The role of the basal ganglia in the control of motor timing.

A thesis submitted to the University of Manchester

for the degree of Doctor of Philosophy

in the Faculty of Medicine.

1994

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Abstract

Clinical evidence suggests that patients with Parkinson's disease (PD) and Huntington's disease (HD) have difficulty in producing sequences of repetitive movements (e.g. whilst walking, speaking or writing), implicating the basal ganglia in the control of such movements. As such movements require a timing component, the present work investigated the role of the basal ganglia in motor timing by testing the ability of PD and HD patients to perform finger tapping tests. In the first set of experiments, the ability of 34 PD patients (11 of whom were tested twice, 'on' and 'off' their usual L-dopa medication), 14 HD patients and 36 age-matched control subjects to produce *mean tapping frequencies* (MTFs) in the presence and subsequent absence of auditory cues was measured over a range of target frequencies (1-5 Hz). When compared to controls, PD patients produced MTFs, in the presence of cues, which were too fast at the lower target frequencies (1-3 Hz) and too slow at the higher target frequencies (4-5 Hz). These abnormalities were exaggerated after cue cessation, causing further increases at lower target frequencies and further decreases at higher target frequencies. HD patients tapped, in the presence of cues, too slowly at higher target frequencies (3-5 Hz) but no further deterioration in performance was noted on cue removal. In the second set of experiments, Wing and Kristofferson's (1973) model of motor timing was employed to analyse the *variability* of the inter-response intervals (IRIs) produced during the non-cued tapping phase (after an initial synchronisation phase with fifteen auditory signals of interval duration 550 msec) of those runs during which the major assumptions underlying the model were not violated. Using the appropriate expressions, the total variance (TV) was decomposed into variance attributable to a hypothetical 'clock' (CV) and that attributable to a hypothetical and independent 'motor-implementation' system (MISV). Twenty-four

PD patients were studied; 12 who showed asymmetric clinical signs (group 1) were tested in both hands and 12 were tested twice, 'on' and 'off' normal L-dopa medication (group 2). Five HD patients and 12 age-matched controls were also tested. Significantly higher levels of TV were associated, in group 1, with the hand more affected by PD and, in group 2, with abstinence from L-dopa, which for both groups were significantly higher than control values. In both PD groups, raised TV was attributable to significant increases in both CV and MISV, which were higher than control values. However, in the 'on' conditions of PD patients in group 2, a significantly higher level of TV, compared to control values, was attributable to CV alone. In HD patients, TV was significantly higher than in PD or control data and was attributable to pronounced increases in both CV and MISV. The third set of experiments tested the ability 6 PD patients and 6 control subjects to *synchronise* their responses with trains of 120 metronome events (700 msec interval duration). Both groups tended to respond in advance of the metronome, the PD patients produced more anticipatory synchronisation errors than did the control subjects. When asked to rate the degree of asynchrony associated with a response, PD patients produced estimates which suggested that they were consciously unaware of their synchronisation errors. Control subjects showed a tendency towards a positive correlation between the subjective and objective synchronisation errors. Data presented in this thesis implicate the basal ganglia in the operation of an internal 'clock' and suggest that the basal ganglia may be involved in sensorimotor integration within such a central timing system.

Key words: Basal ganglia, Parkinson's disease, motor timing, repetitive movements.

Declaration

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The author graduated for the University of Leeds in July 1991, obtaining a B.Sc. degree with Honours in Pharmacology.

for my wife Lorraine

Acknowledgements

I would like to thank my supervisor Dr F.W.J. Cody (School of Biological Sciences, University of Manchester), and Dr D.J. O'Boyle (Department of Psychology, University of Manchester) for their support, guidance and advice throughout my research. I would also like to thank Dr C. Rickards and Dr P. Goulding (Department of Neurology, Manchester Royal Infirmary) for performing the clinical examinations. The Parkinson's Disease Society and Professor Neary, Dr R.G. Lascelles, Dr W. Schady (Department of Neurology, MRI) and Dr D. Craufurd (Department of Medical Genetics, MRI) were of invaluable help in recruiting patients. I would like to thank all the subjects for their cheerful cooperation.

CHAPTER 1: GENERAL INTRODUCTION.

CHAPTER 1.1: THE BASAL GANGLIA.

1.1.1. Basic anatomy.

The basal ganglia are a poorly understood set of nuclei. Marsden (1982) remarked upon "this mysterious region of the brain" while almost sixty years earlier, Wilson (1925) concluded his Croonian Lecture by reporting that "the ganglia situated in the base of the brain still, to a large extent, retain the characteristics of basements - viz., darkness." However, the last decade has vastly improved the basic understanding of the basal ganglia.

It is now generally accepted that the basal ganglia comprise of five nuclei; the caudate, putamen, globus pallidus, subthalamic nucleus and substantia nigra. These interconnected nuclei span the telencephalon, diencephalon and the upper regions of the midbrain. The basal ganglia do not have any direct connections with either sensory inputs or motor outputs but form part of various multi-structured loops (see section 1.1.2).

The main part of the basal ganglia is made up of three of the aforementioned nuclei, the putamen, caudate and globus pallidus. The caudate and putamen are together termed the striatum (or neostriatum), and are anatomically divided in man by the internal capsule. The term striatum describes the appearance of the two nuclei in myelin stains, as a number of nerve fibre bundles (Wilson's pencils) span the nuclei to produce a *striped* appearance. The striatum is phylogenetically newer than the globus pallidus, whose name is derived from the fact that unstained, it appears *paler* than the striatum. The globus pallidus is sub-divided into two parts, the lateral or external globus pallidus (GPe) and the medial or internal globus pallidus (GPi). Anatomically, the GPi and GPe are separated by the medial

medullary lamina.

The remaining two nuclei which make up the basal ganglia are the subthalamic nucleus (STN) and the substantia nigra. The STN is a small lens-shaped nucleus situated ventral to the thalamus on the dorsal surface of the internal capsule. Continuous with the STN and caudal and ventral to it, is the substantia nigra. The cells of the substantia nigra are densely packed with melanin and as the nuclei is well developed in man, dark stripes can be seen above the cerebral peduncle with the naked eye. Like the globus pallidus, the substantia nigra can be divided into two parts which have quite separate connections and functions within the basal ganglia. In the dorsal part of the nuclei (the boundaries are not clear), the cells are more densely packed and this area is termed the substantia nigra pars compacta (SNc) while the ventral region is known as the substantia nigra pars reticulata (SNr). The primary output structure(s) of the basal ganglia are the GPi and the SNr and these structures are often considered to be homologous (see Figure 1.1). These nuclei are separated by the fibres of the cerebral peduncles in man, but contain cytologically similar neurons (Albin *et al*, 1989b).

1.1.2. The connections of the basal ganglia.

The major input to the basal ganglia is from the cerebral cortex and the principal afferent structure of the basal ganglia is the striatum. The major output is via the thalamus, back onto the same areas of the cortex (Rothwell, 1987). An example of this cortico-basal ganglia-cortex loop is shown in Figure 1.1, a diagrammatic representation of the structures involved.

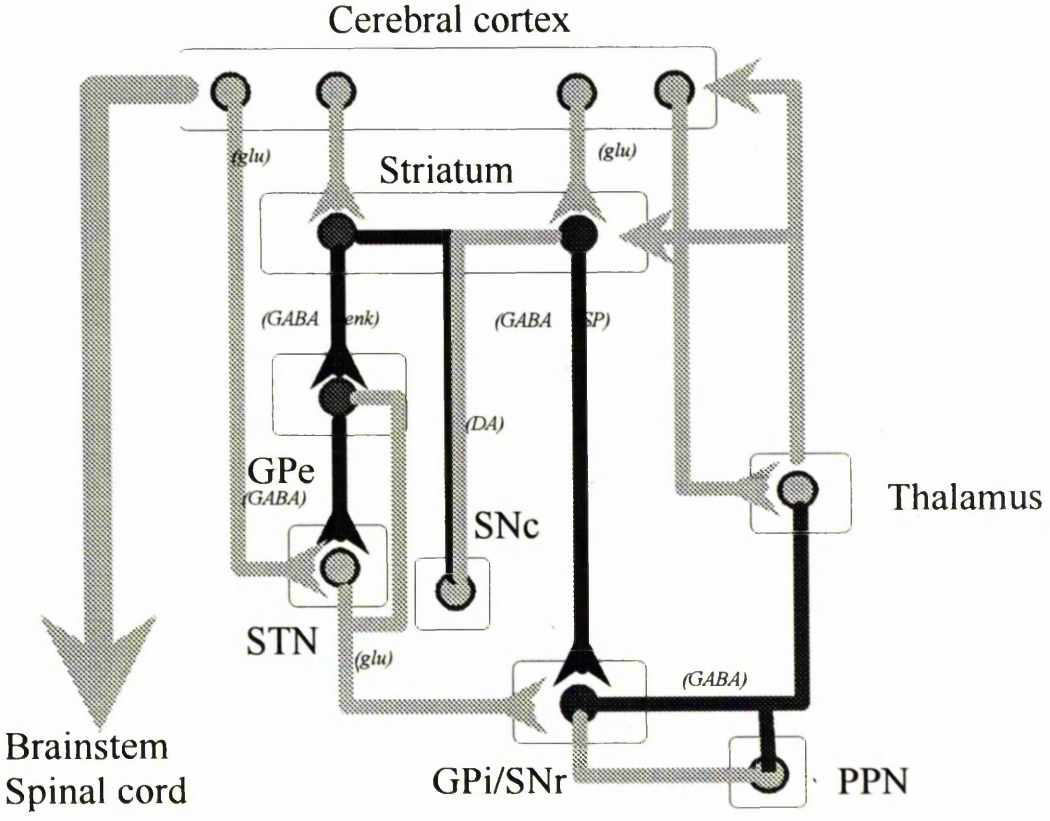

Figure 1.1. Schematic diagram of the circuitry and neurotransmitters of the cortico-basal ganglia-cortex circuit, highlighting the parallel 'direct' and 'indirect' pathways from the striatum to the basal ganglia output nuclei. Inhibitory neurons are depicted as black symbols, excitatory are shown as grey symbols. Abbreviations: DA, dopamine; enk, enkephalin; GABA, τ-aminobutyric acid; GPe/GPi, external/internal segments of globus pallidus; glu, glutamate; PPN pendunculopontine nucleus; SNc/SNr, substantia nigra pars compacta/reticulata; SP, substance P; STN subthalamic nucleus (from Alexander and Crutcher, 1990).

The striatum is the largest and major receptive component of the basal ganglia, and receives massive projections from the cerebral cortex. Most cortical areas project topographically to the striatum (Parent, 1990). Input from the cortex to the putamen and caudate is glutaminergic and excitatory. The main output nuclei of the basal ganglia (GPi and SNr) send most of their efferent fibres to several regions of the thalamus, the most important being the ventral tier and the mediodorsal thalamic nuclei (Albin *et al*, 1989b). From the thalamus, fibres project to the motor cortex with robust projections to the supplementary motor area (SMA). Other projection targets from the basal ganglia include the superior colliculus and the pendunculo-pontine nucleus.

The striatum is primarily composed of projection neurones (Parent, 1990) which both receive and project. From the striatum there are two separate pathways, the *direct* and *indirect*, in which axons are sent to the output nuclei, GPi/SNr. In the direct pathway, neurones project directly onto the GPi/SNr from the striatum. This pathway is inhibitory and contains GABA, co-localised with substance P as neurotransmitters. Figure 1.1 shows that in following the inhibitory and excitatory projections of the direct pathway, it can be seen that the overall effect of this pathway is cortical excitation. Cortical input to the striatum causes disinhibition of the thalamus.

The second pathway is indirect. Efferent fibres from the striatum take the route of GPe, STN and finally, GPi. Like the direct pathway, projections from the striatum to the GPe are inhibitory and GABA-ergic but now the neurotransmitter co-localises with enkephalin. Figure 1.1 shows that when the indirect pathway is followed, the overall effect is opposite to that of the direct pathway, that is, an inhibitory effect on the thalamus and cortex.

Striatal neurones receive further dopaminergic input from the SNc. Dopamine has an opposite action on the modulation of the direct and indirect pathways. Dopaminergic input is excitatory to neurones projecting directly to GPi/SNr and this may be due to D1 receptor stimulation. However, probably due to D2 receptor stimulation, dopamine is inhibitory to the neural projections to GPe in the indirect pathway.

1.1.3. The motor circuit.

Inputs are processed separately throughout their passage through the basal ganglia. Inputs from different cortical regions form *distinct* loops within the basal ganglia which are processed in a parallel manner (Alexander and Crutcher, 1990). In my research, the most important was the motor circuit, which comprises the largest flow of information through the basal ganglia. The inputs to the basal ganglia portion of the motor circuit are focused principally on the putamen. This part of the striatum receives topographic projections from the primary motor cortex and two premotor areas, the arcuate premotor area and the SMA (Jones *et al*, 1977). The putamen also receives topographic projections from somatosensory cortex. These projections result in a somatotopic organisation that consists of the leg being represented in the dorsal region of the putamen, the face in a ventromedial region and the arm in a midregion. There is very little homogeneity between the projections in these areas. However, the neurones of the striatum are not homogenous and form two sub-populations, the striosomes and the matrix, which do not correspond to the direct and indirect pathways (Graybiel, 1990). The striosomes receive cortical afferents from the prefrontal and limbic cortices, while the matrix receives cortical afferents from the primary motor and somatosensory cortex as well as frontal, parietal and occipital cortex. The substance P containing matrix neurons project mainly upon the GPi or SNr, while those

containing enkephalins project mainly to the GPe. Substance P containing striosomes project mainly upon the SNc.

From the SNc, there are topographic projections to the output nuclei of both the direct (GPi/SNr) and indirect pathways (GPe). In turn, the respective motor sections of the GPi and SNr send topographic projections to specific thalamic nuclei including nucleus ventralis lateralis pars oralis (VLo), nucleus ventralis anterior pars parvocellularis (VApc) and magnocellularis (VAmc) and the centromedian nucleus (CM). The motor circuit is closed by means of the thalamocortical projection from VLo and VAmc to the SMA, from VApc (and VLo) to the premotor cortex and from VLo and CM to the motor cortex.

The flow of discrete loops of information, sometimes termed *parallel processing*, may actually be even more refined. Alexander and Crutcher (1990) postulated that within the somatotopic channels of the motor circuit (leg, face and arm) there may be a further level of organisation. Sub-channels of neurones may process selectively, in parallel, information about motor behaviour such as target location, muscle patterns and limb movement.

1.1.4. Models of movement disorders of basal ganglia origin.

The primary symptom of all human disorders of the basal ganglia is movement dysfunction. The output nuclei (GPi/SNr) have an inhibitory effect on the ventrolateral thalamus and the GPi cells fire at sustained high frequencies (DeLong and Georgopoulos, 1981). Evidence suggests that during the execution of specific motor tasks, phasic decreases in GPi/SNr discharge play a vital role in motor control by disinhibiting the thalamus (see 1.1.3). This will facilitate cortically initiated movements via excitatory

thalamocortical connections (DeLong, 1990). Phasic increases will have the opposite effect. If both systems controlled the same GPi/SNr neurons, the indirect system would have a "braking" or "smoothing" effect on cortically initiated motor patterns.

It can be seen that the basal ganglia allow highly organised information to flow through the various nuclei, which form part of a larger circuit incorporating various higher structures. Predictions about the functions of the basal ganglia can be made by the observation of the symptoms associated with lesions of the various nuclei. Movement disorders associated with basal ganglia dysfunction are separated into two main categories (for review, see Lakke, 1981). *Hyperkinesia* is characterised by excessive involuntary movements (seen in patients with HD or ballism), while a deficiency of spontaneous movement is termed *hypokinesia* (seen in patients with PD). Both types of movement disorder can be explained by specific disturbances (for example, lesions) within the motor circuit. Some workers postulate (Albin *et al*, 1989b; DeLong, 1990) that for movement to occur, the inhibitory output of the basal ganglia must be removed. Therefore, increased pallidal inhibition leads to hypokinesia, while reduced pallidal inhibition results in hyperkinesia. Evidence for this can be found from the aetiology of three main basal ganglia disorders:

a) Ballism is a consequence of infarction of the STN causing violent, flinging motions of the extremities. Figure 1.2 shows that a lesion of the STN will produce a loss of excitatory output to GPi/SNr, reducing inhibitory output to the thalamus and therefore, as has been suggested, releasing additional movement.

b) HD is the classic hyperkinetic movement disorder. The main symptom of HD is chorea, characterised by excessive, fast, involuntary movements which interrupt normal

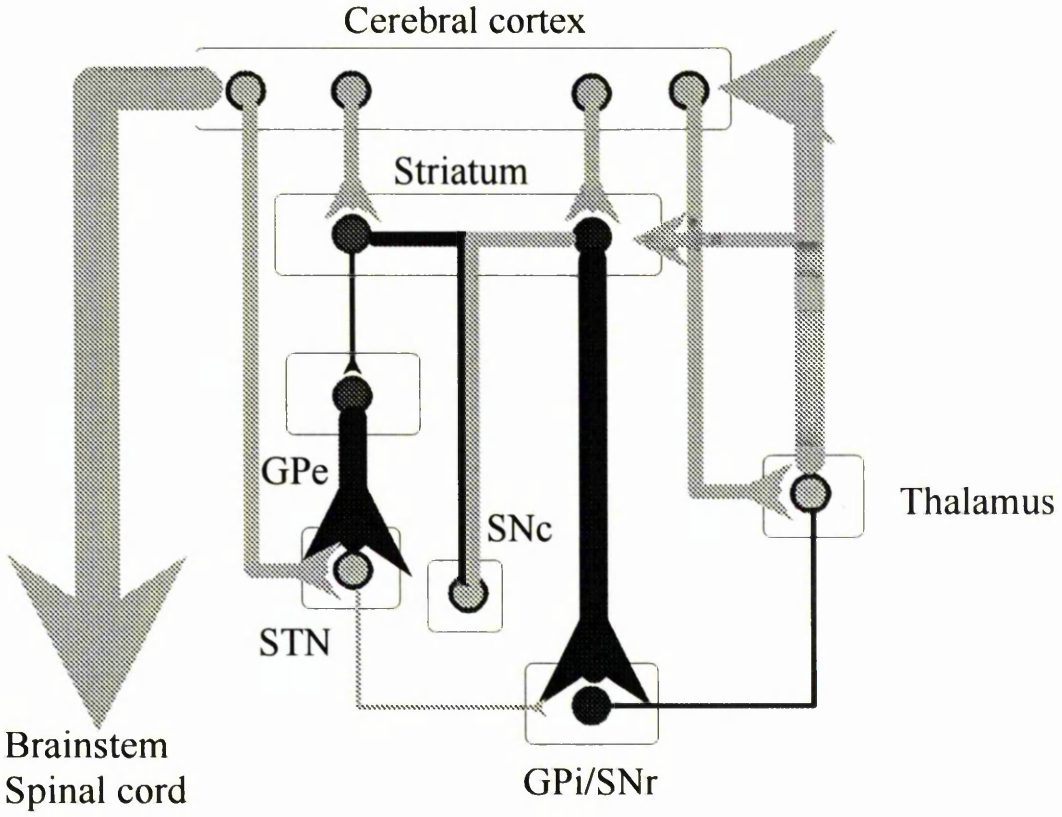

Figure 1.2. Schematic representation of the 'motor' circuit in hyperkinetic disorders. Reduced excitatory projections from the STN to GPi, due either to STN lesion (hemiballismus) or reduced striatopallidal inhibitory influences along the indirect pathway (Huntington's disease or L-dopa-induced dyskinesias) lead to reduced inhibitory outflow from GPi/SNr and excessive disinhibition of the thalamus, and excessive positive feedback to the motor cortex. Inhibitory neurons are depicted as black symbols, excitatory are shown as grey symbols. Abbreviations: same as Figure 1.1 (from DeLong, 1990).

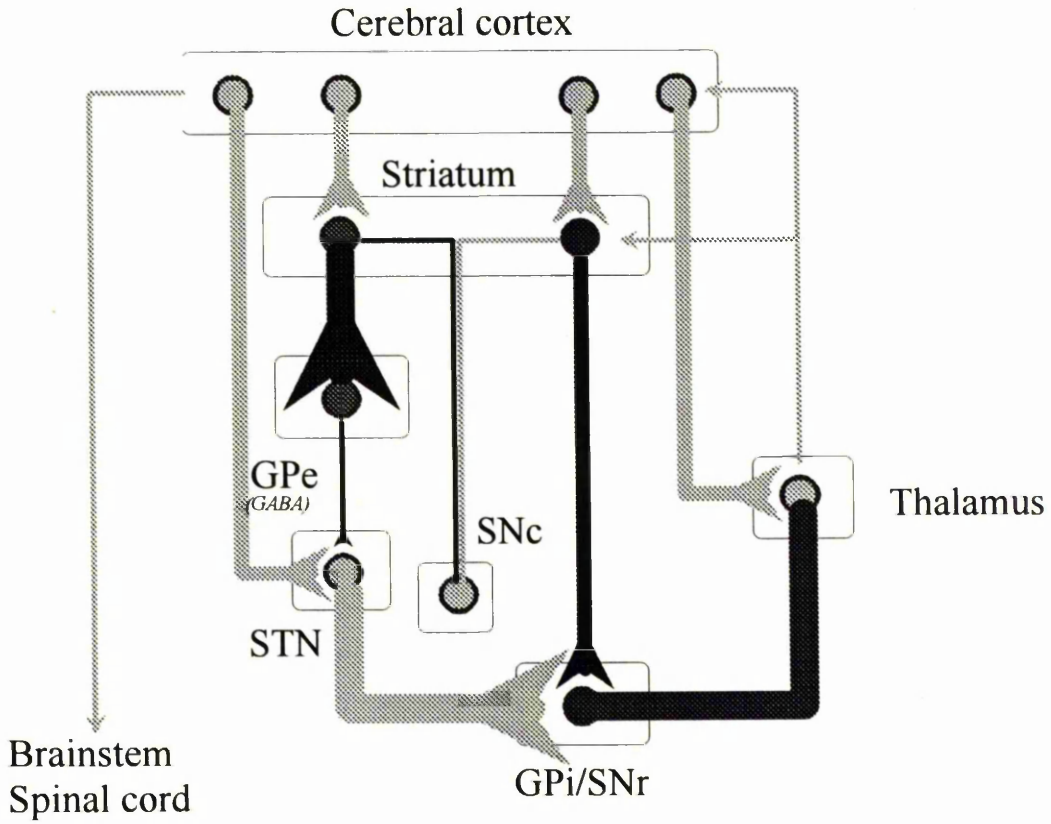

Figure 1.3. Schematic representation of the activity in the 'motor' circuitry in hypokinetic disorders. Excessive inhibition of GPe within the indirect pathway leads to disinhibition of the STN, which provides excessive excitatory drive to GPi/SNr, leading to excessive thalamic inhibition. This is augmented by reduced inhibitory input to GPi/SNr through the direct pathway. Inhibitory neurons are depicted as black symbols, excitatory are shown as grey symbols. Abbreviations: same as in Figure 1.1 (from DeLong, 1990).

movement. Chorea is often accompanied by athetosis which has a slower, writhing appearance. In early HD, where chorea is more prominent, post mortem studies show a selective loss of striatal GABA/enkephalin neurons to GPe in the indirect pathway (Albin *et al*, 1989a). Figure 1.2 shows the effect that this will have on thalamic inhibition. The consequent loss of inhibition of GPe neurons would result in excessive inhibition of the STN. The presence of a lesion and an increase in inhibition to the STN will have a similar overall effect, an increase in unwanted movements. This model explains why bicucculine, a GABA receptor antagonist, injected into the GPi on monkeys produces hyperkinetic movement disorders (Crossman *et al*, 1988). In late HD, rigid akinetic signs are associated with additional loss of the GABA/substance P direct striatal pathway to the GPi. This would add, by removal of the inhibitory effect of the direct pathway on GPi/SNr, to the increased inhibition of the thalamus by GPi/SNr (again for clarification, see Figure 1.2).
c) PD, the classic hypokinetic disorder, is characterised by slowness of movement and poverty of spontaneous movement and is caused by degeneration of dopaminergic neurons in SNc which innervate the striatum. Figure 1.3 shows the effect that such a loss will have on the basal ganglia model. The effect is twofold; a decrease of dopaminergic excitation of the projection of the GPi (direct pathway) and a decrease in dopaminergic inhibition to the GPe (indirect pathway). The net effect is that there is an increase in GPi/SNr inhibition of the thalamus, due to reduced inhibition in the direct pathway and excess excitation in the indirect pathway, which may lead to the symptoms associated with hypokinesia. Evidence for this finding was uncovered in an unlikely manner.

Drug abusers from California, USA first unwittingly discovered N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) when administering "home-made" narcotics. MPTP

ingestion produced severe irreversible parkinsonian symptoms almost immediately. When isolated, MPTP represented one of the first pharmacological models with features that closely resembled the characteristics of a brain disorder (Tetrud and Langston, 1989b). MPTP, being a tertiary amine, easily crosses the blood-brain barrier and is converted in the brain to the toxin MPP+ (a pyridinium ion) by the enzyme monoamine oxidase B. MPP+ is then selectively taken up by nigrostriatal neurons, via catecholamine uptake mechanisms, and destroys them by interference with mitochondrial oxidation and redox reactions (Forno *et al*, 1986). Animals treated with MPTP exhibit the classic aetiology of PD, destruction of the melanin-containing neurons of the SNc. Studies show that there is a significant increase in tonic neural discharge in GPi and STN neurons, and decrease in the GPe neurons, in animals after MPTP treatment (Crossman *et al*, 1985).

CHAPTER 1.2: MOVEMENT DISORDERS OF THE BASAL GANGLIA; PARKINSON'S DISEASE AND HUNTINGTON'S DISEASE.

1.2.1. Parkinson's disease.

Sir James Parkinson (1817) was the first to describe this neurodegenerative disease which now bears his name. PD is the most prevalent example of human basal ganglia dysfunction. The disease is typically first diagnosed in the fifth or sixth decade, and epidemiological studies suggest an occurrence as high as 1 in 100 in people over the age of sixty-five, and 1 in 1000 for the population as a whole. Global variation in incidence and prevalence studies, for example higher in North American than African blacks, support an environmental factor being the major aetiological factor (Rothwell, 1987) in PD. There is a strong body of evidence to suggest no direct genetic contribution in PD

(Ward, 1991). The discovery of MPTP (see 1.1.4.) showed that relatively simple compounds could, in certain circumstances, produce PD. Tetrud and Langston (1989b) suggest that substances similar to MPTP may occur in the environment and that repeated exposure to small quantities of such chemicals, combined with ageing, may be factors in the aetiology of the disease.

PD is a hypokinetic disorder of the basal ganglia, with a degeneration of dopaminergic neurons in the SNc and corresponding loss of dopaminergic innervation to the striatum (see section 1.1.4. and Figure 1.3). Hornykiewicz (1982) noted that 80% of the dopaminergic neurones must degenerate in order for symptoms to appear. If the percentage is less, then the striatum seems to be able to compensate for the shortage. Apart from the SNc, degeneration can be seen in other parts of the brain, but these deficiencies are not thought to be responsible for the motor deficits of the disease. The striatum contains some cholinergic neurones, and the balance between these neurones and the dopaminergic neurones is important in PD. When dopaminergic neurones have degenerated below a certain critical level, the inhibitory influence of dopamine will be reduced and the excitatory effects of the cholinergic neurones will dominate (Hornykiewicz, 1982). There are several forms of parkinsonism. Idiopathic Parkinson's disease (referred to as Parkinson's disease) is the most common form of parkinsonism and is the type which afflicts all the patients in the present work. It is regarded as a specific disease entity with characteristic pathology, but with a poorly understood aetiology. Drug-induced parkinsonism is caused by unwanted adverse effects of anti-schizophrenic medication in which dopamine receptors are blocked within the striatum (Ayd, 1961; Ross, 1990). Other forms include post-encephalitic parkinsonism (Sacks, 1990) and parkinsonism due to head

trauma.

The four main signs of PD are bradykinesia, akinesia, rigidity and tremor. In any one patient, any connotation of these signs may, or may not, be present. These signs usually occur with a number of associated features including; postural abnormalities, dysarthria, characteristic facies, autonomic dysfunction, micrographia and seborrhoea. Marsden (1982) considers akinesia and bradykinesia as the core symptoms in PD as they are negative symptoms. This is because they involve pure loss of function thereby representing the negative manifestations of the underlying pathology. Bradykinesia is defined as "slowness of movement" while akinesia is defined as "a lack of spontaneous or associated movement" (Rothwell, 1987). These symptoms will be discussed further in section 1.3.4.

Rigidity and tremor are the major positive symptoms in PD and are thought to be less central to the pathophysiology, as they are likely to arise from over-activity of the lower motor centres (Marsden, 1982). Rigidity is manifest as an increase in resistance to passive manipulation around a joint and may be accompanied by the "cogwheel" phenomenon, in which may be due to superimposition of tremor, the examiner feels as if he is moving the joint through a ratchet mechanism. Tremor is usually seen at rest, at a frequency of 4-6 Hz (Hallett, 1991) and is usually manifest early on in the disease process (Gresty and Findlay, 1984). Tremor is commonly seen in the hands of parkinsonians, where a characteristic opposition and abduction of the thumb towards the index finger ("pill-rolling" tremor) can be noted.

1.2.2. Assessment and treatment.

The diagnosis of PD is very much a clinical one and depends on the recognition of a characteristic pattern of symptoms and signs (Koller, 1992). In the assessment of PD patients it is important to have objective clinical grading scales, which permit the overall severity, prognosis and relative magnitude of the component features to be rated. The clinical grading for the current work was assessed by a qualified neurologist using two widely used scales; those of Webster (1968) and Hoehn and Yahr (1967). Webster's scale defines current functional ability on a range of sub-components of the disease. Ten parameters are individually scored on a four-point scale and an assessment of the overall severity of the illness can be obtained from the total score. The Hoehn and Yahr scale emphasises the disease staging and the long term prognosis and is scored over four categories (I - mild, IV - severe).

Anticholinergic drugs such as orphenadrine, benzhexol and procyclidine were successfully used to treat PD before the realisation of the importance of dopamine. After the discovery that there was a dopamine deficiency in the basal ganglia of PD patients, attempts were made to use replacement therapy (for review, see Fahn, 1989). As dopamine itself does not cross the blood-brain barrier, the introduction of the amino acid precursor to dopamine, L-dopa or levodopa (L-3,4-dihydroxyphenylalanine) in the late 1960's revolutionised the treatment of PD, reducing the mortality and raising the standard of life (Yahr, 1975). Various refinements of L-dopa which include controlled release preparations (MacMahon *et al*, 1990) and concurrent administration with peripheral decarboxylase inhibitors have increased the effectiveness of the drug and reduced side effects (LeWitt, 1993). The main serious long-term adverse effect of L-dopa is a breakdown in the dose-

response relationship. Nutt *et al* (1984) reported patients fluctuating within a single dosage regimen from a state of over-treatment, in which abnormal hyperkinetic movements are seen, to one of under treatment which results in profound akinesia. This situation usually occurs after several years of L-dopa treatment and so this form of treatment is delayed for as long as possible after diagnosis (Marsden, 1990).

Other treatments employed are the direct dopamine agonists such as bromocriptine, pergulide and lysuride, which stimulate the dopamine receptors. Amantidine, an antiviral agent, is effective in treating PD. The mechanism of action is unclear, but it has been shown to increase dopamine release from the nerve terminals (Forssman *et al*, 1972). Selegiline which reduces neuronal re-uptake of dopamine, may offer a degree of neuro-protection as well as slowing the progress of the disease, by virtue of its anti-oxidant properties (Tetrud and Langston, 1989a). This is usually the drug of choice for newly-diagnosed patients before the introduction of L-dopa.

Future modes of treatment may involve surgical techniques. As hyperactivity in the STN projections to GPi has been established as a crucial feature of PD, recent experiments have tested the effects of blocking the STN glutaminergic output to GPi in animals (for review, see Guridi *et al*, 1993) or more importantly, lesioning the STN in patients (DeLong, 1993), in both cases produced a dramatic reversal of parkinsonism.

1.2.3. Huntington's disease.

HD is a autosomal dominant (Gusella *et al*, 1983), neurodegenerative disorder characterised by a progressive atrophy of the caudate within the basal ganglia, and then

of cortical structures (Martin and Calne, 1986). It results from the loss of specific sets of cholinergic neurones and neurones that synthesize GABA, as shown by the reduced levels of glutamic acid decarboxylase in HD patients, which is an enzyme involved in GABA synthesis (Bird *et al*, 1973; Burnett and Jankovic, 1992). As stated in 1.1.4. and Figure 1.2. there is a selective loss of the GABA/enkephalin striatal neurones which project to GPe.

The disease is comparatively rare, affecting 1 in 10-20,000 of the population (Hayden, 1981). The onset is delayed, the first symptoms appearing between the ages of 30-45, by which time the next generation may have been born (of which half will inherit the disorder), and death usually occurs within fifteen years. HD is a genetic disorder with a mutation occurring on chromosome 4 (for review, see Gusella *et al*, 1993).

HD begins with disturbances in mood and personality (Burns *et al*, 1990). The disease causes depression and dementia, the latter thought to be of cortical origin (Cummings and Benson, 1984; Butters *et al*, 1978). Although changes in mood and personality are usually the first signs of HD, disturbance of movement is the most obvious clinical feature. A number of motor signs are associated with HD. The most predominant sign is chorea which is defined by the World Federation of Neurology as "a state of excessive, spontaneous movements, irregularly timed, randomly distributed and abrupt" (Lakke, 1981). HD patients also show rigidity and hypotonia, muscle tone being simultaneously enhanced in some muscles and reduced in others, depending on the age of the patient (Bruyn, 1968). Akinesia and bradykinesia are important features of HD (Hamilton, 1908; Denny-Brown, 1960; Starr, 1967; Girotti *et al*, 1984; Hefter *et al*, 1987; Thompson *et al*,

1988). This paradox, in which an excess of involuntary movements is coupled with hypokinetic voluntary movements shows the considerable overlap between movement deficits in PD and HD. Other motor deficits in HD include abnormalities of postural control (Tian *et al*, 1991; 1992) and gait (Koller and Trimble, 1985).

Whereas PD is associated with a reduction in the activity in the dopaminergic system, HD is partly associated with an increase in levels of the activity of dopaminergic activity within the basal ganglia (Stelmach and Phillips, 1991). Spokes (1980) observed increased levels of dopamine in the putamen and caudate, while Melamed *et al* (1982) reported only increased levels in the caudate. Whereas PD patients respond to dopamine agonists (L-dopa and bromocriptine), these drugs exacerbate the symptoms of HD. Instead, certain aspects of HD such as the involuntary movements respond to dopamine antagonists. Dopamine antagonists such as pimozide and the amine depleting tetrabenazine have been used with relative success to treat choreiform movements (Albin *et al*, 1989b).

CHAPTER 1.3: THE FUNCTION OF THE BASAL GANGLIA IN THE CONTROL AND THE TIMING OF MOVEMENTS.

1.3.1. Repetitive timed movements.

The present work is primarily concerned with functional role of the basal ganglia in simple repetitive timed movements. Anecdotal, clinical and experimental evidence of deficiencies of performance of repetitive movements in patients with basal ganglia disorders suggests some form of modulation by these structures (Ward, 1991). Repetitive movements encompass everyday activities such as locomotion, mastication and writing, as well as the

movements required whilst, for example, playing musical instruments. All movements require some form of timing component. Repetitive movements are conceptually different to other movements in that they require a series of timed, relatively discrete individual movements. A simplistic overview is that to perform repetitive movements accurately, not only does each movement have to be executed accurately, but the set of movements must be accurately timed which must require modulation by some timing system. Inaccuracies in either, or both, of these systems will produce deficits in repetitive movements and the present work aims to investigate the degree of involvement of the basal ganglia in motor timing. However, in order to understand the role of the basal ganglia in the timing of repetitive movements, a general understanding of the control and production of movements is required.

