
The evidence which has been presented so far shows that neuronal activity in all parts of the motor circuit precedes the voluntary movements which cause perturbation of balance. Moreover, this activity has a close temporal correlation with that of postural musculature. Reference was also made to the fact that striatal neurones increase their firing rate during the maintenance of posture. Taking these facts into account together with our current knowledge of the structure and neurochemistry of the basal ganglia [reviewed by Cooper et al, (1986)], it is clear that the model of basal ganglia function proposed by Penney

and Young (1983) has some similarities with the hypothesis put forward by Simpson (Simpson & Khuraibet, 1987) [see below].

The model of Penney & Young proposes a dual function for the components of the motor circuit with the nigrostriatal pathways regulating the cortico-striato-pallido-thalamo-cortical circuit. Thus, the striatum selects, facilitates and maintains the motor behaviour generated by the cerebral cortex and, at the same time, suppresses other conflicting motor activity. A sustained activity is an essential prerequisite for normal motor behaviour (Evarts, 1967). This is ensured by the pathways depicted as circuit A and B in figure 3/1. Accordingly, collateral fibres from the motor cortex excite the ventral anterior (VA) and ventral lateral (VL) thalamic nuclei which in turn re-excite the motor cortex neurones (circuit A). Similarly, circuit B provides a positive feedback on the on-going motor behaviour: cortical neurones excite striatal cells which inhibit the substantia nigra pars reticulata (SNr) and the internal pallidal segment (GPi). The latter neurones inhibit VA and VL thalamic nuclei (and, therefore, the motor cortex). Thus the striatum facilitates motor behaviour by inhibition of the motor activity inhibitors, i.e. SNr and GPi.

The nigrostriatal pathways synapse on the same cells of the striatum as the corticostriatal fibres. These are the dopaminergic projections affected in Parkinson's disease and they constitute one of the three inhibitory neurones of circuit C. This circuit regulates the ease of

Figure 3/1 : Basal ganglia function (after Penney & Young, 1983)



Exitatory

◇ glutamate
○ acetylcholine

Inhibitory

◆ dopamine
● GABA

Abbreviations as in text.

transmission through circuit B. It either facilitates the transmission (and, therefore, maintains the on-going activity) or suppresses it (and hence overrides on-going activity and establishes a new one). In this way the striatum functions as a gate control mechanism for motor behaviour, an integral part of which is the maintenace of posture.

There is a time delay between activation of the primary motor cortex and the EMG responses. In Evarts' experiments (1973) which we referred to earlier the response latencies were 24 ms for precentral pyramidal tract neurones and 12, 30-40 and 80 ms for EMG activity (the first phase of EMG potential is due to a muscle stretch reflex as discussed above). The model proposed by Penney and Young does not explain these findings.

Simpson's model differs from that of Penney and Young in a number of respects. He does not regard the cerebral cortex as the initiator of intended movement but only as a "fine tuner" of movement started at subthalamic level with striato-thalamo-cortical control projected to the SMA and transcortical driving of area 4 from the prefrontal and postcentral cortices. These two drives are gated at striatal and SMA levels (Simpson, unpublished, 1986, Simpson & Fitch, 1988).

The additional features of Simpson's model, to account for premovement cortical potential and the delay of the "voluntary" component of a willed movement (not implicit in the Penney-Young model) is that the striatum acts on the SMA to delay area 4 activation until the postural

set has been initiated. Accordingly, the 30-40 ms EMG discharge could be due to the muscle activity associated with postural set, while the 80 ms response represents the discharge related to the voluntary movement.

These morphological, physiological and neurochemical data which show the regulatory role of the basal ganglia in postural stabilization are in total accord with the clinical observations of impairment of postural mechanisms that occur in basal ganglia disease and also with the effects of therapy on these disorders. This will be discussed next.

CHAPTER FOUR

CLINICAL OBSERVATIONS WHICH SUGGEST THE ROLE OF THE BASAL GANGLIA IN POSTURAL CONTROL

a) Impairment of postural reflexes in basal ganglia disorders

b) Effects of treatment of Parkinson's disease on postural mechanisms.

Clinical observations which suggest the role of the basal ganglia in postural control.

1. Impairment of postural reflexes in basal ganglia disorders:

In his classic "The basal ganglia and posture", Purdon Martin (Martin, 1967) drew attention to the fact that all postural reflexes except those concerned with antigravity mechanisms are impaired in basal ganglia disease. All and each of these reflexes (which include postural fixation of body segments, righting reflexes, reactions to tilting and locomotion) are intimately related to the maintenance of equilibrium during stance and gait. There are two ways in which basal ganglia disorders may interfere with equilibrium:

a) loss or impairment of postural righting reflexes as occurs in Parkinson's disease (PD). [Stretch reflexes are increased in PD (McLellan, 1975).

b) increased sensitivity of the basal ganglia to postural stimuli which is seen in chorea and drug-induced dyskinesias (Martin, 1967, Yassa, 1989, Huttunen & Homberg, 1990).

Postural instability in basal ganglia disease is clearly not due to motor cortex or pyramidal tracts involvement as there is no muscle weakness in these patients and the plantar response is always flexor.

Moreover, loss of postural fixation in patients with basal ganglia disorders could be overcome by voluntary movements.

Parkinson's disease:

Impairment of righting reflexes is one of the cardinal features of PD (Barbeau, 1986). This "negative" symptom of parkinsonism is more likely to give insight into the function of the basal ganglia than tremor and rigidity (Martin, 1967, Marsden 1982). The anatomical substratum for postural mechanisms has been described in a previous chapter. However, it is worth noting that the peripheral structures which subserve righting reactions, i.e. proprioceptive, visual and vestibular organs and their fibre connections, are not affected in patients with PD. Since the fundamental neuropathological abnormality in these patients is degeneration of the dopaminergic nigrostriatal neurones, it is reasonable to assume that the lesion which interferes with postural reflexes in PD must lie in these neurones or their connections. Interestingly, postmortem examination of patients with post-encephalitic parkinsonism had shown a positive correlation between the degree of impairment or loss of postural reflexes in these patients and the amount of degenerative changes in the pallidum, substantia nigra and their efferent fibres (Martin, 1967).

Chorea:

The brunt of pathological changes in chorea (including drug-induced forms) and Wilson's disease is in the caudate and putamen, whilst hemiballismus results from lesions of the subthalamic nucleus. These disorders of basal ganglia function are accompanied by variable degrees of postural instability and serve as good examples which support our hypothesis.

For example in these patients reactions to tilting were found to be of normal pattern but they were greatly increased (Martin, 1967). This led to the suggestion that choreiform movements are exaggerated reactions to instability and are due to extreme sensitivity of the basal ganglia to postural stimuli. This clinical observation is substantiated by further experimental evidence.

Gait analysis has confirmed that postural instability is a consistent finding in Huntington's disease (HD), occurring in 12 out of 13 patients in one study (Koller & Trible, 1985). HD is a hereditary degenerative disorder of the striatum which is characterized by dementia and choreiform movements. A functionally normal presynaptic dopaminergic system in association with reduced dopamine receptor binding in the striatum was demonstrated in vivo with positron emission tomographic scanning in this condition (Leenders et al, 1986a), a finding which is consistent with earlier neuropathological reports (Spokes, 1980). It

would appear, therefore, that in HD there is an exaggerated response to normal dopamine concentrations despite a reduction in the number of post-synaptic receptors. These data suggest postdenervation supersensitivity in the striatum as a possible pathophysiological mechanism underlying this exaggerated response. Similar findings were demonstrated in other forms of chorea (Cunha et al, 1981).

Drug-induced dyskinesias:

Drug-induced choreiform movements whether resulting from chronic administration of neuroleptic drugs (tardive dyskinesia) or levodopa preparations (peak-dose and diphasic dyskinesia) are probably triggered by the same neurophysiological mechanism and are due to morphological and / or functional abnormalities of the dopaminergic neurones in the striatum. Impairment of postural reactions is a consistent feature of these forms of chorea and contributes to the disability in affected individuals (Weiner et al, 1978)

In tardive dyskinesia withdrawal of the offending neuroleptic agent has the same effect in these patients as the administration of levodopa or its agonists (e.g. amphetamine), i.e. worsening of the involuntary movements (Crane et al, 1969, Klawans & Weiner, 1974). On the other hand, further blockade of striatal dopaminergic receptors or dopamine depletion improve the dyskinesia. These observations suggest increased sensitivity of striatal dopamine neurones in tardive dyskinesia.

A similar conclusion can be drawn with regard to levodopa-induced dyskinesias from a recent elegant study (Mouradian et al, 1988). In this experiment levodopa was given by continuous intravenous infusion to patients with various stages of PD following a washout period. The patients were grouped into four different categories according to their pre-study motor response to oral levodopa therapy. These were:

i) patients not previously exposed to levodopa,

ii) those with stable response to levodopa,

iii) those with end of dose deterioration and

iv) a group with the "on-off" effect.

It was found that although the threshold dose for the optimal antiparkinsonian effect was the same for all groups of patients, the dose which produced dyskinesias became progressively smaller from those with stable response to the "on-off" group. These results were interpreted to indicate a marked increase in the sensitivity of striatal neurones to small fluctuations of dopamine concentrations at post-synaptic receptor sites.

From this account it is clear that basal ganglia disorders such as PD,

Wilson's disease, the choreas and ballismus all intefere with postural reactions, albeit by different mechanisms.

2. Effects of treatment of PD on postural mechanisms:

Although a complete and lasting resolution of the postural deficiency seen in basal ganglia disorders has been reported following surgical treatment (Leenders et al, 1986b, Koller et al, 1989), the impairment of postural reflexes which occurs in PD responds to treatment with levodopa drugs and dopamine agonists, as a rule, less favourably than bradykinesia and rigidity (Barbeau, 1986). This is probably due to the differences in the functional organization of the various dopaminergic systems within the basal ganglia and depends on the different functions of dopamine receptors.

There are two types of dopamine receptors which differ in their distribution, functional and pharmacological properties. These are D1 receptors which are linked to adenylate cyclase and increase prolactin secretion and D2 receptors which inhibit the enzyme adenylate cyclase and prolactin release (Kebabian & Calne, 1979, Stoof & Kebabian, 1984). D1 receptors have the highest density in the prefrontal cortex, substantia nigra and nucleus accumbens. By contrast, the striatum is rich in both D1 and D2 receptors. Interestingly, there is a gradient of increasing D2 receptor density in the striatum from a lateral-to-medial

and from a rostral-to-caudal direction, whereas D1 receptors are uniformly distributed (Boyson et al, 1986).

The functional significance of the different types of dopamine receptors is not fully understood. However, selective stimulation of these receptors has been shown to result in activation of different dopaminergic pathways. For example, there was a dose-dependent response to D2 receptor agonists but no discernable effect on D1 receptors in monkeys rendered parkinsonian with methyl-phenyl-tetrahydropyridine (MPTP) (Barone et al, 1987). Similarly, treatment with either D1 or D2 receptor agonists selectively increased regional glucose utilization in different dopaminergic systems, an observation which was thought to reflect the physiological activity in the corresponding region (Trugman & Wooten, 1987).

The antiparkinsonian drugs levodopa and bromocriptine are potent D2 receptor agonists but also bind to D1 receptors, albeit weakly (Calne, 1982). The clinical effect of these drugs, therefore, depends mainly on their interactions with D2 receptors. However, the simultaneous stimulation of D1 and D2 receptors appears to be essential for the optimal response of the motor system since the co-administration of D1 and D2 receptor agonists results in better symptomatic control of MPTP-induced parkinsonism in animals than treatment with D2 agonists alone (Barone et al, 1986, Barone et al, 1987). At present there are no potent D1 receptor agonists for the treatment of PD in man and only a

submaximal clinical response is achieved by using the currently available drugs, especially in the later stages of the disease. This probably explains the discrepancy in response of the various symptoms of PD to these agents. The partial improvement of postural instability with treatment in PD, therefore, may be due to the inadequate activation of D1 receptor systems.

Conclusion:

The evidence reviewed here clearly shows that a number of diverse basal ganglia disorders cause a variable degree of impaired postural stability and also that this effect is mediated by dopaminergic mechanisms.

CHAPTER FIVE

MATERIALS AND METHODS

Materials and methods

Reference was made in previous chapters to the fact that the Bereitschaftspotential (BP) reflects the functional activity of cortical area 6. In this study, it is postulated that the basal ganglia regulate the response of cortical area 6 (supplementary motor area) via dopaminergic pathways to delay the activity of the primary motor cortex (i.e. area 4) so that the appropriate adjustments of postural muscle set is complete before the forthcoming self-paced movement. The present project tests this hypothesis by studying the functional organisation of the righting reflexes during the performance of a motor task which causes perturbation of balance in patients with Parkinson's disease (PD). The temporal relationship of the onset of electromyographic (EMG) activity in the "prime mover" to that of the appropriate postural muscles and their relationship to the BP in patients with idiopathic parkinsonism is examined. Details of the experiments which were used in this study and their justification are described in this section.