1.3.2. Anatomical overview of movement control.

Different neural pathways have been shown to control movements in different effector systems (Stein, 1982). The motor cortex and lateral corticospinal (pyramidal) tract are thought to be primarily concerned with voluntary control over the most distal muscles. This pathway may control, for example, independent finger movements. The red nucleus and lateral reticular formation of the brainstem with their lateral descending projections, control voluntary and postural movement of the limbs, for example, shoulders and elbows. The vestibular system and medially descending pathways are thought to control axial musculature and therefore posture. The cerebellum is thought to contribute to each of these systems in evolving strategies for movements of the extremities, execution of whole limb movements and in aiding the control of body posture (Rothwell, 1987). The basal ganglia are thought influence each of these pathways as basal ganglia disorders show

symptomology in fine movements as well as posture. Both cerebellum and basal ganglia employ motor cortex and brain stem motor structures to execute their actions (the basal ganglia output is via the thalamus, see section 1.1.3).

1.3.3. Types of movement.

1.3.3.i. Voluntary and reflex.

Movements willed by the individual are termed voluntary, while movements which occur without requiring thought are termed reflex. However, the distinction is not clear-cut and there is a significant overlap between the two extremes. Marsden (1982) defined reflex movements as "anything not under the control of the will" although not all reflexes will be as stereotyped as the tendon jerk. By contrast, voluntary movements were defined as "anything that requires an effort or will for its execution or that can be abolished or enhanced by an effort or will". It should be noted that some voluntary movements may occur without much "thought".

1.3.3.ii. Ballistic and ramp movements.

Voluntary movements can be split up into two further categories; ballistic and ramp. Ballistic movements are fast movements which have been pre-programmed, so that they are completely independent of events during their execution. Such movements are, therefore, feedback-free and operating in an open-loop mode (DeLong and Strick, 1974). A characteristic triphasic electromyography (EMG) pattern is seen during a ballistic movement (Hallett and Marsden, 1979) which remains remarkably constant from one individual to another. Firstly, there is a short burst of activity of fixed duration in the agonist, which then silences as the antagonist fires. The antagonist silences as the agonist

starts firing again. This second agonist burst may prevent oscillations around the terminal position (Marsden *et al*, 1983a). The speed and size of a ballistic movement can be modified by altering the amount of activity in the initial agonist burst and the subsequent antagonist burst facilitates the movement to discontinue (braking the movement).

Ramp or slower movements are, by contrast, subject to continual correction from feedback control and are thought operate under closed-loop conditions (Stein, 1982). Sensory signals about the position of the limb and the actual position of the target are compared and used to match the target and limb movement.

There is overlap between ballistic and ramp movements as the ballistic performance of a fast movement may be improved by incorporating information about how the movement was performed last time. The present work is concerned with series of ballistic movements and the degree of feedback present within the set of movements. However, the focus of the present studies concerns the timing of these movements as opposed to their force or trajectory.

1.3.4. The modulation of movements by the basal ganglia.

In order to understand the role of the basal ganglia in producing accurate repetitive sequences of movements, it is important to understand what is known about the function of the basal ganglia in the control of movement. The nuclei may have a modulatory effect at a number of stages of movement, either at the motor planning stage, in the initiation and/or execution of movements or during the dynamics of the actual movement (for example, speed of movement). Deficiencies in any of these stages in patients with basal

ganglia disorders gives clues to the level of control invoked by these nuclei.

1.3.4.i. Speed of movement.

Bradykinesia is a common symptom in both PD and HD patients. Evarts *et al* (1981) showed that during a simple reaction time test, movements were almost three times slower in PD patients than in normal subjects. Studies have shown a certain degree of change in muscle firing. Glendinning and Enoka (1994) showed that in PD patients, motor unit behaviour is altered so that the discharge patterns of motor units are irregular and intermittent and a number of the motor units are recruited at a lower threshold as compared to control subjects. These results were interpreted as evidence of an imbalance in excitatory and inhibitory inputs to the motor neurons from the basal ganglia via cortical circuits.

Various workers have studied EMG patterns in patients during simple ballistic wrist movements (Benecke *et al*, 1986; 1987a; Berardelli *et al*, 1985; 1986; Brown and Cooke, 1984; Hallett *et al*, 1975; Sheridan and Flowers, 1990). Hallett and Khoshbin (1980) reported that breakdown in the normal agonist-antagonist-agonist cycle occurred in longer ballistic movements in PD patients (see section 1.3.3.ii). Berardelli *et al* (1985, 1986) found that the first agonist burst was smaller than in control subjects which results in the movement failing to achieve the final intended end position. Also, almost all patients made some movements requiring additional cycles of alternating agonist and antagonist activity. The authors suggest that the basal ganglia energise the appropriate muscles required to make a movement. Rothwell (1987) suggested that because the overall size of the movement in PD patients is smaller, patients often make large amplitude movements in

a series of small steps. Thompson *et al* (1988) showed that although EMG bursts were elongated in patients with HD (also seen in other choreiform disorders, Hallett and Kaufman, 1981), the bradykinesia seen during complex simultaneous and sequential movements is remarkably similar in both HD and PD patients.

However, there is not a strong correlation between performance in simple wrist movement experiments and clinical scores for bradykinesia. This is because clinical assessment for bradykinesia (for example, in the Webster scale, see section 1.2.2.) usually employ more complex movements such as touching each finger with the thumb. Therefore studies using more complex movement sequences may be more highly correlated with clinical scores for bradykinesia. Benecke *et al* (1986; 1987a) found that during tasks in which PD patients were asked to produce movement with or without a force component, the movement was made even more slowly than usual. This extra slowing in complex movements suggests a role for the basal ganglia in motor sequencing.

It may appear paradoxical that bradykinesia occurs in both HD and PD, whose neuropathology appears to be so different. Thompson *et al* (1988) have postulated that (as discussed in section 1.1.4.) in HD under-activity in the direct pathway to GPi is important in producing bradykinesia. This would be a consistent explanation in PD (see Figure 1.1). Lack of dopamine results in the under-activity in the direct striatal projection to the GPi and, via an opposite action on the indirect pathway, to excess excitatory output from the STN.

1.3.4.ii. Initiation of movements.

PD patients have difficulty initiating movements and akinesia is also manifest in patients with HD (Stelmach and Phillips, 1991). The difficulty in initiation and execution of movements seen in PD patients does not seem to be due to perceptual impairment. Stelmach *et al* (1989) used distance judging tasks that were systematically varied in perceptual and motor difficulty. They found that patients were not affected by perceptual variations but were affected by variations in the motor requirements of the task.

Electrophysiological studies by DeLong and Georgopoulos (1981) showed that in animals, unlike a neurone in the motor cortex, the firing of the neuron in the basal ganglia occurs later in relation to the onset of movement on the contralateral side. Also, they found that the firing of units in the basal ganglia is better related to the direction of movement rather than the pattern of muscle activity necessary for achieving the movement. Therefore, the basal ganglia are unlikely to be intimately involved in either producing the onset of a movement or processing the precise pattern of muscle activity. The basal ganglia must be involved at a "higher" level of motor preparation.

Work by Dick *et al* (1989) suggested that movement preparation is impaired in PD. Electroencephalogram (EEG) studies have shown that the initial phase of the movement related potential (MRP), the Bereitschaftpotential (BP), is smaller in PD patients than controls. The MRP is a slow, rising EEG potential, probably be caused by excitation in the SMA and motor cortex, comprising of two phases; one which begins 1.5 seconds before movement onset (BP) and one which lasts from between 0.6 seconds before movement onset until movement onset. Dick *et al* (1989) interpreted these results as

suggesting that in PD there is a reduced output from the basal ganglia to the cortex in this preparatory stage.

Many workers have studied the role of the basal ganglia in movement preparation (Flowers, 1978; Evarts *et al*, 1981; Marsden, 1982; Montgomery *et al*, 1991; Stelmach *et al*, 1989). Simple and choice reaction times were used by Evarts and colleagues. In common with other workers they found that simple reaction time is increased in PD patients compared to normal subjects while choice reaction time is less affected. Simple reaction time is also prolonged in patients with HD (Hefter *et al*, 1987; Girotti *et al*, 1988). In normal subjects, the choice reaction time is much longer than simple reaction time because in the simple reaction time test, subjects have some time to prepare for the movement in advance. This will reduce the time needed for preparation of the movement and, therefore, decrease reaction time. In PD patients, the similarities between choice and reaction times are thought to be due a deficiency in the use of advance information, that is, movement preparation (for review, see Stelmach and Phillips, 1991). However, Stelmach *et al* (1989) concluded from a set of complex choice reaction time experiments, that PD patients could use advance information to some degree.

Simple and complex choice reaction time experiments in PD patients is an area of confusion between various workers. Different inferences may be drawn because different techniques study the *preparation of a movement* as opposed to the *accessing of a motor program or plan.* There is still some ambiguity concerning the role of the basal ganglia in these two conceptually different processes.

1.3.4.iii. The motor plan.

Clinical signs such as akinesia and bradykinesia in basal ganglia disorders may indicate problems in accessing and/or activating motor programs and plans (Stelmach and Phillips, 1991). Indeed, PD patients exhibit deficits during the acquisition of skills, but also benefit from practice (Frith *et al*, 1986). The question is whether these signs are the result of problems in accessing motor plans such that movements cannot be performed in a sequence. However, the first question to be answered must be: what is a motor plan and a motor program?

Marsden (1982) defined a motor program as a "set of muscle commands that are structured before a movement sequence begins, and that allows the entire sequence to be carried out uninfluenced by peripheral feedback". Motor planning is slightly more difficult to define as it comprises of interaction of several sensory modalities as well as sensorimotor interactions. The motor plan is the concept of a motor action, the execution of which requires the sequential operation of a number simple motor programs. Bernstein (1967) noted that no one movement is quite like another, and that although timing and distribution of muscle patterns may differ, the objective was achieved with the same degree of accuracy. Marsden (1982) suggests that the basal ganglia have an important role in running sequences of motor programs to complete a motor plan, and a breakdown in this function is manifest as akinesia in basal ganglia disorders.

Much research has studied motor programming in PD patients using a variety of sequencing experiments. Early evidence suggested that once a predictable movement was initiated, PD patients could carry out the motor program if the movement was externally

guided (Bloxham *et al*, 1984; Day *et al*, 1984). Some studies have shown that PD impairs the ability to use advance information to initiate and select movements (Bloxham *et al*, 1984; Stelmach *et al*, 1987), but others have found no such deficit (Rafal *et al*, 1987). Harrington and Haaland (1991) found that PD patients showed different types of programming deficits depending on the complexity of sequences and concluded that this was suggestive of abnormalities in several levels of motor programming. When subjects must independently construct an internal motor representation to guide movement, cognitive deficits seem to be more evident (Flowers, 1978). Although there is a consensus that PD patients can construct a motor program, it is not clear whether the output from motor programs is qualitatively similar to that of normal subjects or whether motor programs are used optimally during movement.

Motor planning in PD has been less well studied using tasks that require more organisational processing. Although one study of finger sequencing (Rafal *et al*, 1987) found that PD patients used advanced information to retrieve subprograms from a motor program, which was presumably constructed before the reaction time interval, others have shown that PD patients do not show normal programming of repetitive finger key presses (Stelmach and Teulings, 1987).

There is, therefore, a wealth of (sometimes conflicting) evidence as to the role of the intact basal ganglia in movement control, from motor unit control to deficits at the motor planning stage. Marsden (1982) concluded that the basal ganglia are responsible for "the automatic execution of learned motor plans". The nuclei automatically and subconsciously run the sequence of motor programs that comprise a motor plan. These programs may

have been learned and stored and may be assembled in other parts of the brain, but the initiation and sequencing of motor programs required in the implementation of a motor plan may depend on the basal ganglia (Rafal *et al*, 1987). Brotchie *et al* (1991) postulated that the basal ganglia control more automatic movements and that as these motor plans became better learned, they would pass from cortical to basal ganglia control. They showed in primate studies that activity in the basal ganglia was higher during movements made with the least cortical intervention.

1.3.5. Motor timing and the basal ganglia.

There are many human activities that occur in which the timing is fundamental to execution; for example walking, speaking, writing, dancing and playing musical instruments. Irregularities in such movements may arise from deficits in the assimilation or production of motor programs or in the *timing* of these motor programs. Vorberg and Hambuch (1978) separated timing from the motor program and postulated that during repetitive movements some timing function may signal the execution of the motor program.

The finding that patients with PD show deficits in timed repetitive movements implicates the basal ganglia in the timing of movements. Common clinical observations show that patients with PD experience difficulty in performing repetitive voluntary movements (Ward, 1991). Ward (1991) summarised the performance of parkinsonian patients in a repetitive finger pointing task as "he may continue to perform well for some minutes but will then his hand will fall way and the movements peter out, this deficit being enhanced if the subject closes his eyes". An extreme example of this is the symptom of 'freezing'

in PD patients (see 2.1.2). Freezing is a specific phenomenon characterised by difficulty in starting or continuing rhythmic, cyclical movements such as walking, speaking or writing (Andrews, 1973; Kanazawa, 1986). Koller and Trimble (1985) noted that HD patients displayed freezing or festination of gait, while Folstein *et al* (1986) reported difficulties in performing repetitive finger movements in HD patients. Therefore, the basal ganglia may have some role in the control of motor timing.

Within the theoretical framework of the control of motor timing, much research has focused on finger tapping and synchronisation (Vorberg, 1992). Other investigators have addressed the correlation between timing in different effectors, for example, wrist, shoulder and leg (for review, see Keele and Ivry, 1987). This present study is concerned solely with the ability of patients with basal ganglia disorders to perform timed repetitive movements using a single effector. Therefore, to study motor timing a simple timing task is required. All the tapping tasks performed have been designed so as to minimise any other requirements. Each finger tap requires a minimal force component and a minimal spatial accuracy. The task must employ only the simplest of motor programs. This is vital when studying motor timing in basal ganglia disorders. Previous sections cite the numerous deficiencies in motor control in patients at various phases of motor control such as the muscular and the motor planning level. In order to test the ability of patients to time their movements, the required movements should be simple to execute, with little emphasis on muscular control.

Semjen (1992) puts forward the reasoning that each finger tap constitutes a simple motor program. A series of finger taps, therefore, needs a motor plan to execute a series of these

simple motor programs. However, the motor plan is simple in that no choice about the serial utilisation of effectors is required, but a timing component is required. Marsden (1982) stated that the basal ganglia are important in motor planning, but to what degree is the motor timing of these plans functionally deranged in patients with basal ganglia disorders?

The tapping tasks in this thesis are typical of those used in motor timing research and fall into two categories (Vorberg, 1992). During *continuation* experiments, subjects are firstly asked to synchronise finger taps to auditory cues and then to continue tapping at the same speed after cessation of the cues. In a typical *synchronisation* task, subjects simply synchronise their finger taps with an external cue or metronome. The subject's performance is described in terms of the means of the intervals produced; variability and statistical dependence structure of the response intervals are usually characterised by their serial auto-covariance function (see 3.1.3).

To date, the most influential model for finger tapping has been the two process model proposed by Wing and Kristofferson (1973) for the generation of intervals during the continuation phase. The model assumes that tapping precision is bounded by two kinds of variability, one due to a hypothetical central clock, the other due to temporal 'noise' in the peripheral motor system. The clock is assumed to trigger a succession of motor programs. Execution of the programs by the motor system introduces delays between the clock 'ticks' and the corresponding overt responses. In experiments in which performance is analysed using Wing and Kristofferson's model, the cued phase simply ensures that subjects are producing accurate intervals.

In synchronisation tasks, subjects must synchronise their finger taps to sequences of auditory tones. Synchronisation tasks can be classified with respects to the properties of the metronome that the subject must shadow. In the simplest case, the metronome produces series of regular intervals, all with exactly the same inter-click interval. More challenging for the subject is when the metronome produces small random variations of intervals around a mean, or when the period undergoes abrupt changes or systematic drifts in intervals. Interest centres on two aspects of subject performance. Firstly, the size and variability of synchronisation errors, the time difference between the subject's response and the corresponding metronome click and secondly, the statistical dependence relations between metronome and response intervals which is usually stated in terms of the cross-correlation or the cross-covariance function between the two time series (see 4.2.4). There have been several models for synchronisation (for example, Michon, 1967; Fraisse and Voillaume, 1971; Hary and Moore, 1985, 1987a, 1987b). All agree that the subject's performance is based on the perceived synchronisation errors. The models differ in their assumptions about whether and how the subject uses the information of the synchronisation error for achieving and maintaining synchronisation.

This body of work is split up into three main sections, each reporting work which aims to study different aspects of motor timing in simple finger tapping tasks. Patients with PD and HD were compared with age-matched controls in order to ascertain the effect of basal ganglia disease on motor timing.

The experiments in Chapter 2 demonstrated the ability of PD and HD patients to produce mean tapping rates in the presence and absence of auditory cues. Various cue frequencies

were employed and subjects were asked to make finger movements in the synchronisation and continuation phases of the experiment. Mean tapping frequencies were studied as these were deemed to be the simplest parameter, and the one most likely to have been used by the subject to consciously monitor their performance.

In Chapter 3, performances in further finger tapping experiments were analysed using Wing and Kristofferson's (1973) model for timing in repetitive movements. Variability around the mean inter-response interval was decomposed into that which was attributable to a central clock and that which was attributable to temporal noise within the peripheral motor system. A detailed study including the effect of medication and sign asymmetry in PD as well as a longitudinal fifteen-month study on a newly diagnosed PD patient was described. A short study using HD patients was also described.

Chapter 4 described experiments of finger tapping and synchronisation with auditory cues. Various protocols were described, including regular and random metronome intervals. The performance was analysed with respect to synchronisation errors and patterns seen after the time series analysis of trials utilising auto- and cross-correlograms. The aim of this set of experiments was to characterise patient performance and to make initial predictions about the synchronisation strategy used by PD patients.

CHAPTER 2: THE EFFECT OF AUDITORY CUE REMOVAL ON THE ABILITY TO GENERATE MEAN TAPPING FREQUENCIES.

CHAPTER 2.1: INTRODUCTION.

2.1.1. Mean tapping frequency.

In order to study the role of the basal ganglia in the control of motor timing I have designed experiments to answer the following questions. In a simple finger tapping task, are patients with PD and HD able to duplicate accurately a range of target speeds, and then maintain these speeds after the target cues have been removed? How accurate are the patients in comparison with control subjects?

The variable measured was *mean tapping frequency* (measured in taps per second, Hz). Subjects were asked to produce mean tapping frequencies which accurately duplicate trains of target frequencies which were presented as auditory cues. The variable of mean tapping frequency was used as a starting point into this body of research as it represented the most simple parameter available in timing studies. Semjen (1992) noted that the parameter of "mean tapping speed" is most likely to be used *consciously* by subjects to monitor and improve their performance both during and after a series of finger taps. Intuitively, one feels that the concept of 'mean speed' or 'overall speed' is more likely to be fully understood by all subjects compared to, for example, variability of response intervals. Subjects are likely to ask themselves questions such as "Was I tapping too quickly or too slowly?" or "Did I slow down for a period?".

To study the ability of patients to produce accurate mean tapping frequencies seemed logical in that the subject was likely to have the maximum understanding of any improvements to be made in their performance.

2.1.2. Freezing in PD patients and the 'hastening phenomenon'.

Work by Nakamura and colleagues equated abnormalities in mean tapping frequency and freezing in PD patients. Freezing in voluntary movements is characterised by difficulty in beginning or, once begun, maintaining repetitive timed movements such as gait, speech and handwriting (Narabayashi and Nakamura, 1985). Although freezing can often co-exist with tremor, rigidity or other akinetic manifestations in most PD patients, it can be seen as an isolated sign and therefore is considered by Giladi *et al* (1992) and Kanazawa (1986) as an independent feature of the disease. The phenomenon is frequently encountered in cases where other symptoms have been effectively suppressed by drug therapy (Narabayashi *et al*, 1984). Freezing is not usually manifest early on in the disease process, but tends to become more prominent after 5-15 years of the disease process (Narabayashi and Nakamura, 1981). While the existence of the freezing phenomenon in the symptomology of parkinsonism is acknowledged, the underlying mechanisms are not yet fully understood.

The freezing phenomenon is most manifest in gait (Nagasaki *et al*, 1988). When a patient begins walking an oscillation with a high frequency in the region of 5 Hz is unwillingly released in the leg muscles. This high frequency muscle oscillation is manifest as very short, shuffling steps and prevents the subject moving forward and causes them to freeze. Freezing is, therefore, characterised by difficulty in performing repetitive movements leading Narabayashi and Nakamura (1985) to suggest that freezing is due to "the failure in the rhythm formation adequate to maintain repetitive movements in daily activities".

Nakamura *et al* (1976, 1978), Nagasaki *et al* (1978) and Nagasaki and Nakamura (1982)

used a simple finger tapping test to analyse the freezing phenomenon in a quantitative fashion. They likened freezing to a peculiarity of mean frequency production seen in parkinsonian patients. In their tapping tasks, subjects were instructed to respond synchronously to a periodic sound signal by tapping their index finger. Auditory signal frequencies ranged from 1 to 7 Hz and subjects were asked to produce between 50-100 responses. It was found that a high percentage of the patients (72%, Narabayashi and Nakamura, 1985) were unable to synchronise their responses to the external cues and exhibited hastened tapping of between 5-6 Hz (that is, at a rate higher than the given stimulus). Hastened tapping began to occur at one of two critical frequencies (2 or 4 Hz). Some of the patients exhibited hastened tapping at all frequencies of 2 Hz and higher, while others at all frequencies of 4 Hz and higher. This disturbance characterised by an abrupt failure of synchronisation and appearance of a hastened response of rhythmic movements seen in this set of parkinsonian patients was called the "hastening phenomenon" by Nagasaki *et al* (1978). Narabayashi and Nakamura (1981) regard the hastening phenomenon as representing a disturbance of rhythm formation in voluntary repetitive movements, since patients who exhibit the phenomenon are unable to form a desired rhythm exactly and steadily, being disturbed by the "unwilling release" of the abnormal rhythm even when they were consciously aiming to produce repetitive movements at a slow rate. Nakamura *et al* (1976) interpreted the hastened tapping as representing an intrinsic oscillation present throughout the central nervous system, which had been released in patients with PD, but was concealed in normal subjects. They proposed that a random oscillation of mean frequency 5-6 Hz may have existed and which was excited in PD and caused the abnormalities of rhythm formation.

The hastening phenomenon was encountered frequently in other diseases of the central nervous system. Nagasaki *et al* (1981) reported instances in patients with Huntington's disease and nigrostriatal degeneration but rarely in patients with lesions confined to the thalamus or cerebellum. Consequently, Narabayashi and Nakamura (1985) proposed that the disturbances in rhythm formation that produce the hastening phenomenon can be attributed to organic or functional deficits in the striatum.

Nagasaki *et al* (1978) and Nakamura *et al* (1976, 1978) believed that the clinical features of freezing or festination of repetitive movements were quantitatively represented by the hastening phenomenon. Narabayashi and Nakamura (1985) found that "without exception" the hastening phenomenon was observed in patients in whom freezing was manifest. As freezing during walking has been described as high frequency, short steps at about 5 Hz Nagasaki *et al* (1988) regarded the hastening phenomenon found in finger tapping tests as revealing, quantitatively, festination in finger movements in PD patients.

2.1.3. Tremor and repetitive movements.

Tremor at rest, with a frequency of 4-6 Hz, is a classic symptom in PD (see 1.2.1). It is reasonable to question the level of interference by tremor while patients produce repetitive movements. Hallett *et al* (1977) showed that patients with parkinsonian resting tremor timed single, voluntary limb movements so that their voluntary agonist EMG bursts would coincide with their tremor bursts. Logigian *et al* (1991) studied the influence of tremor on repetitive voluntary movements by comparing the frequency of isometric force tremor generated by the index finger with the frequency of voluntary alternating isometric contractions. It was argued that if single, rapid, voluntary movements are preferentially

timed to coincide with tremor cycles, then it might be predicted that repetitive, voluntary movements have preferred frequencies which may coincide with resting tremor frequencies.

Frischer (1989) suggested relative co-ordination between tremor and repetitive movements and proposed two possible mechanisms. Firstly, superimposition, which involved representing movements as the sum of two sinusoidal oscillators or secondly, a 'magnet' effect in which repetitive movements are bound and attracted to underlying tremor frequencies (Logigian *et al*, 1991).

2.1.4. External stimuli and rhythm formation in Parkinson's disease.

Marsden (1982) suggested that basal ganglia function had a primary role in the production of internally guided movements. The freezing phenomenon provides evidence for this hypothesis. There is much anecdotal and clinical evidence to suggest that freezing in PD patients may be both triggered and terminated by external sensory inputs (Ward, 1991; Kanazawa, 1986). For example, a frozen parkinsonian may resume walking if asked to step over their carer's foot placed on the ground in front of the patient. In addition to visual cues, auditory cues in the form of a metronome, or proprioceptive cues in the form of a gentle push may also be effective in starting repetitive motor acts.

Gait can be improved if external signals are provided. PD patients are less likely to freeze *while* walking if they are asked to walk across a pattern of stripes painted on the ground rather than a plain surface. Similarly, instances of freezing will be reduced if patients walk in time with a metronome as opposed to walking in silence (Rothwell, 1987). In contrast,

many patients freeze when trying to walk through a doorway. Even if the door is held open, they stop on the threshold and find it impossible to pass through. This anecdotal and clinical evidence generates an interesting question. How would patients with basal ganglia disorders perform after the removal of external auditory cues, compared with performance in the presence of the cues in a simple finger tapping task? Narabayashi and Nakamura (1981) briefly mention that when the signals were interrupted "mid course" patients tapping frequency rose to the frequency seen during hastening. Even when the target frequency was 1 or 1.5 Hz, cue cessation evoked hastening.

The aims of the experiments in this chapter, was to measure quantitatively (using mean tapping frequencies as the measurement of accuracy) the degree of precision with which patients with PD and HD could duplicate series of auditory target cues, over a range of cue frequencies, and then maintain the same tapping speed on cue removal. These findings would be compared with results from neurologically-intact age-matched controls. Also, postural tremor would be measured using accelerometry, in order to deduce any correlation between tapping performance and tremor.

It was hoped that the results would give initial indications of the types of abnormalities of performance seen in patients with basal ganglia disease and provide insight into further experiments required to study the functional role of the basal ganglia in motor timing.

CHAPTER 2.2: METHODS.

2.2.1 Subjects.

A total of eighty-four subjects were studied. This included thirty-four PD patients of which eleven were studied using the 'on-off' medication protocol (see section 2.2.1ii) and fourteen HD patients. All experimental protocols were controlled for using age-matched, healthy, neurologically intact volunteers. The protocols were approved by the Local Ethics Committee and the subjects participated in accordance with the provisions of the Declaration of Helsinki.

2.2.1.i Parkinsonian patients.

Twenty-three PD patients (10 male, 13 female) aged 63.0 (7.0) years, mean (SD), range 50-72, and twenty-four healthy subjects (12 male, 12 female) aged 62.3 (7.8) years, range 50-75 were studied. A further eleven PD patients (3 male, 8 female) aged 65.0 (6.5) range 56-72, were studied in the 'on-off' medication trial.

The diagnosis of PD was made by a consultant neurologist on the basis of the classic triad of tremor, rigidity, and bradykinesis and the absence of any atypical signs or symptoms. The larger PD patient group undergoing the standard trial (i.e. those who were <u>not</u> being studied under the 'on-off' trial) were investigated while on their routine therapy, which in all cases included standard levodopa formulations and in some case additional medication. No distinction was made between 'on' or 'off' phases. All patients had sufficient voluntary control both to perform the experiment and to continue to live at home, rather than be permanently institutionalised. Thus, the study was carried out on patients with mild to

Init.	Age (yrs)	Sex	Duration (yrs)	Clinical grading	Treatment
IW	63	F	4	7 (I)	LD;Se
PM	63	M	3	8 (II)	LD;DA;Se
GT	69	M	13	14 (II)	LD;DA;Se
LC	50	M	7	8 (I)	LD;AC;Se
EM	58	F	10	8 (II)	LD;AC;Se
JM	54	F	7	12 (II)	DA;AC;Se
WY	62	M	9	11 (II)	LD;AC;Se
MH	72	F	9	15 (III)	LD
MM	58	M	6	12 (II)	LD
AG	68	M	4	6 (I)	LD;DA;Se
TC	69	M	3	8 (I)	LD;DA;Se
FC	51	M	<1	7 (I)	None
MP	67	F	3	11 (II)	None
EM	56	F	11	9 (II)	LD;DA;AC;Se
EA	72	F	2	15 (III)	LD;Se
GW	70	M	5	5 (I)	LD
ED	71	F	12	9 (I)	LD;DA
JS	58	F	3	10 (I)	LD;Se
SN	57	F	3	5 (I)	LD
VM	70	F	1	10 (II)	DA
DR	62	F	2	6 (I)	AC
DB	71	F	6	15 (III)	LD;Se
BP	58	M	7	17 (III)	LD;Se;Am

Table 2.1. Clinical details of the twenty-three PD patients tested on the standard protocol of the finger tapping test. The clinical grading represent the Webster (1968) disability rating, and in parentheses the Hoehn & Yahr (1967) staging (for details refer to Methods). Abbreviations:- Init = initials; yrs = years; duration = duration of illness since initial diagnosis; LD = L-dopa; DA = dopamine agonist; AC = anticholinergic; Se = selegiline and Am = amantidine.

Init.	Age (yrs)	Sex	Duration (yrs)	Clinical Grading	Treatment
HB	69	M	9	10 (I)	LD;Se
NK	66	M	4	6 (I)	LD;AC;Se
GR	56	F	2	11 (II)	LD
MY	72	F	11	15 (III)	LD;Se
AC	71	M	12	9 (I)	LD;DA;Se
HV	71	F	5	5 (I)	LD;AC;Se
JF	57	F	9	5 (I)	LD;DA
EB	56	F	10	10 (I)	LD
JS	70	F	5	10 (I)	LD;Se
MM	69	F	6	19 (III)	LD;AC
EW	58	F	6	18 (III)	LD;Se

Table 2.2. Clinical details of the eleven PD patients tested on the 'on-off' medication protocol of the finger tapping test. All parameters and abbreviations are similar to those used in Table 2.1 (previous page).

moderate symptoms, rather than those with severe disabilities. The average duration of the patients disease at the time of testing was 5.9 (3.6) years. Patients underwent a clinical assessment performed by a neurologist immediately before the experimental sessions. Patients were assessed for rigidity, bradykinesia and gait, each scored on a four-point scale (Webster, 1968) in which 0 = normal or absent and 3 = severely disturbed. Clinical features, together with drug therapy are summarised in Table 2.1 for patients undergoing the standard protocol. Postural tremor was measured accelerometrically at both wrists in nine PD patients (the first nine patients in Table 2.1). Mean peak frequencies for the left and right wrist were, respectively, 6.0 (1.5) Hz and 6.1 (1.5) Hz. The incidence of freezing of gait during everyday activities was also scored for individual patients according to a four-point scale: 0, never; 1, several times per month; 2, several times per week; 3, daily.

2.2.1.ii 'On-off' medication trial.

Eleven PD patients participated in the trial, all of whom were prescribed L-dopa in either the form of Sinemet or Madopar on a daily basis. Table 2.2 shows the clinical features and daily medication for the patients. The patients essentially underwent the standard finger-tapping test twice in order to study the effects of medication. Patients were asked to attend a morning session having refrained from taking L-dopa for 12-15 hours. This was considered to be the 'off' state. Patients then performed the experiments. On completion of the tests the patient took a single dose of their normal medication. After a further period of 45 minutes the patient was considered to be 'on'; that is, less parkinsonian than during the 'off' state. The experiments were then repeated and the results compared using patients as their own controls.

2.2.1.iii HD patients.

Fourteen HD patients (7 male, 7 female) aged 50.8 (11.5) years, range 31-70, and twelve healthy subjects (5 male, 7 female) aged 53.0 (8.3) years, range 30-64 were studied. The patients were drawn from the North-West Regional Genetic Register of HD families. Diagnosis of HD was established on the basis of clinical features and a family history of the disease. Clinical features pertaining to motor function, together with drug therapy of the patients are summarised in Table 2.3. The mean time since diagnosis of the HD patients was 4.8 (3.3) years. Immediately prior to study, patients underwent standard neurological examination and were assessed on a range of tests of cognitive function. None of the patients exhibited clinical rigidity. Only two had clinical tremor and in both cases it was graded as mild (grade 1 on a standard 4-point scale). Clinical bradykinesia, although absent in the majority of patients, was present to a moderate (grade 2 on a 4-point scale) degree in one and a mild (grade 1) degree in five cases. Chorea, of varying severity, was present in all patients. The mean score for overall chorea rating (Folstein *et al*, 1983, 0 = absent, 25 = maximal severity) was 9.9 (3.3) whilst the corresponding score for chorea during voluntary movements (0 = absent, 5 = maximal severity) was 2.2 (0.7).

2.2.2 Apparatus.

The aim of the experiment was to analyze the mean tapping frequencies achieved by subjects when asked to maintain synchrony with given auditory cues and to sustain the rhythm on removal of these external stimuli. The analogue equipment used in the experiment was as follows;

Amplifier (Neurolog) x2

Digitimer (Devices type 3290) x2

Case	Sex	Age	Dur	Chor	BK	Tr	Rg	RF	Medic.
1	M	51	9	9(2)	100(1)	0	0	0	CPZ
2	F	52	5	4(1)	104(1)	0	0	2	AT/Su
3	F	31	2	14(3)	270(2)	0	0	3	TB/Ch
4	M	38	NA	NA	NA	NA	NA	NA	NA
5	M	39	2	11(2)	70(0)	1	0	0	None
6	M	51	12	14(3)	85(0)	0	0	2	None
7	F	56	2	9(2)	120(0)	1	0	0	None
8	M	38	8	13(3)	72(0)	0	0	2	AT
9	M	59	3	9(2)	88(0)	0	0	0	CPZ
10	F	49	0.5	5(1)	59(0)	0	0	0	Pr
11	F	47	5	14(3)	87(1)	0	0	2	None
12	F	62	3	9(2)	53(1)0	0	0	1	St
13	F	70	4	10(2)	92(1)	0	0	1	None
14	M	62	7	8(2)	61(0)	0	0	1	Su

Table 2.3. Clinical data and medication of the HD patients. Abbreviations and scoring conventions:- Age (years); Dur = time since diagnosis (years); Chor = chorea (initial value is overall clinical score, absent 0, maximal severity 25; value in brackets is score for chorea during voluntary movements, absent 0, maximal severity 5, Folstein *et al*, 1983); BK = bradykinesia (initial value is simple dealing time in seconds for the Nelson (1976) modification of the Wisconsin card sorting test; value in brackets is clinical score on a 4-point scale); Tr = tremor, Rg = rigidity and RF = rapid finger-thumb movements each scored on standard 4-point clinical scales. Medication refers to drug treatment (CPZ = chlorpromazine, AT = amitriptyline, Su = sulpiride, TB = tetrabenazine, Ch = choral hydrate, Pr = paroxetine and St = stelazine).