5.1 Patients and control subjects:

We studied 20 patients with PD and two groups of age and sex-matched controls subjects. The control groups consisted of 16 healthy volunteers and 18 patients with neurological diseases other than parkinsonism. The purpose of the study was explained to all patients and control subjects who took part in the experiment and their consent was obtained in all

cases. Only patients with idiopathic parkinsonism, i.e. PD were studied. Those with symptomatic parkinsonism or multi-system degeneration were excluded. The sample of patients studied was chosen at random and was representative of the group of PD patients as a whole as it included patients with various stages of parkinsonism and contained all the age groups which are usually affected by the disease. However, some degree of patient selection was unavoidable. For example, patients with marked tremor were not suitable for this study as moderate or severe tremor causes false and premature triggering of the recording electronics, usually before the onset of EMG activity in the prime mover. For this reason patients with predominantly the akinetic-rigid type of PD were selected for this study. However, there is no reason to assume that the righting reflexes (which are the subject of the present study) in this subgroup of patients are different from others with PD. None of the patients was demented and all were able to follow the instructions and performed the task satisfactorily and without undue discomfort.

The patients' mean age was 57.65 years (range 40-73 years). There were 17 males and 3 females. The duration of illness varied from 2 to 16 years (mean = 6.6 years).

Severity of PD was assessed immediately before the experiment in each case using the Hoehn and Yahr (1967) and the Webster (1968) disability rating scales. These disability scales were chosen because the former

takes into account impairment of balance (which is one of the cardinal features of PD) and the latter evaluates a large number of various symptoms (10 altogether) which are likely to be present in PD. Details of these methods of assessment of the severity of parkinsonism are given in tables 5/1 and 5/2, respectively.

There were two groups of controls: 15 healthy subjects and 18 patients with neurological diseases other than idiopathic or symptomatic parkinsonism.

The healthy controls were recruited mainly from the laboratory staff but in a few cases patients' relatives were also studied. Of the 15 healthy individuals 11 were males and 4 were female. The mean age in this group was 52.4 years (range 30-80 years).

Details of the patients comprising the second group of controls are given in table 5/3. These were 11 males and 7 females with a mean age of 46.5 years (range 23-72). This control group included patients with a wide range of neurological conditions, some of which are associated with disturbances of balance.

5.2 Electrodes:

Small, shallow silver cup electrodes were used for recording the BP. The electrodes had a cup rim diameter of 9 mm and a hole at the bottom of

the cup. The electrode lead was a 100 cm long flexible copper wire. To prevent their polarization, i.e. change of chemical composition during the passage of direct current the electrodes were coated with silver chloride. These electrodes were used because of their:

a) low electrode-electrolyte impedance

b) very stable half-cell potential, i.e. low noise.

Needle electrodes were not used in this study for recording the BP because they have a larger impedance during EEG recordings than disc electrodes (Zablow & Goldensohn, 1969), a property which leads to attenuation of the response to signal. Needle electrodes are also inconvenient for patients and are more likely to fall off during the performance of a ballistic movement as in our present experiments.

For the same reasons EMG activity was recorded with silver strip surface electrodes applied to the contracting part of muscle and secured with elastoplast.

5.3 Amplifiers:

These are electronic devices which increase the strength of the electric current or voltage signal fed into them. Thanks to modern semi-conductor technology, extremely low currents flowing into the electrodes can now

Table 5/1 Webster disability scale

i Bradykinesia of hands (including writing):

0 = no involvement

1 = detectable slowness

2 = moderate slowness

3 = severe slowness, unable to write or button clothes.

ii Rigidity:

0 = none detectable

1 = mild rigidity only detectable on reinforcement

2 = moderate rigidity - present at rest

3 = severe resting rigidity

iii Posture:

0 = normal posture, i.e. head flexed forward < than 4"

1 = begining poker spine, head flexed up to 5"

2 = one or two arms flexed but still below waist

3 = "simian posture"

iv Upper extremity swing:

0 = arm swing preserved bilaterally

1 = arm swing decreased on one side

2 = one arm fails to swing

3 = both arms fail to swing

v Gait:

0 = stride length 18-30". No difficulty on turning round

1 = stride length 12-18 ". Takes several steps to turn

2 = stride length reduced to 6-12", both heels strike floor

3 = shuffling gait and/or festination or freezing

Webster disability scale (continued)

vi Tremor:

0 = no tremor

1 = mild, small amplitude, usually asymptomatic

2 = severe but intermittent, not causing disability

3 = severe and constant. Writing and feeding impossible

vii Facies:

0 = normal, fully animated

1 = detectable hypomimia

2 = moderately immobile, drooling may be present

3 = "frozen" facies, stare, drooling

viii Seborrhoea:

0 = none

1 = increased sweating

2 = obvious oiliness present

3 = marked seborrhoea covering face and head

ix Speech:

0 = clear, loud and well modulated

1 = hoarseness and loss of resonance but easily understood

2 = dysarthria, hesitancy and stuttering. Difficult to understand

3 = dysphonia, very difficult to understand

x Self-care:

0 = no impairment

1 = independent, difficulty with dressing

2 = independent for most activities, requires some help

3 = dependent on others for daily living activities

Table 5/2

Hoehn and Yahr rating scale

Stage i	Unilateral involvement only, minimal or no functional impairment.
Stage ii	Bilateral or midline involvement without impairment of balance.
Stage iii	First sign of impaired righting reflexes. Unsteadiness when patient turns or when pushed from standing equilibrium. Functionally restricted but may have work potential. Physically capable of leading independent life. Mild - moderate disability.
Stage iv	Fully developed PD. Severe disability. Still able to stand and walk unassisted.
Stage v	bed- or chairbound.

Table 5/3

Characteristics of control patients with neurological diseases other than PD

Name	Age/Sex	Diagnosis	Postural instability
T.S.	42 M	tension headache	0
J.D.	60 M	temporal arteritis	0
J.C.	60 M	mild Lt. hemiparesis	+
J.C.	76 F	motor neurone disease	0
J.S.	51 M	cervical radiculopathy	+
L.Mc.	23 F	mild Lt hemiparesis (AVM)	+
C.W.	55 M	postviral fatigue syndrome	0
D.G.	44 M	parietal lobe tumour	0
A.B.	52 F	syringomyelia	++
A.R.	36 M	spasmodic torticollis	0
A.G.	49 F	peripheral neuropathy	+
I.S.	27 M	postviral spastic paraparesis	0
A.D.	43 M	? multiple sclerosis	0
C.F.	68 M	peripheral neuropathy	0
E.C.	41 F	? multiple sclerosis	+
Y.A.	50 F	trigeminal neuralgia	0
D.H.	45 M	cervical spondylosis	0
C.F.	53 F	cervical cord compression	++

be amplified. The first stage of the amplifier is usually connected directly to the electrode and any AC coupling is inserted in the later stages. This reduces noise and allows a better common mode signal rejection. In this study we used AC amplifiers with relatively long time constants (Digitimer Ltd, England). These had the following high frequency cut off filter, time constant (tc) and sensitivity:-

Recording	HC filter	tc	sensitivity
BP	30 Hz	5 s	50 uV/V
EMG	1 kHz	30 ms	1 mV/V

5.4 Accelerometer:

To record the head movements (acceleration) associated with postural adjustments an EGAXT-*-10Z model accelerometer (Entran Ltd, Crowthorne, Berkshire, England) was used. Its active elements are piezoresistive forming a full bridge circuit. It has the following specifications:

Nominal sensitivity	= 5.98 mV/g at 15 V bridge excitation
Input impedance	= 838 ohms
Output impedance	= 451 ohms
Range	= +,- 10 g
Over range	= +,- 10000 g
Resonant frequency	= 600 Hz
Useful frequency range	= DC - 180 Hz

The output from the accelerometer was fed into the amplifier with time constant of 10 s and upper frequency limit of 50 Hz. The complete circuit was calibrated by turning the accelerometer 180 degrees in the earth's gravitational field.

5.5 Computer:

Following amplification, the EMG activity of the anterior deltoid, tibialis anterior (TA) and tensor fascia lata (TFL) muscles as well as the BP and accelerometer signal were fed into a Supersystem Advanced Digital Computer. The computer operated on a specially written programme. The programme was menu-driven to facilitate easy set-up of parameters and aquisition and storage of data. During aquisition the computer performed opisthochronic averaging implemented with software delay so that a two second period prior to the trigger event was included in the analysis. A total of three seconds was displayed on the monitor screen over 512 points (sampling frequency 170 Hz).

To avoid corruption of data the latter were immediately transferred into a "backup" floppy disc and were later retrieved for on line analysis and / or printing.

5.6 Choice of postural muscles:

As a rule a ballistic movement of a body segment leads to perturbation

of balance and is usually preceded by activation of limb and trunk muscles. Activation of these muscles prior to the intended movement is necessary to insure postural stability. As reviewed earlier (Nashner et al, 1985, Horak & Nashner, 1986) the initial position of the subject's centre of gravity and also the nature of the intended movement (the velocity and direction of movement etc) determine the sequence of activation and the specific muscle groups which are used for the given task.

For example, in the experiments of Lipshits et al (1981) the subjects moved quickly from the standing position to standing on tiptoe in response to a signal. The forward displacement of the body's centre of mass caused by this movement was confirmed by stabilograph recordings. The earliest change recorded in lower limb muscles was in the soleus muscle and was characterized by EMG silence (i.e. inhibition of spontaneous activity). This was closely followed by an EMG burst in the TA. Further postural instability caused by the addition of a 2 kg load attached to the subject's body increased the EMG amplitude of TA. However, when the same experiment was repeated with the subject's trunk initially tilted forward no similar anticipatory postural activity was observed. From these results the authors concluded that the functional role of anticipatory lower limbs muscle activity is to stabilize posture by displacing the centre of gravity of the body in advance of the forthcoming movement.

On the other hand EMG recordings from several lower limb and trunk muscles have shown that the TFL contralateral to the side of the body which is affected by the perturbation is a more sensitive index of anticipatory postural adjustments than TA (Bouisset & Zattara, 1981, Zattara & Bouisset, 1988).

In our experiments perturbation of balance was precipitated by shoulder flexion. This task causes forward displacement of body mass in a way similar to that just described. It is, therefore, reasonable to assume that TA and TFL are the muscles most likely to show early changes in relation to postural instability in this task. This was confirmed in our pilot studies.

5.7 Placement of electrodes:

To record the cerebral evoked potentials or EEG activity the difference of electrical potential between two points is measured. There are two methods which are commonly used: bipolar electrodes and monopolar with a common reference electrode. Bipolar electrodes are both "active" and, therefore, they record potential gradients, whereas monopolar electrodes measure the difference between an "active" electrode and a reference point (non-neural tissue). Since electric phenomena depend only on differences of potential, the position of the reference electrode (i.e. the zero point) is of no consequence as long as it remains constant during the experiments. It is preferable, however, that the reference

electrode should be placed on an "inert" point. We chose the ipsilateral mastoid as this point. We used this monopolar derivation because it has many advantages over bipolar electrodes for recording evoked potentials (MacGillivary, 1974). These include good definition of the wave form (because the reference electrode is inactive), good localisation of low voltage activity and, more importantly, good display of the shallow gradient of the Bereitschaftspotential (BP).

The BP was recorded from the right or left motor hand areas (Rt MHA and Lt MHA, respectively) as defined by Shibasaki et al (1980), i.e. 2 cm in front of the somatosensory hand area. The latter lies 7 cm lateral to the midline on a line drawn from a point 2 cm posterior to the vertex [CZ according to the 10-20 system (Jasper, 1958)] to the external auditory meatus (active electrode). The reference electrode was applied over the mastoid area on the same side as the active electrode.

For application of the cup electrodes we used the method described by Rosenfeld et al (1969) with minor modifications. Briefly, the Rt or Lt MHA was marked with a red pencil and the hair overlying this area was cleared away with a finger to expose the scalp. The scalp was cleaned with a Medi-swab to remove skin debris and the electrode was then placed and collodion (a biological cement) was applied round the rim of the electrode. The collodion was dried for approximately two minutes with warm air delivered through an electrode applicator which was attached to an air pump. A blunted needle was then introduced into the hole at the

bottom of the electrode cup and then rotated 2-3 times to scratch the scalp slightly. The slight abrasion thus caused reduces the electric resistance at the electrode-skin interface. Further improvement of current conduction was also achieved by filling the cup with electrode jelly. The impedance was then checked. In cases where the impedance was found to be more than 1 kohm the electrodes were removed and the same process of electrode application was repeated. The electrodes were easily removed with a few drops of acetone applied to a piece of cotton wool.

The electromyogram (EMG) was also recorded with surface electrodes. A small amount of electrode jelly was applied to the electrode which was then placed over the long axis of the contracting part of the muscle and held in place with elastoplast. Another electrode was placed 3 cm distal to the first. For the anterior deltoid and the TA muscles the contracting part was determined by palpation of these muscles during shoulder flexion and ankle dorsiflexion, respectively. EMG recording from the TFL was made from the antero-lateral aspect of the thigh at the point joining the upper and middle thirds.

5.8 Experimental design:

Subjects stood erect and unsupported and with their feet together and their body weight equally distributed between the two legs. Their arms were hanging loosely by their side. They were asked to fixate gaze on a

light signal on the wall approximately one metre in front of the eyes. In each case the position of the light signal was adjusted to the patient's height. Blinking, swallowing and other movements were not allowed during the test. Patients and control subjects were continuously watched during the experiment and when such movements occured the trials were rejected. The experiment was interrupted from time to time to allow patients to rest. At regular intervals they were also allowed to sit down for a few minutes if they so wished but the recording electrodes were not disconnected.