Stimulator (SRI)

Audio amplifier (Neurolog)

Loudspeaker

Tap pulses and auditory cues were converted and stored on a PC. The system used is explained in the next section. Figure 2.1 shows the experimental setup for the tapping experiment.

2.2.2.i The computer system configuration.

Data collection and analysis was performed using a system designed by Ms. Frances Caulshaw. The programming language used was "ASYST" (version 2.0) which is specially designed for scientific applications. Since the layman will have had little or no experience of ASYST, it was considered unnecessary to include program listings. The computer system used in this body of work comprised the following elements:

Olivetti M240 PC (with maths co-processor)

Metrabyte DASH 16 data acquisition card

Dataq waveform scroller card

Roland DXY-880A pen plotter

ASYST 2.0 software package

Applications software

The PC contained the data acquisition and waveform scroller cards. The maths co-processor (8087) was located inside the PC and was a requirement of the ASYST software package. As ASYST is a copy protected software package, a copy protection block

Figure 2.1. Photographic representation of the experimental setup. On the left of the photograph, from top to bottom, the loudspeaker, audio-amplifier, digitimers and amplifiers are shown, the stimulator being shown adjacent to the PC. The position of the hand whilst performing the tapping experiments is also shown.

("dongle") provided with the ASYST package was attached to the parallel port printer socket at the back of the printer.

The DASH 16 data acquisition card was fitted inside the PC and contained the analogue-to-digital converter (ADC) which provides the interface between the transducer/amplifier and the PC. The DASH 16 card was set to have an input range of +/- 5 V.

2.2.3 Finger tapping test.

Subjects sat in a chair with one forearm resting comfortably on a table which was placed in front of them. The hand placed palm downwards on a wooden board upon which was mounted a metal plate. A metal loop was securely placed around the index finger, distal to the terminal interphalangeal joint, of the subject's hand. Subjects tapped their index finger, by making alternating flexion and extension movements of the wrist, so that the metal loop struck the contact plate. Subjects were instructed to make distinct movements, raising the finger about 5 mm above the contact plate between strikes. Small movements were chosen for study to minimise any effects of bradykinesia upon patients' performance. Each time the metal loop attached to the index finger struck the contact plate, an electrical circuit was completed. A brief voltage pulse was generated, signifying the precise instant of the 'tap'. A tap contact activated a stimulator which then triggered a Digitimer to produce standard length -12 V pulses. These pulses were then converted to the correct amplitude (5 V) and polarity by the amplifier before being channelled into the ADC.

Auditory cues of target tapping frequencies were presented to the subjects. These consisted of sequences of regularly spaced 'clicks' (100 ms duration, -12 V amplitude) at frequencies

of 1, 2, 3, 4 or 5 Hz. Cue pulses were produced by a signal generator (Digitimer; type 3290) and played through an audioamplifier and loudspeaker. The electrical signal from the Digitimer was also channelled into the ADC having first been reversed in polarity and attenuated to an amplitude of +5 V (see Figure 2.1). Cues of a single frequency were presented in a given trial. Separate trials involving each of the five different target cue frequencies were presented in a pseudo-random manner.

Two protocols were employed. In protocol 1, tapping performance was recorded over a series of 30 s trials throughout each of which auditory cues were continuously presented at one of the five target frequencies. Subjects were asked to tap in rhythm to the auditory cues. In protocol 2, tapping performance was again recorded over 30 s trials, but auditory cues were abruptly switched off after 10 s. Subjects were asked to tap in rhythm with the cues during the initial 10 s period and then to continue tapping at the same rate during the remaining 20 s 'silent' period. All recording periods were separated by gaps of about 1 min to allow subjects to rest. Both protocols were performed on each hand in both the patient and control groups.

For the HD patients and their control subjects, a measure of the maximum tapping frequency (MTF) of each individual was obtained. Subjects were exhorted to tap, in the absence of auditory cues, at the fastest rate of which they were capable for a period of 10s and the resultant mean rate was calculated.

2.2.4 Data analysis and statistics.

The PC was used to store and analyze tapping data. Pulse trains corresponding to tap and

cue events were sampled at 100 Hz by separate channels of the computer ADC. Any tap pulse which followed its predecessor by an interval of <50 ms was ignored to eliminate counting artifactual contacts. The mean (SD) tapping frequency was calculated for each sampling period. Regression analysis was applied to the data of individual subjects to obtain values for the slope and y-intercept of the relationship between mean tapping rate and cue frequency. These two measures were used to evaluate the overall accuracy of a subject's rate tapping performance. In addition, the difference in mean tapping rates between cued and uncued phases of trials (protocol 2) was determined. The SD of each subject's tapping rate, which measures the dispersion around the mean value of the instantaneous frequencies (reciprocal of inter-tap intervals) in a sequence of taps, was used as an index of the variability of tapping rhythms. Non-parametric statistical tests were routinely used since preliminary analysis indicated that many of the data did not conform to a Gaussian distribution and, thereby, precluded conventional parametric methods. Available non-parametric analysis of variance techniques (e.g. Friedman's ANOVA) are not applicable to the numbers and combinations of data sets of the present investigation. Therefore, intra-group and inter-group comparisons were performed using, respectively, Wilcoxon's signed-rank, matched pairs test and the Mann-Whitney U test. These comparisons each involved five sets of dependent tests. In this situation there is an increased risk of false positives (type I errors) and a compensatory α adjustment procedure (for example, Bonferroni) may be applied. In the present analyses, Bonferroni adjustment dictates that a p value of 0.01 should be interpreted at the $\alpha = 0.05$ level of significance. However, it should be noted that many statisticians (see Cohen, 1990) consider the Bonferroni adjustment to be excessively conservative and that its use leads to an unacceptable loss of power (increase in type II errors, that is, false negatives). In this

chapter, Bonferroni corrected p values of 0.01 are taken to indicate statistical significance. Spearman's rank correlation test was used to determine whether correlations existed between measures of rate tapping deficits in HD (see above) and clinical scores of motor signs.

2.2.5 Tremor recordings.

A standard way of collecting data on an oscillating body is with the aid of a light accelerometer which produces a voltage proportional to acceleration. Tremor was measured using a small piezoelectric accelerometer (Bruel & Kjaer; type 4393; weight 2.2 g) coupled to a light metal plate. This plate was then strapped to the back of the hand by velcro bands. The signal from the accelerometer amplified by linkage to a charge amplifier (Bruel & Kjaer; type 2635) and then digitised by the DASH 16 ADC. The signal was then captured by the PC and stored on magnetic disk. Both postural and resting tremor were recorded from the wrists of both hands. Resting tremor was measured with the subject's forearm lying pronated along a horizontal support, with the hand dangling freely. Postural tremor was measured with the hand extended, so that the metacarpus was maintained in the horizontal plane with the forearm still supported. Both resting and postural tremor were recorded for five 10 s periods from both hands.

Tremor recordings were sampled at 50 Hz by one channel of the ADC via the accelerometer and charge amplifier. Recordings were then analyzed by Fourier transform to determine the power spectrum, peak frequency and overall power.

2.3. RESULTS.

2.3.1 Externally signalled rhythm generation in PD and healthy subjects.

Figure 2.2 compares the ability of a healthy subject and a representative PD patient to duplicate the rhythm of a sequence of evenly-spaced auditory cues, presented at 3 Hz, by making voluntary wrist movements to produce tapping of the index finger over a 30 s time period. In the figure, taps are represented by crosses (+). The height of each point is indicative of the tapping frequency at that instant, relative to the preceding tap (calculated as a reciprocal of the inter-tap interval). There are characteristic differences in performance between the healthy subject (Figure 2.2A) and the PD patient (Figure 2.2B). The tapping performance of the healthy subject reproduced far more accurately the rhythm of the auditory cues, both regarding the mean frequency (3 Hz) and the regularity. In this example, the PD patient is tapping at a higher rate than is required (mean tapping rate 3.28 Hz). Also, while the points representing successive taps made by the healthy subject are closely grouped around the cue frequency for the full 30 s recording, while those of the patient show greater variability, indicated by a broader scatter about the mean.

Figure 2.2 also shows two other features of tapping performance in this study. Firstly, both the healthy subject and the PD patient were able to immediately establish a tapping rhythm approximating to the cue frequency upon onset of the auditory signal. Secondly, in neither case is there any sign of a transition in performance such as might result from a loss of concentration or physical tiredness. Comparison of the tapping performance of individual subjects during the first and last 10 second period of the 30 s trials confirmed that in neither patient nor control was there a systematic deterioration in accuracy as trials

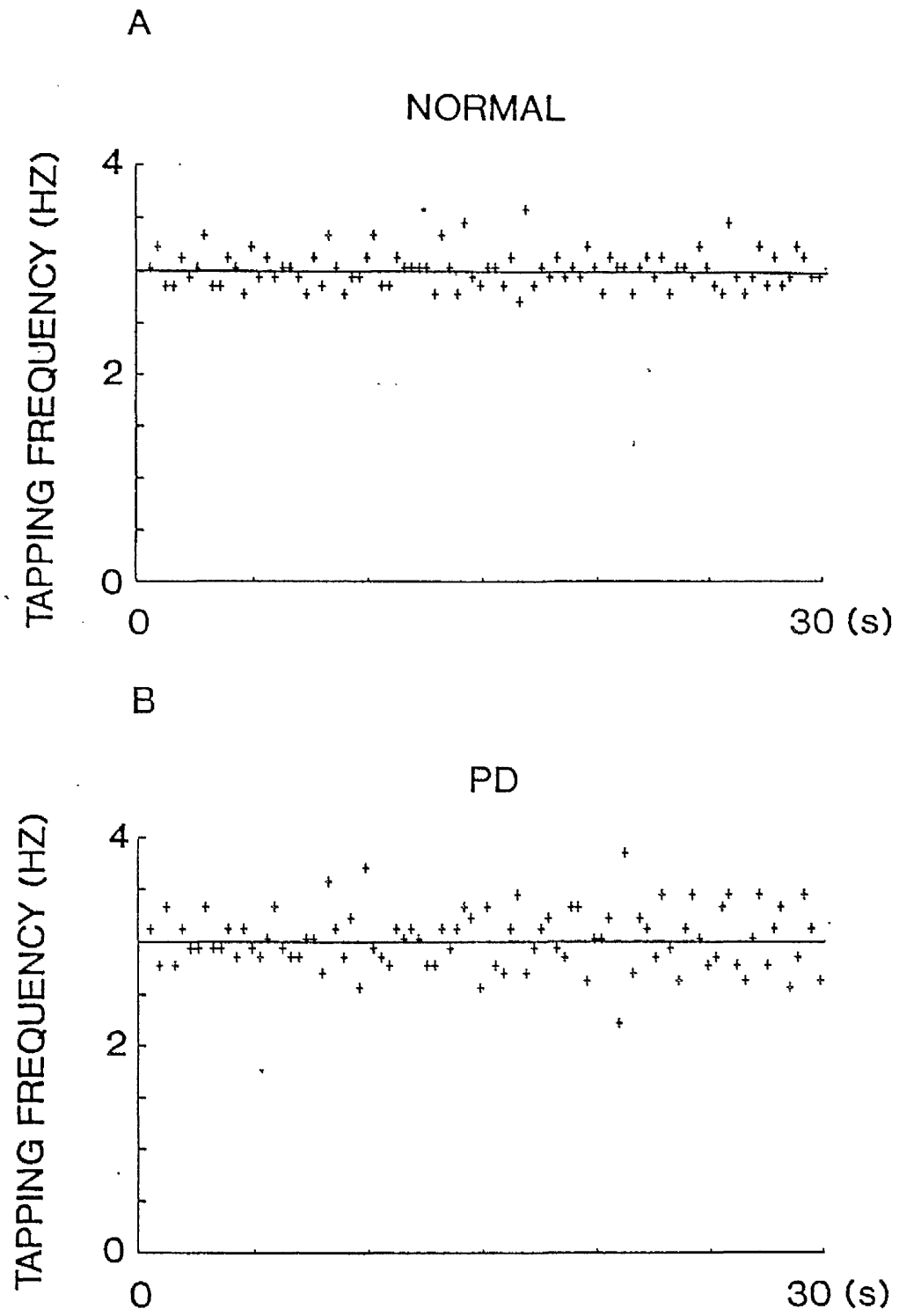

Figure 2.2. Plots of instantaneous frequency of finger tapping in a healthy subject (A) and a representative PD patient (B) in the continuous presence of 3 Hz auditory signals. Each point represents the occurrence of a single tap. The height of each point indicates its instantaneous frequency in relation to the immediately preceding tap and was calculated from as the reciprocal of the inter-tap interval. The solid line indicates cue frequency.

progressed. In particular, if fatigue was setting in it would be expected that the PD patients' tapping response would decline progressively, but this was not the case. Similar findings were obtained at all frequencies.

Figure 2.3 shows a plot of mean tapping frequency, measured over a 30 s period for the entire range of target frequencies for the healthy subject (Figure 2.3A) and the representative PD patient (Figure 2.3B) featured in Figure 2.2. In this example, the healthy subject demonstrated a high degree of accuracy between mean tapping frequency and auditory cue frequency over the entire range. In contrast, the mean tapping frequencies of the patient showed obvious differences from the corresponding cue frequencies which were typical found in the group. The patient, in this example, tapped too quickly at the lower target frequencies (1-3 Hz) and too slowly at the higher target frequencies (4-5 Hz). Additionally, at all cue frequencies, the patients' inter-tap intervals showed far greater variability within a single trial, indicated by the relatively large standard deviations seen in Figure 2.3B.

Figure 2.4 illustrates that when data from the whole group was analyzed, similar findings were noted between PD and normal subjects. Plots of tapping performance of the two groups confirm that, in the presence of auditory cues, PD patients were less exact in replicating the cue frequency. Figure 2.4 shows results from the preferred hand. The relatively larger S.D. values of the patient group suggest that tapping performance within the group showed more variability than in that of the control group. Figure 2.4 shows that the PD patients as a whole tended to tap more rapidly than healthy subjects at low intermediate target frequencies and less rapidly at the highest frequency investigated (5

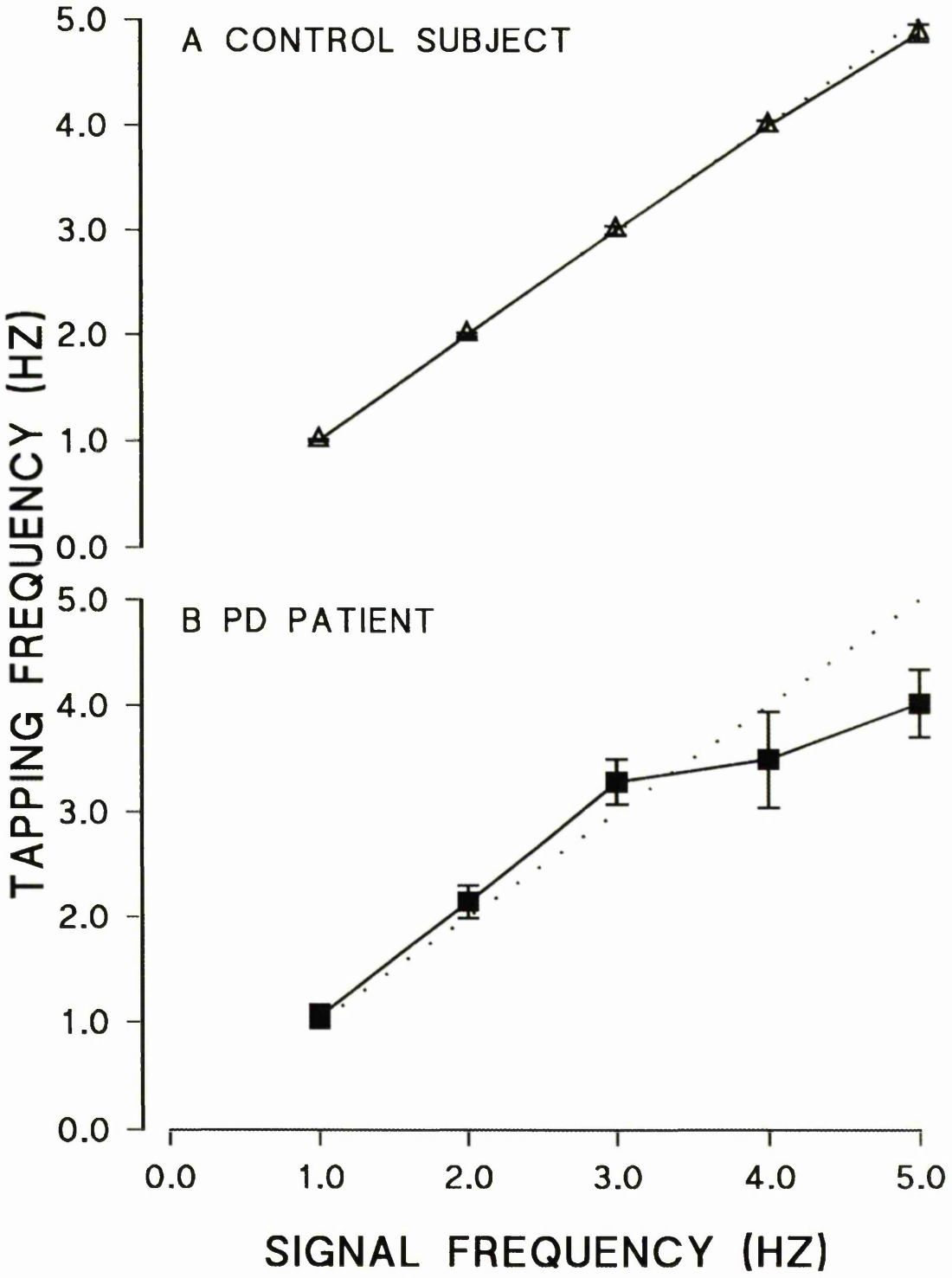

Figure 2.3. Mean (S.D.) tapping frequencies for one healthy subject (A) and one PD patient (B) for the range of signal frequencies. Each trials was conducted over a 30 s period in the continued presence of the auditory cues. Dotted lines, with unity slope, indicate an ideal performance in which there would be an exact correspondence between tapping and cue frequencies.

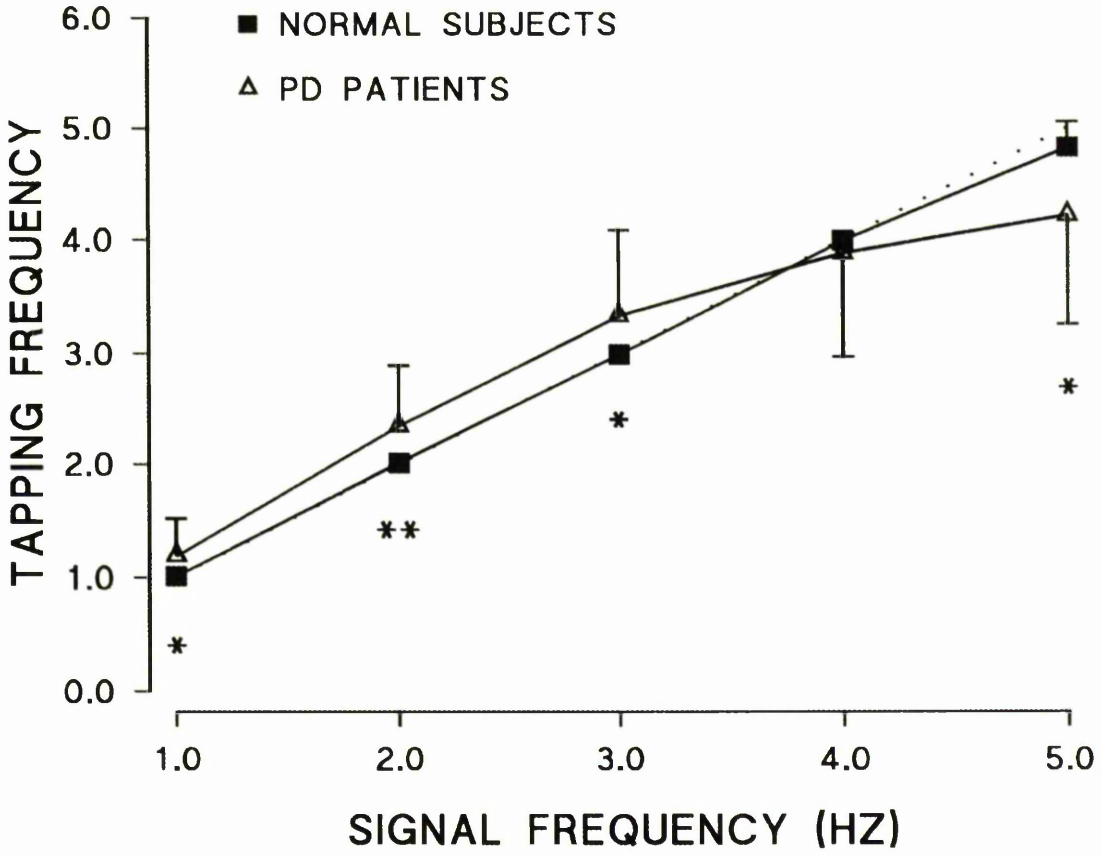

Figure 2.4. The relationship between finger tapping frequency and the frequency of auditory cue signals in the preferred hands of 24 healthy subjects and 23 PD patients. Mean (S.D.) tapping frequencies are shown and auditory cues were presented throughout the 30 s trials. The dotted lines indicate unity slope. The mean tapping rates of the PD group were significantly different at 1, 2, 3 and 5Hz (** $p<0.001$, * $p<0.01$, Mann-Whitney) when compared with the control group.

Hz). The mean preferred hand tapping rates of the patient group were statistically significantly higher than those of the control group for cue frequencies of 1, 2 and 3 Hz and lower for the 5 Hz signals (p values, respectively, 0.009, 0.0005, 0.006 and 0.004, Mann-Whitney). Essentially similar findings were obtained for the non-preferred hand, where tapping frequency was significantly higher at 1 and 2 Hz (borderline significance) and lower at 5 Hz (p values, respectively, 0.006, 0.01 and 0.009, Mann-Whitney). In neither patient nor control groups were there any significant differences between the mean tapping rates of left versus right hands at any of the target frequencies.

2.3.2. Rhythm generation in the absence of external signals in PD and healthy subjects.

Figure 2.5 shows instantaneous frequency plots of tapping performance of a representative healthy subject (A) and a PD patient (B) during 30 s periods in which a 3 Hz auditory cue signal was removed after 10 s, and the subjects required to maintain their tapping frequency. Figure 2.5A shows that the tapping performance of the healthy subject was relatively unaffected by withdrawal of the auditory signals. By contrast, the performance of the patient (Figure 2.5B, note different scale) underwent a clear alteration following removal of auditory cues. There was an increase in mean tapping frequency and the rhythm became far more irregular. Similar trends were noted for the 3 Hz target frequency in the patient group as a whole (see below). These changes seem certain to have resulted from withdrawal of cue signals, since they did not occur in the presence of auditory cues (see Figure 2.2B).

The plots in Figure 2.6 compare the tapping performance of healthy and PD groups in the

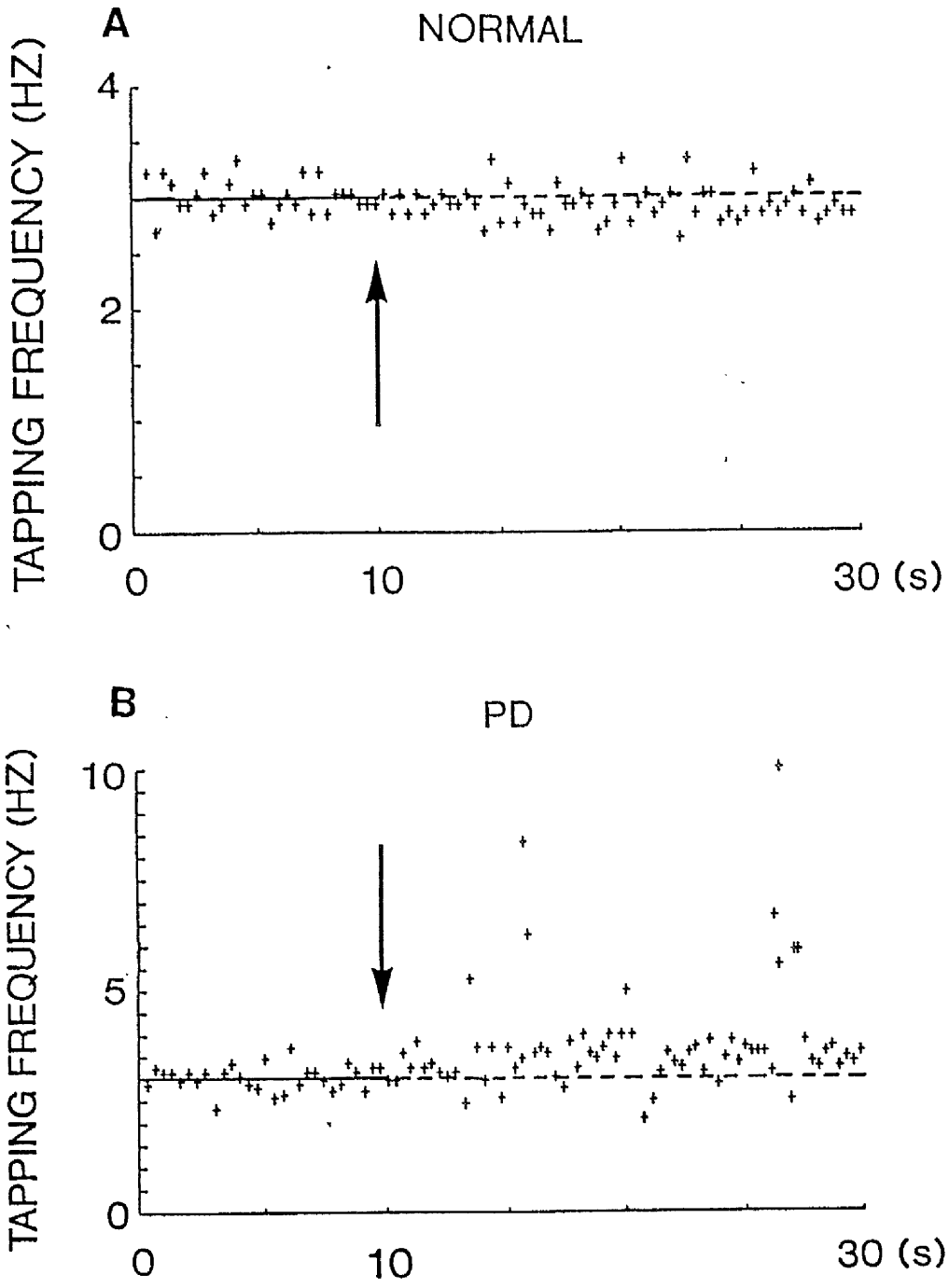

Figure 2.5. Plots of instantaneous frequency of finger tapping in a healthy subject (A) and one PD patient (B) in the presence and then sudden removal of 3 Hz auditory signals after 10s during a single 30 s trial. Each point represents the occurrence of a single tap and its height represent the frequency at that instant. Arrows indicate the point at which the auditory cue was removed which becomes dashed in the 'silent' phase. Tapping during the remaining 20 s period was in the absence of cues. The scales on the vertical axes differ in A and B.

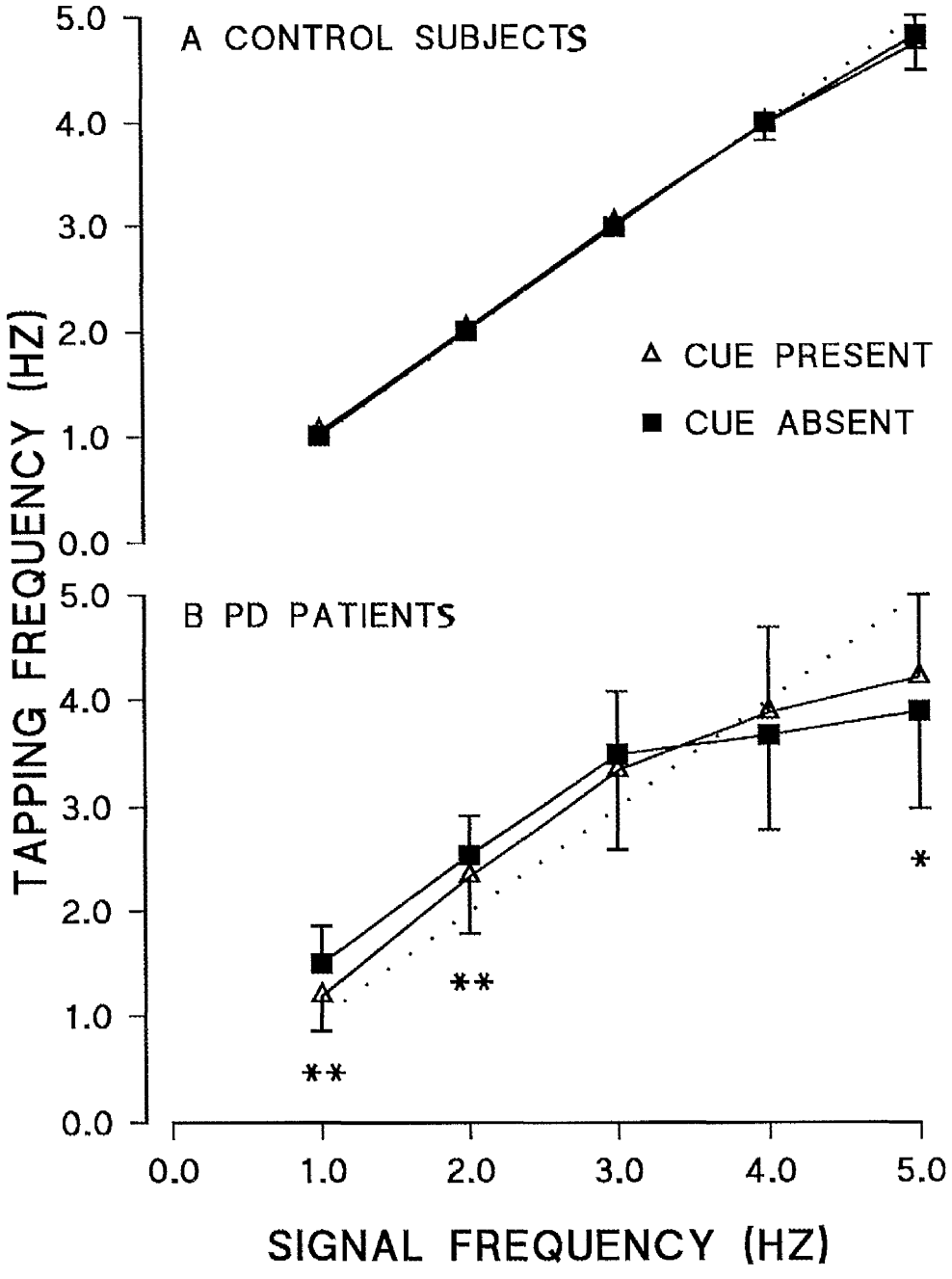

Figure 2.6. Plots comparing the tapping performance of the subjects in the presence and absence of auditory signals for the group of 24 healthy subjects (A) and the group of 23 PD patients (B). Mean (S.D.) values for preferred hand are given. Dotted line indicates unity slope. The mean tapping rates on cue removal of the PD group were significantly different at 1, 2 and 5 Hz (** $p<0.001$, * $p<0.01$, Wilcoxon) when compared to data during the period of auditory feedback.

presence of auditory cues and following there sudden removal once the rhythm had been well established. Results for the preferred hand are shown. Figure 2.6 shows that the withdrawal of external cues had a pronounced influence on the performance of the patients (Figure 2.6B) whereas it had little effect on that of the healthy subjects (Figure 2.6A). Cue suppression resulted in the patients' mean tapping frequencies increasing at the two lowest target frequencies (1 and 2 Hz) and declining at the 5 Hz target (p values, respectively, 0.0005, 0.001 and 0.007, Wilcoxon). Similar findings were obtained for the non-preferred tapping performance. Withdrawal of cue signals caused significant increases in mean tapping rates at targets of 1, 2 and 3 Hz and a reduction at 5 Hz (p values, respectively, 0.009, 0.005, 0.01 and 0.01, Wilcoxon). In all cases, these changes represented a further reduction in accuracy. In the control group, cue removal had no significant effect on mean tapping performance at any of the target frequencies ($p > 0.1$, Wilcoxon).

Figure 2.7 shows the actual changes in mean tapping frequency between performance during the cued and subsequent uncued periods at each target frequency for the control and PD groups, which allowed direct comparison between the groups, of the effect of cue removal. When the differences in mean tapping performance were analysed it was found in the PD group, that there was significantly more change at 1 and 2 Hz (this was a positive increase; patients were tapping more rapidly on cue removal) and at 4 Hz (a negative increase; patients were tapping more slowly on cue removal) than those seen in the control group (p values, respectively, 0.0005, 0.001 and 0.004, Mann-Whitney).

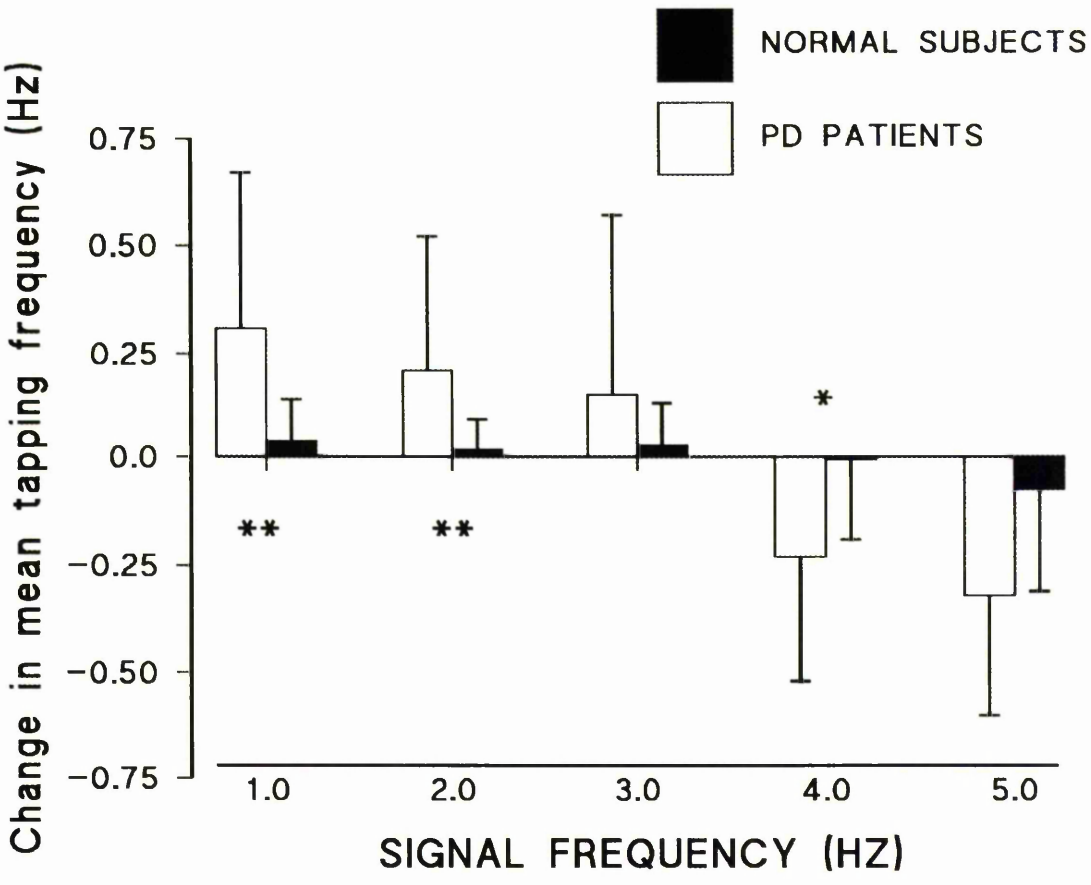

Figure 2.7. Actual changes in mean tapping frequency (Hz) between cued and subsequent uncued periods. Mean (S.D.) group data from 24 healthy subjects and 23 PD patients is shown. A positive value shows an increase in tapping frequency on cue removal, while a negative value shows a decrease in tapping frequency on cue removal. ** $p<0.001$, * $p<0.01$, Mann-Whitney, indicate significant differences between normal and PD groups.

2.3.3. The relationship between clinical symptoms of PD and abnormal rhythm generation.

The slope and the y-intercept of the regression line of the relationship between mean tapping rate and cue frequency were calculated for all subjects as measures of their tapping performance in the presence of external cues (see 2.2.4.). Healthy subjects, who were accurately able to match tapping rates to cue frequencies, consistently had slopes close to unity and y-intercepts near to the origin. The corresponding regression lines of individual PD patients typically had slopes of <1 and a positive y-intercept due to an increase at lower cue frequencies and a decrease at the higher frequencies. The slope of the tapping-cue rate regression line was adopted as the best overall index of tapping performance. The mean (S.D.) value of the slope in this relationship in the PD group was 0.76 (0.28), range 0.30-1.32.

Correlations between the patients' tapping rate indices and their clinical scores for other aspects of motor function obtained during standard neurological examination were tested (see table 2.1). No significant correlations were found between tapping indices and the duration of the disease ($p=0.345$, Friedman's Rank correlation) or total clinical score ($p=0.420$). There was no correlation between tapping indices and tremor, either when tremor was defined as a clinical score ($p=0.065$) or when peak frequency of postural tremor was measured ($p=0.212$). Individual instances of abnormal tapping performance were noted in the absence of appreciable tremor, while in other instances tapping accuracy was "within normal limits" despite the presence of pronounced, low frequency tremor. Similarly, there was no correlation between clinical scores for rigidity ($p=0.998$), bradykinesia ($p=0.509$) or gait ($p=0.693$).

When asked about 'freezing' of gait (see 2.2.1.i), ten patients reported the most severe score (3 or daily), six reported a score of 2, three reported a score of 1 and four reported a score of 0 (freezing never occurred). There was no correlation between the score for freezing and patients' tapping indices ($p=0.101$).

2.3.4. The effect of medication on the ability to generate repetitive movements in PD patients.

Figure 2.8 shows a plot of mean tapping frequency, measured over a 30 s period in the continued presence of the auditory cues for the entire range of target frequencies. Mean (S.D.) group data is shown for eleven PD patients. This group of patients performed the tests twice; first, after abstinence from their normal L-dopa medication for 12-15 hours and secondly, forty-five minutes after ingestion of one dose of medication.

The graph in Figure 2.8 shows that essentially similar results were found in this patient group as were found with the patient group in section 2.3.1. PD patients tended, in the presence of the cue, to tap too quickly at lower target frequencies and too slowly at higher target frequencies (see also Figure 2.4). However, medication seems to have had little effect on the tapping performance of PD patients in the presence of auditory signals. There was no significant difference in the mean tapping frequency at any target frequency, between trials conducted when patients were 'off' medication and when they were 'on' medication ($p>0.063$, Wilcoxon).

Patients also underwent trials in which the auditory cue was abruptly removed. Figure 2.9 shows the effect of medication on the change in mean tapping frequency between the cued

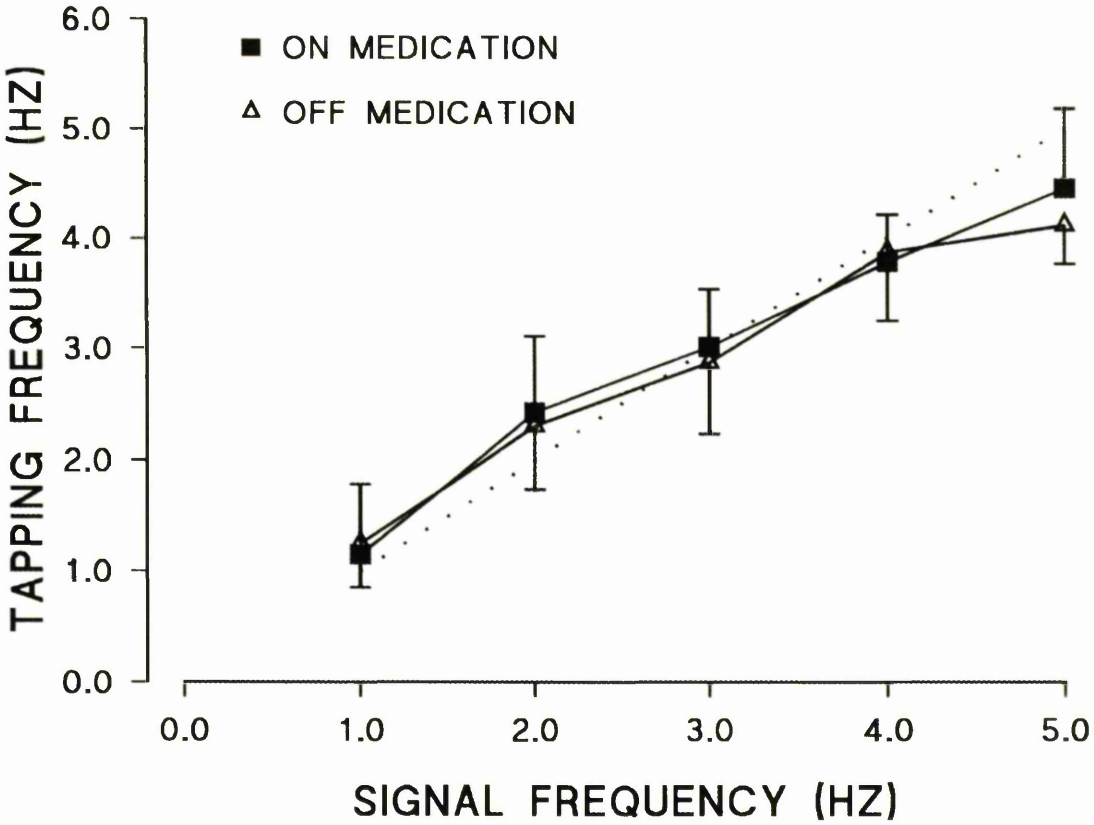

Figure 2.8. The relationship between finger tapping frequency and the frequency of auditory cue signals in the preferred hands of 11 PD patients 'on' and 'off' medication. Mean (S.D.) tapping frequencies are shown and auditory cues were presented throughout the 30 s trial period. There was no significant difference in mean tapping frequencies when performances 'on' and 'off' were compared (Wilcoxon).

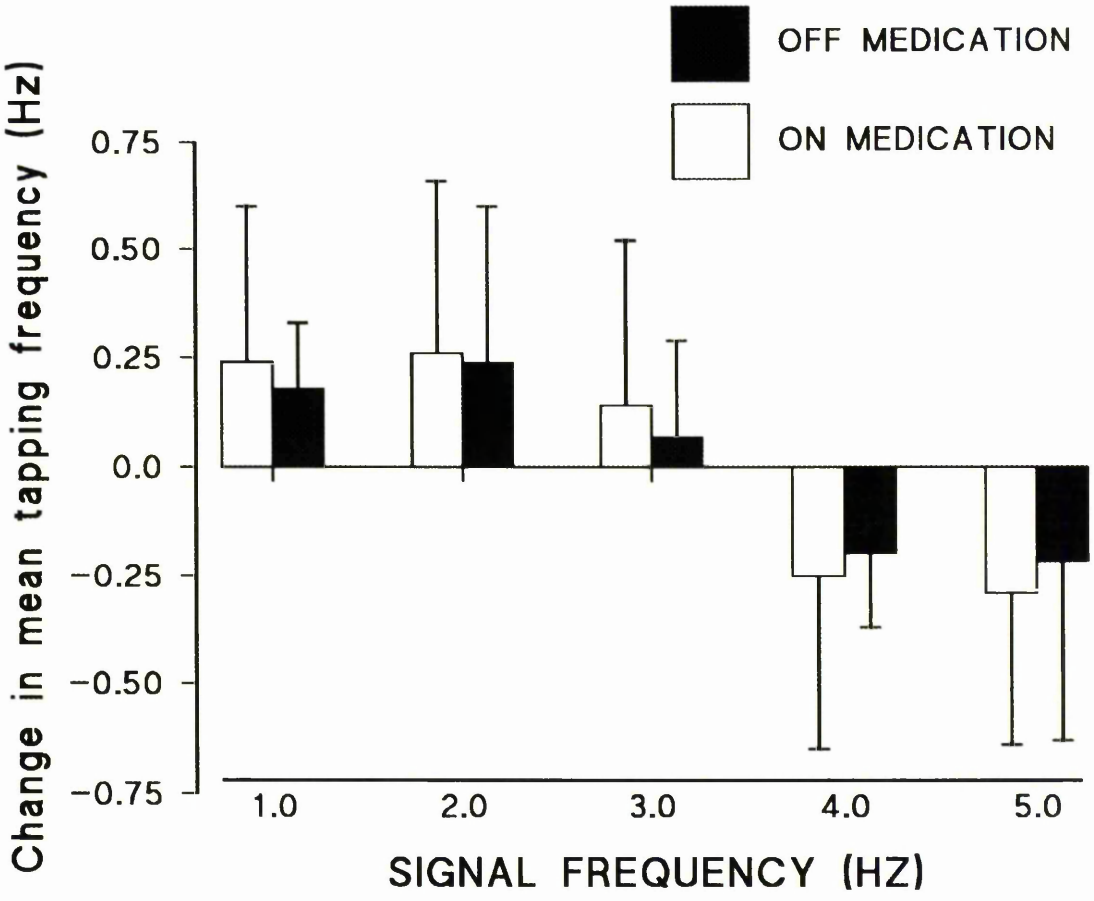

Figure 2.9. Actual changes in mean tapping frequency (Hz) between cued and subsequent uncued periods. Mean (S.D.) group data from 11 PD patients who performed the trials 'on' and 'off' medication is shown. There is no significant difference in the changes in tapping frequency on cue removal between 'on' and 'off' conditions (Wilcoxon).

and subsequent uncued tapping periods. Again, essentially similar results for the PD group to those observed in Figure 2.7 are seen. PD patients became more inaccurate on cue removal, tapping more quickly at lower target rates and more slowly at higher frequencies. However, medication seems to have had little effect on the change in tapping performance on cue removal. Again, there was no significant difference in the change in mean tapping frequency on cue removal at any target frequencies between trials conducted when patients were either 'on' or 'off' their medication ($p > 0.593$, Wilcoxon).

Patients underwent a clinical examination, performed by a neurologist, when 'off' treatment and again, one hour after ingestion of their medication, when they were deemed to be 'on'. Table 2.4 shows the clinical scores for bradykinesia, rigidity and tremor. These were the signs which were likely to be most affected by medication. In all patients, ingestion of a normal dose of their daily medication reduced the overall severity of the three signs ($p = 0.003$, Wilcoxon).

2.3.5. Rhythm generation in HD patients and healthy subjects in the presence of external timing cues.

Figure 2.10 illustrates the tapping behaviour, with the preferred hand, of a healthy individual (A) and a HD patient (B) during 3 Hz target frequency (the middle frequency of the 1-5 Hz range tested) trials. The instantaneous frequency plot of the tapping performance of the control subject indicates that the target rhythm was accurately duplicated both in terms of mean rate and regularity. By contrast, the patient's mean tapping rate (2.2 Hz) fell well below the target frequency. In addition, the patient's tapping rhythm was highly inconsistent. Whilst the majority of taps were of an instantaneous

	OFF			ON		
Init.	Brad	Rigid	Trem	Brad	Rigid	Trem
HB	2	2	1	1	1	0
NK	2	2	2	1	1	1
GR	2	2	0	1	1	0
MY	3	2	3	2	1	1
AC	1	1	0	0	0	0
HV	2	1	1	1	0	1
JF	2	1	1	1	0.5	1
EB	1	1	1	1	0	1
JS	2	2	2	1	2	2
MM	2	3	1	1	2	1
EW	3	1	0	1	0	0

Table 2.4. Clinical gradings for eleven PD patients tested 'on' and 'off' their routine L-dopa medication. The signs were scored using the Webster disability rating scale (Webster, 1967). The three signs shown, bradykinesia (Brad), rigidity (Rigid) and tremor (Trem) were deemed to be most likely to be affected by a single dose of L-dopa. When totalled, the clinical gradings of the three signs were significantly different when 'on' was compared with 'off' ($p=0.003$, Wilcoxon). Further clinical details are given in Table 2.2.

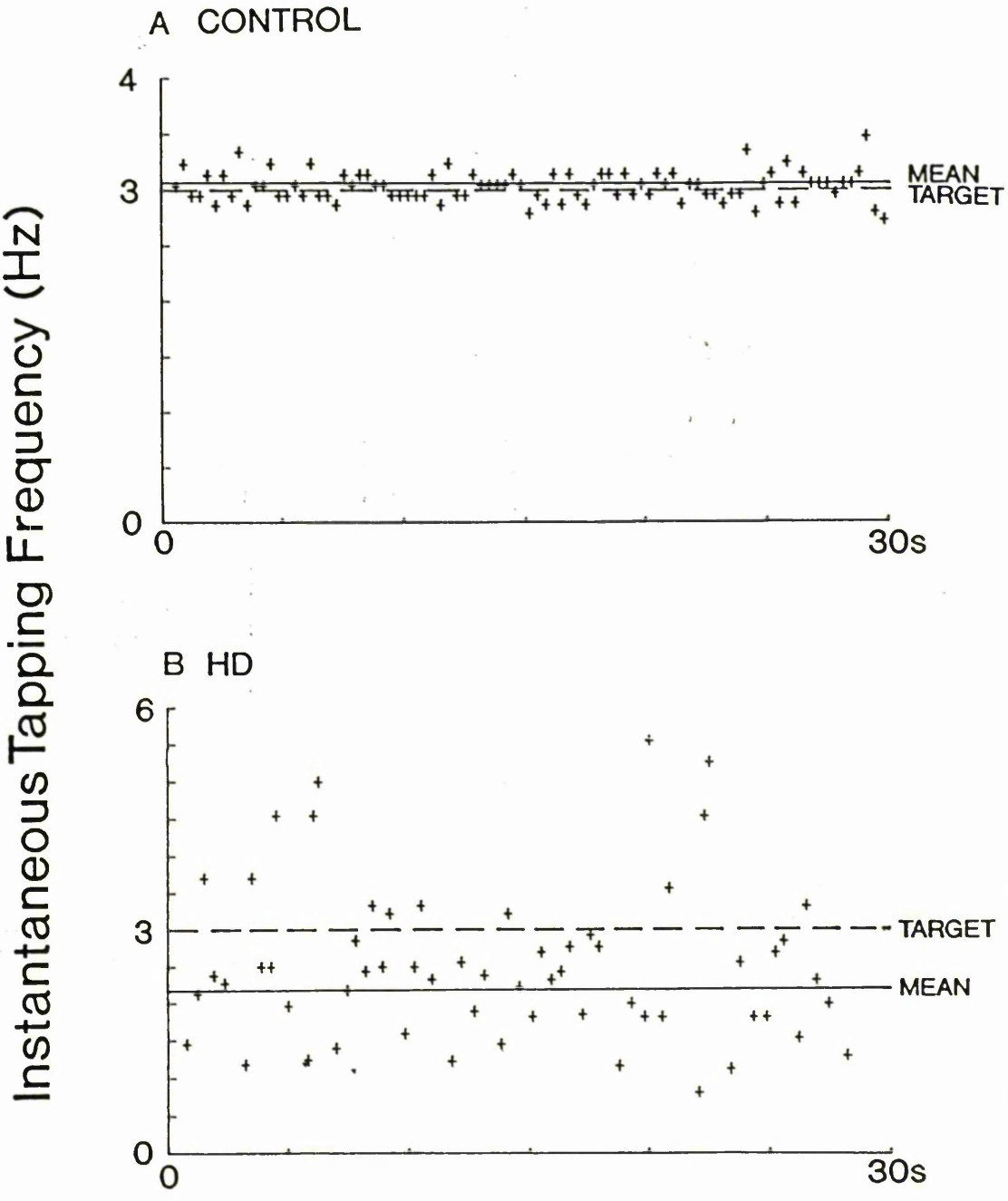

Figure 2.10. Plots of instantaneous frequency for finger tapping in a healthy subject (A) and a HD patient (B) in the continuous presence of 3 Hz auditory signals. Each point represents the occurrence of a single tap. The height of each point indicates its instantaneous frequency in relation to the immediately preceding tap and was calculated from as the reciprocal of the inter-tap interval. The solid horizontal line indicates mean tapping rate over the 30 s trial whilst the dashed horizontal line indicates the target frequency.

frequency of <3 Hz, some very short inter-tap intervals sporadically occurred which produced instantaneous rates of almost 6 Hz. In neither the control subject's nor the HD patient's records is there any indication of a systematic alteration in tapping performance as the trials progressed, such as might result from fatigue or loss of concentration.

Figure 2.11 compares the accuracy with which the tapping behaviour of HD and control subjects matched the rate of external cues over a range (1-5 Hz) of target frequencies. The mean (S.E.M.) tapping rates, recorded over 30 s trials, of each group are plotted. These plots indicate that the HD patients were, on average, less accurate than healthy subjects in generating finger tapping movements which reproduced the cue frequency. This disturbance of tapping behaviour of the HD group was most pronounced at the higher (3-5 Hz) target frequencies. For these target frequencies, the mean tapping rates of the HD group fell well below those of the controls. Statistical analysis confirmed that the patients, as a whole, tapped more slowly than the control group at 3, 4 and 5 Hz cue frequencies (p values, respectively, 0.01, 0.004 and 0.006, Mann-Whitney). By contrast, HD patients tended to tap at a higher rate than healthy subjects at the lowest target frequency (1 Hz), although not significantly so.

The relatively large S.E.M. values associated with the mean tapping rates of the HD group indicate a subsidiary feature, namely, that the tapping performance of individual patients showed a far broader scatter than was observed amongst the control subjects. Thus, at higher cue rates not only did the accuracy of rate tapping of the HD group progressively deteriorate but greater inter-patient differences in behaviour emerged.

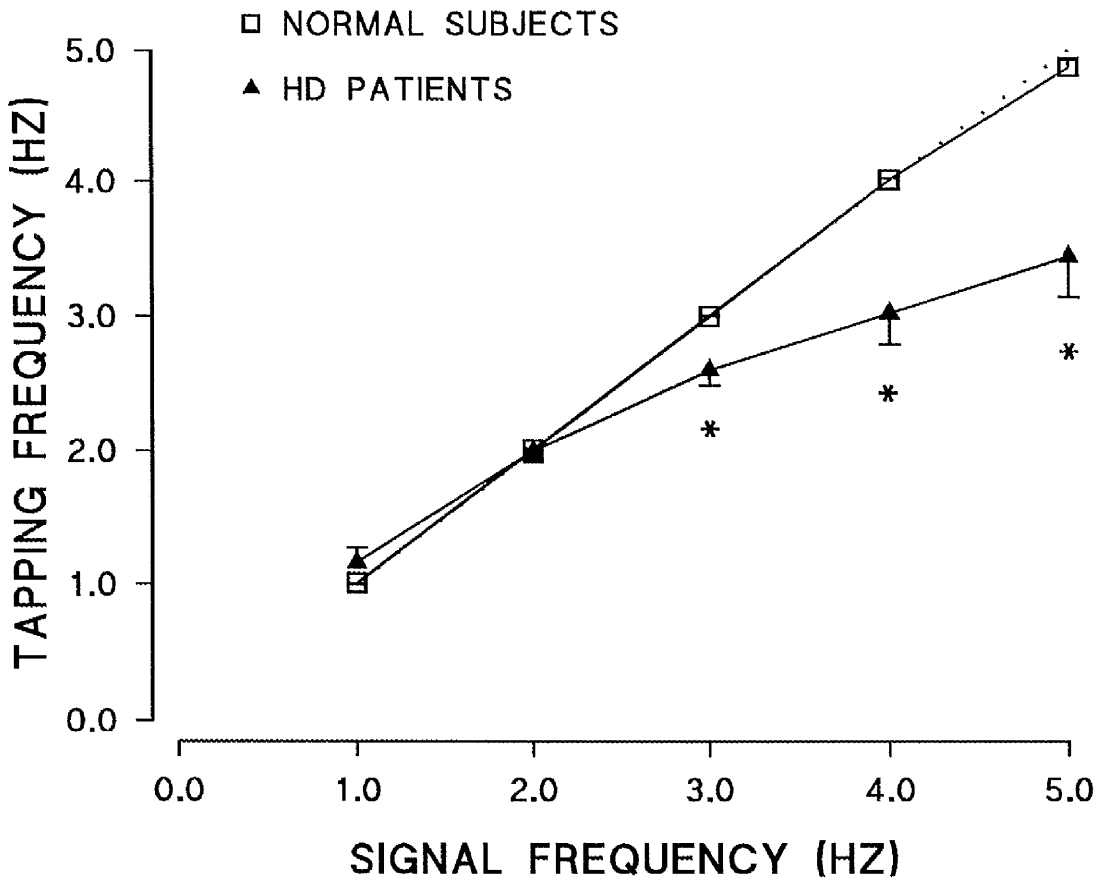

Figure 2.11. The relationship between tapping rate and the frequency of auditory cue signals in 12 healthy subjects and 14 HD patients. Mean (S.E.M.) tapping rates are shown for the group data. The dotted line indicates unity slope. Asterisks indicate statistically significant (* $p < 0.01$, Mann-Whitney) differences between the mean tapping rates of the patient and control groups.

As noted above, the most severe disturbances of HD patients rhythm generation occurred at the 3-5 Hz target frequencies. To test whether their abnormal depression of tapping rates over this range in HD was due to an inability to generate an adequate movement tempo, maximum tapping frequencies (MTF) were determined for individual subjects (see section 2.2.3). The mean (S.E.M.) MTF values of the HD and control groups were, respectively, 4.07 Hz (0.25) and 5.27 Hz (0.08). Statistical analysis indicated that the MTF values of the HD patients were significantly lower than those of healthy subjects ($p<0.01$, Mann-Whitney). The MTF values of individual HD patients were found to be greater than their mean tapping rates at 1-4 Hz cued target frequencies ($p<0.005$ at 1, 2 and 3 Hz, $p=0.009$ at 4 Hz, Wilcoxon). Only at the 5 Hz target, was there no significant difference ($p>0.1$, Wilcoxon) between individual patient's MTF scores and their mean tapping performance.

2.3.6 Rhythm generation by HD patients and healthy subjects in the absence of external timing cues.

Figure 2.12A compares the ability of the HD group to sustain the rate of externally-cued tapping performance following the sudden withdrawal of auditory signals. Removal of timing cues had little obvious effect upon the mean tapping rates of the HD group over the range of target frequencies studied. Statistical analysis confirmed that in the patient group the mean tapping rates significantly differed between cued and uncued conditions at none of the target frequencies ($p>0.360$, Wilcoxon). Again, in the control group, there was no significant difference between performance during the cued and uncued periods ($p>0.493$, Wilcoxon). In addition, Figure 2.12B plots the changes in mean tapping rates which were induced by cue suppression, there was no significant difference between the patient and

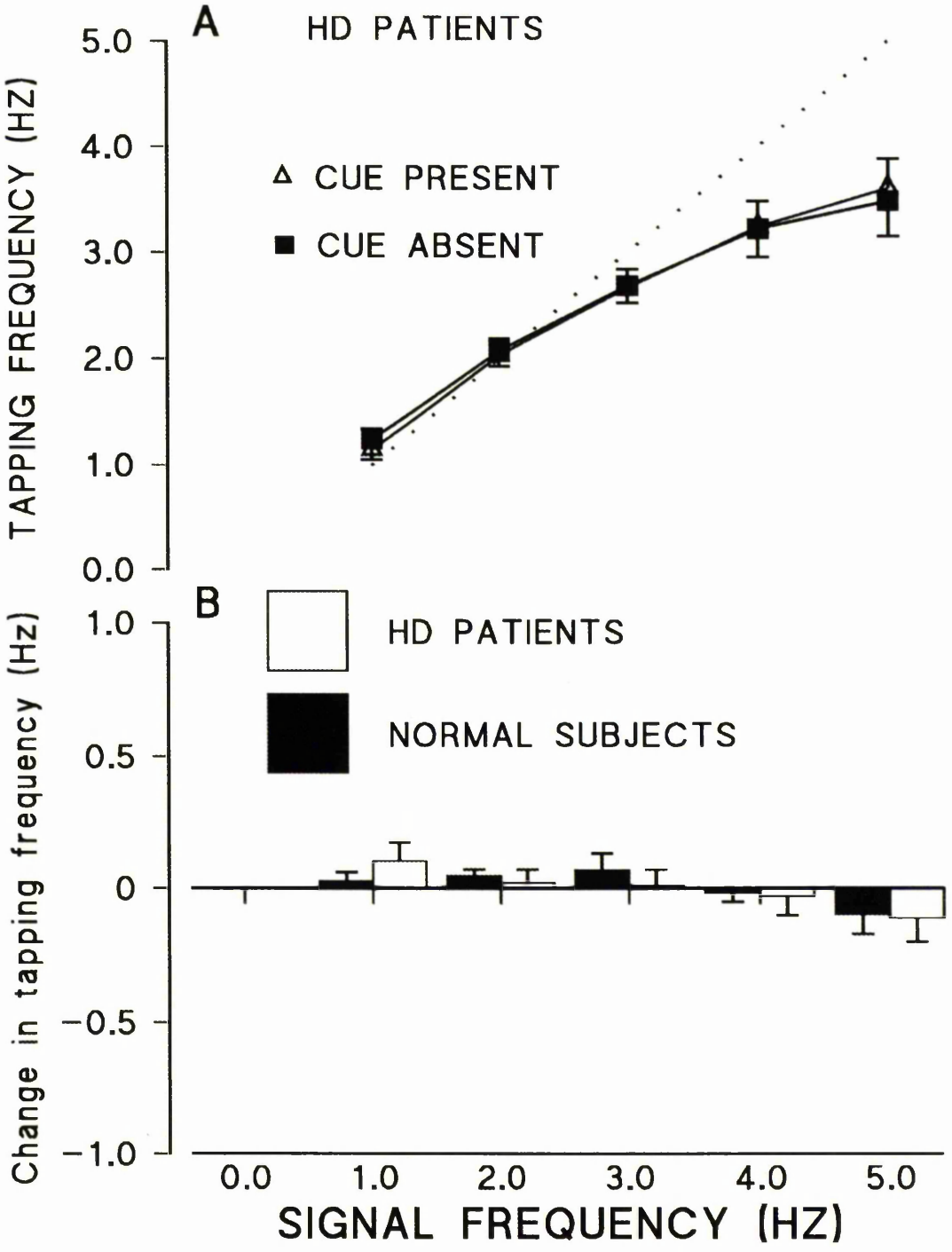

Figure 2.12. **A** shows plots comparing mean tapping rates in the presence and absence of auditory cues for HD patients. Mean (S.E.M.) values are given, with the dotted line indicating unity slope. The mean tapping rates of HD patients was not significantly affected by cue suppression ($p > 0.402$, Wilcoxon). **B** shows actual changes in mean tapping frequency (Hz) between cued and uncued periods. Mean (S.E.M.) group data from 12 healthy subjects and 14 HD patients is shown. There was no significance difference between normal and HD groups at any of the target frequencies (Mann-Whitney).

control groups over the range of cue frequencies studied ($p > 0.402$, Mann-Whitney). Therefore, although the HD patients' mean rate tapping performance was inherently inaccurate at higher signal frequencies (3,4 and 5 Hz), they, like healthy subjects, were well able to maintain established tapping rates in the absence of continuing timing cues.

2.3.7. Relation of impairment of tapping performance to motor deficits in HD.

The slope and y-intercept of the regression line of the relationship between mean tapping rate and cue frequency were calculated for individual patients as measures of their tapping performance (see section 2.2.4). The corresponding regression lines of individual HD patients typically had slopes of < 1 and positive y-intercept values due to a depression of tapping rates at the higher cue frequencies. Generally in the HD group, lower values of slope (and higher y-intercept values) equated with more severe disruptions of tapping accuracy. Slope of the tapping-cue rate regression line was adopted as the best overall index of rate tapping accuracy. The average value of slope of this relationship in the HD group was 0.55 (range -0.11 to 0.96).

Correlations between the patients' rate tapping indices and their scores for other aspects of motor function obtained during standard neurological examination and cognitive testing (see Table 2.3) were tested. No significant correlations were found between tapping indices and the duration of disease ($p > 0.746$, Friedman's Rank correlation), chorea (overall chorea score, $p > 0.618$; chorea score during voluntary movements, $p > 0.492$), bradykinesia (clinical grade, $p > 0.400$; card sort time, $p > 0.301$) or rapid finger movements (clinical score for finger-thumb movements, $p > 0.373$). None of the patients showed clinical rigidity and only two had clinical tremor, which in both cases was mild.

CHAPTER 2.4: DISCUSSION.

The ability of healthy subjects and patients with either PD or HD to produce finger tapping movements in synchrony and after removal of auditory cues have been reported in this chapter. Subjects' performance was measured using mean tapping frequency (average taps per second) as the calculated parameter. Semjen (1992) postulated that subjects were most likely to use 'overall speed' of mean tapping frequency to consciously monitor and correct tapping performance during a trial. Mean tapping frequency was therefore taken as the starting point to study the role of the basal ganglia in the control of repetitive movement.

The present findings demonstrate that the ability of PD patients to generate simple, rhythmic voluntary movements is impaired in two distinct respects. First, and in agreement with previous studies (Nakamura *et al*, 1976, 1978; Nagasaki *et al*, 1978), patients are less able than healthy subjects to synchronise accurately their movements to extrinsic timing cues. Secondly, the patients exhibit a greater reliance on the external cues for rhythm formation, as removal of the cues causes further deterioration of mean tapping frequencies. Thus, in PD there appears to be a deficit of external guidance coexisting with a probably more fundamental derangement of internal sequence generation for stereotyped, repetitive, voluntary movements. This is evidence for the general conclusion from numerous studies of more complex motor tasks, that central programming is disrupted in PD (see 1.3.4.; Flowers, 1978; Stern *et al*, 1983; Bloxham *et al*, 1984; Day *et al*, 1984; Benecke *et al*, 1987a; Sheridan *et al*, 1987; Stelmach & Teulings, 1987). The present study shows that routine medication has little effect on the ability to produce mean tapping frequencies. L-dopa did not improve the ability to synchronise finger taps with auditory cues or enhance

the tapping performance on removal of the cues.

The present observations indicate that in HD two principal disturbances of repetitive movement generation exist, as exemplified by the ability to generate mean tapping frequencies. Firstly, HD patients show an impaired ability to replicate the mean rate of externally-cued rhythms over the range 3-5 Hz. Secondly, HD patients are unable to utilise the external cues to improve their tapping performance. Removal of the external cues causes no further deterioration in mean tapping frequencies. These findings raise questions firstly, concerning the neural origin of deficits of repetitive movement in HD and secondly, whether comparison of the different patterns of rhythm disruption in HD and PD provides new clues to how the basal ganglia contribute to motor timing.

2.4.1. Abnormalities of synchronisation of movements to external cues in PD.

The findings of the present study generally confirm earlier observations of Nagasaki *et al* (1978) for finger tapping and Logigian *et al* (1991), for repetitive isometric contractions of finger muscles, that PD patients show two separate types of synchronisation abnormalities. The first is an elevation in tempo at low to intermediate target frequencies (1-3 Hz) and the second a depression of mean tapping frequency at the 5 Hz target frequency.

The present results differ from those of Nakamura and colleagues in one respect. These authors placed considerable emphasis on the "hastening phenomenon" in PD. This was characterised by a clear-cut transition frequency at either 2 or 4 Hz, at which the mean tapping frequency suddenly jumped to a new plateau level of 5-6 Hz which was

independent of cue frequency. In only one hand in two different individuals from the 23 patients (i.e. 2/46 possible occasions or 4.3%) was such well developed hastening observed. Instead, a less pronounced form of increased mean tapping frequencies was more commonly observed which lacked clear transition and plateau phases.

A straightforward explanation to the reason why PD patients show a decrease in mean tapping frequency at the 5 Hz target is bradykinesia, since slowness of movement is a common feature in PD. The possibility that an inherent inability of some of the patients to maintain an adequate pace of movement contributed to their synchronisation errors for the 5 Hz target cannot be excluded. However, all of the four patients who produced mean tapping frequencies which exceeded 5 Hz showed significant signs of bradykinesia on clinical examination. There was no correlation between tapping indices (the slope of the tapping-cue rate regression line) and clinical score for bradykinesia. Similarly, bradykinesia would not explain the increased mean tapping frequencies at the low and intermediate target frequencies. Thus, slowness of movement was not a universal limiting factor in the PD group and a more basic synchronisation deficit was probably responsible.

2.4.2. Dependence of PD patients on external cues for rhythm formation.

One of the main new findings work reported in this chapter is that mean tapping frequencies of PD patients deteriorates following withdrawal of external timing cues. Tapping rates increased for low to intermediate frequencies and decreased for high target frequencies. These changes correspond to an exaggeration of pre-existing patterns of inaccuracies found in the presence of timing cues.

PD patients' increased dependence on external timing cues for generation of mean tapping frequencies may be broadly interpreted as an inherent deficit of internal guidance of movement. Psychophysical models of repetitive movement generation by the nervous system comprise two conceptually distinct elements, namely an internal timekeeper or oscillator component and an implementation or effector component (Wing & Kristofferson, 1973). It should be noted that this model is derived from movements after the external cue has been removed (i.e. self-paced) but conceptually the two components of the model must still exist in some form during cued periods. It can be argued from a simple, conceptual standpoint that although movement implementation itself is abnormal in PD (tremor, bradykinesia and rigidity will cause inaccuracies in this system), inaccuracies of repetitive movement arising from this source are likely to occur equally in both the presence and absence of external timing cues. The increased dependence of PD patients on the external timing cues for formation of repetitive movements, therefore, argues strongly in favour of a deficit of internal timekeeping. Since, healthy subjects are able to generate motor programmes for ongoing repetitive movements by extrapolating temporal parameters from previously similar movements (Schmidt *et al*, 1979), this capacity must be assumed to be impaired in PD.

On quite separate grounds, Nakamura and colleagues have also proposed a disturbance in internal rhythm generation in PD. The authors suggest that an intrinsic oscillation at a frequency of 5-6 Hz occurs within the healthy nervous system, which is unmasked in PD and leads to a convergence of rhythmic movements towards this rate. In addition, such hastening in PD was seen as being relatively independent of external timing cues. As already stated, definite signs of such a convergence were very rarely observed in the

present study. Mechanical factors, such as the resonant frequency of the wrist, being important in determining tapping performance also seem to be ruled out by this finding. Pure 'hastening' to 5 Hz could possibly be an extreme form of dysfunction of rhythm formation found in relatively few patients. It was noted that whilst the removal of external cues caused a clear deterioration in the tapping performance of the PD group as a whole, there was relatively little effect in the two patients who did show classic 'hastening' in the presence of the cues.