Patients and control subjects were instructed to point at the aforementioned light signal in their own time after they saw a flash of red light. We took another precaution to avoid a reaction time response by randomly varying the interval between trials. The subject's arm was kept straight at the elbow during the performance of the task. To ensure maximum perturbation of balance subjects were instructed to perform the task with a single rapid movement. In 6 patients the experiment was repeated with the subject holding a book (weight 300g) in his hand. This additional load increases the perturbation of balance and, hence, the postural requirements.

5.9 Recording and storage of data:

5.9a Artefacts:

The following methods to eliminate or minimize contamination of the

biological signals under study by artefacts and electrical interference were rigorously followed in all our experiments:

1. To reduce movement artefacts subjects were instructed to stand still and not to blink or swallow saliva during performance of the task. [swallowing results in glosso-kinetic artefacts (Mackay, 1984)]. When such movements occurred the trials were rejected. Eye movements are known to cause slow scalp potentials and subjects were, therefore, instructed to fixate gaze on a target directly infront of them. Talking was not permitted during the experiments because slow evoked potentials have been described to occur before speech (Grozinger et al, 1976).

2. To minimize external electrical interference all experiments were carried out in a physiology laboratory where no other electrical equipment, e.g. electric kettles, was in use at the time of experiments.

3. Electrodes were glued firmly to the underlying skin to ensure good contact and electrode jelly was used to improve current conduction. In addition, experiments were started at least 10-15 minutes after application of electrodes to allow contact potentials to stabilise. These measures reduce the electrical impedance to a minimum and in all our experiments it was reduced to 1 kohm.

"Noise" was minimized by averaging 30 "clean" trials for each experiment (see below).

5.9b EMG activity:

Onset latencies and duration of EMG activity of TA and TFL muscles were recorded relative to a predetermined zero point which corresponded to the onset of the EMG activity in the prime mover, i.e. the anterior part of the deltoid muscle. Latency recordings started two seconds before and ended one second after the onset of shoulder flexion which caused the perturbation, thus allowing the detection of anticipatory TA and TFL contractions as well as delayed (i.e. postperturbation) postural correction.

Each single trial was visually inspected on the computer display unit before it was included in the average. Trials in which EMG activity of the prime mover preceded the zero point, e.g. due to poor relaxation of shoulder girdle musculature, and those contaminated with movement or other artefacts were rejected. To facilitate this process the zero point was displayed on the monitor screen as a vertical line. A total of 30 trials was averaged in each experiment.

5.9c Bereitschaftspotential (BP):

Evoked potentials (including BP) are an electrical manifestation of the brain's perception of an external stimulus and its response to it. Because of their low amplitude (0.1 - 20 uV) they are "hidden" in alpha rhythm (amplitude 20 - 60 uV) and also in various artefacts in the routine EEG record. However, all evoked potentials are triggered by

psychological or external factors and, therefore, they are time-locked to the stimulus. By contrast, EEG activity and artefacts are random with respect to the stimulus. Thanks to this property it is possible to record evoked potentials using computer averaging methods. During the averaging process the signal component (the BP in this case) remains relatively unchanged (because it is time-locked to the stimulus), whereas the noise component (which is random) progressively attenuates.

In our experiments we used the computer-assisted method of Shibasaki et al (1980) for averaging the BP (see below). This method utilizes the EMG activity of the prime mover as the fiducial marker for averaging the cortical evoked potentials and does not have the shortcomings of the previously described methods, for example the use of an electrical signal derived from the interruption of a light beam or electric circuit by the part of the body which moved. In the former method the trigger pulse completely coincides with the EMG activity because it is related to a constant physiological event (i.e. EMG onset) in association with each movement included in an average. Consequently, it enables reliable measurements of latency and duration of the evoked potential in question. It also has the advantage of reducing the signal to noise ratio by allowing the experimenter to reject trials due to spurious trigger pulses, e.g. resting EMG activity. An additional advantage of this method is that it unequivocally demonstrates the temporal relationship of EMG activity in postural muscles to that of the prime

mover and, hence, discriminates between anticipatory (preperturbation) and corrective (postperturbation) postural adjustments.

In this laboratory, Khuraibet (1984) has found that averaging as few as 24 trials was adequate for recording the BP. Averaging of 15 - 30 trials also gave satisfactory recordings of slow potentials under different experimental conditions (Dick et al, 1987). We chose the arbitrary number of 30 artefact-free trials per experiment for averaging in each patient and control subject. It was felt that exceeding 30 "clean" trials might introduce more artefacts as the patients become tired. Indeed there was no need to exceed this number of trials because our results were always reproducible on repetition of these experiments in healthy volunteers in our pilot study. The averaged trials were inspected on the computer display unit and then written into an 8" computer floppy disc for future analysis.

5.9d Head movements:

We studied the acceleration of head movements which occurred in relation to postural adjustments in all patients and control subjects. These were recorded in the antero-posterior rather than the lateral plane for two reasons. First, because the ballistic arm movement used to cause perturbation of balance in this task results in antero-posterior displacement of body mass (Martin, 1967, Bouisset & Zattara 1981, Zattara & Bouisset, 1988) and, secondly, because displacement in this

plane is invariably greater than lateral body sway under conditions of poor balance in patients and healthy individuals alike (Diener et al, 1984).

The recording part of the accelerometer was mounted loosely on the vertex and was allowed to move freely with the subject's head. The cable connecting the accelerometer to the amplifier was about 2½ metres long and, therefore, it did not impede the subject's performance of the task.

5.10 Measurements:

There is no agreement on the reference point and baseline at which latency and amplitude measurements of movement-related potentials should begin. However, it is clear that at least two factors must be considered when deciding on this point. First, the point at which measurements begin must lie outside the expected range of the evoked potential and, secondly, it must be in close proximity to this potential. The latter condition is essential to reduce contamination with noise, electrical interference and artefacts.

Previous work in this department has demonstrated that the BP preceded the onset of the associated movement by an average of 850 msec. (Simpson & Khuraibet, 1987). Taking these observations into account and also allowing for the possible effects of disease on the duration of this potential, we chose the part of the recording between two points 1500

and 1250 ms. before the onset of the EMG burst of the prime mover to define the baseline. The latter was then determined by computing the average of the integrated evoked potential signal for the 250 ms. between these two points. The first potential shift on this line was taken as the start point for latency measurements. A method similar in principle was previously described by Fox and Rosenfeld (1972). To obtain a baseline these authors averaged 10-50 ms of data prior to the stimulus onset. Subsequently, Shibasaki et al (1980) adopted the same principle to determine the baseline for measurements of onset latencies of movement-related cortical potentials. This method was also used in the present study to determine the baseline and for latency measurements of EMG potentials and accelerometer signals. In all cases amplitude and latency meaurements were made to peak of wave using a computer cursor programme which gave a numerical display of these values.

9.5.11 Nomenclature:

It is conventional to refer to the upward and downward EEG deflections associated with movement-related cortical potential shifts as negative or positive, respectively. This nomenclature was adopted in the present study.

We use the same nomenclature of Shibasaki et al (1980) to define the waves which constitute the BP. Hence, the first part of the BP, i.e. the slowly rising negative wave, is referred to as the BP proper and the

more steeply rising negative wave which follows the BP proper as the NS' (negative slope). The positive deflection which immediately precedes the onset of EMG activity of the prime mover (pre-motion positivity) is named here P -50, while the re-afferent potential is called P +50. The various components of movement-related cortical potentials are schematically shown in figure 5/1.

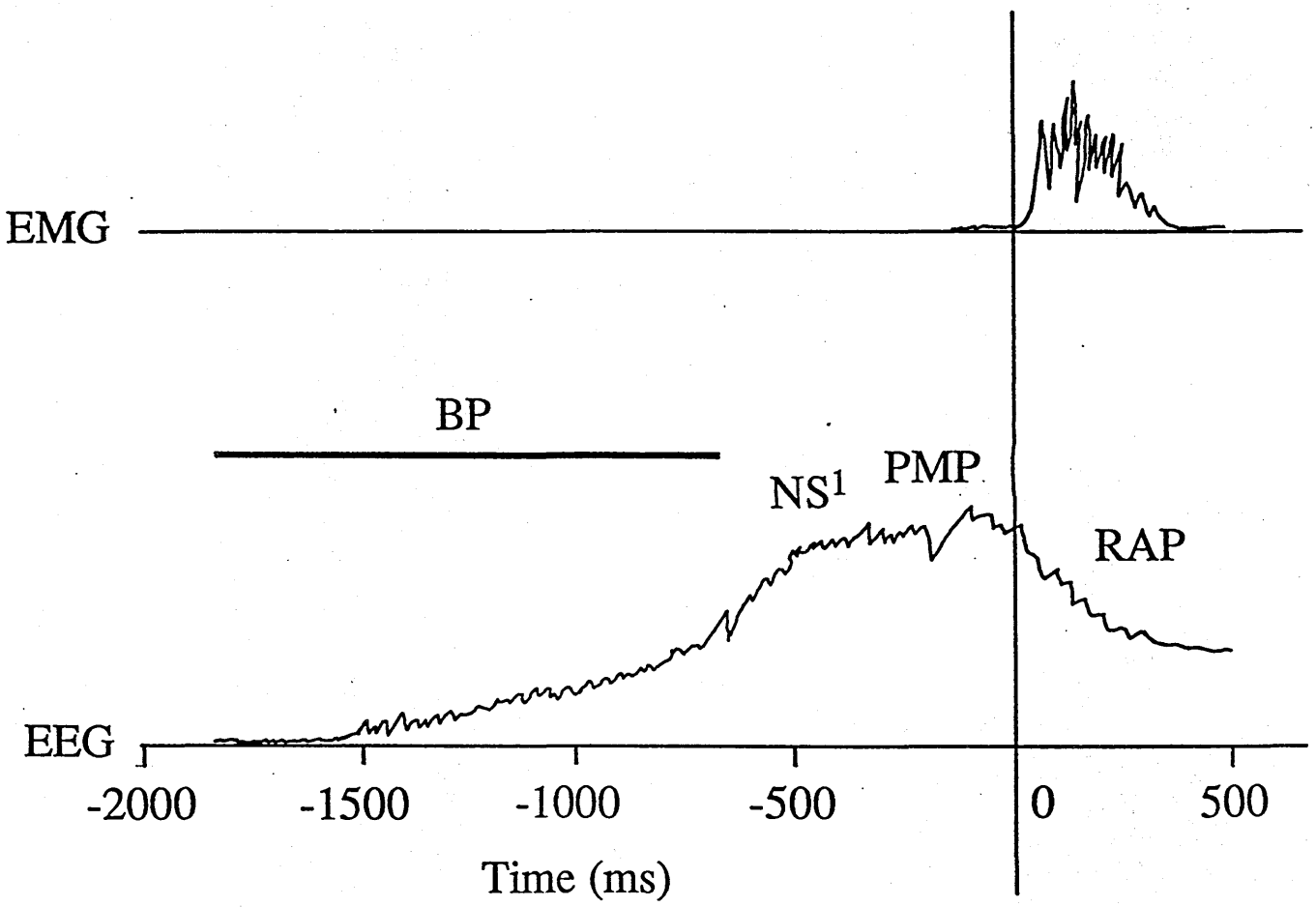
12 Parameters measured:

Onset latencies, duration and amplitudes of BP, EMG activity in TFL and TA and also head acceleration were measured from the baseline as defined earlier. These were then compared to the latencies and amplitudes observed in the two control groups. In some patients with PD these parameters were compared in the same patient when performing the test under the standard experimental conditions and under conditions of increased postural instability (while holding a book weighing 300 g. in the right hand).

The possible effects of age, duration and severity of PD on the righting reflexes, i.e. relationship of the BP components, i.e. wave form, onset latency, duration and amplitude, to the EMG activity of postural muscles were also analysed.

Figure 5/1

Schematic illustration of the various components of movement-related cortical potentials



BP - Bereitschafts potential

NS' - negative slope

PMP - premotion positivity

RAP - reafferent potential

5.13 Statistics:

Inspection of our results shows that they do not follow a normal Gaussian distribution. For this reason the following non-parametric statistical methods were used.

a) Spearman's rank correlation test (Olds, 1949, Mood, 1954). This method was used to compare simultaneously the latencies, durations and amplitudes of postural muscle EMGs and of BP in patients with PD and the two control groups. It was also used to analyse the effects of the duration and the severity of PD on postural muscle activity.

b) The Mann-Whitney U test (Mann & Whitney, 1947) was used to compare the same variables referred to in the section above between the two control groups on the one hand and, on the other hand, between patients with PD and each control group separately.

c) Wilcoxon signed rank test (Wilcoxon, 1945). This test was useful in the analysis of the effects of various degrees of postural instability on the activity of postural muscles, i.e. TFL and TA in our experiments.

The data were processed on an IBM computer using commercially-available software (Statistical Package for the Social Sciences [SPSS/PC+], system PC-DOS/MS-DOS, 1989).

CHAPTER 6

RESULTS

6.1 Introduction:

The data which are being analysed here are of those patients and control subjects who completed the experiments satisfactorily. These were 20 patients with Parkinson's disease (PD), 18 patients with neurological disorders other than PD and 15 healthy subjects. Results of the pilot study are not included in the analysis.

The patients and control subjects were comparable in terms of age and sex distribution. The raw values of the onset latency, duration and amplitude of the electromyographic (EMG) activity of the tensor fascia lata (TFL) and tibialis anterior (TA) muscles and of the Bereitschaftspotential (BP) in patients with PD, and in patients with other neurological illnesses and healthy subjects are given in tables 6/1 - 6/3, respectively.