2.4.3. Relation of abnormalities in production of mean tapping frequencies to other motor symptoms in PD.

Tremor is a common feature of PD (see 1.2.1), occurring at frequencies of 4-6 Hz (Findley *et al*, 1981) and is believed to result from oscillatory discharges of neurones in the ventrolateral thalamus (Alberts, 1972; Lee & Stein, 1981). Logigian *et al* (1991) have proposed that in PD the neural oscillators for repetitive voluntary movement and for tremor become synchronised. The general tendency for our patients' mean tapping frequency to shift towards the PD tremor band (and to shift closer to this band on cue removal) is consistent with this "attractor theory". However, in the present study, none of the patients showed a dominant frequency in their tapping behaviour such as would be expected if a powerful entrainment occurred. More importantly, there was no correlation between tapping indices and tremor, when tremor was either defined as a clinical score or as peak frequency of postural tremor. In addition, clear instances of deficits in mean tapping frequencies were seen in patients lacking appreciable tremor. This echoes the finding of Narabayashi & Nakamura (1985) that disturbances of repetitive tapping persist in PD patients following alleviation of tremor (amongst other symptoms) by medication

or surgical thalamotomy. Therefore, while the tapping performance of our patients was presumably influenced to some extent by coexisting tremor (and its pathological neural generator), the balance of evidence favours a more fundamental disruption of an independent internal oscillator for repetitive voluntary movement.

As discussed earlier, slowness of voluntary movement does not appear to be responsible for inaccuracies of repetitive tapping movements in PD. Equally there was no correlation between tapping indices and the clinical score of bradykinesia. Similarly, inability to produce accurate mean tapping frequencies in PD patients seem unlikely to be due to rigidity. There was no correlation between tapping indices and the clinical scores for this symptom.

Nakamura *et al* (1976, 1978) regarded the hastening phenomenon they observed in rhythmic finger tapping to be closely related to PD freezing. A relationship between hastening and freezing is also suggested by the observation that PD patients often show a freeze-release-hasten-freeze cycle in gait and speech in which, for example, freezing episodes in walking are immediately preceded by a quickening of pace and shortening of step (Ward, 1991). However, in the present experiment it was found that there was no correlation between tapping indices and either the amount of freezing reported by the patients or the clinical score for gait. Two patients showed hastening in the form of that described by Nakamura, one patient reported daily instances of freezing, the other reported that freezing never occurred. Therefore, the evidence is inconclusive as to whether some common pathological process predisposes to disturbances of rhythmic hand movements and freezing in PD. It would be premature to assume a single causative mechanism.

2.4.4. The effect of L-dopa on the mean tapping frequencies of PD patients.

The present study shows that L-dopa has little effect on the ability of PD patients to synchronise mean tapping frequencies with external cues. Also, L-dopa, does not stop the deterioration in mean tapping frequency on cue removal. The medication, however, did improve all patients clinical scores for bradykinesia, tremor and rigidity.

Previous workers have found that L-dopa medication does improve patients' ability to perform motor tasks. Girotti *et al* (1986) noted obvious changes in patient motor status in the 'on-off' stages of PD, with a significant lengthening of movement time in the 'off' stage, even though reaction time remained unaffected. Velasco & Velasco (1973) demonstrated the efficacy of L-dopa in the amelioration of programming and execution of ballistic movements. Benecke *et al* (1987b) showed that during the 'off' stage, patients produced slower movements on a simple task and this deficit was magnified on performance of a complex task. These results were thought to "reflect general bradykinesia and akinesia". It seems that L-dopa facilitates movements simply by reducing levels of bradykinesia, rigidity and tremor. Why, therefore, does L-dopa have such little effect on the generation of mean tapping frequencies?

Work has been performed on the effect of medication on rhythm regulation and motor function. Karlsson *et al* (1992) observed that medication enhanced the performance of rhythmic jaw movements in PD patients. However, they postulated that parts of the masticatory cycle and not the fundamental rhythmical pattern were affected by dopamine transmission. It was reported by Narabayashi & Nakamura (1985) that L-dopa had no beneficial effect on freezing in PD, and often makes the condition worse, while it had little

effect on patients who showed 'hastening'. Kanazawa (1986) noted that freezing continued in patients whose other symptoms (rigidity, tremor and akinesia) had been successfully treated with L-dopa. If PD freezing is a breakdown in rhythm generation (see 2.1.2) and finger tapping is a valid means of investigating rhythm generation, then it may be expected that abnormal tapping performance would be unaffected the absence of L-dopa.

As L-dopa reduces the severity of motor symptoms in the PD patients, it would seem that its' ineffectiveness at facilitating mean tapping frequency production is further evidence for tapping abnormalities in PD to be due derangement of an internal 'clock' or neural oscillator. L-dopa reduces motor symptoms in PD but does not alleviate the underlying pathological dysfunction (see 1.2.2). It may be that abnormalities of mean tapping frequency formation are similar to the negative symptoms and, therefore, more central to the pathology of PD than motor signs such as tremor or rigidity, which Marsden (1982) defined as being positive symptoms (see 1.2.1.)

2.4.5. Origin of impairment of rhythmic movement in HD.

As stated in 2.4.2, current theories of repetitive movement production propose a two-process model comprising a central neural timekeeper or oscillator which sets the basic tempo and an effector system which implements the movements (Wing & Kristofferson, 1973). Disturbances of either or both components could produce impairments of rate. Thus, there are two sorts of potential explanation of the observed abnormalities of finger tapping performance in HD. One possibility is that they result from a primary malfunction of an internal, neural rhythm generator. Alternatively, they might simply represent secondary consequences of other motor deficits e.g. bradykinesia, rigidity, chorea or

tremor.

Thus, the first issue is whether the abnormal depression of mean tapping rates of our HD patients at target frequencies of 3-5 Hz was due to bradykinesia since slowing of finger (Hefter *et al,* 1987) and wrist (Thompson *et al,* 1988) movements in the disease is well established. In keeping with these reports, it was found that the maximum tapping frequencies of our patients were significantly below those of control subjects. None of the patients exhibited clinical rigidity confirming the view of Hefter *et al* (1987) that slowing of movement in HD is not due to abnormalities of tone. Although the HD patients were bradykinetic, observations, both on a group and individual basis, indicated that their mean tapping rates at targets of 3 and 4 Hz were substantially lower than their maximum tapping frequencies. Thus, it seems highly unlikely that slowness of movement was limiting patients' performance at these target frequencies. The situation for the 5 Hz target is less clear. The patients' maximum tapping rates were, on average, less than 5 Hz and in many individuals an inability to achieve an adequate tempo probably prevented their attaining the target frequency. Nevertheless, on average group basis, the actual mean rate achieved was still far short of maximal capability whilst most individuals had maximal tapping frequencies appreciably in excess of their 5 Hz test scores. In addition, sporadic groups of high frequency taps (see Figure 2.11) featured in many patients records. These factors suggest that even at the highest target some factor other than slowness *per se* was acting to suppress patients' tapping rates. Furthermore, considering individual patient's tapping performance over the entire range (1-5 Hz) of target frequencies, there was no association between indices of tapping performance and clinical bradykinesia rating or card sorting time (see Table 2.3).

Chorea is often the most obvious motor sign in HD (Hayden, 1981) and might plausibly interact with voluntary movement to influence patients' tapping behaviour. Single choreiform movements, although differing in form, are usually slow (<2 Hz) and occur at well-spaced, randomly-timed intervals (Wilson, 1925; Hallett and Kaufman, 1981; Marsden *et al,* 1983b; Hefter *et al,* 1987). These considerations, combined with a lack of correlation between individual patients' clinical chorea scores and either their measures of mean tapping accuracy or variability, argue against involuntary choreiform movements having markedly interfered with tapping performance. Equally, we doubt that tremor appreciably modified HD patients' tapping rhythms. Although a downward shift in the peak frequency of physiological tremor to ca. 6 Hz has been reported in HD, amplitude seems largely unaffected (Hefter *et al,* 1987) and pronounced, pathological tremor is not generally regarded as a characteristic feature of the disease. Indeed, only two of our patient sample had an abnormal clinical tremor grading and in both of these cases tremor was scored as 'mild'.

Hence there appears to be a motor programming defect in HD which produces profound disruption of rate and regularity of finger tapping over and above that readily explicable by difficulties in movement implementation. This may be representing a disturbance of neural timekeeping due to slow and unstable running of a central rhythm generator.

2.4.6. Comparison of deficits in mean frequency production in HD and PD.

Comparison of the present novel findings in HD with those for PD indicates that both similarities and dissimilarities exist regarding the patterns of disruption of rhythmic finger tapping in these two related diseases. Both patient groups show an inability to accurately

replicate the rate of auditory cues, in the range 1-5Hz, by tapping movements. However, whereas in HD the sole form of error of mean rate was abnormal depression of tapping tempo at 3-5Hz cue frequencies, PD patients tended to tap too rapidly at <3 Hz targets and too slowly at targets of 5Hz and above (Nakamura *et al,* 1978; see section 2.4.1.).

Parkinsonian tremor is believed to be associated with abnormal, cyclic discharge of neurones in the ventrolateral thalamus (Alberts, 1972), and although strict analogies between tremorogenic mechanisms and disorders of rhythmic voluntary movements are unlikely to be valid, some common features probably exist. Such oscillatory firing of thalamic neurones presumably arises, in part, from the enhancement of pallido-thalamic inhibition which is thought to be the major consequence of nigro-striatal degeneration in PD (see 1.1.4 and De Long, 1990). However, whilst parkinsonian tremor is often abolished by thalamotomy, it is rarely alleviated by surgical lesions of the globus pallidus alone (Stein, 1982). This suggests that other modulatory influences, e.g. from the cerebellar dentate nucleus, are crucial in controlling the firing patterns of thalamic neurones and that an imbalance may predispose towards abnormal cyclic movements. Thus, increased pallido-thalamic inhibition in PD may favour hastening of rhythmic movements. Conversely, the faltering of HD patients' tapping, which was far more pronounced and regularly found than in PD, may reflect a suppression of pallido-thalamic inhibition. Such a disinhibition of thalamic neurones is predicted to result from a loss of striatal output neurones in early HD (De Long, 1990).

The present results in both PD and HD patients, in combination with earlier findings in PD (Nakamura *et al,* 1978; Nagasaki *et al,* 1978; Keele and Ivry, 1987), lead to the

general conclusion that lesions of the basal ganglia disrupt the normal running of an internal clock for rhythmic movements. It remains uncertain, however, whether this effect is direct or indirect. Case studies reported by Keele and Ivry (1987) indicate that damage to the cortex, basal ganglia and cerebellum can all produce deficits of rhythm generation. Thus, an interactive loop involving these structures, and possibly with a common relay in the ventrolateral thalamus, may be suspected.

Although distinguishing patterns of cued-tapping deficits were found in HD and PD, the most striking difference in tapping behaviour between the two diseases concerned the influence of external timing signals. The present results show that removal of cues had rather little effect on the, albeit imprecise, tapping rates of HD patients. By contrast, cue withdrawal elicited a profound, further deterioration in the accuracy of PD individuals.

The normal role of external cues in timekeeper regulation is equivocal. The ability of healthy subjects accurately to sustain mean tapping rates following cue withdrawal favours the clock having an effective 'memory', whilst the experiments of Wing (1977b) suggest that individual cue signals are not employed to correct the duration of the immediately succeeding inter-tap interval. Thus, the lack of influence of timing cues in HD might seem to correspond to 'normal' behaviour and the reliance on cues found in PD to represent a departure. It remains quite conceivable, however, that the intact CNS utilises cues when available but that they exert minimal detectable effect if the clock itself is inherently accurate. From this perspective, HD patients have a more profound deficit of rhythm control than do parkinsonians. In any event, the ability of PD patients continuously to employ external timing cues to modulate or reinforce their tapping rhythms allows them

to improve their inherently poor performance in a manner which HD patients do not.

Impairment of cognitive functions is a major sign of HD (Bruyn, 1968), which is evident for perceptual-motor and attention tests (Girotti *et al,* 1988). Thus, the failure of HD patients to benefit from continuous auditory pacing cues in regulating tapping rhythms may result from a relatively more severe disturbance of cognitive function in HD than PD. However, both patient groups were able to utilise external cues of differing target frequencies to establish tapping rates which, although often imprecise, were in an appropriate rank order. This implies an understanding of the task and an ability to recognise and extract basic temporal parameters from the cue sequences. Thus, whilst difficulties in processing auditory cue information cannot be discounted in HD, other factors must be considered. A possible clue lies in the common clinical observation that HD patients, unlike parkinsonians, are often unaware of their own involuntary movements and impaired voluntary performance (Hayden, 1981). Therefore, HD patients may be less capable of synthesising an adequate, temporal profile of their actual movements, from proprioceptive feedback or corollary discharges, to serve as a template against which extrinsic cues might be compared. Evidence of reduced cortical somatosensory evoked potentials (Ehle *et al,* 1984; Bollen *et al,* 1985; Thompson *et al,* 1988; Abbruzzese *et al,* 1990) and long-latency stretch reflexes (Noth *et al,* 1983; Thompson *et al,* 1988) in HD indicates an impairment in central processing of proprioceptive inflow which is compatible with this idea.

2.4.7. Conclusions.

The results presented in this chapter suggest deficits in the production of mean tapping

frequency in both the presence and absence of external stimuli in the form of auditory cues in patients with basal ganglia dysfunction. These deficits appeared to be more functionally deranged in patients with HD, as PD patients were able to utilise the external cues to attain some degree of synchronicity and, therefore, improve the accuracy of the mean frequency produced. These findings are interesting as a novel piece of research in quantifying defects of motor timing in basal ganglia disorders, but do not resolve the actual nature of source of the timing deficit.

Numerous workers have suggested that a structure which would act as a 'clock' within the CNS (for review, see Keele and Ivry, 1987). It seems plausible that this clock will have an important role in mean frequency production, as the variable which produces changes in mean frequency is the *time* between two successive intervals. This is slightly different from *variability* within sets of intervals (which has not been measured in the experiments in this chapter). Variability may arise in an inherent inability in the clock structure to produce similar intervals, and therefore an accurate speed or, from fluctuations in the precision of the system which produces a response.

The results shown in this chapter may be explained by a number of deficits. Patients with basal ganglia disorders are known to have certain deficits of motor programming so that there may be problems in the execution of each finger tap, although workers have found that simple movements (e.g. a finger tap) are programmed relatively normally (see 1.3.4.iii; Rafal *et al*, 1987). Motor planning is thought to be impaired in PD (Marsden, 1982) so that the production of a *series* of finger taps may be inefficient. What is not known, is whether this inefficiency would be in producing a set of temporally ordered

movements in the correct sequence or in the timing aspects of this sequence. The former would seem to have less relevance because the sequencing is of less importance as all the movements are the same and force and spatial accuracy demands during the task have been kept to a minimum. This would lead me to suggest that the timing of the set of finger movements is impaired in patients with basal ganglia disorders. However, this is speculation with no direct evidence for such a theory. What is needed is a method of studying the cause of these deficits in motor timing. How would this cause encompass what is already known about basal ganglia anatomy?

In order to perform experiments to find answers to the above questions, I feel it is necessary to dissociate finger tapping in the presence of auditory cues from that in the absence of the cues. Initially, it may be perceived that tapping in the presence of cues is a more simple task than tapping without the aid of external stimuli. However, tapping in the presence of cues could be construed as adding the task demand of synchronisation. Not only do subjects have to generate mean tapping speeds, or mean intervals, which are accurate but they have synchronise them with the auditory tones. This adds another parameter to the internal clock, that is, the timing of the tapping series in relation to the metronome series as opposed to the timing of each discrete motor act. Although PD and HD patients have deficits in both tasks, it can be argued that inabilities to produce mean tapping frequencies in the absence of external cues, albeit after a period of synchronisation, is the more fundamental deficit.

Therefore, the next set of experiments have been designed to study the cause of deficits of motor timing in PD and HD patients in the continuation (uncued) phase of similar

tapping tasks. To do this I have analysed data using Wing and Kristofferson's (1973) influential model for the control of repetitive movements. It is supposed, within the model, that the production of unpaced finger taps is controlled by two hypothetical processes; a clock or timekeeper which determines when a response should be made, and an implementation system which executes the response. Variability within a series of inter-tap intervals can be attributed to either of these processes. Therefore, this may provide more direct (if the model is valid and applicable to the study of basal ganglia disorders) evidence as to the nature of deficits in motor timing in PD and HD patients.

CHAPTER 3: THE ANALYSIS OF MOTOR TIMING DURING THE CONTINUATION PHASE USING WING AND KRISTOFFERSON'S (1973) MODEL FOR THE CONTROL OF REPETITIVE MOVEMENTS.

CHAPTER 3.1: INTRODUCTION.

3.1.1. Wing and Kristofferson's (1973) model for timing of repetitive movements.

This chapter presents a detailed study of the source of the deficit in motor timing in patients with PD and HD using Wing and Kristofferson's (1973) psychophysical model for the control of repetitive movements. In the last twenty years, the model has been influential in the understanding of motor timing. However, until five or six years ago the model was confined to experimental psychology; since then neurophysiologists have tried to map the mysterious 'timekeeper' aspect of the model on to structures within the CNS. The logic used, similar to that used throughout this thesis, was that differences in performance between control subjects and patients with neurological disorders must be due to the abnormal functioning of the lesioned structure, and as a corollary this structure would be implicated in normal motor timing.

The model is primarily concerned with the underlying statistical structure of a series of unpaced repetitive movements (usually finger taps), during a task involving two sequential and continuous phases. Subjects are asked to tap in synchrony with a series of metronome beats ('synchronisation' phase) and continue to reproduce the metronome interval on cessation of these external cues ('continuation phase'). Analysis using the assumptions of the model is only applicable during the latter unpaced phase, and by definition is not valid during cued movements. Also, analysis using the model is centred on the variability within a series of inter-response intervals; mean intervals or mean tapping frequency are peripheral to the central analysis.

3.1.2. Basic assumptions of the model.

The advanced analysis of the continuation phase of the tapping data collected in experiments reported in this chapter, was based on the theoretical model for the timing of repetitive movements developed by Wing and Kristofferson (1973). The basic assumption of the model is the supposition that there are two processes which are involved in endogenously-timed, repetitive movements. One of the processes functions as a timing device, a clock or timekeeper, determining when a response should occur. The clock, having been more or less accurately-entrained to the frequency of the pacing cues, subsequently ticks, with successive clock-intervals (C_j, with mean μ_C), which are subject to random temporal variation (σ^2_C). However, this process requires a second process as determining the response is not sufficient to execute the response. This second process is deemed to be the implementation system and actually produces the motor response. The implementation system includes all the processes which are involved in activating the central control signal, and, peripheral processes involved in control of the appropriate effector. Thus, there is a delay between the instruction being given and the response being produced; the time it takes the implementation system to execute the timekeeper command, the motor delay (D_j, with mean μ_D), is itself subject to independent random temporal variation (σ^2_D).

The Wing and Kristofferson model postulates that during a series of finger taps, the variability of the inter-response-intervals (IRIs) will arise from variability in both the central timekeeper and the motor implementation system. In other words, the total variability observed during a repetitive movement task represents the independent contribution of the two independent sources; random variation in the timing mechanism

which signals when a response should be initiated and the variability in the implementation system which executes the motor command. The model assumes that each process behaves as an independent random variable with normal variance. The model further assumes that these two processes operate independently of each other. The central timekeeper or clock determines when a response should be initiated, but has no knowledge of whether the motor implementation system has faithfully executed the command. Similarly, the implementation system cannot perceive the accuracy of the clock since this would require both systems to have timing capabilities. These assumptions promote the concept that the system operates on an open-loop (feedback-free) mode (see 1.3.3.ii). Therefore, the duration of a clock interval and the duration for the impending implementation delay associated with that clock interval are assumed to be independently determined for each IRI.

It is possible, therefore, to decompose total variability (TV) within a repetitive motor task, using the principles of the Wing and Kristofferson model, into that which is attributable to variability derived from the central timekeeper system (clock variance - CV) and that which can be derived from the motor implementation system (motor implementation system variance - MISV) from variability in the motor delay intervals.

3.1.3. Decomposition of variability by calculation.

Figure 3.1 depicts the two underlying processes in the Wing and Kristofferson model in two sets of hypothetical series of timekeeper signals and their associated responses. In Figure 3.1A the variability of the timekeeper is zero. Each IRI is the sum of a timekeeper interval plus the differences in delays due to the motor implementation system associated

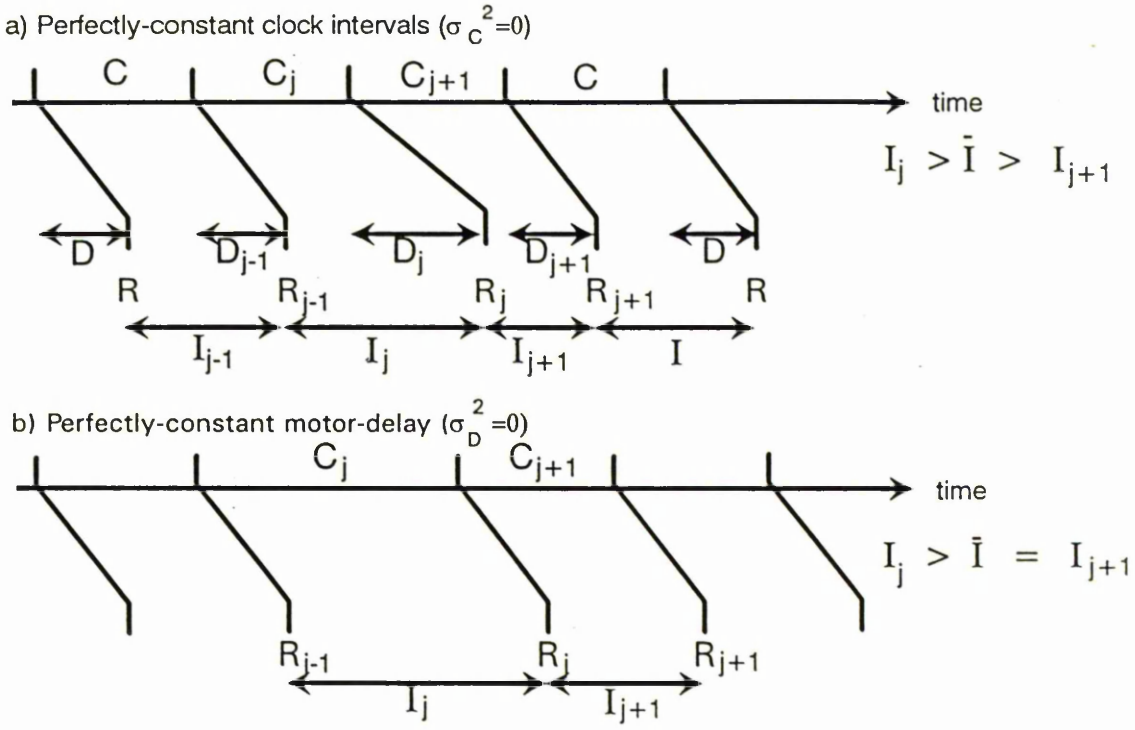

Figure 3.1. Schematic depiction of Wing and Kristofferson's (1973) model, in which C represents a clock interval, D an implementation delay, R the time occurrence of a response and I a response interval. In Panel A is shown a hypothetical situation in which associated with one of a series perfectly-accurate clock pulses there occurs one randomly-long implementation delay (D_j), resulting in a long (relative to the mean) associated response interval (I_j). As the clock and the motor implementation systems are assumed to be independent, this necessarily results in the following interval (I_{j+1}) being short (relative to the mean). That is to say, random variation in motor-delays will tend to produce negative covariation between successive response intervals. Such negative covariation between successive response intervals does not necessarily result from random variation in successive clock intervals (Panel B).

with the initiation and termination of that response interval. The duration of a response interval, j, can be calculated from the following equation.

$$I_j = C_j + D_j - D_{j-1} \quad \text{.....(equation 1).}$$

where *I*, *C* and *D* symbolise the interval, clock and motor implementation delay durations, respectively. Since, as the model assumes, the two sources of variance are independent the following equation applies;

$$\sigma^2_I = \sigma^2_C + 2\sigma^2_D \quad \text{.....(equation2).}$$

σ^2_I (or TV) can be directly obtained from the subject's data and is simply the variance of all the responses around the subject's generated mean interval. The central principle underlying the Wing and Kristofferson model is, assuming the validity of the assumptions, that both sources of variance (i.e. that attributable to the central clock and that attributable to the motor implementation system) can be estimated from the autocovariance function of the series of responses. As shown in Figure 3.1A a randomly large motor implementation delay will propagate both a long preceding response interval and a short succeeding response interval (as shown by I_j and I_{j+1} in Figure 3.1A). Therefore, if there is an increase in σ^2_D (MISV) there will be an increase in negative covariance at successive intervals, that is, negative lag one autocovariance. The magnitude of this variance serves to estimate MISV.

It should be noted that although the hypothetical process shown in Figure 3.1A may appear

to be a corrective process it is actually the result of the independence between timekeeper and the implementation system, as, during the long motor implementation delay the clock signal for the next interval will already be running. Although the two *variances* are independent of each other, it is not strictly true that the two *processes* are completely independent. While the clock is indeed completely independent of the implementation system, initiation of a response relies entirely upon a command given by the clock. This one-way dependence is the reason for variation in the motor implementation system producing negative covariation of successive intervals.

Figure 3.1B shows a series of responses in which there is only inaccuracy in the central clock system (i.e. $\sigma^2_D = 0$); it can be seen that there is no similar dependency between successive intervals. Therefore, variance attributable to the clock does not cause negative covariation at successive intervals. These observations allow calculations to be made to decompose total variability during a finger tapping task into that attributable to the two processes which the model assumes underlie repetitive movements. An estimate of σ^2_D can be obtained from the lag-one autocovariance function (in the present analysis, the autocovariance was calculated using equation 5 in section 3.2.6ii);

$$-\text{autocov}(1) = \sigma^2_D \quad \text{.....(equation3)}$$

By making the appropriate substitution in equation 2, σ^2_C (CV) can now be calculated. Therefore, estimates for the two supposedly independent processes are not calculated independently.

3.1.4. Autocorrelation.

Some workers report lag-one auto*correlation* instead of lag-one autocovariance. The lag-one autocorrelation (see Wing and Kristofferson, 1973) is given by the following equation, assuming that, according to the model, the two processes (C and D) are mutually independent for all j, and that the jth inter-response interval is given by equation 7. According to the assumptions of the model, the value of this function is bound between 0 and -0.5. Positive lag-one covariance will be associated with positive functions of the values of the function, and negative clock variance with values of less than -0.5, as shown in equation 4.

$$p(1)=\frac{\gamma_I(1)}{\gamma_I(0)}=-\frac{1}{2+\frac{\sigma_C^2}{\sigma_D^2}}$$

(equation 4)

where p is autocorrelation and γ is autocovariance.

3.1.5. Evidence for the validity of the model.

Evidence for the validity of Wing and Kristofferson's two process model has been received from three important experimental paradigms. There are several predictions of fundamental importance to the model which are upheld under experimental conditions. Firstly, in Wing and Kristofferson's (1973) original paper it was found that predictions for the general autocovariance functions were upheld. They found, in neurologically-intact subjects, that in a vast majority of cases, correlations at successive intervals (lag-one covariance) to be negative and that covariances at lags greater than zero to be minimal (also see Turvey *et al*, 1989). Secondly, the model predicts that if adjustments are made to the base interval

differences in variance should be attributed solely to the central clock. MISV should remain constant, irrespective of base duration. Wing (1980) found this to be the case, in that, on changing base interval duration only CV was affected. It was also found that CV was more stable than MISV if the effector was changed, for example, in tasks requiring repetitive movements using fingers, arms or feet (Wing, 1977a, 1980).

The third important piece of experimental evidence concerns the assumption that the two processes are independent. If this were to be true then it should be possible to create experimental situations in which a differentiation between CV and MISV could be observed. Ivry *et al* (1988) showed that patients with cerebellar disease performing simple finger tapping tasks could produce different results depending on the position of the lesion. On decomposing variability using the model, poor performance of patients with lateral cerebellar lesions could be attributed to a increase in CV, while those with medial cerebellar lesions showed an increase in MISV. Therefore, Ivry *et al* were able to show independent differences in both processes.

3.1.6. Predictions of the model.

According to Wing and Kristofferson's (1973) model, various predictions can be made about the statistical structure underlying a series of finger taps. Autocovariance at lag zero should be large and positive as this represents the total variance within the system and therefore must, presumably, have some relatively large, positive number. Autocovariance at lag one should be *negative* and small in relation to lag zero, as predicted by the assumption that total variability will be partially composed of variance (calculated from the lag one autocovariance function, see 3.1.3) which can be attributed to the motor

implementation system. Figure 3.2 shows covariance plotted against lag (for lags 0-5) as predicted by the model.

The model makes one further prediction, namely, that the covariance at all lags greater than one should be zero. This prediction can be visualised in Figure 3.1. The impact of variability of the central timekeeper is confined solely to lag zero and does not contribute to covariance estimates at higher lags. Similarly, variability in the motor delay will produce non-zero covariance estimates at lag one but not at lags greater than one. That is, neither process will affect non-neighbouring intervals because the effect of each process are limited to the intervals bordered by a single response.

3.1.7. Violations of predictions underlying the model.

Certain questions arise from the predictions of the model. Are the predications ever violated when a single trial is analysed and, if they are, how are they violated? More importantly, if they are violated, how should the results be interpreted. Ivry and Keele (1989) reported that certain violations had occurred in some trials during their experiments. The main type of violation reported was that during the analysis of certain trials, a positive lag-one autocovariance was reported (the model predicts the value to be negative and attributable to variability within the motor-implementation system). Positive lag-one autocovariance may occur if a subject systematically speeds up or slows down during a trial producing a positive correlation between adjacent responses. A more minor violation was negative CV, in which (presumably) negative lag one covariance was so large that when doubled in the calculation of CV (see equation 2), it was larger than σ^2_I (TV). Therefore, substitution in equation 2 would render CV negative.

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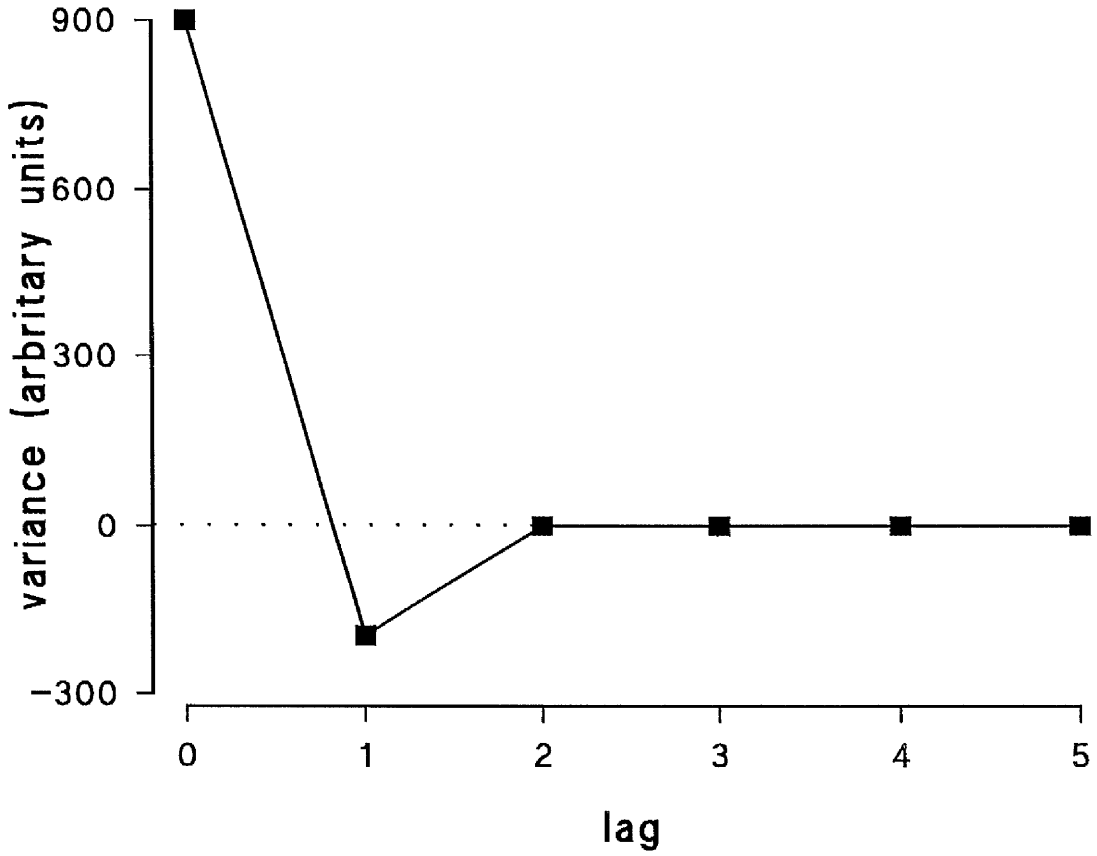

Figure 3.2: Predictions for the values of autocovariance function at lags 0-5 when series of uncued repetitive movements are analysed using Wing and Kristofferson's (1973) model. The prediction underlying the model are that a relatively high, positive value is associated with lag zero, a relatively low and negative number is associated with lag one, while autocovariance at lags 2-5 should be very close to zero.

The incidence of these violations, which may be due to positive lag one autocovariance, varied between subject groups in Ivry and Keele's (1989) study. They reported the percentage of tapping blocks in which one or more trials contained violations. A tapping block constituted "either six 'error-free' or six 'unsuccessful' trials. A trial was considered unsuccessful if "any IRI was less than or greater than 50% of the base duration" (see 3.2.3). The percentages of blocks which contained violations were 12.8% in a control group, 21% in patients with peripheral neuropathy, 18% in PD patients, 14.3% in cortical disease patients and 26% in patients with cerebellar disease. Ivry and Keele attributed these violations to the "relatively small data sets of six trials per block".

There are various methods for dealing with violations of the predictions underlying the model when collecting data from a number of trials. One method would be simply to take the average of a block of trials; this may produce a higher probability of the average lag-one autocovariance being negative. Another method was used by Ivry and Keele (1989) who minimised the effect of any violations by recording a value of zero for the motor delay estimate, and hence rendering the MISV zero, in trials in which lag-one autocovariance was positive. This resulted in all the variability in such trials being attributed to CV. Ivry and Keele argued that such a transformation "did not change the tenor of the conclusions" but stated that "the high percentage of violations, especially for the cerebellar group, dictates that these clock and motor delay estimates be considered cautiously".

In the main analysis in this chapter, I have simply discarded any trials which produced violations of predictions of the model (either positive lag-one autocovariance or negative

CV). I believe that this was the most correct procedure as it produced a set of data in which deductions can be made. In my opinion, including trials which contain violations in any form will only dilute a set of data and confuse interpretation. For example, Ivry and Keele's (1989) method of attributing all variability to the timekeeper in trials in which lag-one autocovariance is positive should be viewed cautiously. They report that "it is unreasonable, of course, to expect that the subjects with positive lag-one (auto)covariance had no variability in their implementation process". In the light of this statement, their use of the transformation seems unjustified.

In using only trials which are violation-free, the data set remains fundamentally more open to interpretation within the context of Wing and Kristofferson's model, as every run conforms to the predictions of the model. I believe that the percentage of violations between groups is a separate and interesting topic, and one which may question the validity of the model. The percentage of trials which contain violations of either positive lag-one autocovariance or negative CV will be reported in this chapter.