The EMG activity of the prime mover, i.e. the anterior deltoid muscle, was recorded and displayed on the computer's monitor screen simultaneously with the BP, head acceleration and EMG activity of TFL and TA. These data were also stored in a floppy disc. However, the amplitude and duration of EMG activity of the prime mover were not analysed because only the onset of EMG activity of this muscle was useful as an indicator of the onset of movement which caused the perturbation of balance in our experiments.

Table 6/1

Onset latency, duration and amplitude of postural muscles' activity and of Bereitschaftspotential in patients with Parkinson's disease.

Name	Tensor fascia lata			Tibialis anterior			Bereitschaftspotential		
	latency	duration	amplitude	latency	duration	amplitude	latency	duration	amplitude
MF	+ 206	794	310.0	+ 218	782	388.1	1570	952	- 6.34
JS	+ 83	627	39.06	+ 324	229	26.85	1124	324	+ 4.7
CM	+ 142	858	100.0	+ 318	735	63.47	1747	935	- 13.42
MB	+ 565	465	53.71	+ 112	524	31.71	1482	282	- 3.66
MMcI	+ 583	9	7.32	0	0	0	1329	593	+ 7.08
GF	+ 124	635	449.2	- 1424	576	129.3	1394	1147	+ 6.95
CS	- 153	854	31.73	+ 89	711	17.09	1488	982	+ 21.11
JH	+ 195	803	119.9	0	0	0	1453	1235	+ 22.90
JD	+ 200	800	253.9	0	0	0	1265	341	- 1.95
DA	+ 36	964	65.91	0	0	0	1353	723	- 6.95
WMcC	0	1000	659.1	+ 200	800	485.8	1700	676	+ 6.95
TR	- 1218	2218	95.21	- 1147	2147	4.88	1253	776	- 8.17

* Onset latency and duration were measured in ms; amplitude was measured in uV.

Table 6/1 (continued)

Name	Tensor fascia lata			Tibialis anterior			Bereitschaftspotential		
	latency	dutation	amplitude	latency	duration	amplitude	latency	duration	amplitude
AF	- 1347	2347	117.1	0	0	0	1412	647	- 4.63
JG	- 1518	2518	212.4	- 1512	2512	34.18	1541	729	- 7.08
WG	- 1218	2218	397.9	+ 330	400	9.76	1376	652	+ 6.46
WMcN	- 1341	2341	190.4	- 1329	1629	2.44	1447	365	- 6.22
WF	- 1129	2129	107.4	0	0	0	1362	662	- 1.83
RI	- 1259	2259	300.2	0	0	0	1376	776	+ 9.26
EC	- 1106	2106	532.2	0	0	0	1353	553	+ 2.80
HB	- 1353	2353	126.9	- 1335	1794	7.23	1382	499	+ 5.24

Table 6/2

Onset latency, duration and amplitude of postural muscles' activity and of Bereitschaftspotential in healthy subjects.

Name	Tensor fascia lata			Tibialis anterior			Bereitschaftspotential		
	latency	duration	amplitude	latency	duration	amplitude	latency	duration	amplitude
RD	0	0	0	0	0	0	1494	829	- 9.15
PK	+ 330	141	56.15	+ 353	65	36.62	1312	372	+ 2.31
CR	- 1917	2864	107.4	0	0	0	1294	600	- 13.06
BW	- 1670	2670	437.0	- 1829	2617	12.20	1341	988	- 15.38
AK	- 1876	2876	241.6	0	0	0	1553	400	- 4.76
AS	- 912	1506	56.15	- 606	500	4.88	959	359	- 3.76
DL	- 1617	2617	56.0	- 401	200	18	1300	706	- 12.0
RW	- 1492	2092	74.2	- 121	80	10.1	1290	815	- 16.4
JW	- 2000	2120	19.6	0	0	0	1410	940	- 19.2
TB	- 1918	2480	70.8	- 460	510	19.8	1206	820	- 27.0

* Onset latency and duration were measured in ms; amplitude was measured in uV.

Table 6/2 (continued)

Onset latency, duration and amplitude of postural muscles' activity and of Bereitschaftspotential in healthy subjects .

Name	Tensor fascia lata			Tibialis anterior			Bereitschaftspotential		
	latency	duration	amplitude	latency	duration	amplitude	latency	duration	amplitude
AL	– 1760	2190	68.4	– 310	412	7.4	1461	842	– 6.0
MB	– 1900	1980	35.2	– 90	80	13.6	980	810	– 14.0
AW	– 1748	2143	98.0	– 20	96	12.0	1110	960	– 9.27
MP	– 1948	2248	40.1	– 120	14	37.0	989	808	– 15.7
ME	– 1952	2000	36.4	– 18	40	12.2	1002	906	– 13.6

Table 6/3

Onset latency, duration and amplitude of postural muscles' activity and of Bereitschaftspotential in patients with neurological disorders other than Parkinson's disease .

Name	Tensor fascia lata			Tibialis anterior			Bereitschaftspotential		
	latency	duration	amplitude	latency	duration	amplitude	latency	duration	amplitude
AR	- 1964	2964	4.88	0	0	0	1335	341	- 15.8
TS	- 1776	2776	85.44	+ 83	455	36.62	1341	447	- 11.1
CW	- 1888	2888	31.73	- 1035	1835	7.32	1232	611	+ 3.41
AG	- 2000	3000	358.8	- 1406	1877	34.18	1412	665	- 12.45
AB	- 1553	2361	87.89	0	0	0	1623	317	- 2.19
AD	- 1812	2724	46.38	0	0	0	1817	411	- 3.90
DG	- 1306	2306	170.8	- 1382	1835	14.64	1341	847	+ 5.49
JS	- 1565	2565	131.8	- 1423	2041	26.85	1618	624	- 17.2
CF	- 1500	2500	70.8	- 1482	6	2.44	1570	558	- 2.56
LMcN	- 1418	2418	95.21	0	0	0	1429	352	- 7.93

* Onset latency and duration were measured in ms; amplitude was measured in uV.

Table 6/3 (continued)

Onset latency, duration and amplitude of postural muscles' activity and of Bereitschaftspotential in patients with neurological disorders other than Parkinson's disease .

Name	Tensor fascia lata			Tibialis anterior			Bereitschaftspotential		
	latency	duration	amplitude	latency	duration	amplitude	latency	duration	amplitude
IS	- 1376	2376	217.2	- 1229	1900	17.08	1382	382	- 2.93
EC	- 1341	2341	246.5	- 1324	2324	2.4	1359	506	- 4.63
YA	- 1035	2012	241.6	- 1065	1283	9.76	1259	518	- 2.93
DH	- 1300	2300	97.66	- 1282	2257	7.32	1312	388	- 4.39
CF	- 1435	2435	73.24	- 1441	2441	34.0	1488	611	- 26.12
JC	- 1423	2423	327.1	- 1418	2418	31.73	1560	817	- 9.27
JCa	- 1347	2347	185.5	- 1147	1859	2.44	1706	277	- 2.07
JD	- 1423	2423	310.0	- 1412	1464	2.44	1618	700	- 5.37

The effects of the duration and severity of PD (as measured by the Webster and the Hoehn and Yahr disability scales) on the impairment of righting reflexes which is observed in patients with PD were studied by analysing the effects of each of these parameters on the onset latency of TFL and TA (table 6/4).

How the varying degrees of postural instability might influence the anticipatory and corrective activity of lower limb postural muscles (in this case TFL and TA) in patients with PD was examined by comparing the onset latency, duration and amplitude of these muscles in the same patient under two different experimental conditions. The task was first performed under the standard experimental conditions described earlier (we refer to this here as experiments "with no load") and then repeated after a rest period with the patient carrying a book weighing 300 g in his / her hand. The latter set of experiments is referred to as experiments "with load". The raw data for these experiments are presented in table 6/5.

6.2 Waveform of BP:

The BP, first described independently by Kornhuber and Deecke (1964) and Walter et al (1964), is a slowly rising negative potential shift with a characteristic scalp distribution and which precedes self-paced movements by 1.0 - 2.0 s. It has a mean duration of 1300 ms in healthy individuals (for review see Tamas and Shibasaki, 1985). The abrupt and steep rise of the negative potential shift which follows the BP has been named NS' by

Table 6/4

Effects of duration and severity of Parkinson's disease on the onset latency of postural muscles' activity.

Name	onset latency (ms) TFL	TA	duration of PD (years)	severity of PD Webster scale	Hoehn & Yahr scale
MF	+ 206	+ 218	2½ – 3	3	3
JS	+ 83	+ 324	3	10	2
MB	565	+ 112	14	5	2
CM	+ 142	+ 318	7½	13	3
MMcI	+ 583	0	4½	4	1
GF	+ 124	+ 424	4	10	3
CS	– 153	+ 89	16	13	3
JH	+ 195	0	8½	4	3
JD	+ 200	0	2½ – 3	5	3
DA	+ 36	0	2½	3	2
WMcC	0	+ 200	13	9	2
TR	– 1218	– 1147	3	5	1

Table 6/4 (continued)

Effects of duration , and severity of Parkinson's disease on the onset latency of postural muscles' activity .

Name	onset latency TFL	TA	duration of PD (in yeats)	severity of PD Webster scale	Hoehn & Yahr scale.;
AF	- 1347	0	2	5	1
JG	- 1518	- 1512	4	6	2
WG	- 1218	+ 330	½	6	1
WMcN	- 1341	- 1329	1	9	1
WF	- 1129	0	10	8	2
RI	- 1259	0	11	7	2
EC	- 1106	0	6	3	2
HB	- 1353	- 1335	16	7	2

TFL = tensor fascia lata
TA = tibialis anterior
PD = Parkinson's disease

Shibasaki et al (1980). The latter merges into a positive potential shift known as the premotion positivity.

All healthy individuals who participated in this study except one had a BP waveform similar to that just described. This was a 35 year old male who had a positive BP on all occasions when he was tested. Interestingly, this subject had a significantly delayed onset latency of his postural muscles, a pattern which was frequently observed in this study in patients with PD (see below). A typical example of the BP in a healthy individual is shown in figure 6/1.

The BP was also found to be positive in two patients. One had a parietal lobe tumour and the other suffered from postviral fatigue syndrome. By contrast, it was positive in 10 patients with PD who were examined. In the remaining parkinsonian patients the negative deflection of the waveform was only just perceptible. The mean amplitude in the latter subgroup of patients was - 6.02 uV and the mean amplitude of BP for the whole group of PD patients was + 1.66 uV compared with a mean of - 11.8 uV in healthy subjects. These results are consistent with previous reports which showed that in patients with PD the BP was of small amplitude, absent or even positive in the majority of cases (Simpson & Khuraibet, 1986 & 1987).

Head acceleration followed the EMG activity of the prime mover in all patients and control subjects and there was no significant difference between the three groups.

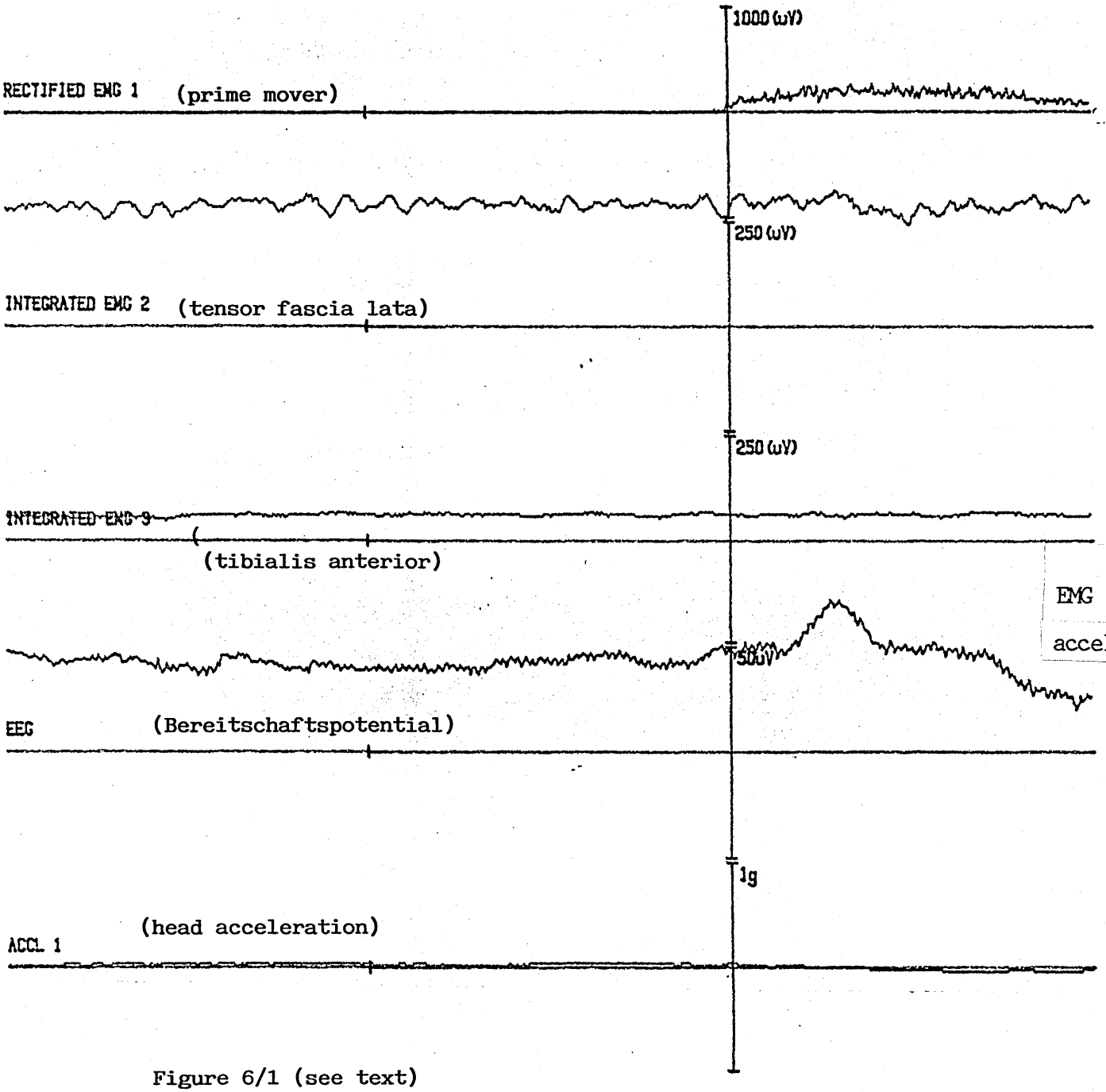
Table 6/5

The effects of the degree of perturbation of balance on the onset latency of postural muscles

Name	with load*		with no load*	
	TFL	TA	TFL	TA
MB	+ 565	+ 112	- 471	- 77
WG	- 1218	+ 330	- 1612	- 971
WMcN	- 1341	- 1329	- 1080	- 1382
WF	- 1129	0	- 1271	0
RI	- 1259	0	-1512	0
EC	- 1100	0	- 1100	0

* see text.