Further violations may, potentially, occur at lags two and onwards which may be significantly different from the predicted value of zero. Little mention of this possibility can be found throughout the literature and it is issue one which is discussed in detail in section 3.2.6. In order to assess the degree of violation of the predictions in trials performed by PD patients between lags 2-5 the theoretically predicted value (0 for $k > 1$) must be compared with the observed value. However, whereas the theoretically-predicted autocovariance function is unbiased, the observed (calculated) autocovariance function is biased in relation to the size of the sample. Bias in the estimator is of order 1/N, where

N is the number of response intervals (Anderson, 1971). As the bias can be large, especially for small N (<50; Vorberg and Hambuch, 1978), one should correct for the bias in the estimated function, or else compare the biased estimate with a biased expected (theoretical) value of the estimate. An explanation of the analysis undertaken is provided in 3.2.6iii.

3.1.8. Previous studies in which the model is applied to the performance of PD patients.

There have been several studies of specific relevance to the present work, in which the performance of PD patients during repetitive movement tasks has been analysed using Wing and Kristofferson's model. However, the studies have proven to be both inconclusive and confusing.

The first study (Wing *et al*, 1984; Wing and Miller, 1984) investigated a single patient, a 44 year-old, right-handed female (M.F.) who had been diagnosed as having PD four years earlier and exhibited symptoms which were principally right-sided. She was tested seven times over a one-year period, while taking (albeit inconsistently) a low daily dose of L-dopa. Each testing session comprised 24 runs of a trial, in which the subject was asked to tap (pressing a touch sensitive plate with the index finger) in synchrony with 20 pacing signals (at two target intervals; 450 msec and 550 msec) and then to produce a further 31 taps on cessation of the cues. Six trials were run for each hand at each target frequency. Over the test period, TV and CV were significantly higher in trials using the right (more affected) hand. MISV was larger in the right-hand but over the complete experimental session the difference between the two hands was not significant. Also, it is

clear from the published data, although neither commented upon nor statistically analysed by the authors, M.F. consistently tapped more slowly, in the continuation phase, when using the right hand than when using the left hand. This is in direct contrast with my findings in the previous chapter, in which on cessation of the cues PD subjects on average tended to tap more quickly at similar entrainment frequencies (1-3 Hz as opposed to 450 msec intervals or 2.22 Hz and 550 msec or 1.82 Hz).

Ivry and Keele (1989, see also Ivry, 1986) reported details of three further studies. These studies, using similar versions of the tapping task, tested the ability of PD patients to produce series of uncued taps after a period of entrainment by pressing a microswitch. In all three studies, the target interval was 550 msec (1.82 Hz) and subjects were required to produce 31 taps following a synchrony period of 12 metronome signals. All subjects completed at least 12 trials (two blocks of six trials).

In one of the studies reported (Ivry and Keele, 1989) both mean TV and CV were larger, and the tapping rate slower, when using the "impaired effector" rather than the "unimpaired effector". The authors reported "little difference" in MISV between hands. However, the significance of these findings is questionable as one of the subjects used was M.F. (Ivry, 1986, p. 22) whose data has already been discussed and was published by Wing *et al* (1984) and Wing and Miller (1984). Also, the comparison in the case of another subject concerned "pre- versus post-medication". Although the identity of this subject was unclear from the report, it may be suspected that the subject was B.A.U. (Keele and Ivry, 1987, pp. 207-208; Ivry, 1986, pp. 41-42). B.A.U. was a 75 year-old PD patients who was tested shortly after diagnosis over a period of two weeks and on one

occasion prior to beginning L-dopa medication. In this subject, MISV remained "fairly" constant over the six sessions while CV declined over the first three sessions after medication to a lower more stable state. Another problem with the data was that no statistical analysis of the aggregated data was provided, probably due to the small number of subjects involved.

In the second of Ivry and Keele's (1989) studies, the performance of a group of seven PD patients maintained on L-dopa ('on') was compared to that after abstaining from taking their normal medication ('off'). These two sessions were conducted one week apart, three subjects initially being tested 'on' and four 'off'. The authors reported no differences in mean IRI, TV, MISV or CV on the tapping task although there were clear differences between the severity of clinical signs on the two test sessions. Again, no statistical analysis was reported.

In the third study, Ivry and Keele (1989) examined, using a between-subjects design, the performance of 29 PD patients (mean age 65.4) and 21 elderly controls (mean age 66.7). The PD group included 21 patients who were receiving some form of L-dopa medication at the time of testing plus the 'off' data from the 7 subjects described in the 'on-off' study (Ivry, 1986, p. 19 and Table 1). The authors reported no difference in mean TV, CV or MISV between groups although the PD patients did tap significantly faster during the continuation phase than controls (in agreement with my results in chapter 2). However, for TV, CV and MISV no results of statistical comparisons were reported.

In a recent paper, Pastor *et al* (1992b) attempted to address the discrepancies between

results of these different studies. They studied the ability of PD patients to produce repetitive alternating 80-degree, flexion-extension movements of the wrist, following 48 hr of withdrawal of L-dopa medication and compared the results with those of age-matched controls. Subjects were tested both during and following (for 30 movements) the presentation of 30 auditory pacing stimuli at inter-stimulus intervals, on different trials, of 400, 500, 667, 1000 and 2000 msec (2.5, 2, 1.5, 1, and 0.5 Hz). Each subject was tested on one trial at each pacing frequency (in ascending order of speed) and the IRI was defined as the interval between two successive flexion movements as indicated by EMG recordings from the forearm flexor. Subjects in the PD group were split into subgroups classified by their response to L-dopa therapy. Fourteen PD patients were classified as 'mild', while twenty-six were 'moderate or severe'. The authors reported that TV, CV and MISV were all significantly higher, at all movement frequencies, for PD patients than for control subjects. However, although mean values for all three variables were higher in the 'moderate/severe' group than in the 'mild' group, only at a target frequency of 1.5 Hz was the difference statistically significant. However, the interpretation of these data is quite problematic for two main reasons.

Firstly, as Wing and Kristofferson's (1973) model is concerned specifically with the control of motor *timing*, the application or testing of the model should ideally involve the use of task in which the task-demand is primarily that of timing, with minimal competing demands for the generation or modulation of force, or for spatial accuracy, about the control of which the model has nothing to say. In the performance of the task employed by Pastor *et al* (1992b), however, subjects were required to flex and extend their wrist not only at a given frequency, but through 80 degrees of arc for each flexion and each

extension. It seems likely that the severity of this demand for spatial accuracy varied as a function of target frequency, and therefore would be most severe at the highest frequencies. The authors do not discuss the degree to which this potentially important task demand may have affected patient performance. The task employed by Pastor *et al* (1992b) differed from the free finger-tapping task utilised by other workers and that used in the present work.

A second problem in appropriately interpreting the data of Pastor *et al* (1992b) appropriately arises from the fact that the authors ran only one trial per subject at each target frequency. Aside from the unaddressed issue of within-subject sampling error, this feature of the authors' experimental design had unfortunate consequences when combined with their strategies for dealing with apparent violations of the assumptions underlying Wing and Kristofferson's (1973) model. The authors found that on many trials the calculated values of lag-one autocovariance were positive, and not negative as predicted (see 3.1.7). The proportion of the trials on which violations occurred was high, ranging between 28.6% and 59.5% among the PD patients. In addressing this problem, the authors chose to restrict subsequent analyses to data collected during trials in which the assumptions were not violated. As the authors only ran one trial per subject at each target frequency, the adoption of this procedure had the consequences that in subsequent comparisons between controls and PD patients, and between mild and severe PD groups, a) the number of subjects was severely reduced, b) for any given target frequency groups were unbalanced in respect of previously-controlled independent variables and c) the size and constitution of groups varied with target frequency. It is difficult to assess the potential import of these considerations as no details about the size or constitution of the groups are

given by the authors. Nevertheless, the magnitude of the problem is indicated by the fact that in the case of the eight PD patients tested both when on and when off L-dopa, statistical analyses were not possible because acceptable data were produced during both conditions only at target frequencies of 1.5 Hz (three subjects) and at 2 Hz (four subjects).

It seems that the literature which describes work studying PD with respect to Wing and Kristofferson's (1973) model is sometimes contradictory and at best nebulous. This may be due to unfortunate experimental protocol. Therefore, the aims of the study reported in this chapter were:-

1) To ascertain the source (either 'timekeeper' and/or 'implementation' system) of deficits of motor timing during the continuation phase of finger tapping tasks in patients with PD and HD using the analysis described by Wing and Kristofferson (1973). Until now, HD patients have not been studied in this way. Subjects were required to tap at one target frequency (1.82 Hz or 550 msec intervals) which was deemed slow enough for PD patients to follow easily (Ivry and Keele, 1989). However, as previously described in Chapter 2, deficits in mean frequency production can occur in PD patients at 1 and 2 Hz.

In the PD group, three studies were performed. The performance of PD patients was compared with age-matched controls in two group studies; a 'medication' study in which patients were tested twice, while 'off' and 'on' L-dopa, and in an asymmetry study in which patients with asymmetrical neurological signs were tested using both hands. A further longitudinal study, in which one PD patient was tested monthly over a fifteen month period was made.

2) To study the effect of using different methods of analysis, regarding the manipulation of trials containing violations of the assumptions of the model, on overall result trends.

3) To investigate the validity of using Wing and Kristofferson's model in the study of patients with neurological disorders by calculating the degree to which the autocovariances at lags 2-5 in series of response intervals differ from the values predicted by the model.

CHAPTER 3.2: METHODS.

3.2.1. Subjects.

3.2.1.i. Parkinsonian subjects.

A total of twenty-four PD patients were studied. Twelve patients (7 male, 5 female) aged 64.0 (4.7) years, mean (S.D.), range 57-71 were investigated on the 'asymmetry' trial (see 3.2.4.i) and a further twelve patients (7 male, 5 female) aged 63.5 (10.5), range 48-85, on the 'medication' trial (see 3.2.4.ii). Twelve healthy volunteers (6 male, 6 female) aged 63.6 (6.7), range 55-74, were studied as control subjects. Again, all subjects participated with informed consent and the protocols were approved by the local ethics committee.

The average duration of the patients' disease at the time of testing was 5.1 (2.5) years in the 'asymmetry' trial and 6.7 (3.8) in the 'medication' trial. Patients underwent a clinical assessment performed by a neurologist immediately before testing, and in the case of the medication trial patients forty-five minutes to 1 hr after ingestion of a normal daily dose of levodopa medication. Patients were assessed using the Webster (1968) disability rating and the Hoehn and Yahr (1967) staging evaluation (see 1.2.2). Clinical features, together with drug therapy are summarised in Table 3.1 for both sets of patient groups.

All subjects were tested for (i) handedness, using a simple questionnaire to derive a Laterality Quotient (LQ) and (ii) cognitive function using the 'Mini-Mental State' test derived by Folstein *et al* (1975) in which the maximum score for intact cognitive function is 30. Speed and accuracy of movement was tested further in all subjects in a Reciprocal Aimed Tapping test (Wing *et al*, 1984). Using a pencil, subjects were asked to tap, with

Trial	Init.	Age (yrs)	Sex	Dur.	Clinical grading	MMS	Treatment
A	TC	69	M	4	11 (II)	30	LD;AC
	JS	57	M	8	8 (II)	30	LD;Am
	WY	64	M	10	10 (I)	28	LD;Se
	GM	66	M	7	10 (I)	30	LD;Se
	DF	71	M	3	15 (II)	29	LD;Se
	PM	65	M	4	11 (II)	29	LD;Se;DA
	HW	59	F	6	7 (II)	30	LD;Se
	MB	65	F	6	7 (II)	30	LD
	FR	68	M	3	7 (I)	27	LD;Se
	PN	67	F	5	9 (I)	30	Am
	MN	59	F	0.5	4 (I)	30	None
	LT	58	F	5	8 (I)	30	LD
B	DR	56	M	6	6 (I)	30	LD;Se
	MK	48	M	5	10 (II)	27	LD;Se
	CW	63	F	4	5.5 (I)	30	LD
	AB	85	M	1	8 (II)	26	LD
	TH	67	M	8	10 (III)	29	LD;Se
	ED	71	F	12	9 (II)	30	LD
	GW	70	M	5	7 (I)	29	LD;Se
	EA	72	F	2	10 (II)	29	LD;Se
	EW	58	F	7	17 (III)	30	LD;DA
	HV	66	M	14	12 (II)	28	LD;DA
	LC	51	M	9	9 (I)	30	LD;Se
	DB	55	F	7	10 (II)	27	LD

Table 3.1. Clinical details for the twenty-four PD patients tested on either **A** the 'asymmetry' protocol or **B** the 'medication' protocol of the finger tapping test. The clinical gradings represent the Webster (1968) disability rating, and in parentheses the Hoehn & Yahr (1967) staging (for details refer to Methods). Abbreviations:- Init = initials; yrs = years; dur = duration of illness since initial diagnosis; MMS = mini-mental score (Folstein *et al*, 1975); LD = L-dopa; AC = anticholinergic; DA = dopamine agonist; Se = selegiline; Am = amantidine.

one hand, alternately in pairs of target squares. The pairs of squares were either 5 mm or 20 mm wide and either 51 mm or 205 mm apart. The number of taps made during a 10 s trial was recorded for each of the four combinations. In the 'medication' trial, patients were tested on the same hand before and after taking medication, while in the 'asymmetry' trial patients were tested on both hands, prior to the main tapping experiments. Control subjects were tested on the preferred hand alone, prior to the main experimental session.

3.2.1.ii. HD subjects.

Five HD patients (3 male, 2 female) aged 50.6 (13.9) years, range 33-66 were studied, having been recruited from the North-West Regional Genetic Register of HD families. All patients were diagnosed on the basis of exhibiting clinical signs and a family history of the disease. A summary of clinical features is given in Table 3.2. Prior to testing, all patients underwent neurological and psychological tests to estimate clinical and cognitive function.

3.2.2. Apparatus.

The aim of these experiments was to analyse the mean IRI and serial autocovariances produced by subjects on removal of external auditory cues after initial internalisation of the external cue pattern. An Apple IIe computer was used to produce the auditory cues and to record the times that movements were made. Finger movements were recorded using a small rectangular box (11 x 6 x 3 cm). Figure 3.3 shows a diagram of the box. An infra-red beam was positioned 7 mm above the box surface and breaking the beam recorded this occurrence on the computer with 1 msec temporal resolution.

Case	Sex	Age	Dur	Chor	BK	Tr	Rg	RF	Medic.
1	M	61	7	8(2)	120(0)	0	0	2	CPZ
2	F	33	4	14(3)	290(2)	0	0	3	TB
3	F	40	2	9(2)	83(0)	0	0	1	None
4	M	66	4	8(2)	72(0)	0	0	1	None
5	M	53	3	9(2)	63(0)	0	0	0	CPZ

Table 3.2. Clinical data and medication of the HD patients. Abbreviations and scoring conventions:- Age (years); Dur = time since diagnosis (years); Chor = chorea (initial value is overall clinical score, absent 0, maximal severity 25; value in brackets is score for chorea during voluntary movements, absent 0, maximal severity 5, (Folstein *et al*, 1983); BK = bradykinesia (initial value is simple dealing time in seconds for the Nelson (1976) modification of the Wisconsin card sorting test; value in brackets is clinical score on a 4-point scale); Tr = tremor, Rg = rigidity and RF = rapid finger-thumb movements each scored on standard 4-point clinical scales. Medication refers to drug treatment (CPZ = chlorpromazine, TB = tetrabenazine).

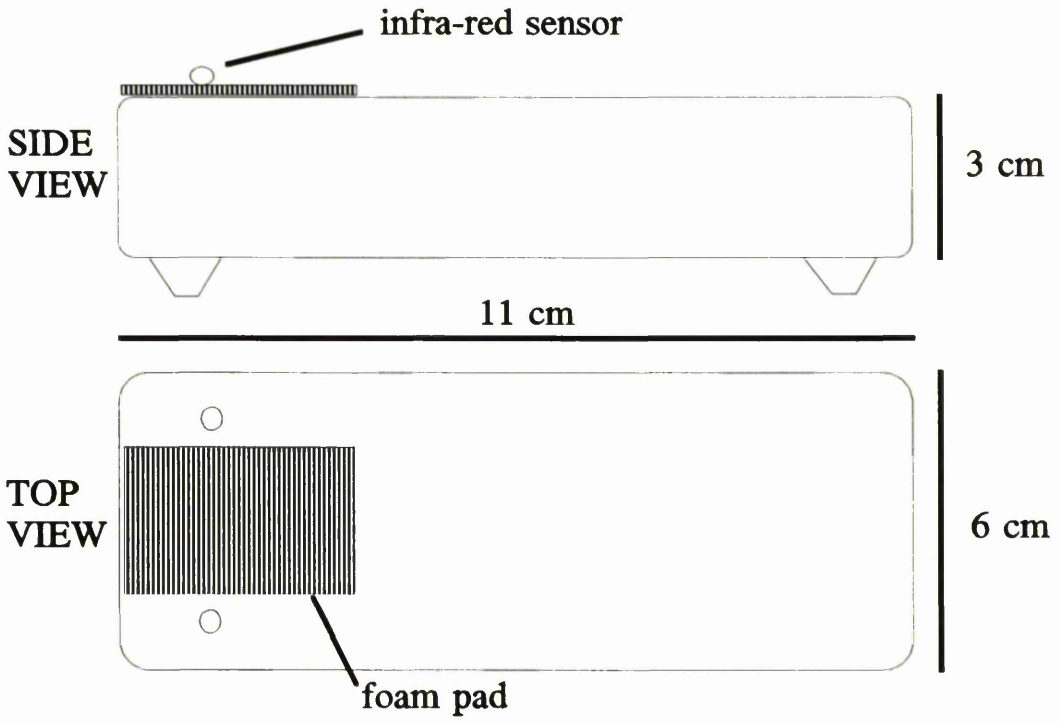

Figure 3.3. Diagram to show the top and side views of the tapping box apparatus used in the present set of experiments. Subjects held the box, comfortably, and proceeded to tap their index finger on the foam pad. On tapping, the breaking of an infra-red beam which passed between to two infra-red sensors caused a TTL (Transistor-Transistor Logic) pulse to be detected by the Apple IIe computer.

3.2.3. Experimental task.

The subject was seated at a table with the arm to be used resting on the table. The subject held the rectangular box on the table surface and placed the designated effector (in all cases, the index finger) on the foam patch at the end of the box furthest from the wrist. Subjects were instructed to make discrete tapping responses by producing flexion-extension movements of the metacarpophalangeal joint. On tapping, the finger broke the infra-red beam the occurrence of a response was registered on a computer.

Each trial consisted of a series of fifteen 50 msec, 1000 Hz tones presented at an easily audible level and occurring at a fixed interval of 550 ms. This pace was deemed sufficiently slow to minimise any effects of bradykinesia, which may be seen in PD or HD patients, and had been used by workers previously (Ivry and Keele, 1989). Subjects were asked to first establish the desired rate internally and then to proceed to tap in time with the cues. After the fifteen auditory tones, subjects were instructed to continue tapping at the same rate without any pause or hesitation. After 31 self-paced taps (which would produce 30 intervals) a single tone indicated the end of the trial. Figure 3.4 shows a representation of the experimental task. Subjects were blindfolded throughout the experiment so as to remove any visual feedback. Subjects were given immediate feedback of their performance on the computer screen, in the form of the mean and S.D. of the response intervals. It was established that they understood this feedback.

For parkinsonian and control groups, each block of trials was concluded when subjects had produced either eight or ten error-free trials. A trial was considered to contain an error if any of the 30 self-paced intervals were less than or greater than 50% of the 550 ms base

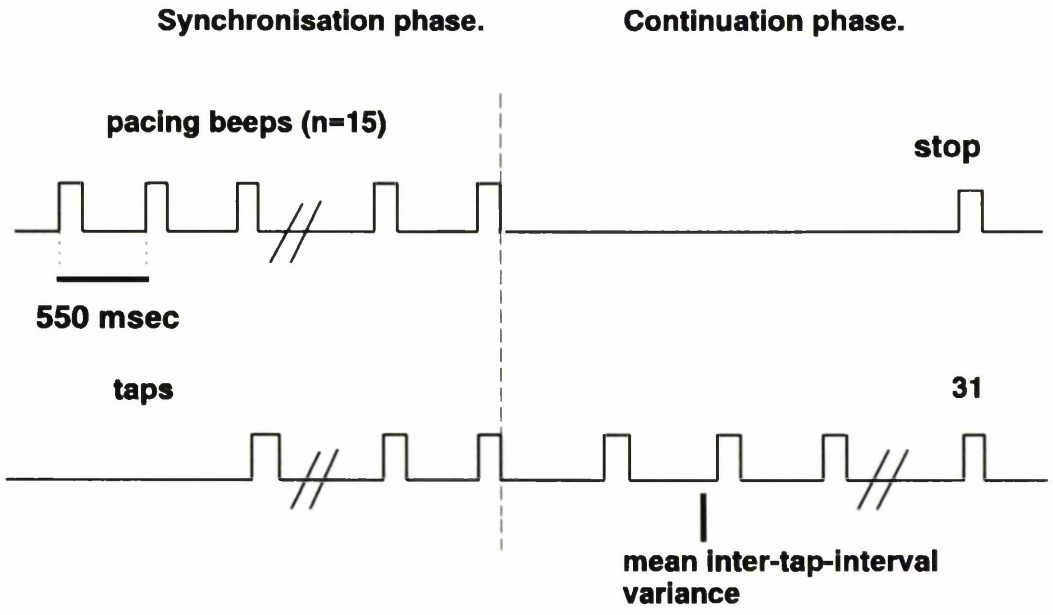

Figure 3.4. Diagram to explain the experimental procedure. Subjects were asked to internalise and then synchronise finger tapping movements ('synchronisation' phase) to 15 auditory cues (50 msec duration, 1000 Hz and easily audible) and then continue tapping at the same speed for a further 31 responses on cessation of the cues ('continuation' phase). A single auditory tone signalled the end of a trial. Immediately afterwards subjects were provided with feedback in the form of mean and S.D. of their produced intervals.

duration (i.e. less than 275 ms or greater than 825 ms). This criterion was used to eliminate artefactual intervals which may have been due to tremor, which may have produced abnormally short intervals, or an inability to ensure that the tap broke the infrared beam (Ivry and Keele, 1989). The data from such trials were discarded.

3.2.4. Clinical studies undertaken.

3.2.4.i. PD 'asymmetry study'.

Two PD patient groups were studied. The first group (the 'asymmetry study', see Table 3.1A) comprised patients who, on clinical examination, possessed definite asymmetrical signs. Patients performed four blocks of trials each containing between 8-10 trials. The first block of trials was performed using the right hand (irrespective of handedness) and the second block using the left hand. The third and fourth blocks were performed approximately one hour after the first two blocks, with the left hand being tested before the right in order to counteract any practice effect. Patients produced 14-20 error-free trials with each hand.

3.2.4.ii. PD 'medication study'.

A second group of PD patients ('medication study', see Table 3.1B) were tested twice (each involving 11-20 error-free runs), once after 12-15 hour abstinence from normal L-dopa medication ('off') and again one hour following ingestion of a single normal dose ('on'). In the medication study, the designated hand was the preferred hand except in two cases in which the neurological deficit dictated otherwise.

For both PD studies the same control group was used for comparison. In the control

group, subjects were tested on one hand only and completed 23-24 error-free runs in four blocks of trials. Approximately one hour separated the first and last two blocks.

3.2.4.iii. A longitudinal study in a PD patient, before and during a period of L-dopa medication.

The motor timing accuracy of a 59 year-old PD patient was also studied over a period of 15 months. The patient (M.N., Table 3.1A) was included in the asymmetry study and the data from the first session were used in the group study. I have tested M.N.'s performance with each hand, at intervals of approximately one month, over a 15-month period, starting shortly (six months) after she had been diagnosed. Throughout this time, M.N.'s neurological signs were consistently worse on her right, and dominant, side. The first five testing sessions ('pre-medication' phase) were conducted prior to M.N. being prescribed a daily dose of L-dopa (two 62.5 mg tablets during the period of sessions 6-9 inclusive, and three tablets thereafter). On each occasion during this 'medication' phase, M.N. was tested following an abstinence of 15 hr from L-dopa.

3.2.4.iv. HD study.

In the HD group one block of trials was concluded when subjects had completed between 8-12 trials. In three of the HD patients, only error-free runs were accepted, while in two patients all runs, regardless of any errors, were analysed.

3.2.5. Preliminary data analysis and statistics.

Data collection and analysis was performed using programs written by Dr. D.J. O'Boyle and Mr. Ivan Todd (Department of Psychology, University of Manchester) using Applesoft

Basic and running on the Apple IIe. Timing routines were written in machine code, giving 1 msec accuracy, by Kevin Rowley (Department of Psychology, University of Manchester). Copies of all programs can be obtained from Dr. O'Boyle.

All the analysis was performed on the 31 responses produced during the continuation phase (after initial internalisation during the synchronisation phase). Response times were recorded as both 'up' and 'down' times as the finger passed through the infra-red beam. Inter-response-intervals were measured as the time difference between two successive 'down' times. Variance of a single run was calculated as the standard deviation of the thirty intervals. The program also contained algorithms which enabled the calculation of serial autocovariances from lag zero to lag five. TV was deemed to be the variability at lag zero while MISV was calculated as negative lag one autocovariance (see 3.2.6.ii, equation 5). CV could therefore be calculated from equation 2 (see section 3.1.3). However, as was discussed in 3.1.7., violations in the form of positive lag one autocovariance or negative clock variance have been managed in different ways, by different workers. I have, therefore, further analysed the data using four different methods of analysis. These results are reported in section 3.3.5. The main analysis was performed by using only those trials which contained none of the above violations. This method was used when reporting findings from the various clinical studies performed. A second form of analysis was performed by taking the average of a block of trials, irrespective of violations. The third method, as was used by Ivry and Keele (1989) and Ivry *et al* (1988) in which any trials containing violations in which lag one autocovariance was positive, involved attributing all variance to CV (MISV is zero). The last method, as was used by Pastor *et al* (1992b), involved analysing only one trial, the first to contain no violations,

was analysed.

Statistical comparisons between experimental conditions within a subject group, and between patient and control groups, were effected using, respectively, Wilcoxon's matched-pairs signed-rank test and the Mann-Whitney *U* test. Non-parametric procedures were preferred because the characteristics of sample distributions did not invariably satisfy the assumptions underlying the use of parametric tests. All test were two-tailed, uncorrected alpha per-comparison (α_{PC}) was set at 0.05 and exact *p*-values were reported. We exerted some degree of control over the inflation of the probability of alpha-error, occasioned by multiple planned comparisons, by using Keppel's (1982) modified Bonferroni test (*cf* Ivry and Keele, 1989). Accordingly, the statistical significance of comparisons was assessed against a corrected value of α_{PC} of 0.025.

Keppel (1982) suggested that it is reasonable to correct for family-wise (FW) error only when the number of planned comparisons exceeds *c*-1 (where, in the present study, *c* = the number of experimental conditions). To do so, the maximum FW error for planned comparisons, $\alpha_{FW\ planned} = (c\text{-}1)(\alpha)$, is divided by the number of planned comparisons (*c*) to yield $\alpha_{planned}$ which is then used in assessing the statistical significance of comparisons. A slightly conservative version of this procedure was adopted, in maintaining $\alpha_{FWplanned}$ at 0.20, rather than allowing it to rise, unconstrained with *c*. In the present study, a *family* of comparisons was defined as all comparisons conducted in respect of a particular dependent variable. The total number of conditions employed in the study was seven (two for each of the patient groups and three, including data combined across sessions 1 and 2, for controls) and the total number of planned comparisons within a family was eight

(three within-group and five between-group). Therefore, the statistical significance of comparisons was assessed against $\alpha_{planned} = 0.20/8 = 0.025$.

3.2.6. Extended analysis: the autocovariance function in relation to the validity of the use of Wing and Kristofferson's (1973) model in the study of neurological disorders.

In order to assess the validity of using the model to analyse performance of patients with neurological disorders further analysis was performed. The aim of the further analysis was to elucidate the degree to which series of taps produced by all subjects contained violations of the prediction that the autocovariance function at lags 2-5 should be zero (see 3.1.6). The (auto)covariance, at different lags, of a sequence of intervals is calculated using an expression referred to as an *estimator*. Several such estimators, which are roughly analogous, are provided in the following sections. The principal concern is with providing details of estimators which have been used by investigators who are primarily interested in the model devised by Wing and Kristofferson (1973). As described below, such estimators are biased (see section 3.2.6ii) because, in practice, one invariably estimates the autocovariance function on the basis of a small number (N) of intervals whereas, ideally, N should be infinite. In addition, bias may be introduced by violation of the assumption of *stationarity* (see section 3.2.6iv).

An estimator is theoretically-neutral, in the sense that no assumptions are made about the structure of the underlying process(es) which give rise to the sequence of intervals, or about particular statistical relations which may obtain between successive intervals at different lags. Thus, the estimator simply allows calculation of the degree to which successive intervals at different lags covary. However, one is usually interested in

estimating the covariance function within the context of a particular theoretical model which, on the basis of specific assumptions about the nature of the statistical structure of successive intervals (perhaps reflecting the operation of specific underlying processes), will make specific predictions about what the estimated autocovariances at different lags should be. The observed estimations are compared with the predicted values, at different lags, in order to assess the validity of the model which has generated the predictions. Then the model is used to generate a theoretical autocovariance function the predictions of which are compared with the observed autocovariance estimates. This theoretical function is *unbiased*.

One such model is that of Wing and Kristofferson. In their basic model (Wing and Kristofferson, 1973), they assume that CV and MISV are two random, independent variables. Thus, to highlight the independence assumption, Wing and Kristofferson assume, in this version of their model, that (1) clock intervals are independent of each other at any lag, (2) motor delay intervals are independent of each other at any lag and (3) clock intervals are independent of motor delay intervals at any lag. On the basis of these assumptions, they then generated a theoretical autocovariance function (equation 9 in section 3.2.6iii). If this model is correct, it should be found that the estimated autocovariance at different lags does not significantly differ from those predicted. More specifically, the basic model predicts that lag zero covariance should be 'large' and positive, that lag one should be relatively small and negative, and that covariances at all lags greater than one should be zero (see 3.1.5).

In a later paper, Wing (1977a) examined the validity of several alternative models in which

some degree of dependence is hypothesised to exist between successive clock intervals or between successive motor implementation intervals (the assumption of independence between clock and motor implementation intervals being retained throughout). On the basis of comparison of the observed estimated autocovariance function with the theoretical autocovariance functions associated with each model, Wing concluded that the basic model of Wing and Kristofferson (1973) had to be modified to include some degree of dependence of successive motor implementation intervals.

The important methodological point of this finding, in the comparison outlined above, is that Wing compared the observed estimated autocovariance function, which is *biased*, with the theoretically-predicted autocovariance function, which is *unbiased*. As bias in the estimate can be large, especially for small N (<50), and as originally pointed out by Vorberg and Hambuch (1978), one should either correct for the bias in the estimated function, or else compare the biased estimate with a 'biased' version of the theoretical function.

As it was computationally more convenient, both Wing (1979) and Vorberg and Hambuch (1978) chose the latter alternative. They compared, at each lag, the biased estimate with the biased *expected value of the estimate*. This expected value was calculated using an expression in which the theoretical function was employed to produce predicted values for a sample of N intervals. For each analogue of the estimator, there was the appropriate form of this expression. For example, the biased expected value of the estimator (equation 3) given in section 3.2.6ii would be calculated using the expression shown in equation 6 in section 3.2.6iii.

3.2.6i. Unbiased estimator of the autocovariance function.

Given the population mean-interval (μ), an unbiased estimate of the covariance of a sequence of intervals is provided by (see Anderson, 1971):-

$$\gamma_I(k) = \frac{\sum_{j=1}^{N-k} (I_j - \mu)(I_{j+k} - \mu)}{N-k}$$

[for $k = 0,1\ldots, N\text{-}1$] (equation 1)

where I_j is the jth interval, N is the number of intervals , k is the lag number and μ is the population mean.

In practice, it is not possible to know the population mean; rather, an unbiased estimate is given in the form of the sample mean (see Anderson, 1971);

$$\bar{I} = \frac{\sum_{j=1}^{N} I_j}{N}$$

(equation 2)

3.2.6ii. Biased estimators of the autocovariance function.

As the population mean is unknown, the sample covariance cannot be calculated using equation 1, rather, an estimator must be used. For small N, the estimator will be biased (see section 3.2.6iii). Of a number of analogue estimators which are available, the most

commonly-used involves the definition of sample covariance in terms of deviations from the sample mean. Hence, from Anderson (1971):-

$$\hat{\gamma}_I(k) = \frac{\sum_{j=1}^{N-k} (I_j - \bar{I})(I_{j+k} - \bar{I})}{N-k}$$

[for $k = 0, 1...., N\text{-}1$] (equation 3)

This is almost identical to the estimator used by Wing (1980):-

$$\hat{\gamma}_I(k) = \frac{\sum_{j=k+1}^{N} (I_j - \bar{I})(I_{j-k} - \bar{I})}{N-k}$$

[for $k = 0, 1, 2, 3, 4$ and 5] (equation 4)

In the programs used for analysis of data obtained in this chapter, the sample autocovariance is estimated using the same expression as that used by Anderson (1971; equation 8, page 440), except that the denominator is N-k-1. The identical estimator is given by Ivry and Keele (1989):-

$$\hat{\gamma}_I(k) = \frac{\sum_{j=1}^{N-k} (I_j - \bar{I})(I_{j+k} - \bar{I})}{N-k-1}$$

[for $k = 0, 1, 2, 3, 4$ and 5] (equation 5)

3.2.6iii. Correcting for estimator bias.

All of the estimators given in section 3.2.6ii are biased. According to Vorberg and Hambuch (1978), for example, "estimates of the autocovariance function from finite response sequences may be heavily biased, depending on the estimator used and on the shape of the theoretical function" and, "for small samples, with N as small as 30, the bias involved may be so large as to make estimates useless for quantitative tests of models". This issue is also addressed by Wing (1979). As mentioned in section 3.2.6, the problem of bias needs to be addressed, especially if estimates are to be compared with theoretical functions derived from particular models of underlying processes. In the following equations a strategy is described for calculating a biased expected value of the autocovariance function (rather than correcting the bias of the in the estimate).

The (biased) *expected*, or *predicted*, value of the estimator given in equation 3 is (equation number 50, p. 448, Anderson, 1971; also given by Wing, 1979):-

$$E(\hat{\gamma}_I(k)) = \gamma_I(k) - \frac{1}{N(N-k)} \sum_{n=1}^{N-k} \sum_{m=1}^{N} [\gamma_I(n-m) + \gamma_I(n+k-m)] + \frac{1}{N^2} \sum_{n=1}^{N} \sum_{m=1}^{N} \gamma_I(n-m)$$

(equation 6)

where $\gamma_I(k)$ is the theoretical (unbiased) serial covariance function for lag k. Note that the bias in this estimator is of the order of $1/N$ (Anderson, 1971, p. 449)

In the case of Wing and Kristofferson's (1973) model, in which it is proposed that:-

$$I_j=C_j-D_{j-1}+D_j$$

(equation 7)

(see chapter 3.1.3.) the theoretical serial covariance function, which involves no assumptions about the statistical dependence or independence between C and D, is given by Wing (1977a) as:-

$$\gamma_I(k)=\gamma_C(k)+2\gamma_D(k)-\gamma_D(k-1)-\gamma_D(k+1)-\gamma_{CD}(k+1)-\gamma_{CD}(-k+1)+\gamma_{CD}(k)+\gamma_{CD}(-k)$$

[for $k = 0, 1, 2...$] (equation 8)

In the case of the basic model (Wing and Kristofferson, 1973) in which it is assumed that clock intervals and the motor implementation intervals are all mutually independent, this expression resolves to (Wing, 1977a):-

$$\gamma_I(k) = \sigma_C^2 + 2\sigma_D^2, \text{ for } k=0$$
$$-\sigma_D^2, \text{ for } k=1$$
$$0, \text{ for } k>1$$

(equation 9)

Therefore, substitution of equation 9, appropriate for a given lag, in equation 6 will give the expected value of the estimator given in equation 3.