** Onset latency of postural muscles was measured in ms.



EMG activity, Bereitschaftspotential and head acceleration in a healthy subject.

Figure 6/1 (see text)

6.3 Correlation between the onset latency of TFL and TA and the amplitude of BP:

There was a statistically significant correlation between the amplitude of the BP and the latency of TFL. However, no similar correlation was found between the amplitude of the BP and TA onset latency.

Correlation between amplitude of BP and onset latency of TFL:

T = 58

Wilcoxon one-tailed test: $p < 0.05$

Correlation between the amplitude of BP and the onset latency of TA:

T = 96

Wilcoxon one-tailed test: p not significant

Wilcoxon two-tailed test: p not significant

6.4 Onset latency, duration and amplitude of TFL:

Statistical analysis of our results shows that the onset of the EMG activity in TFL was significantly delayed in patients with PD in comparison with that of healthy subjects and also of patients with neurological disease other than idiopathic parkinsonism ($p < 0.001$ in both cases). By contrast, there was no statistically significant difference in the onset latency of TFL between the two control groups. Details of this analysis are given below.

Onset latency of TFL in PD (group 1) versus healthy subjects (group 2)

Mann-Whitney U test.

Rank sum of group 1 = 471.5

rank sum of group 2 = 158.5

n1 = 20

n2 = 15

U = 38.50

z = - 3.717

$p < 0.001$

Onset latency of TFL in PD (group 1) versus patients with neurological disease other than parkinsonism (group 3)

Mann-Whitney U test.

Rank sum for group 1 = 541.0

Rank sum for group 3 = 200.0

n1 = 20

n2 = 18

U = 29.00

z = - 4.415

$p < 0.001$

Onset latency of TFL in healthy subjects (group 2) versus patients with neurological diseases other than parkinsonism (group 3):

Mann-Whitney U test.

Rank sum for group 2 = 209.5

Rank sum for group 3 = 351.5

n1 = 15

n2 = 18

U = 89.5

z = - 1.645

p not significant

Interestingly, although the duration of EMG activity of TFL was not significantly different between parkinsonian patients and healthy subjects, the amplitude was greater in patients with PD ($p < 0.05$, see below).

TFL duration: PD (group 1) versus healthy subjects (group 2)

Mann-Whitney U test.

Rank sum for group 1 = 313.0

rank sum for group 2 = 317.0

n1 = 20

n2 = 15

U = 103.00

z = - 1.567

p not significant

TFL amplitude: PD (group 1) versus healthy subjects (group 2)

Mann-Whitney U test.

Rank sum for group 1 = 431.5

Rank sum for group 2 = 198.5

n1 = 20

n2 = 15

U = 78.50

z = - 2.383

$p < 0.05$

6.5 Onset latency, duration and amplitude of TA:

There was no statistically significant difference in the onset latency of TA muscle between parkinsonian patients and healthy subjects. However, the onset latency of TA was found to be significantly earlier in patients with neurological diseases other than parkinsonism than in patients with PD and healthy subjects as illustrated below.

Onset latency of TA: PD (group 1) versus healthy subjects (group 2)

Mann-Whitney U test.

Rank sum for group 1 = 409.0

Rank sum for group 2 = 221.0

n1 = 20

n2 = 15

U = 101.00

z = - 1.633

p not significant

Onset latency of TA: PD (group 1) versus patients with other neurological diseases (group 3)

Mann-Whitney U test.

Rank sum for group 1 = 482.5

Rank sum for group 3 = 258.5

n1 = 20

n2 = 18

U = 87.50

z = - 2.704

$p < 0.01$

Onset latency of TA: Healthy subjects (group 2) versus patients with neurological diseases other than parkinsonism (group 3)

Mann-Whitney U test.

Rank sum for group 2 = 315.0

Rank sum for group 3 = 246.0

n1 = 15

n2 = 18

U = 75.00

z = - 2.169

p = <0.05

6.6 The effects of the severity and the duration of PD on the onset latency of TFL and TA:

The severity of PD was assessed in this study by using the Webster (1968) and the Hoehn and Yahr (1967) disability scales. As expected, there was no correlation between the Webster and the Hoehn and Yahr scales when the severity of PD was assessed in the same patient by these two different methods. (Spearman's rank correlation test: rho = 0.232, t = 1.010, p not significant). This is discussed further in chapter 7.

Also there was no correlation between the onset latency of TFL and the severity of PD as assessed by the Webster scale, whereas a statistically significant correlation was demonstrated when the Hoehn and Yahr disability scale was used. On the other hand, the onset latency of TA in parkinsonian patients did not correlate with disease severity when either disability scale was used:

Correlation between the onset latency of TFL and severity of PD on the Webster scale

Spearman's rank correlation test.

rho = - 0.222

t = - 0.967

p not significant

Correlation between the onset latency of TFL and severity of PD on the Hoehn and Yahr scale

Spearman's rank correlation test.

rho = 0.502

t = 2.464

$p < 0.05$

Correlation between TA onset latency and severity of PD on the Webster scale

Spearman's rank correlation test.

rho = 0.324

t = 1.451

p not significant

Correlation between TA onset latency and severity of PD on the Hoehn and Yahr scale

Spearman's rank correlation test.

rho = 0.423

t = 1.980

p not significant

There was no statistically significant correlation between the onset latency of TFL or TA and the duration of PD as shown in the following illustration:

Correlation between the onset latency of TFL and the duration of PD

Spearman's rank correlation test.

rho = 0.056

t = 0.240

p not significant

Correlation between the onset latency of TA and the duration of PD

Spearman's rank correlation test

rho = - 0.001

t = - 0.005

p not significant

6.7 The effects of different degrees of postural instability on the onset latency of TFL and TA:

To test the response of postural muscles (measured here by the onset latency of TFL and TA) in situations of increased perturbation of balance the experiments were conducted "with load" and "with no load" (see above for definitions of these terms). There was no difference in the onset latency of TFL in the two experiments (Wilcoxon signed ranks test, T = 9.00) but the onset latency of TA was significantly earlier in "with load" experiments:

Onset latency of TA in experiments " with load" versus experiments "with no load".

Wilcoxon signed ranks test.
T = 0.00
One-tailed test: $p < 0.025$
Two-tailed test: $p < 0.05$

6.8 Summary of the results:

* Head acceleration followed the onset of EMG activity of the prime mover in all patients and control subjects and there was no statistically significant difference between these groups.

* The amplitude of the BP correlated with the onset latency of TFL (Wilcoxon one-tailed test, $p < 0.05$) but not with the onset latency of TA.

* The duration of BP was shorter in patients with PD than in control subjects but this did not reach statistical significance.

* The onset latency of TFL was significantly delayed in patients with PD (Figure 6/2) in comparison with healthy subjects (Mann-Whitney U test, $p < 0.001$) and patients with neurological disorders other than idiopathic parkinsonism (Mann-Whitney U test, $p < 0.001$) and there was no statistically significant difference between the two control groups.

* The duration of the EMG activity of TFL in patients with PD was not significantly different from that of healthy subjects, but the amplitude was greater in parkinsonian patients (Mann-Whitney U test, $p < 0.05$).

* There was no difference in the onset latency of TA between PD patients and healthy subjects. However, the onset latency was earlier in patients with neurological diseases other than parkinsonism when compared with healthy subjects or parkinsonian patients (Mann-Whitney U test, $p < 0.05$ & $p < 0.01$, respectively).

* There was no correlation between the Webster and the Hoehn and Yahr disability scales when the two methods were used to assess the severity of parkinsonism in the same patient. There was also no correlation between the onset of EMG activity of TFL and the severity of PD on the Webster scale but there was a significant correlation on the Hoehn and Yahr scale (Spearman's correlation rank test, $p < 0.05$).

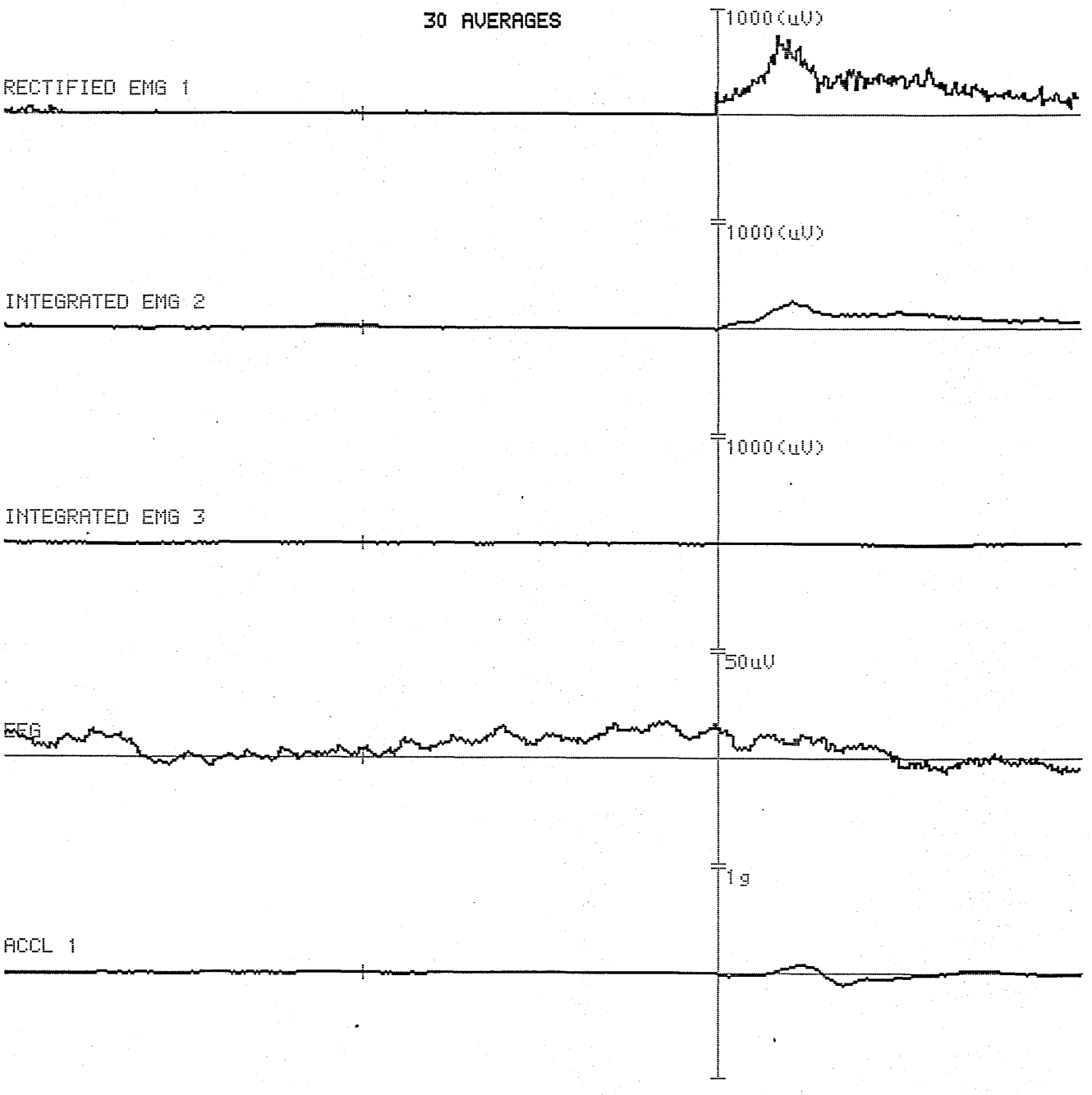


Figure 6/2
Electromyographic activity of prime mover (EMG 1), tensor fascia lata (EMG 2) and tibialis anterior (EMG 3) and of Bereitschaftspotential (EEG) and head acceleration (Accl1) in a patient with Parkinson's disease. Note delayed EMG activity of tensor fascia lata.