In order to test the degree to which violations occur between lags 2-5, I have tested,

following Vorberg and Hambuch (1978), for significant departures of the estimated covariance from the respective biased expected value, calculated after insertion of the obtained observed estimates for the autocovariance function at lag 0 and lag 1 in Anderson's (1971, p.448) expressions (equation 6). The prediction of the model, at any of lags 2-5, was considered to be violated if, at that lag, the corrected expected value of covariance did not fall within the bounds of 2 standard errors either side of the obtained value (that is, within the approximate 95% confidence interval of the obtained value).

3.2.6iv. Stationarity.

Estimation of the autocovariance function proceeds on the assumption that the series of intervals (of underlying process(es)) is *stationarity*, that is in general terms, its probabilistic structure does not change with time (Vorberg and Wing, 1994). Checks for stationarity of the means have been employed by Wing (1979), by Ivry and Keele (1989), by Vorberg and Hambuch (1978) and by Pastor *et al* (1992b) by fitting regression lines to the means or by comparing the first N/2 intervals with the mean of the second N/2 trials. These authors universally agreed that stationarity usually obtained or that correlations made on the basis of such procedures made little or no difference to calculations of autocovariance.

However, in the present work the data have been analysed in order to estimate the degree of stationarity in trials performed by subjects in the various experimental groups (except the HD group. Various analyses were performed. Two of the methods used by Wing (1979), Ivry and Keele (1989), Vorberg and Hambuch (1978) and Pastor *et al* (1992b) were employed, namely, comparing the mean of the first N/2 intervals (in the present

work - fifteen) with the mean of the second N/2 intervals and fitting regression lines in which the intercept, slope and r^2 values were obtained. I have also performed a further analysis in which the means of the first, second and third ten intervals (N/3) were compared.

CHAPTER 3.3: RESULTS.

3.3.1. Motor timing in PD patients with asymmetrical neurological signs - the 'asymmetry' study.

Figure 3.5 compares the ability of 12 control subjects and 12 PD patients to produce mean IRIs of 550 msec in the continuation phase of a tapping task. The PD patients all exhibited asymmetrical neurological signs on examination, with six being more affected on the right side and six being more affected on the left side; data for both the more and less affected side are shown. All patients and control subjects were right-handed. Table 3.3 shows the clinical scores (Webster, 1968) for bradykinesia, rigidity and tremor for the patients, which were deemed to be most likely to exhibit asymmetry. In all patients, a higher total clinical score was given for the three signs on the more affected side. In reciprocal tapping tests all patients were shown to be able to produce IRIs of shorter length than the 550 msec target interval (minimum interval produced; 337 (66.7), group mean (S.D.), msec per tap in the less affected hand and 437 (87.9) msec per tap in the more affected hand). Two main findings are exhibited in the mean (S.D.) group data shown in Figure 3.5. Firstly, and in agreement with data reported in the previous chapter, PD patients are less accurate in producing mean IRIs of 550 msec than control subjects during the continuation phase. On average, patients produced shorter intervals (tapping more quickly than required) than control subjects who produced intervals which are closer to the target interval of 550 msec. However, there are no statistically significant differences between mean IRI produced by controls and either the more or less affected hand in the patient group (p=0.1841 and 0.2364, respectively, Mann-Whitney). Secondly, within the patient group, there was no significant difference in mean IRI produced between the more and less

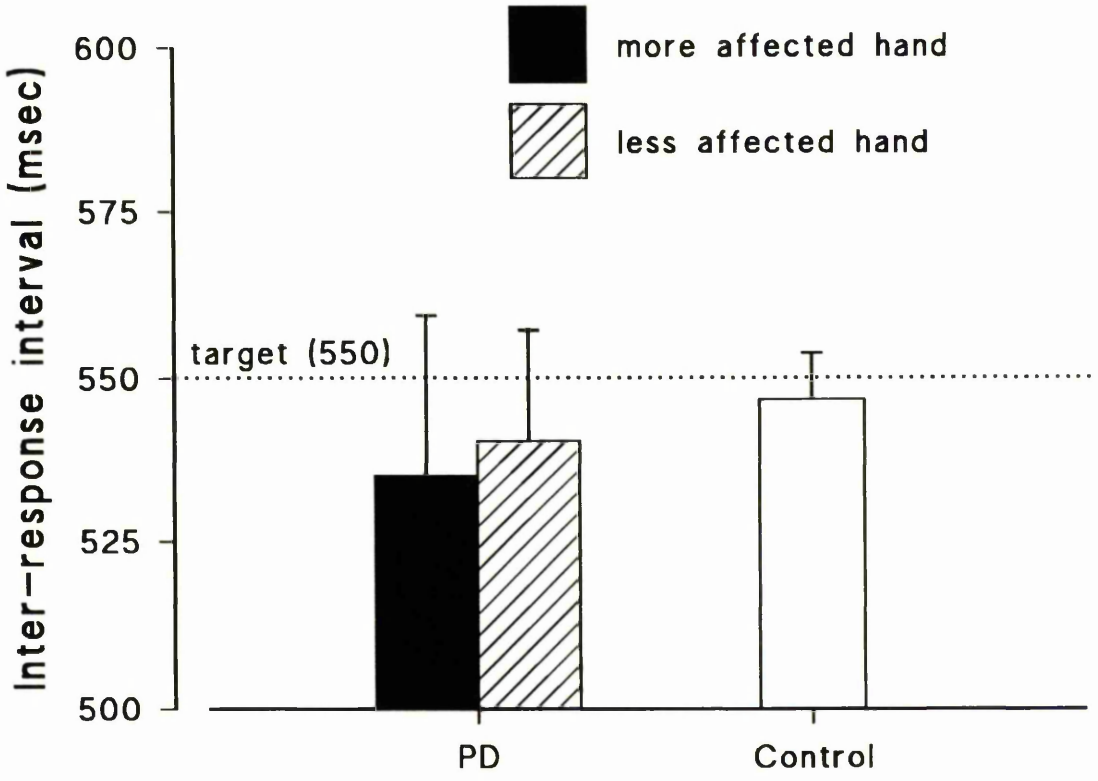

Figure 3.5. Mean (S.D.) group data for the mean IRI produced during the continuation phase of the tapping task, in 12 control subjects and 12 PD patients who exhibited asymmetrical neurological signs on examination. For the PD group, results for both the more and less affected hand are shown. There was no statistically significant difference between the more and less affected hand in the PD group ($p=0.2094$, Wilcoxon) or between controls and the more or less affected hand in the patients ($p=0.1841$ and 0.2364, respectively, Mann-Whitney).

	MORE			LESS		
Init.	Brad	Rigid	Trem	Brad	Rigid	Trem
A TC	2	2	0	1	0.5	0
JS	2	1	1	1	1	0
HW	1	1	0	0	0.5	0
FR	1	0	1	0	1	0
MN	1	1	1	0	1	0
LT	1	2	1	0	2	0
B WY	2	2	0	1	0.5	0
GM	1	2	2	0	1	0
DF	2	2	1	1	2	0
PM	2	2	2	0	2	0
MB	1	1	1	0	0.5	0
PN	1	2	2	0	1	0

Table 3.3. Clinical gradings (Webster, 1968) for 12 PD patients who exhibited asymmetrical neurological signs for the more and less affected hands. **A** shows the scores for patients in whom the right hand was more affected while **B** shows the scores for patients in whom the left hand was more affected. Scores for three signs are reported, bradykinesia (Brad), rigidity (Rigid) and tremor (Trem). When the three clinical scores were added, a higher total was observed in the more affected hand in each patient. Further patient details are given in Table 3.1.

affected hand (p=0.2094, Wilcoxon). Thus, PD patients produced similarly short intervals with the less affected or 'less' parkinsonian' hand and the more affected hand.

Figure 3.6A shows group mean (S.D.) for TV in the asymmetrical PD patients and control subjects. TV was calculated as lag-zero autocovariance using the autocovariance function shown in equation 5 in 3.2.6ii. TV was significantly higher for the more affected hand of the PD patients than when compared with the less affected hand (p=0.0005, Wilcoxon). When compared to that produced by control subjects, TV was significantly higher for the more affected hand of PD patients (p=0.0005, Mann-Whitney) but there was no significant difference between the TV in control subjects and that of the less affected hand of patients (p=0.6033, Mann-Whitney).

Differences in TV produced by the more and less affected hands of the PD patients depended on whether the right or left hand was the more affected. Figure 3.6B shows that when the *difference* in TV between the more and less affected hand (i.e. TV more affected minus TV less affected) was analysed a significant contrast was found between patients whose right *versus* left hand was more affected (p=0.0374, Mann-Whitney). That is, patients who were more predominantly more affected in the left hand showed a greater contrast with the less affected hand. As all patients were right-handed, a handedness factor may have been involved. However, the six patients who exhibited more severe neurological signs on the left side, had a longer duration of illness than patients whose right side was more affected (5.8 (2.5), mean (S.D) years compared to 4.4 (2.6)). Patients with the left side more affected also had higher overall scores for clinical severity (Webster, 1968) than patients with the right side more severely affected (10.33 (2.7), mean

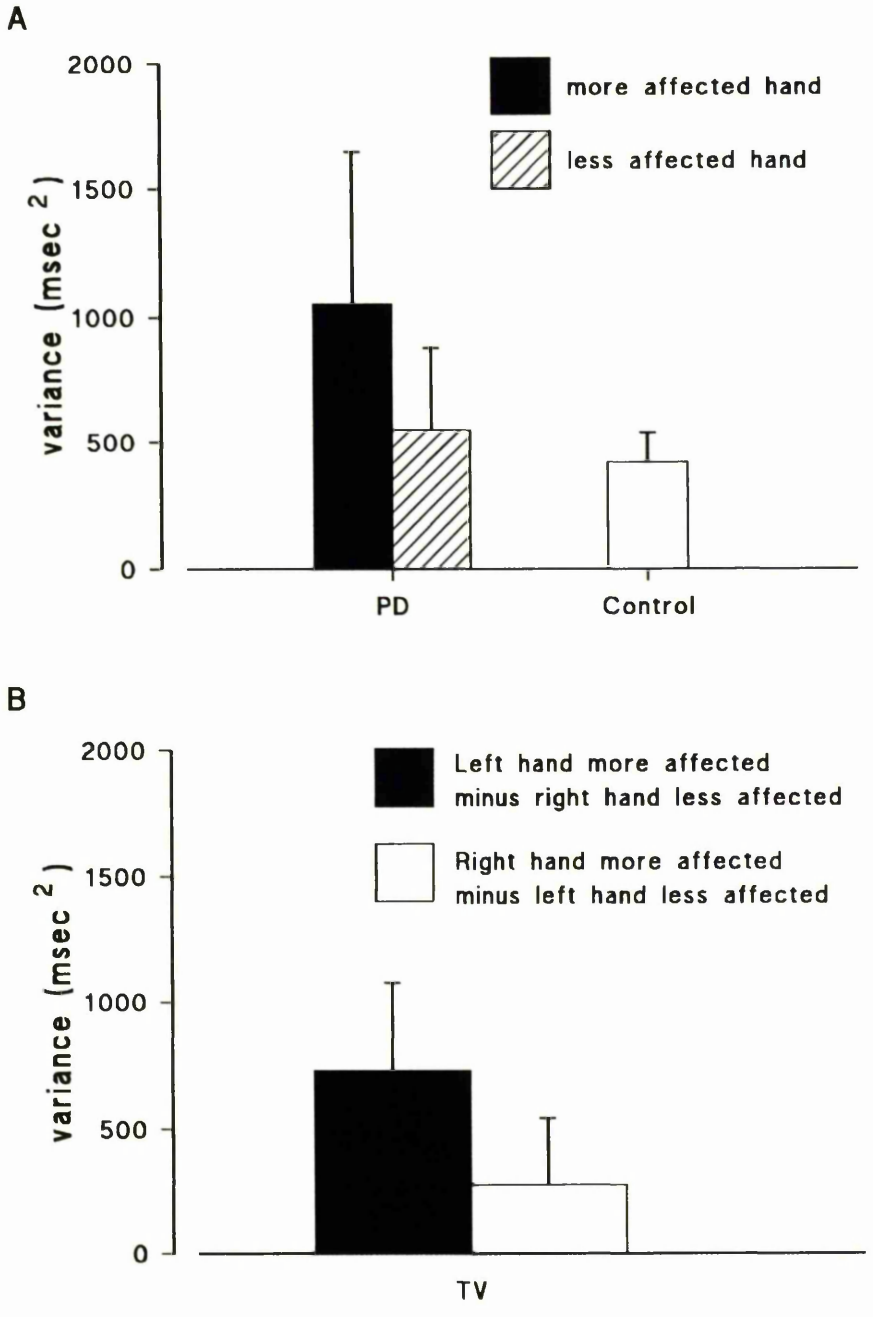

Figure 3.6. In **A**, mean (S.D.) group data for TV for 12 PD patients who exhibited asymmetrical neurological signs on examination, and 12 control subjects. Significant differences were found in the PD group between performance with the more and less affected hand (p=0.0005, Wilcoxon) and between the more affected hand, but not the less affected hand, in the PD group and controls (p=0.0005 and 0.6033, respectively, Mann-Whitney). In **B,** the contrast between 6 PD patients who more affected on the right, and 6 patients who were more affected on the left. There was a significant difference in mean (S.D.) TV between the left hand more affected minus the right less affected, and the right hand more affected minus the left hand less affected (p=0.0374, Mann-Whitney).

(S.D.) compared to 7.5 (2.3)). However, the results for both duration of illness and overall clinical score did not differ significantly between the patients sub-groups.

The plots in Figure 3.7A compare mean (S.D.) group data for PD patients and controls when TV is decomposed into CV and MISV using Wing and Kristofferson's (1973) model for motor timing. Methods of calculations were explained in 3.1.3. Both CV and MISV were significantly higher in the more affected hand than in the less affected hand of the patient group (p=0.0005 and 0.0047, respectively, Wilcoxon). However, when compared to control subjects CV and MISV were significantly higher only for the more affected hand of the patient group (p=0.0003 and 0.0067, respectively, Mann-Whitney). Neither CV nor MISV values differed significantly between the less affected hand in the patient group and the corresponding values of the control subjects (p=0.2727 and 0.9081, respectively, Mann-Whitney).

Figure 3.7B compares the *differences* in (i) CV and (ii) MISV between the more and less affected hands of patients in whom the right versus left hand was more affected. There was a larger difference in CV and MISV between the more and less affected hand when the more affected hand was the left. However, only the difference in CV, and not MISV, was significant (p=0.0374 and 0.2623, respectively, Mann-Whitney).

3.3.2. The effect of L-dopa on motor timing in PD patients - the 'medication' study.

A further twelve PD patients were tested twice, firstly after a 12-15 hour abstinence from their normal L-dopa medication ('off') and approximately one hour after ingestion of a single normal dose ('on'). Table 3.4. shows the clinical scores (Webster, 1968) for

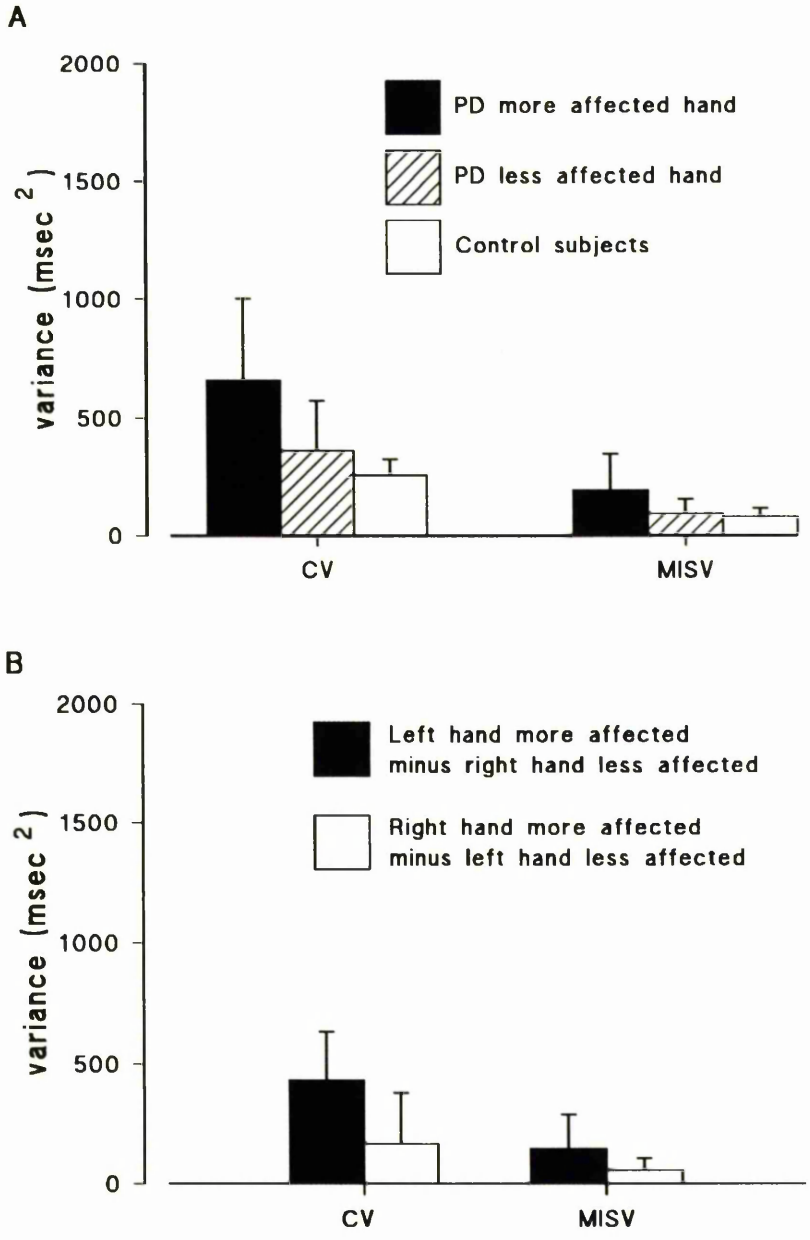

Figure 3.7. In **A**, mean (S.D.) group data for variability when decomposed into CV and MISV when using Wing and Kristofferson's (1973) model, for 12 PD patients with asymmetrical neurological signs and 12 control subjects is shown. Significant differences were found between the more and less affected hand in the PD group for both CV and MISV (p=0.0005 and 0.0047, respectively, Wilcoxon) and between the more affected hand in the PD group and the control group for both CV and MISV (p=0.0003 and 0.0067, respectively, Mann-Whitney). In **B**, the contrast between 6 PD patients who were more affected on the right, and 6 who were more affected on the left. There was a significant difference in CV but not MISV (p=0.0374 and 0.2623, respectively, Mann-Whitney) between the left hand more affected minus the right less affected hand, and the right hand more affected minus the left hand less affected.

	OFF			ON		
Init.	Brad	Rigid	Trem	Brad	Rigid	Trem
DR	0	1	0	0	0	0
MK	2	2	3	1	2	1
CW	1	1	1	0	0.5	0
AB	2	2	1	1	2	0
TH	3	1	1	0	1	0
ED	2	2	2	0	1	1
GW	1	1	2	0	0	1
EA	2	2	1	0	2	0
EW	3	3	3	0	1	0
HV	2	3	0	0	1	0
LC	1	1	3	0	1	0
DB	2	2	1	0	1	1

Table 3.4. Clinical gradings (Webster, 1968) for bradykinesia (Brad), rigidity (Rigid) and tremor (trem) for 12 PD patients who performed the experiments twice; once after abstinence for 12-15 hours from normal their L-dopa medication ('OFF') and one hour after ingestion of a single normal dose ('ON'). When the scores for the three clinical signs were added, a higher total was observed when patients were 'off' medication. Further clinical details are given in Table 3.1.

bradykinesia, rigidity and tremor for PD patients when 'on' and 'off' L-dopa, these signs being most likely to be affected by medication. In the patient group the dominant hand was studied, except in two cases, in which the severity of the neurological deficit dictated otherwise. Reciprocal tapping data showed that all patients were able to produce IRIs of shorter duration than the required 550 msec target interval (minimum IRI produced; 321 (91.0), group mean (S.D.), msec per tap for patients 'on' medication and 446 (118.2) for patients 'off' medication).

As the 'off' data were always collected before the 'on' data in the patient group, and since control subjects performed trials in two sessions on a similar timescale to patients, data from the control group were divided into those obtained in the first and second sessions. This division attempted to compensate for any practice effect which may have occurred between sessions. The performance of patients 'off' (mean (S.D.) number of trials analysed, $n=10.4$ (2.0)) was compared with that of the controls' first session ($n=9.3$ (1.8)) and the performance of patients 'on' $n=11.3$ (1.8) was compared with that of the controls' second session, $n=8.1$ (1.9). Figure 3.8 compares the ability of the PD patients, both 'on' and 'off' medication, and control subjects to produce mean IRIs of 550 msec. It can be seen from Figure 3.8 that PD patients produced shorter intervals than both the target interval (550 msec) and the IRIs of control subjects. There was a significant difference between PD 'off' and the first control session and between PD 'on' and the second control session ($p=0.0377$ and 0.0079, respectively, Mann-Whitney). Figure 3.8. shows that there was no significant difference within groups for mean IRI produced, between either PD 'on' and 'off' sessions ($p=0.9063$, Wilcoxon) or the first and second session in the control group ($p=0.1361$). Thus, ingestion of L-dopa did not

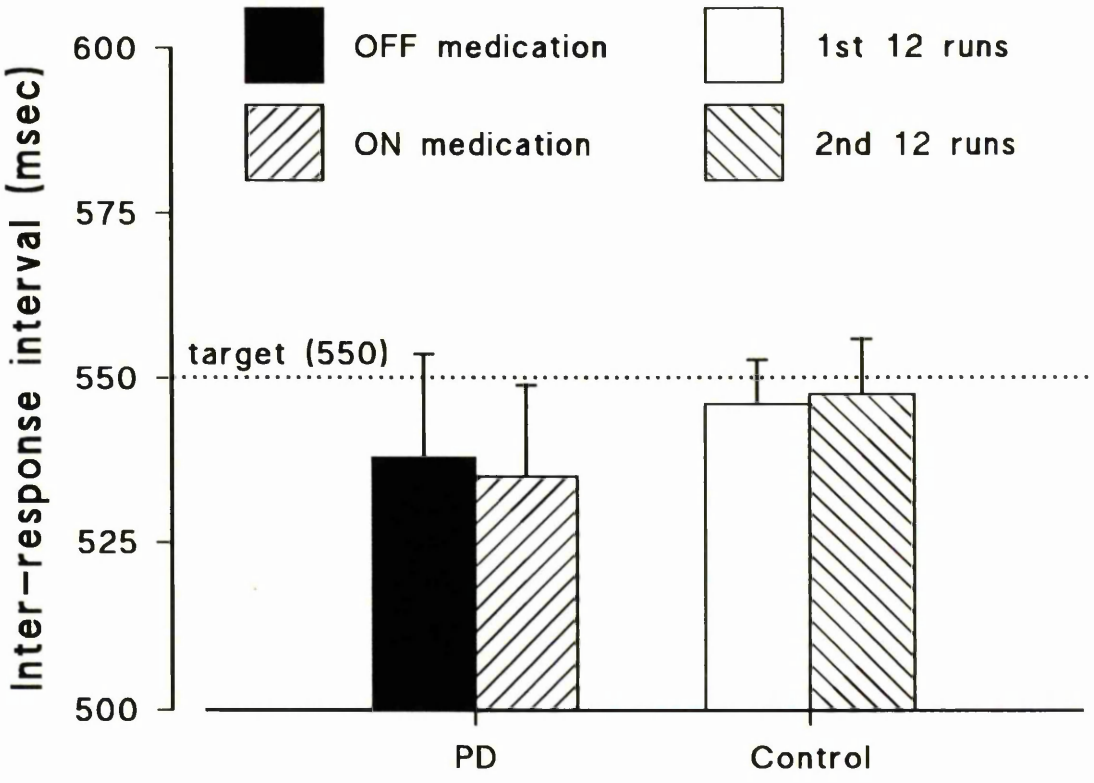

Figure 3.8. Mean (S.D.) group data for the mean IRI produced during the continuation phase of the tapping task, in 12 control subjects and 12 PD patients. Both groups performed two sessions of experiments. In the PD group the first session was performed after 12-15 hours abstinence from their normal L-dopa medication ('OFF') while the second session was performed one hour after ingestion of a single normal dose of L-dopa ('ON'). Control subjects performed the second session (2nd 12 runs) one hour after the first session (1st 12 runs). There was no statistically significant difference in mean IRI within groups, between either 'on' or 'off' in the patient group, or the first and second session in the control group (p=0.9063 and 0.1361, respectively, Wilcoxon). However, there was a significant difference between groups; PD 'off' and control first session, PD 'on' and second session (p=0.0377 and 0.0079, respectively, Mann-Whitney).

alter the production of short IRIs by patients despite an improvement in clinical signs.

The effect of medication on TV (calculated as lag-zero autocovariance) is shown in Figure 3.9. Figure 3.9A shows that the group mean for PD patients was significantly higher when patients were 'off' medication than when they were 'on' (p=0.0005, Wilcoxon). There was no significant difference in mean TV between the first and second control session (p=0.1361, Wilcoxon). However, when data from the PD group were compared with control data it was found that mean TV in the PD 'off' group was higher than that obtained in the first session in controls (p=0.0003, Mann-Whitney); there was no significant difference in mean TV between PD 'on' and the second session in controls (p=0.1190, Mann-Whitney). In order to test for any practice effect, the mean TV for the second control session was subtracted from the first control session. Figure 3.9B shows that a small positive difference in variance was found which may have been attributable to the effect of practice. This difference was compared to the difference obtained when the mean TV of the PD 'on' (second) session was subtracted from that of the PD 'off' (first). There was a significant difference in the mean change in TV occurring between sessions in the two groups; a larger difference was seen in the PD group (p=0.0001, Mann-Whitney).

Figure 3.10A compares mean (S.D.) group data for PD patients and controls when variability is decomposed into CV and MISV using Wing and Kristofferson's (1973) model for motor timing. Both CV and MISV were significantly higher in patients when 'off' medication than when 'on' medication (p=0.0005, Wilcoxon). Neither CV nor MISV differed between the first and second sessions in control subjects (p=0.1167 and 0.8753,

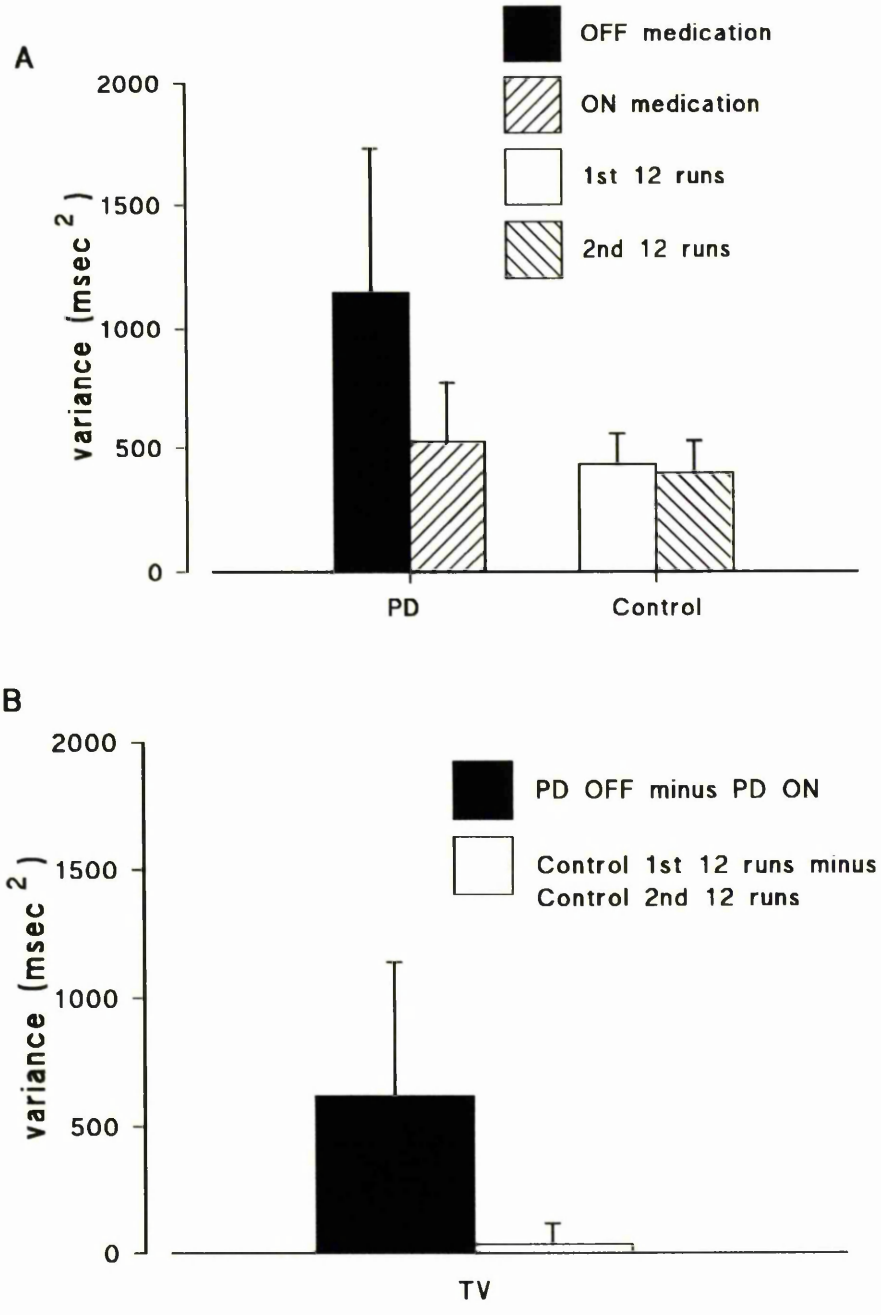

Figure 3.9. In **A**, mean (S.D.) group data for TV for PD patients in the 'medication' study and 12 control subjects are shown. Significant differences were found in the PD group between patients performance 'on' and 'off' medication ($p=0.0005$, Wilcoxon) and between PD 'off' and the 1st 12 runs of the control subjects ($p=0.0003$, Mann-Whitney). In **B**, mean (SD) change in TV between PD 'off' and 'on', and between control 1st and 2nd 12 runs. A significant difference in the amount of change was found between PD and control groups ($p=0.0001$, Mann-Whitney).

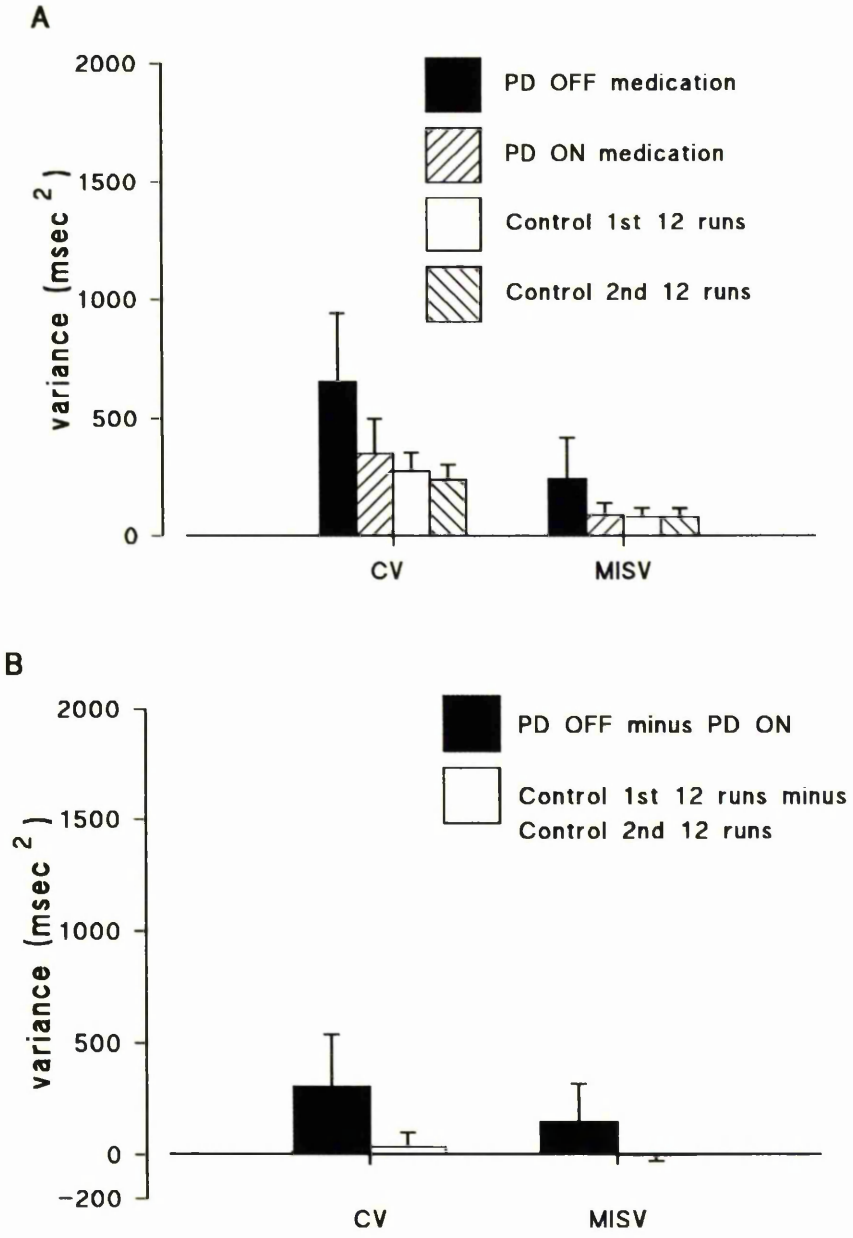

Figure 3.10. In **A**, mean (S.D.) group data for variability when decomposed into CV and MISV using Wing and Kristofferson's (1973) model for the PD 'medication' study and 12 control subjects are shown. Significant differences were found between patients 'on' and 'off' medication for both CV and MISV (p=0.0005, Wilcoxon), between PD 'off' and control 1st 12 runs for both CV and MISV (p=0.0002 and 0.0039, respectively, Mann-Whitney) and between PD 'on' and control 2nd 12 runs for CV alone (p=0.0209). In **B** mean (SD) change in CV and MISV between PD 'off' and 'on' and control 1st and 2nd 12 runs. Significant differences were found in the amount of change between PD and controls for both CV and MISV (p=0.0001 and 0.0003, respectively, Mann-Whitney). significantly greater in the PD patients than in control subjects (p=0.0001, for CV; p=0.0003, for MISV, Mann-Whitney).

respectively, Wilcoxon). When PD data were compared with control data, differences in CV and MISV were observed. When PD 'off' data were compared with those of the first control session, both CV and MISV were significantly higher in the PD group (p=0.0002 and 0.0039, respectively, Mann-Whitney). However, when PD 'on' data were compared with those of the second control session *only* changes in CV and *not* MISV were observed (p=0.0209 and 0.9081, respectively, Mann-Whitney).