* The onset latency of TA did not correlate with the severity of PD when either disability scale was used.

* The duration of PD had no effect on the onset latency of TFL or TA.

* When the perturbation of balance was increased the EMG activity started earlier in TA muscle (one-tailed Wilcoxon signed rank test, $p < 0.025$, two-tailed test, $p < 0.05$) but there was no such effect on TFL.

CHAPTER SEVEN

DISCUSSION

Discussion

The working hypothesis which the present study attempted to test is that the basal ganglia act on the cerebral cortex via dopaminergic pathways to delay the onset of voluntary self-paced movements until the appropriate postural set is established (Simpson & Fitch, 1988). This concept which suggests an important gating function for the basal ganglia in the maintenance of posture and equilibrium is based on the current knowledge of the anatomy and function of the basal ganglia, as well as on clinical observations of the effects of disease of these structures.

Parkinson's disease (PD) - a disorder suitable for studying basal ganglia function:

To gain insight into the possible role of the basal ganglia in the control of equilibrium during stance and gait we chose to study patients with PD. These patients are suitable for the purposes of our study because the brunt of pathological changes which account for the clinical features and neurochemical abnormalities seen in PD are confined to the basal ganglia. Therefore, one could reasonably assume that any abnormalities present in patients with parkinsonism are likely to be due either to a direct loss of function caused by the basal ganglia lesion or to loss of inhibitory control that is normally exerted by the basal ganglia on other structures. As pointed out by Martin (1967) and later

by Marsden (1982) only the "negative" symptoms of PD , i.e. loss of postural (righting) reflexes and bradykinesia are likely to indicate the true function of the basal ganglia, whereas the "positive" symptoms of tremor and rigidity are release phenomena which result from disinhibition of distant neural structures from basal ganglia control. This viewpoint is corroborated by evidence from animal experiments which showed that stimulation and / or destruction of the red nucleus and the areas lateral and dorso-lateral to it and the ventrolateral nucleus of the thalamus resulted in tremor, whereas stimulation of the basal ganglia had failed to do so (Carpenter & McMasters, 1964).

A clinically detectable variable degree of disequilibrium is invariably present in patients with moderately severe and advanced PD. Characteristically, impairment of balance in these patients is initially noticed when they turn round and becomes more pronounced as the disease progresses. In the later stages of parkinsonism postural instability is consistently present during stance and gait and usually leads to significant disability by causing frequent falls.

The organization of righting reflexes:

The underlying pathophysiological mechanism of postural instability in patients with PD is the impairment or loss of righting reflexes. As discussed earlier, stretch reflexes are normal in these patients (McLellan, 1975).

The anatomical organization of the reflex mechanisms which allow man to maintain or regain his erect posture is complex. Afferent input from proprioceptive, visual and vestibular systems relay through the posterior ventral nucleus of the thalamus. Fibres from this nucleus terminate on the small polymorphous striatal interneurones (Kemp & Powell, 1971). Convergence and integration of input to these cells is ensured by the extensive axonal plexuses which cross the dendrites of other cells. Most efferent striato-pallidal fibres (which are axons of the large multipolar striatal neurones) form "closed" loops which terminate in the supplementary motor area (SMA) (Alexander et al, 1986).

The role of the SMA in the control of righting reflexes is evident from the work of Weisendanger et al (1973) who demonstrated that stimulation of this area of the cerebral cortex caused sustained contractions of proximal "postural" muscles. This activity is distinct from and precedes that of the primary motor cortex. Thus posture is adjusted in anticipation of forthcoming willed movements. The net effect is to bring the centre of body mass over the base of support (Martin,1967, Lipshits, 1981)

The anatomical pathways which subserve righting reactions in man are not fully understood. However, it is clear, that the functional stretch reflex (FSR) [also known as the long latency stretch reflex and the transcortical stretch reflex] plays an important role in stabilizing human posture as was shown by Nashner (1976) in a series of experiments.

This author was able to show that the postural sway induced by platform displacements in standing healthy subjects evoked FSR responses with a latency of 120 ms. which attenuated or were completely abolished in the absence of postural instability (e.g. in experiments with direct ankle rotation in the absence of antero-posterior platform displacement). It is also evident that these FSR are not due to vestibular cues because in experiments in which proprioceptive input from the ankle joints was blocked, the EMG latency of postural muscles was 200-300 ms. [responses begining at 200-300 ms. have been shown to be vestibular in origin (Nashner, 1973)].

Movement-related cortical potentials:

Experimental neurophysiological evidence shows that self-paced movements are preceded by slow potential shifts collectively known as movement-related cortical potentials (MRCP). Four components of MRCP have been described. Each of these components has distinct topographical and morphological characteristics and functional significance (see table 7/1). Kornhuber & Deecke (1964) and Gilden et al (1966) have postulated that the negative components of MRCP reflect the preparatory events and the cortical discharge which are associated with a self-paced movement, whilst the positive shift (reafferent potential) is due to the afferent movement-produced feedback. Controversy has surrounded the significance of each of these components of MRCP ever since [for an up to date review see Tamas & Shibasaki, (1985)]. The present study is concerned with the

Table 7/1

The morphological characteristics of movement-related cortical potentials (MRCP).

MRCP	morphological characteristics	topography	functional significance
BP proper	slowly rising negative potential starting 800 - 1000 ms before onset of movement.	diffuse, but maximal at vertex	probably reflects functional activity Of SMA.
NS'	abrupt increase in negativity which follows BP proper & continues with more or less constant slope.	mainly precentral & parietal	? related to functional activation of primary motor cortex.
MP	sharp negative wave occuring just before the onset of movement.	well-localised to contralateral central cortex.	? results from activation of a final common pathway of cortical motor activity.
P300	large, diffuse asymmetrical positive wave, follows movement onset by 300 ms.	maximal precentrally.	appears in response to various stimuli but is independent of stimulus modality.
CNV	slow potential which occurs in the inter-stimulus intervals.	frontal and premotor areas.	seen only in warned movement paradigms "the expectancy wave".

BP = Bereitschaftspotential, NS' = negative slope, MP = movement potential, CNV = contingent negative variation.

BP, which will be discussed in more detail.

The BP is the first of the slowly rising negative potential shifts associated with a self-paced movement and it starts about 800 - 1500 ms before the onset of movement (Simpson & Khuraibet, 1987). It has been postulated that the BP reflects the functional activity of the SMA. Deecke & Kornhuber (1978) suggested that the BP is generated by the SMA and not the primary motor cortex since it is maximal over the SMA but poorly developed over the parietal cortex and frontal areas. Barrett et al (1985) have also found the distribution of the BP to be symmetrical about the midline and concluded that it originates in the SMA which is in agreement with several other reports (e.g. Boschert et al, 1983, Simpson & Khuraibet 1987).

By contrast, in experiments with self-paced finger movements NS' had a maximum slope over the contralateral motor hand area (Barrett et al, 1985), whereas its maximum distribution for foot movements was over the vertex (Shibasaki et al, 1981). Maximum amplitude of NS' (also referred to as N') over the hemisphere contralateral to the self-paced movement and also a clear somatotopic distribution of this component of movement-related potentials has also been reported earlier (Vaughan et al, 1968). These observations suggest that NS' reflects the functional activation of the primary motor cortex.

In PD the BP is absent or positive over the precentral areas and its

duration and amplitude correlated with spontaneous or drug-induced fluctuations of PD (Simpson & Khuraibet, 1987). This indicates that area 6, i.e. SMA, is under cortico-fugal dopaminergic control. The work of Adler et al (1989) supports this viewpoint. These authors have found that the amplitude of the BP is more than two times larger in patients with tardive dyskinesia than in healthy subjects or schizophrenic patients without tardive dyskinesia. The latter condition is known to be associated with enhanced dopaminergic activity.

Simpson postulated that the fluctuations of BP in PD may indicate that the basal ganglia regulate the function of the SMA by "gating" the nigrostriatal-thalamo-cortical input thus delaying the activation of the primary motor cortex until postural muscle set is appropriately adjusted by the SMA and by brain stem-putamen-spinal reflex loops in preparation for the forthcoming movement (Simpson & Fitch, 1988). Therefore, studying the BP in relation to self-paced movements which cause perturbation of balance in patients with PD appears to be a useful approach to examine the validity of the aforementioned hypothesis.

Experimental paradigm:

We used rapid shoulder flexion to induce perturbation of balance in our experiments and recorded the BP from the contralateral motor hand area. Thus, the anterior part of the deltoid muscle was the prime mover in these experiments. Simultaneous recordings of EMG activity in the

"postural" muscles appropriate to this task were also made. These are the tensor fascia lata (TFL) on the side contralateral to the prime mover and the ipsilateral tibialis anterior (TA) muscles. The choice of TFL and TA as the "appropriate postural" muscles for this task was based on observations of other experimenters (see below) and also on the results of our own pilot study.

All who participated in the study were right-handed subjects. Left-handed individuals were excluded because of the reported differences in the MRCP between the two groups: the BP in sinistrals is smaller in amplitude and less asymmetrical than in dextrals (Papakostopoulos & Jones, 1980). Handedness was determined by a modified Edinburgh Inventory scale (Oldfield, 1971). To determine handedness we took into account the following: the hand which the subject uses to write with, to cut bread with and to hold tools in; the foot which he uses to kick a ball with and the eye which he uses for aiming a rifle.

It is worth emphasizing that in our experiments we used self-paced movements to cause the perturbation of balance and not a reaction time paradigm. To avoid a reaction time response (i.e. intentional shift in posture) patients were instructed to respond to the visual signal "in their own time". The signals were also delivered at random intervals to eliminate the factor of anticipation. Avoiding a reaction time situation is essential since the functional organization of a reaction time response differs from that of a self-paced movement. In experiments in

which the focal destabilizing movement was tone-triggered (i.e. a reaction time response was evoked) the response latencies of postural muscles varied from one trial to another depending on the subject's concentration, motivation etc., whereas with self-paced movements no such variations were observed and the response latency of postural muscles was always shorter than that of a reaction time movement in the same individual. An additional important difference between these two responses is also the sequence in which postural muscles are activated. This activation occurs in a proximal-to-distal order in reaction time situations but in the reverse sequence with self-paced movements (Nashner and Cordo, 1981). An interesting observation made by these investigators is that when a subject is presented with a reaction time task at the same time as the balance is being disturbed (by a platform displacement), automatic postural adjustments always occur before the voluntary reaction time movement and proximal muscles activation consistently lags behind that of the distal muscles, indicating a delay of the voluntary movement until the appropriate postural set is established. These authors concluded that automatic postural adjustments are organized at a lower (less adaptive) hierarchical level in the central nervous system than reaction time movements.

The present study has shown that TFL is the main postural muscle responsible for righting reactions when the perturbation of balance is caused by a ballistic forward arm movement with the subject standing

erect. These findings confirm the observations of other investigators. For example in a series of experiments employing the same paradigm while recording the EMG activity simultaneously in several trunk and lower limb muscles it was found that the EMG activity of TFL consistently preceded that of other lower limb and trunk muscles. Furthermore, its amplitude was always greater than that of the other muscles (Bouisett & Zattara 1981, Zattara & Bouisett, 1988).

In all healthy subjects but one and in all patients with neurological diseases other than idiopathic parkinsonism which we studied the EMG activity of TFL preceded that of the prime mover. By contrast, in patients with PD the EMG activity of TFL as a rule followed that of the prime mover and the difference of TFL onset latency between patients with PD and the two control groups was statistically significant (Mann-Whitney U test, $p < 0.001$). As expected, no difference in the onset latency of TFL was found when the two control groups were compared.

Interestingly, the degree of delay of the onset latency of TFL correlated with the severity of PD as measured by the Hoehn and Yahr scale (1967) [Spearman's rank correlation test, $p < 0.05$] but not when the Webster disability scale (1968) was used. This could be explained by the fact that the former method of assessment of severity of PD takes into account the impairment of righting reflexes while the latter does not. In fact, when the severity of PD in the same patient was assessed with the two methods no correlation was found. Therefore, the Hoehn and

Yahr disability scale appears to be a better method of assessment of PD severity than the Webster disability scale, especially when the impairment of righting reflexes is being evaluated. The duration of PD per se does not appear to have any effect on the onset latency of TFL.

In their experiments with a movable platform, Cordo and Nashner (1982) have found that increase in postural requirements, e.g. when platform displacements are increased, has two effects. First, the gain (amplitude) of the associated postural adjustment increases and, secondly, the focal movement is delayed proportionally to the severity of perturbation. In contrast to these findings, the onset latency of TFL did not alter significantly when the requirements for postural adjustments were increased in our experiments by asking the subjects to hold a book weighing 0.3 kg while performing the task. It is possible that this small extra load was not sufficient to increase the perturbation of balance significantly. However, this explanation is unlikely since the same amount of extra weight resulted in a significantly earlier onset of EMG activity in TA (one-tailed Wilcoxon signed rank test, $p < 0.025$; two-tailed test, $p < 0.05$). This apparent discrepancy is probably due to the fact that each of these muscles has a distinct role in postural stabilization in this task: the activity of the TFL is probably preprogrammed and maintains postural stability in anticipation of the forthcoming willed movement, whereas the TA contibutes to the maintenance of posture by correcting postperturbation instability which results from inadequate peripheral stimuli.

The following data from our study support this point of view. In the standard experiments there was no significant difference in the onset latency of TA between PD patients and healthy subjects but it was earlier in patients with neurological diseases other than parkinsonism when the latency was compared with that of PD patients ($p < 0.01$) or healthy subjects ($p < 0.05$). The group of patients with neurological diseases other than parkinsonism in the present study consisted mainly of patients with cervical spondylosis, peripheral neuropathies and syringomyelia. These disorders cause impairment of balance by interfering with the "peripheral" mechanisms of postural control (see chapter 1). The central mechanism of postural control, i.e. the basal ganglia and their central connections, in these patients is intact. Therefore, by inference, the abnormalities observed in these patients could be explained by the failure of the "peripheral" mechanisms of postural control.

The observation of Cordo and Nashner (1982) that the amplitude of the EMG activity of postural muscles increased with an increase in postural requirements is in agreement with our findings.

The EMG activity of TFL and TA in this study are clearly not the result of vestibular stimuli. As stated earlier, when the postural muscles activity is due to vestibular cues the EMG onset latency is between 200 - 300 ms (Nashner, 1973). Furthermore, head acceleration followed the

onset of EMG activity of the prime mover in all patients and control subjects and there was no difference between the three groups.

Our data clearly demonstrate the correlation between the amplitude of the Bereitschaftspotential (BP) and the onset latency of TFL. There was no similar correlation with TA.

Reference has been made earlier to the fact that the BP reflects the electro-cortical activity of the supplementary motor area (SMA) and is closely related to the control of postural mechanisms. The present study has demonstrated a clear correlation between the severity of PD and the amplitude of the BP. The amplitude of the BP can, therefore, be considered a reliable index of basal ganglia dysfunction. This statement is in agreement with previously reported observations. For example, Simpson and Khuraibet (1987) have found a significant correlation between PD severity and the amplitude of the BP. Furthermore, these authors were able to demonstrate an increase in the BP peak amplitude with levodopa therapy. Similar observations were made by Dick et al (1987).

In this study the duration of the BP had a clear tendency to be shorter in patients with PD than in control subjects but this was not statistically significant. In an earlier study in this department Simpson & Khuraibet (1987) have found the duration of BP to be reduced in patients with PD. This discrepancy could be explained by the fact

that the latter investigators have measured the whole of the negative movement-related cortical potential (MRCP) [which includes the slowly rising potential shift, i.e BP proper, and the the more steeply rising potential now known as NS']. In this study we adopted the more recent classification of MRCP of Tamas & Shibasaki (1985). NS' was, therefore, not included in the measurements. In this series the sum of BP proper & NS' tended to be shorter than normal but was not statistically significant.

The data presented here unequivocally show that the EMG activity of the TFL (the main postural muscle in the present experimental paradigm) was significantly later in patients with PD as compared with that of healthy subjects and patients with neurological disorders other than parkinsonism. In other words, activation of the prime mover in these patients occurred much earlier than in control subjects, i.e. before the appropriate postural set is established. This can only be due to basal ganglia dysfunction since these abnormalities were present in patients with PD but not in control subjects. Recently, similar findings have been documented in other basal ganglia disorders. For example, in experiments with sudden toe-up tilt of a movable platform, Huttunen and Homberg (1990) have shown that patients with Huntington's disease have delayed onset latency of EMG activity in lower limb postural muscles in comparison to those of healthy subjects. By contrast, the EMG onset latency of these muscles was similar in both groups when perturbation of balance was minimal (e.g. in experiments with platform displacement while patient was sitting).

Delayed initiation of voluntary movements is a characteristic feature of parkinsonism. For example, when patients with PD were asked to sit up from the supine position, the EMG activity of the rectus femoris muscle on the affected side was found to follow that of the unaffected side by 40 ms. (Wilson, 1925). Although the precise mechanism of the delayed initiation of voluntary movements in parkinsonism is not known, several subsequent studies have confirmed Wilson's observation. The findings of this study that the EMG activity of the prime mover preceded rather than followed postural muscles activity are quite compatible with the phenomenon of the delayed initiation of willed movements in parkinsonian patients since the fiducial point may be considerably delayed from the intention to move. Thus, the pallido-thalamo-cortical circuit, as proposed in this model, is a parallel regulatory one which delays cortical commanded movements until the appropriate postural set is established by brain stem structures.

In conclusion, the present study has demonstrated that the basal ganglia allow a postural set to be established in advance of any movements which are perceived to cause perturbation of balance. Diseases of the basal ganglia result in impairment or loss of this function and consequently lead to the observed abnormalities of righting reflexes in these patients.

CHAPTER EIGHT

CONCLUSIONS

Penney & Young (1983) observed that a number of criteria must be fulfilled in any model which attempts to prove a given hypothesis or to elucidate function of a certain organ. Briefly,

1. it is essential that the model should have an anatomical basis;

2. it should also be consistent with the known physiological and biochemical properties of that organ;

3. the model should also explain how disruption of structure and function produces symptoms of disease; and

4. it must be able to account for the effects of treatment, medical or surgical.

The model of the basal ganglia as a "gate" control mechanism for postural set that this work set out to prove fulfils all these criteria. The evidence has been presented in previous chapters.

The present study confirms the role of the basal ganglia in postural control. This function of the basal ganglia is consistent with the currently accepted theory of the central organization of the righting reflexes and explains the temporal sequence of activation of postural muscles and its relationship to that of segmental musculature which causes perturbation of balance. Our findings would be compatible with

the hypothesis that failure to establish the SMA controlled postural set delays the onset of area 4 activity driven by volition. It was also shown in this study that the length of delay in the onset of the EMG activty of postural muscles in patients with Parkinson's disease is proportional to the severity of basal ganglia dysfunction. This observation is accounted for in our model by the proposed "gating" mechanism. Gating by the basal ganglia will, therefore, depend on the perceived degree of postural requirement. The present work explores yet another function of the fascinating brain stem grey matter masses which are collectively known as the basal ganglia.

REFERENCES

Adler LE, Percevich M, Nagamoto H. Bereitschaftspotential in tardive dyskinesia. Mov. Disord. 1989, 4: 105-112

Alexander GE, De Long MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann. Rev. Neurosci. 1986, 9: 357-381

Allum JHJ, Keshner EA, Honneger F, Pfaltz CR. Organization of leg-trunk-head equilibrium movements in normals and patients with peripheral vestibular deficits. In: Pompeiano O & Allum JHJ (eds). Vestibulospinal control of posture and locomotion. Progress in Brain Research, vol.76, Elsevier, Amsterdam, 1988, pp 277-290

Anderson ME. Discharge patterns of basal ganglia neurones during active maintenance of postural stability and adjustment to chair-tilt. Brain Res. 1977, 143: 325-338

Arikuni T, Kubota K. Substantia innominata projection to caudate nucleus in macaque monkeys. Brain Res. 1984, 302: 184-189

Barbeau A. Parkinson's disease: clinical features and etiopathology. In: Vinken PJ, Bruyn GW, Klawans HL (eds). Handbook of Clinical Neurology, vol. 49 (revised series 5), Elsevier Science Publishers, Amsterdam, 1986, p92.

Barone P, Bankiewicz KS, Corsini GU, Kopin IJ, Chase TN. Dopaminergic mechanisms in hemiparkinsonian monkeys. Neurology 1987, 37: 1592-1595

Barone P, Davis TA, Braun AR, Chase TN. Dopaminergic mechanisms and motor function: characterization of D1 and D2 dopamine receptor interactions. Eur. J. Pharmacol. 1986, 123: 109-114

Barrett G, Shibasaki H, Neshige R. A computer assisted method for averaging movement-related potentials with respect to EMG onset. Electroencephal. Clin. Neurophysiol. 1985, 60: 276-281

Belen'kii VY, Gurfinkel VS, Pal'tsev YI. Elements of control of voluntary movements. Biophysics 1967, 12: 135-141

Boschert J, Hink RF, Deecke L. Finger movement versus toe movement related potentials: further evidence for supplementary motor area (SMA) participation prior to voluntary action. Exp. Brain Res. 1983, 52: 73-80

Bouisset S, Zattara M. A sequence of postural movements precedes voluntary movement. Neurosci. Lett. 1981, 22: 263-270

Bowsher D. Introduction to the anatomy and physiology of the nervous system. 4th ed. Blackwell Scientific publications, Oxford, 1979

Brinkman C, Porter R. Supplementary motor area in the monkey: activity of neurones during performances of a learned motor task. J. Neurophysiol. 1979, 42: 681-709

Brodal A. Neurological anatomy in relation to clinical medicine. 2d ed. Oxford University Press, London, 1969

Boyson SJ, McGonigle P, Molinoff PB. Quantitative autoradiographic localization of the D1 and D2 subtypes of dopamine receptors in the rat. J. Neurosci. 1986, 6: 3177-3188

Burke D. Muscle spindle function during movement. Trends Neurosci. 1980, 3: 251-253

Buser P, Pouderoux G, Mereaux J. Single unit recording in the caudate nucleus during sessions with elaborate movements in the awake monkey. Brain Res. 1974, 71: 337-344

Calne BD. Dopamine receptors in movement disorders. In: Marsden CD, Fahn S (eds). Movement disorders. Butterworth, Boston, 1982, pp 348-355

Carpenter MB. Anatomy of the basal ganglia. In: Vinken PJ, Bruyn GW, Klawans HL (eds). Handbook of Clinical Neurology, revised series 5, vol. 49, Elsevier Science Publishers, Amsterdam, 1986, pp 1-18

Carpenter MB, McMasters RE. Lesions of the substantia nigra in the rhesus monkey. Efferent fiber degeneration and behavioral observations. Am. J. Anat. 1964, 114: 293-320

Cooper JR, Bloom FE, Roth RH. The biochemical basis of neuropharmaclogy. 5th ed. Oxford University Press, New York, Oxford, 1986

Cordo PJ, Nashner LM. Properties of postural adjustments associated with rapid arm movements. J. Neurophysiol. 1982, 47: 287-302

Crane GE, Ruiz P, Kernohan WJ. Effects of drug withdrawal on tardive dyskinesia. J. Neurol. Neurosurg. Psychiat. 1969, 33: 511-512

Crutcher MD, De Long MR. Single cell studies in the primate putamen. 1. Functional organization. Expt. Brain Res. 1984, 53: 233-243

Crosby EC, Humphrey T, Laurer EW. Correlative anatomy of the nervous system. The Macmillan Company, New York, 1962, pp: 365-366

Cunha L, Oliveria C, Diniz M et al. Homovanillic acid in Huntington's disease and Sydenham's chorea. J. Neurol. Neurosurg. Psychiat. 1981, 44: 258-261

Damasio AR, Van Hoesen GW. Structure and function of the supplementary motor area (abstract). Neurology, 1980, 30: 359

Deecke L, Kornhuber HH. An electrical sign of participation of the mesial "supplementary" motor cortex in human voluntary finger movement. Brain Res. 1978, 159: 473-476

De Long MR. Putamen: activity of single units during slow and rapid arm movements. Science 1973, 179: 1240-1242

De Long MR, Georgopoulos AP. Motor functions of the basal ganglia as revealed by studies of single cell activity in the behaving primate. Adv. Neurol. 1979, 24: 131-140

De Long MR, Strick PL. Relation of basal ganglia, cerebellum and motor cortex units to ramp and ballistic limb movements. Brain Res. 1974, 71: 327-335

Dick JPR, Cantello R, Buruma O, Gioux M, Benecke R, Day BL, Rothwell JC, Thompson PD, Marsden CD. The Bereitschaftspotential, L-DOPA and Parkinson's disease. Electroencephal. Clin. Neurophysiol. 1987, 66: 263-274

Diener H-C, Dichgans J. On the role of vestibular, visual and somatosensory information for dynamic postural control in humans. In: Pompeiano O, Allum JHJ (eds). Vestibulospinal control of posture and locomotion. Progress in Brain Research, vol. 76, Elsevier, Amsterdam, 1988, pp 253-262

Diener H-C, Dichgans J, Bruzek W, Selinka H. Stabilization of human posture during induced oscillations of the body. Expt. Brain Res. 1982, 45: 126-132

Diener H-C, Dichgans J, Bacher M, Gompf B. Quantification of postural sway in normals and patients with cerebellar diseases. Electroencephal. Clin. Neurophysiol. 1984, 57: 134-142

Di Fabio RP. Lower extremity antagonist muscle response following standing perturbation in subjects with cerebrovascular disease. Brain Res. 1987, 406: 43-51

Evarts EV. Motor cortex reflexes associated with learned movement. Science 1973, 179: 501-503

Evarts EV. Representation of movements and muscles by pyramidal tract neurones of the precentral motor cortex. In: Yahr MD & Purpura DP (eds). Neurophysiological basis of normal and abnormal motor activity. Raven, New York, 1967, pp 215-253

Everett NB. Functional neuroanatomy. 6th ed. Lea & Febiger, Philadelphia, 1971

Fox SS, Rosenfeld JP. Recording evoked potentials. In: Meyers RD (ed). Methods in psychobiology. Vol. 2. Academic Press, London & New York, 1972, p 365

Gerfen GR. The neostriatal mosaic: compartmentalization of cortico-striatal input and striato-nigral output systems. Nature 1984, 311: 461-464

Gilden L, Vaughan HG, Jr, Costa LD. Summated human EEG potentials with voluntary movement. Electroencephal. Clin. Neurophysiol. 1966, 20: 433-438

Goldman PS, Rosvold HE. Localization of function within the dorsolateral prefrontal cortex of the rhesus monkey. Expt. Neurol. 1970, 27: 291-304

Gray EG. Electron microscopy of excitatory and inhibitory synapses: a brief review. In: Akert K & Waser PG (eds). Mechanisms of synaptic transmission. Progress in Brain Research, vol. 31, Elsevier, Amsterdam, 1969, pp 141-155

Graybiel AM, Ragsdale CW, Jr. Histochemically distinct compartments in the striatum of human, monkeys and cat demonstrated by acetylcholinesterase staining. Proc. Natl. Acad. Sci. USA, 1978, 75: 5723-5726

Graybiel AM, Baughaman RW, Eckensein F. Cholinergic neuropil of the striatum observes striosomal boundaries. Nature 1986, 323: 625-627

Grozinger B, Kornhuber HH, Kriebel J. EEG investigation of hemispheric asymmetries preceding speech: the R-wave. In: McCallum WC, Knotts JR (eds). The responsive brain. Wright, Bristol, 1976, pp 103-107

Hammond PH. Involuntary activity in biceps following the sudden application of velocity to the abducted forearm. J. Physiol. 1955, 127: P23-P25

Hoehn MM, Yahr MD. Parkinsonism, onset, progression and mortality. Neurology, 1967, 17: 427-442

Horak FB, Nashner LM. Central programming of postural movements: adaptation to altered support-surface configuration. J. Neurophysiol. 1986, 55: 1369-1381

Huttunen J, Homberg V. EMG responses in leg muscles to postural perturbations in Huntington's disease. J. Neurol. Neurosurg. Psychiat. 1990, 53: 55-62

Jasper HH. Report of the Committee on Methods of Clinical Examination in Electroencephalography. Electroencephal. Clin. Neurophysiol. 1958, 10: 370-375

Jayaraman A. Organization of thalamic projections in the nucleus accumbens and caudate nucleus in cats and its relation with hippocampal and other subcortical afferents. J. Comp. Neurol. 1985, 231: 396-420

Kebabian JW, Calne DB. Multiple receptors for dopamine. Nature 1979, 277: 93-96

Kemp JM, Powell TPS. The cortico-striate projection in the monkey. Brain 1970, 93: 525-546

Kemp JM, Powell TPS. The connections of the striatum and globus pallidus: synthesis and speculation. Phil. Trans. R. Soc. Lond. 1971, B 262: 441-457

Khuraibet AJ. Cerebral cortical potentials preceding intended movement in Parkinson's disease. MSc Thesis, University of Glasgow, 1984

Klawans HL, Weiner WJ. The effect of d-amphetamine on choreiform movement disorders. Neurology, 1974, 24: 312-318

Koller WC, Trible J. The gait abnormality of Huntington's disease. Neurology, 1985, 35: 1450-1454

Koller WC, Morantz R, Vetere-Overfield B, Waxman M. Autologous adrenal medullary transplant in progressive supranuclear palsy. Neurology 1989, 39: 1066-1068

Kornhuber HH, Deecke L. Hirnopotentialanderungen beim Menschen vor und nack Willkurbewegungen dargestellt mit Magnetbandspeicherung und Ruckwartsanalyse. Pflugers Arch. 1964, 281: 52 (quoted by Tamas & Shibasaki, 1985)

Kunzle H. Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. Brain Res. 1975, 88: 195-209

Labadie EL, Awerbach GI, Hamilton RH, Rapcsak SZ. Falling and postural deficits due to acute unilateral basal ganglia lesions. Arch. Neurol. 1989, 46: 492-496

Leibowitz HW, Johnson CA, Isabelle E. Peripheral motion detection and refractive error. Science 1972, 177: 1207-1208

Lemon RN, Porter R. Afferent input to movement-related precentral neurones in conscious monkeys. Proc. R. Soc. Lond. (B) 1976, 194: 313-339

Leenders KL, Frackowiak RSJ, Quinn N, Marsden CD. Brain energy metabolism and dopaminergic function in Huntington's disease measured in vivo using positron emission tomography. Mov. Disord. 1986a, 1: 69-77

Leenders KL, Findley LJ, Cleeves L. PET before and after surgery for tumour-induced parkinsonism. Neurology 1986b, 36: 1074-1078

Liles SL. Activity of neurones in putamen during active and passive movements of wrist. J. Neurophysiol. 1985, 53: 217-236

Lipshits MI, Mauritz K, Popov KE. Quantitative analysis of anticipatory postural components of a complex voluntary movement. Human Physiol. 1981, 7: 165-173

MacGillivary BB. Traditional methods of examination in clinical EEG. (Derivations and montages). In: Remond A. (ed). Handbook of Electroencephalography and Clinical Neurophysiology, vol. 3, part C, 1974, Elsevier, Amsterdam, pp 3C22-3C57

Mackay DM. Source density analysis of scalp potentials during evaluated action. 1. Coronal distribution. Exp. Brain Res. 1984, 54: 73-85

MacPherson JM, Rasmusson DD, Murphy JT. Activities of neurones in "motor" thalamus during control of limb movement in the primate. J. Neurophysiol. 1980, 44: 11-28

Mann HB, Whitney DR. On a test of whether one of two random variables is stochastically larger than the other. Ann. Math. Statist. 1947, 18: 50-60

Marsden CD. The mysterious function of the basal ganglia. The Robert Wartenberg lecture. Neurology, 1982, 32: 514-539

Martin JP. The basal ganglia and posture. Pitman Medical, London, 1967

Mood AM. On the asymptotic efficiency of certain non-parametric two-sample tests. Ann. Math. Statist. 1954, 25: 514-522

McLellan DL. Clinical and neurophysiological aspects of extrapyramidal system disease in man. Ph D. Thesis, University of Glasgow, 1975

Moore AP. Sensorimotor motor integration in Parkinson's disease. M.D. Thesis, University of Birmingham, 1987

Mouradian MM, Juncos JL, Fabbrini G et al. Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms. Part ii. Ann. Neurol. 1988, 24: 372-378

Nashner LM. Vestibular and reflex control of normal standing. In: Stein et al (eds). Control of posture and locomotion. Plenum Press, New York, 1973, pp 291-308

Nashner LM. Adapting reflexes controlling the human posture. Exp. Brain Res. 1976, 26: 59-72

Nashner LM, Cordo PJ. Relation of automatic postural responses and reaction-time voluntary movements of human leg muscles. Exp. Brain Res. 1981, 43: 395-405

Nashner LM, Diener H-C, Horak FB. Selection of human postural synergies differ with peripheral somato-sensory versus vestibular loss. Soc. Neurosci. Abstr. 1985, 11: 704

Nashner LM. Strategies for organization of human posture. In: Igarashi M & Black FO (eds). Vestibular and visual control of posture and locomotion equilibrium. S. Karger, Basle, 1985, pp 1-8

Nauta WJH, Mehler WR. Projections of the lentiform nucleus in the monkey. Brain Res. 1966, 1: 3-42

Newton RA, Price DD. Modulation of cortical and pyramidal tract-induced motor responses by electrical stimulation of the basal ganglia. Brain Res. 1975, 85: 403-422

Oldfield RC. The assessment and analysis of handedness: The Edinburgh Inventory. Neurophysiologica 1971, 9: 97-113

Olds EG. The 5% significance levels for sums of squares of rank differences and a correction. Ann. Math. Statist. 1949, 20: 117-118

Palmer C, Schmidt EM, McIntosh JS. Cortico-spinal and cortico-rubral projections from the supplementary motor area in the monkey. Brain Res. 1981, 209: 305-314

Pandya DN, Vignolo LA. Intra- and interhemispheric projections of the precentral, premotor and arcuate areas in the rhesus monkey. Brain Res. 1971, 26: 217-233

Papakostopoulos D, Jones JG. The Bereitschaftspotential in left and right handed subjects. In: Kornhuber HH & Deecke L (eds). Motivation, motor and sensory processes of the brain: electrical potentials, behaviour and clinical use. Elsevier, Amsterdam, 1980

Parent A, Mackay A, Smith Y, Boucher R. The output organization of the substantia nigra in primate as revealed by a retrograde double labeling method. Brain Res. Bull. 1983, 10: 529-537

Penney JB, Young AB. Speculation on the functional anatomy of basal ganglia disorders. Ann. Rev. Neurosci. 1983, 6: 73-94

Poppele RE, Kennedy WR. Comparison between behaviour of human and cat muscle spindles recorded in vitro. Brain Res. 1974, 75: 316-319

Preston RJ, Bishop GA, Kitai ST. Medium spiny neurone projection from the rat striatum: an intracellular horseradish peroxidase study. Brain Res. 1980, 183: 253-263

Roland PE, Meyer E, Shibasaki T, Yamamoto YL, Thompson CJ. Regional cerebral blood flow changes in cortex and basal ganglia during voluntary movements in normal volunteers. J. Neurophysiol. 1982, 48: 467-480

Rosenfeld JP, Rudell AP, Fox SS. Operant control of neural events in humans. Science, 1969, 165: 821-823

Rubin AM, Liedgren SRC, Odkvist LM et al. Labyrinthine and somatosensory convergence upon vestibulospinal neurones. Acta Otolaryngol. 1978, 86: 251-259

Schachter M, Bedard P, Debono AG, Jenner P, Marsden CD, Price P, Parkes JD, keenan J, Smith B, Rosenthaler J, Horowski R, Dorow R. The role of D1 and D2 receptors. Nature 1980, 286: 157-159

Schell GR, Strick PL. The origin of thalamic inputs to the arcuate premotor and supplementary motor areas. J. Neurosci. 1984, 4: 539-560

Schneider JS, Denaro FJ, Lidsky TI. Basal ganglia: motor influences mediated by sensory interactions. Expt. Neurol. 1982, 77: 534-543

Sedgwick EM, Williams TD. The response of single units in the caudate nucleus to peripheral stimulation. J. Physiol. (Lond.) 1967, 189: 281-298

Simpson JA, Khuraibet AJ. Readiness potential of cortical area 6 in Parkinson's disease. Evidence for a dopaminergic striatal control of postural set involving supplementary motor area. (Abstract), J. Neurol. Neurosurg. Psychiat. 1986, 49: 475

Simpson JA, Khuraibet AJ. Readiness potential of cortical area 6 preceding self paced movement in Parkinson's disease. J. Neurol. Neurosurg. Psychiat. 1987, 50: 1184-1191

Simpson JA, Fitch W. Applied neurophysiology. Wright, London, 1988, pp 152 & 212-213

Shibasaki H, Barrett G, Halliday E, Halliday AM. Components of the movement-related cortical potential and their scalp topography. Electroencephal. Clin. Neurophysiol. 1980, 49: 213-226

Shibasaki H, Barrett G, Halliday E, Halliday AM. Cortical potentials with voluntary foot movements in man. Electroencephal. Clin. Neurophysiol. 1981, 52: 507-516

Spokes EGS. Neurochemical alterations in Huntington's chorea. A study of postmortem brain tissue. Brain 1980, 103: 179-210

Stoof JC, Kebabian JW. Two dopamine receptors: biochemistry, physiology and pharmacology. Life Sci. 1984, 35: 2281-2296

Szabo J. Organization of the ascending striatal afferents in monkeys. J. Comp. Neurol. 1980, 189: 307-321

Tamas LB, Shibasaki H. Cortical potentials associated with movement: a review. J. Clin. Neurophysiol. 1985, 2: 157-171

Tanji T, Taniguchi K, Saga T. Supplementary motor area: neuronal response to motor instructions. J. Neurophysiol. 1980, 43: 60-68

Trugman JM, Wooten GF. Selective D1 and D2 dopamine agonists differentially alter basal ganglia glucose utilization in rats with unilateral 6-hydroxydopamine substantia nigra lesions. J. Neurosci. 1987, 7: 2927-2935

Uchizono K. Characteristics of excitatory and inhibitory synapses in the central nervous system of the cat. Nature (London), 1965, 207: 642-643

Vaughan HG, Costa LD, Ritter W. Topography of the human motor potential. Electroencephal. Clin. Neurophysiol. 1968, 25: 1-10

Walter WG, Cooper R, Aldridge VJ, McCallum WC, Winter AI. Contingent negative variation: an electrical sign of sensory-motor association and expectancy. Nature 1964, 380-384

Webster DD. Critical analysis of the disability in Parkinson's disease. Mod. Treat. 1968, 5: 257-282

Weiner WJ, Goetz CG, Nausieda PA, Klawans HL. Respiratory dyskinesias: extrapyramidal dysfunction and dyspnoea. Am. J. Intern. Med. 1978, 88: 327-331

Wiesendanger M, Seguin JJ, Kunzle H. The supplementary motor area- a control system for posture. In: Stein RB, Pearson KB, Smith RS, Redford JB (eds). Control of posture and locomotion. Plenum Press, New York, 1973, pp 331-346

Wilcoxon F. Individual comparisons by ranking methods. Biometrics Bull. 1945, 1: 80-83

Wilson SAK. Disorders of motility and muscle tone, with special reference to the striatum. Lancet 1925, 2: 1-53

Yassa R. Functional impairment in tardive dyskinesia: medical and psychosocial dimensions. Acta Psychiatr. Scand. 1989, 80: 64-67

Zablow L, Goldensohn ES. A comparison between scalp and needle electrodes for the EEG. Electroencephal. Clin. Neurophysiol. 1969, 26: 530-533

Zattara M, Bouisset S. Posturo-kinetic organisation during the early phase of voluntary upper limb movement. 1. Normal subjects. J. Neurol. Neurosurg. Psychiat. 1988, 51: 956-965