Figure 3.10B plots the differences in, respectively, CV and MISV between the first and second control sessions. A small reduction in CV was found, possibly associated with a practice effect, whilst the change in MISV was negligible. When these differences were compared to differences in CV and MISV seen when PD 'on' data was subtracted from PD 'off' data, it was found that the group mean (S.D.) changes in CV and MISV were significantly different (p=0.0001 and 0.0003, respectively, Mann-Whitney).

3.3.3. A longitudinal study of motor timing in a single subject with PD; observations before and during a period of L-dopa medication.

Figure 3.11 shows mean (S.E.M.) data for the mean IRI produced over fifteen sessions by M.N., a PD patient who exhibited consistently more severe neurological signs on her right and dominant side. Results from both hands are shown and the patient was tested at approximately monthly intervals. Sessions 1-5 (weeks 0-19) were conducted prior to M.N. being prescribed daily L-dopa medication ('pre-medication'). After this period, daily doses of either two (weeks 20-30) or three (week 30 onwards) 62.5 mg tablets of L-dopa were prescribed ('post-onset medication'). Figure 3.11 shows that in the 'pre-medication' phase M.N. produced intervals which, in the early sessions, were shorter than the target intervals. This phenomenon was observed for both hands. However, by the fourth session

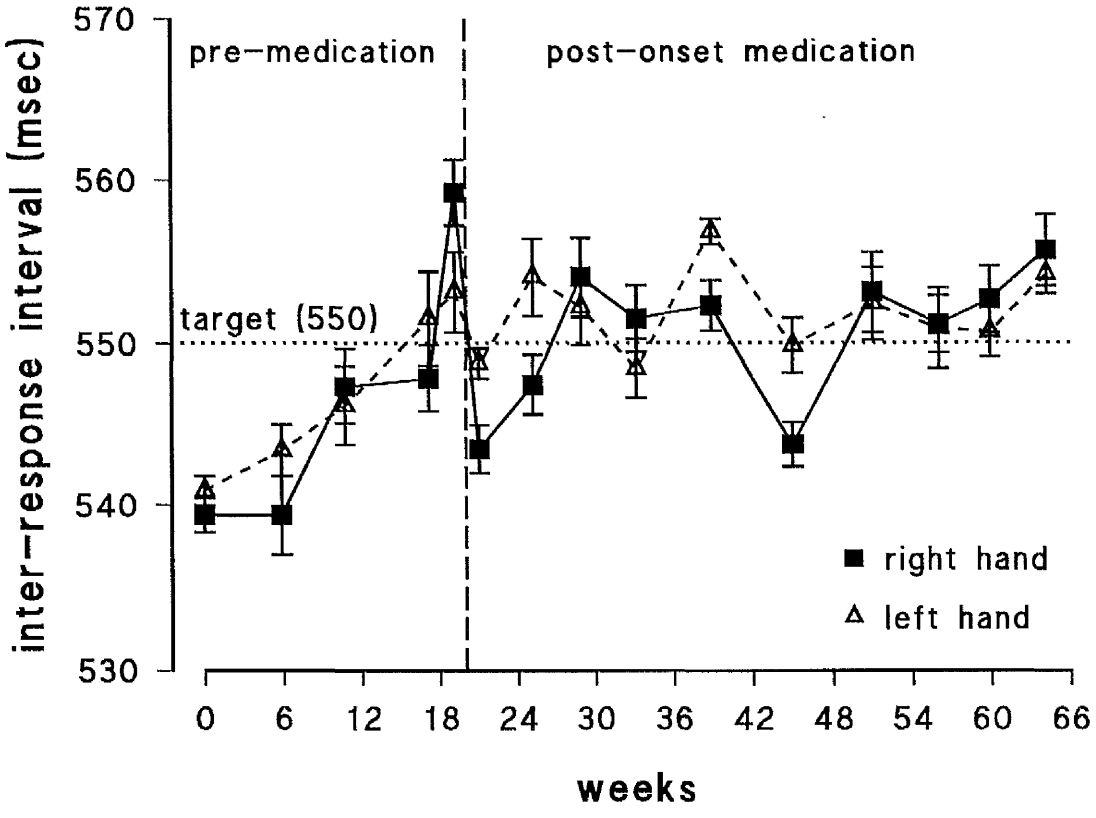

Figure 3.11. Mean (S.E.M.) data for the mean IRI in each of fifteen sessions completed by M.N., a 59 year-old female PD patient who exhibited consistently worse neurological signs on her right, and dominant side, over a fifteen-month period. Both hands were tested, and sessions were approximately one month apart and started approximately six months after initial diagnosis. The first five sessions, weeks 0-19, ('pre-medication' phase) were conducted prior to M.N. being prescribed a daily dose of L-dopa. After this period, daily doses of two 62.5 mg tablets during the period of sessions between weeks 20-30 inclusive, and three tablets thereafter ('post-onset medication' phase) were prescribed.

(week 17), the mean IRIs produced for both hands were relatively accurate. During the 'pre-medication' phase the mean IRIs became longer (M.N. tapped, on average, slower over the five sessions) so that in session five (week 19), M.N. produced mean IRIs which were actually longer than the target interval. In the first 'post-onset medication' session (week 21), mean IRI became markedly shorter for the right hand. In subsequent sessions, mean IRI returned to levels close to the target interval for both hands. Apart from week 21, there did not seem to be a clear difference in production of mean IRIs between the right, and more affected, hand and the left hand in either the 'pre-' or 'post-onset medication' phases of testing.

Figure 3.12 shows mean (S.E.M.) data for TV over fifteen sessions. In the 'pre-medication' phase higher values of TV were observed in the right, and more affected hand, than in the left hand and were consistently higher over the five sessions. Also, in general, during the 'pre-medication' phase levels of TV did not show significant changes for either hand. However, there were definite decreases for both hands in the 'post-onset medication' sessions. For the right hand there was a sudden drop in TV immediately after the onset of medication and the new level remained relatively stable in subsequent sessions. There was a more gradual decrease in the levels of TV for the left hand and, again, the new level (which was lower than in the 'pre-medication' sessions) remained relatively stable throughout subsequent sessions.

Figure 3.13 shows data for CV and MISV calculated using Wing and Kristofferson's (1973) model for motor timing. Figure 3.13 show that in general, in the 'pre-medication' phase, higher levels of CV and MISV were observed for the right hand than the left hand.

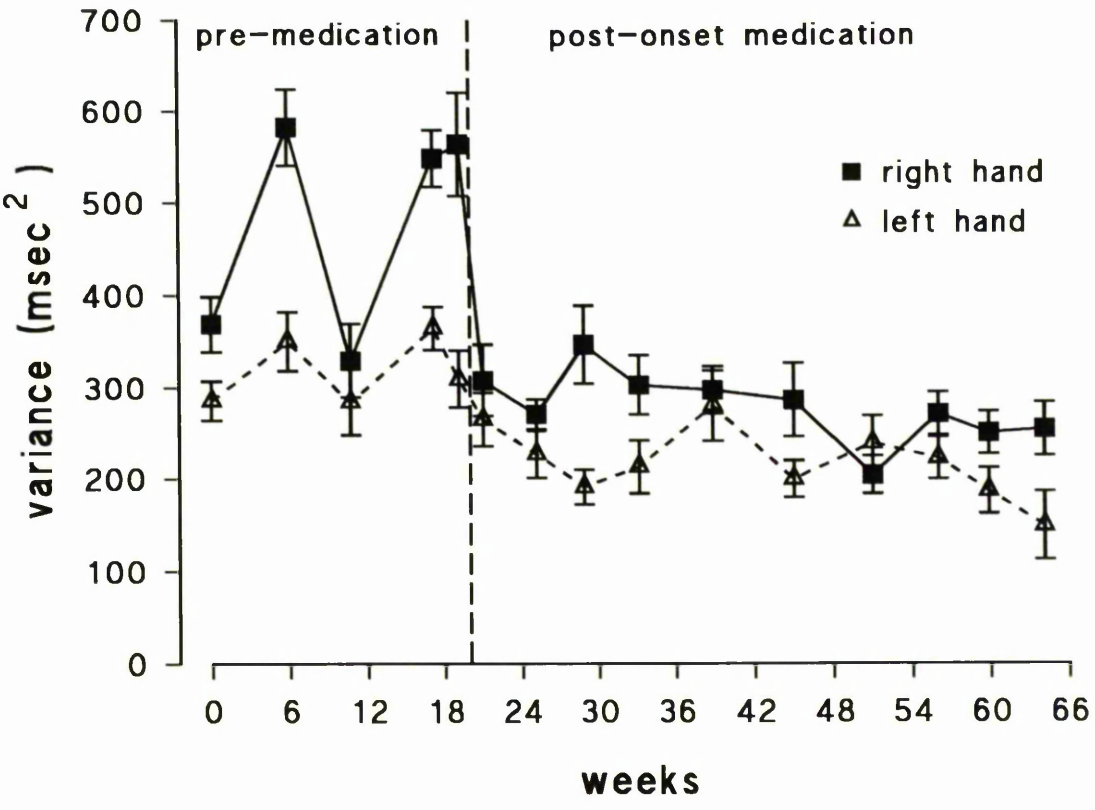

Figure 3.12. Mean (S.E.M.) data for TV in each of fifteen sessions completed by M.N., a 59 year-old female PD patient who exhibited consistently worse neurological signs on her right, and dominant side, over a fifteen-month period. Both hands were tested, and sessions were approximately one month apart and started approximately six months after initial diagnosis. The first five sessions, weeks 0-19, ('pre-medication' phase) were conducted prior to M.N. being prescribed a daily dose of L-dopa. After this period, daily doses of two 62.5 mg tablets during the period of sessions between weeks 20-30 inclusive, and three tablets thereafter ('post-onset medication' phase) were prescribed.

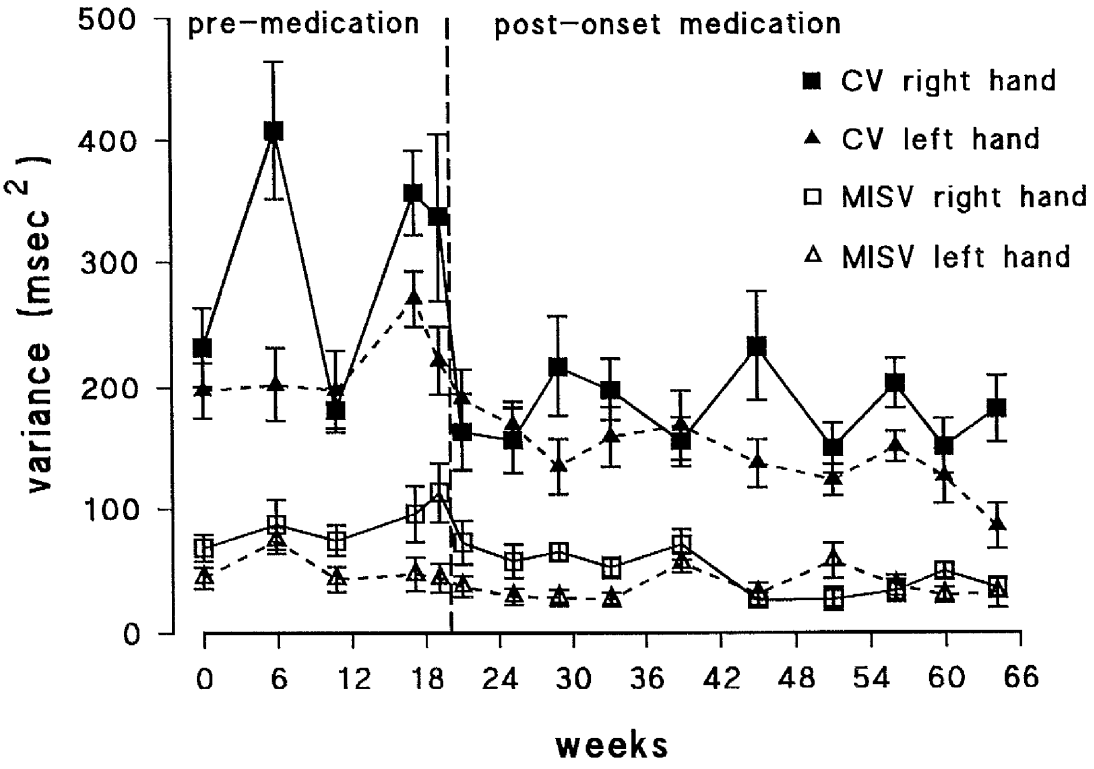

Figure 3.13. Mean (S.E.M.) data for CV and MISV in each of fifteen sessions completed by M.N., a 59 year-old female PD patient who exhibited consistently worse neurological signs on her right, and dominant side, over a fifteen-month period. Both hands were tested, and sessions were approximately one month apart and started approximately six months after initial diagnosis. The first five sessions, weeks 0-19, ('pre-medication' phase) were conducted prior to M.N. being prescribed a daily dose of L-dopa. After this period, daily doses of two 62.5 mg tablets during the period of sessions between weeks 20-30 inclusive, and three tablets thereafter ('post-onset medication' phase) were prescribed.

Again the levels for both CV and MISV remained relatively stable throughout the 'pre-medication' phase (except in CV during session 3). However, in the 'post-onset medication' sessions there were decreases in both CV and MISV for the right hand. Immediately after medication began, there was a relatively large drop in CV and a definite but more gradual reduction in MISV in the right hand. However, an interesting result was that for the left, and less affected hand, a gradual decrease in levels of CV was observed, but little reduction in MISV was noted. After the initial decrease in levels of CV and MISV for the right hand and CV for the left hand, subsequent levels remained relatively stable.

Immediately prior to each experimental session, M.N. was examined by an independent neurologist, who had no knowledge of her daily medication. Table 3.5 shows the clinical gradings for M.N. over the experimental period. In her less affected hand only a score of one for rigidity, on the Webster (1968) rating scale was noted before sessions 4 and 8. In the more affected hand, M.N. was only mildly affected (maximum total Webster rating was between 4-8 out of 30) throughout the experimental period with only a slight increase in the total Webster rating noted during period. Immediately after the onset of medication there seemed little improvement of these, albeit mild, signs.

3.3.4. Motor timing accuracy in HD patients.

Figure 3.14A shows the mean (S.D.) group data for the mean IRIs produced during the continuation phase in five HD patients and compares the findings with mean IRIs produced during the first session (first twelve runs) by the twelve control subjects. The mean IRI of the HD group significantly differs from that of the control group (p=0.0153, Mann-Whitney);

Session	Week	WebTot	Rig	Brad	Trem	H&Y
1	0	4	1	1	1	I
2	6	6	2	1	0	I
3	10	6	2	1	1	I
4	17	6	2	1	0	I
5	19	7	2	1	0	I
6	21	6	1	1	0	I
7	25	6	1	1	0	I
8	29	7	1	1	1	I
9	33	8	2	1	0	I
10	39	6	1	1	0	I
11	45	8	1	1	0	I
12	51	7	1	1	0	I
13	56	8	1	1	1	I
14	60	8	1	2	0	I
15	64	8	1	1	0	I

Table 3.5. Clinical gradings using the Webster (1968) disability rating, and the Hoehn and Yahr (1967) staging (H&Y) for M.N.'s more affected (right) hand over the fifteen experimental sessions. WebTot represents the total Webster rating (ten clinical signs; maximum score, 30), while Rig, Brad and Trem represent the individual clinical scores for rigidity, bradykinesia and tremor respectively. These signs were deemed to be most likely to demonstrate an asymmetry and/or medication effect. The less affected (left) hand a score Webster rating score of 1 for rigidity was noted on sessions 4 and 8; all other clinical signs being scored as zero on other session times.

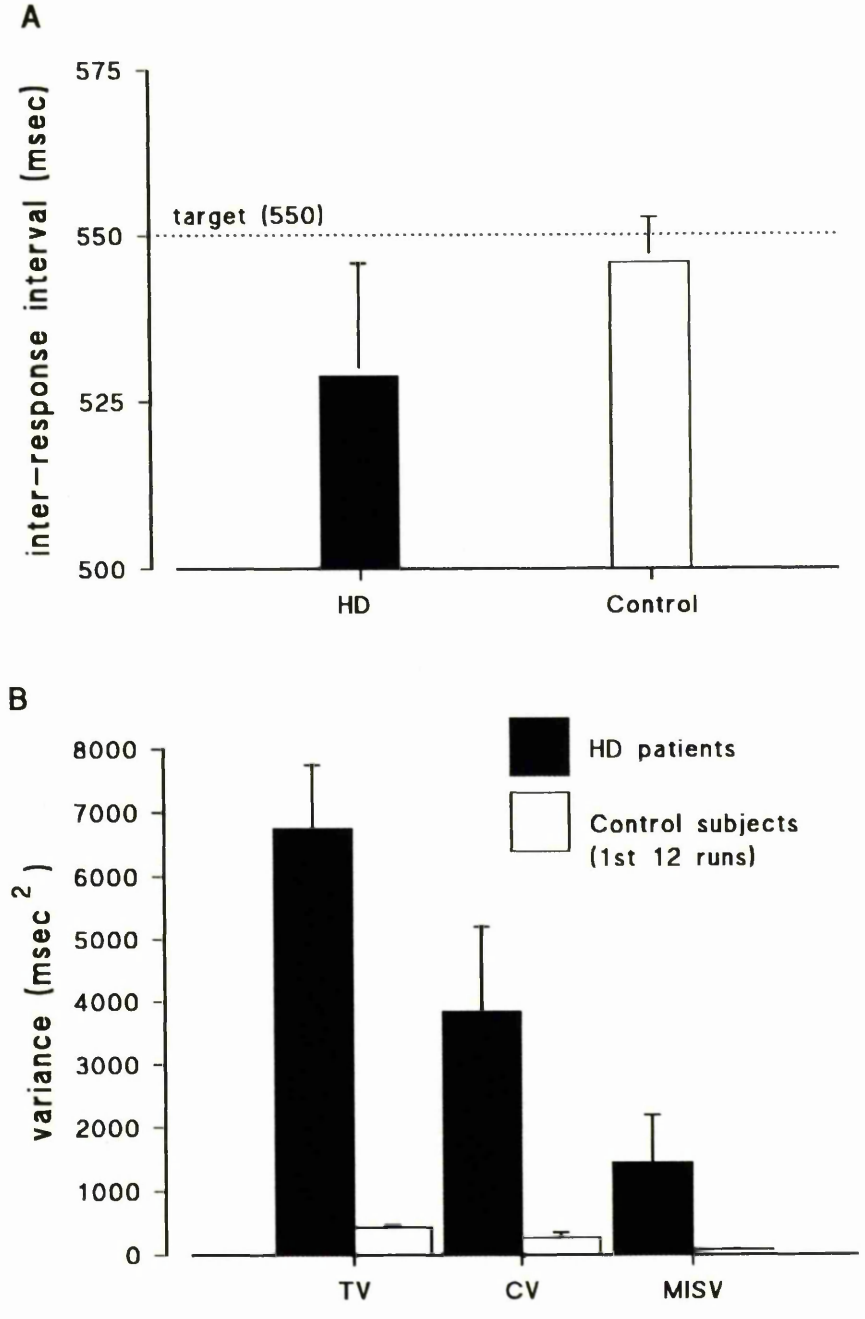

Figure 3.14. Mean (S.D.) group data for mean IRI (**A**) and TV, CV and MISV (**B**), for five HD patients and the first twelve runs obtained from 12 control subjects. Significant differences were found between the HD and control group for IRI (p=0.0153, Mann-Whitney) and TV, CV and MISV (p=0.0016, for each variable, Mann-Whitney).the HD group differed significantly from that of the control group (p=0.0153, Mann-Whitney); the patients produced shorter intervals than both the control group and the required target interval.

the patients produced shorter intervals than both the control group and the required target interval.

Mean (S.D.) values for TV, CV and MISV for the HD and control groups are shown in Figure 3.14B. The mean TV produced by the patients was significantly larger than that produced by the control group (p=0.0016, Mann-Whitney). When TV was decomposed into CV and MISV, using Wing and Kristofferson's (1973) model, it was found that the mean CV and MISV were significantly larger in the patient than the control group (p=0.0016, for both variables, Mann-Whitney).

3.3.5. Violations of predictions underlying Wing and Kristofferson's (1973) model: investigation into four different methods of analysis.

All the results so far reported in this chapter were obtained from those experimental runs, when analysed, contained *no* violations of the predictions underlying Wing and Kristofferson's (1973) model. In other trials, two types of violations were observed, namely, positive lag-one autocovariance and/or negative CV (the model predicts that lag-one autocovariance should be negative and CV should be positive, see section 3.1.6). Indeed, it was found that a significant number of trials performed in the present work contained such violations. Table 3.6 lists the actual number of trials which contained violations and expresses these values as percentages of the total number of trials. Data were shown for control, PD 'asymmetry' and 'medication' and HD group studies.

Table 3.6 shows that the incidence of negative CV is low across the various groups the highest incidence being 1.5% of trials in the PD 'off' group. In the first control session

GROUP	runs *n*	+lag1 *n*	%	-CV *n*	%	either *n*	%
CON (1st 12)	144	33	22.9	0	0	33	22.9
CON (2nd 12)	141	42	29.8	2	1.4	44	31.2
PD 'on'	197	61	31.0	0	0	61	31.0
PD 'off'	195	67	34.4	3	1.5	70	35.9
PD less	216	62	28.7	1	0.5	63	29.2
PD more	212	60	28.3	3	1.4	63	29.7
HD	53	3	5.7	0	0	3	5.7

Table 3.6. Group data pooled for the incidence of two types of violations of the predictions central to Wing and Kristofferson's model for repetitive movements. Violations are shown as actual numbers (*n* is the number of trials) and as a percentage (%) of the total number of trials performed. CON (1st 12 and 2nd 12) represent control group data from the first 12 runs and the second 12 runs (first and second session respectively). PD 'on' and 'off', and more and less affected hand represents pooled data from PD patients on the 'medication study' and the 'asymmetry study', respectively, whilst HD represents results from the study using HD patients. +lag1 represents those trials which violated the predictions of the model by producing positive lag one autocovariances, whilst -CV represents trials which produced negative CV.

and the PD 'on' and HD groups no trials contained negative CV. However, for each group apart from the HD group, a significant percentage of trials contained positive lag-one autocovariances. The highest percentages were seen in the PD 'medication study' in which 34.4% and 31.0% of trials contained such violations when patients were 'off' and 'on' respectively. Similar percentages were seen in the PD 'asymmetry study' and the second control session. However, the percentage was lower (22.9%) in the first control session and considerably lower in the HD group (5.7%).

Different workers have used different methods to analyse data using Wing and Kristofferson's (1973) model with regards to incorporating trials which violate the predictions provided by the model (see 3.2.5). In the present study data for the PD and control groups have been analysed using four different methods. The first method (**A**) was to include only trials, in the final analysis, which contained no violations. This method was used in the previous sections of this chapter. Method **B** involved averaging *all* trials produced by a subject, to increase the possibility of obtaining a final average which did not violate the predictions. Method **C** had been previously implemented by Ivry *et al* (1988) and Ivry and Keele (1989). In this method, any trials which contained negative CV were discarded, but in trials containing positive lag-one autocovariance, all variance was attributed to CV, and MISV was set at zero. Method **D** had been previously employed by Pastor *et al* (1992b), who analysed only one trial; the first to contain no violations.

Figures 3.15, 3.16 and 3.17 show the mean (S.D.) TV, CV and MISV for control, PD 'asymmetry' and PD 'medication' groups respectively, when the data was analysed using the four methods (A, B, C and D) outlined above. In Figure 3.15 (control data), levels of

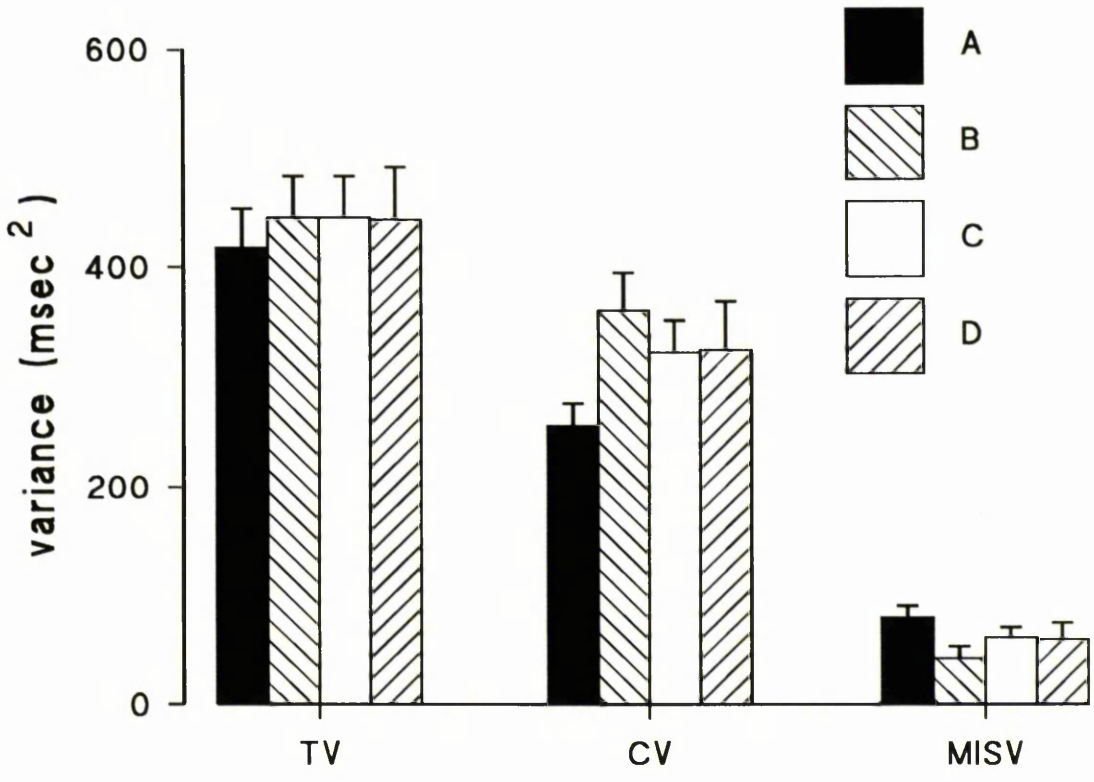

Figure 3.15. Group mean (S.D.) TV, CV and MISV for 12 control subjects using four different methods of analysis. The four analyses (A, B, C and D) comprise of four different methods of managing trials containing violations of predictions of Wing and Kristofferson's (1973) model, either in the form of positive lag-one autocovariance or negative clock variance (see 3.1.6. and 3.2.5). The four methods employed are; A, only using those runs containing no violations, $n=17.3$ (0.9), mean (SEM); B, taking the mean of the total number of trials regardless of violations, $n=23.6$ (0.02); C, on trials which contain positive lag-one autocovariance, all variance attributed to CV (MISV is zero, Ivry and Keele, 1989), $n=23.6$ (0.02); D, analyse the first violation-free trial produced ($n=1$, Pastor *et al*, 1992b).

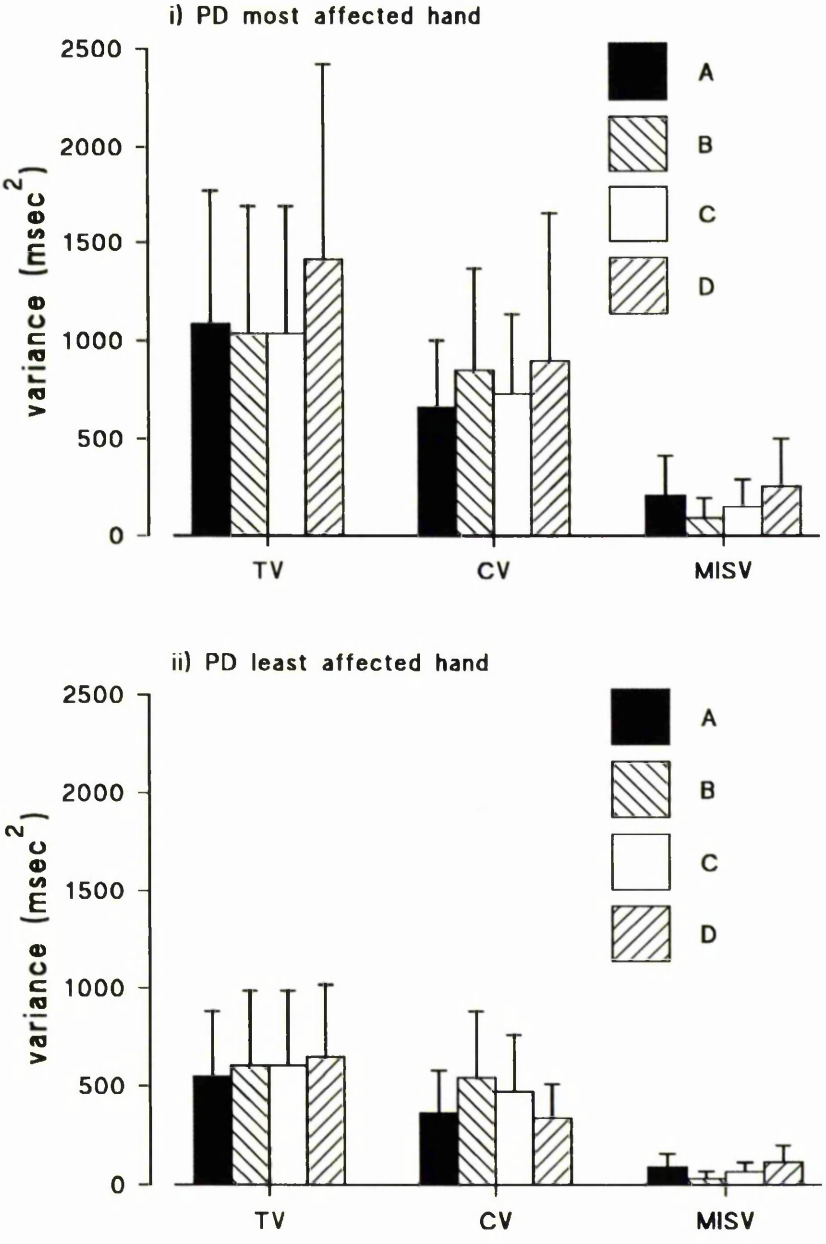

Figure 3.16. Group mean (S.D.) TV, CV and MISV for 12 PD patients who exhibited asymmetrical neurological signs on examination, using four different methods of analyses. In **i)**, results for the more affected hand are shown, while in **ii)**, results for the less affected hand are presented. The four analyses (A, B, C and D) comprise of four different methods of managing trials containing violations of the predictions of the model, either in the form of positive lag-one autocovariance or negative clock variance (see 3.1.6. and 3.2.5). The four methods employed are; A, only using those runs containing no violations, $n=12.5$ (0.7), mean (SEM); B, taking the mean of the total number of trials regardless of violations, $n=17.5$ (0.77); C, on trials which contain positive lag-one autocovariance, all variance attributed to CV (MISV is zero, Ivry and Keele, 1989), $n=17.5$ (0.77); D, analyse the first violation-free trial produced ($n=1$, Pastor *et al*, 1992b).

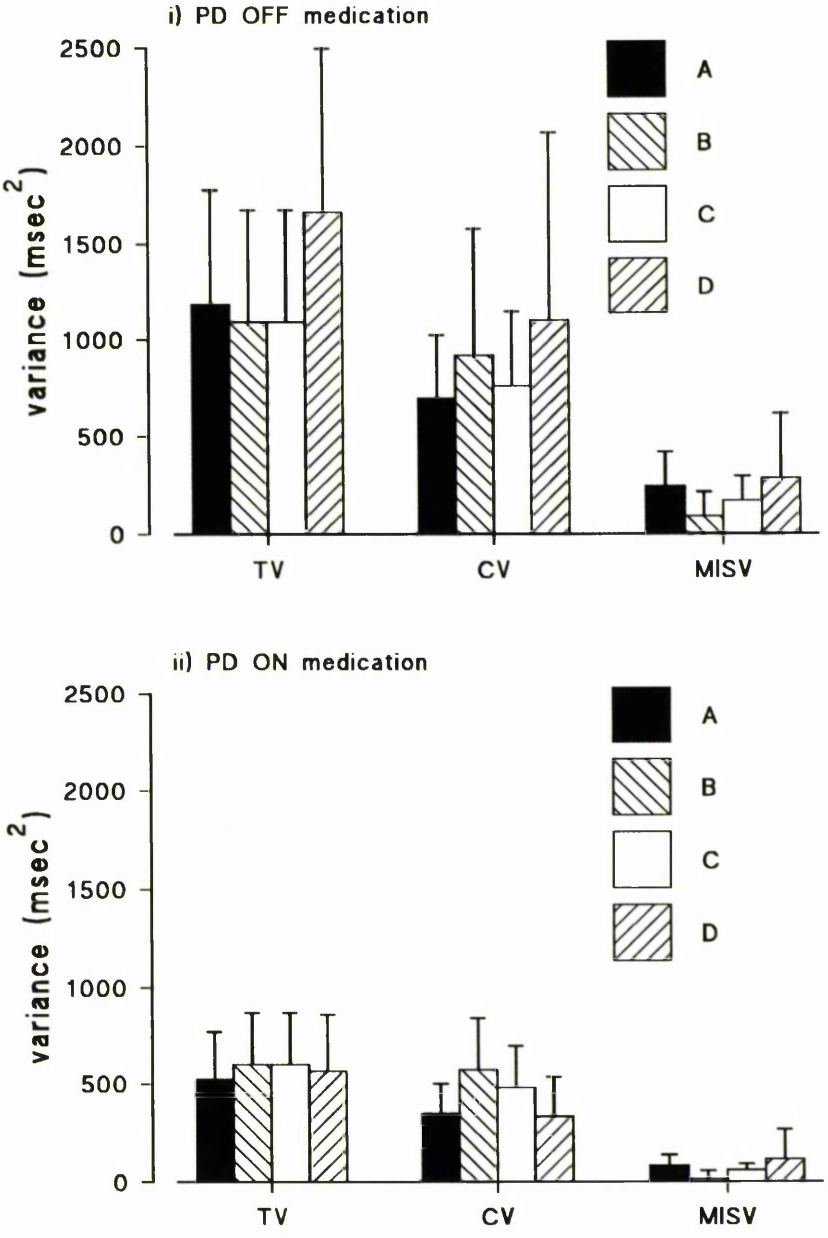

Figure 3.17. Group mean (S.D.) TV, CV and MISV for 12 PD patients, tested twice, once after 12-15 hours abstinence from L-dopa medication ('off', shown in **i**) and once one hour after ingestion of a single normal dose ('on', shown in **ii**), using four different methods of analyses. The four analyses (A, B, C and D) comprise of four different methods of managing trials containing violations of the predictions of the model, either in the form of positive lag-one autocovariance or negative clock variance (see 3.1.6. and 3.2.5). The four methods employed are; A, only using those runs containing no violations, $n=10.5$ (0.6), mean (SEM); B, taking the mean of the total number of trials regardless of violations, $n=16.1$ (0.86); C, on trials which contain positive lag-one autocovariance, all variance attributed to CV (MISV is zero, Ivry and Keele, 1989), $n=16.1$ (0.86); D, analyse the first violation-free trial produced ($n=1$, Pastor *et al*, 1992b).

TV were similar regardless of the mode of analysis. The total numbers of trials analysed using each criteria were 23.6 (0.02), mean (S.E.M.), for B and C, and 17.3 (0.9) for A. The number of trials analysed in D was, by definition, one. CV was higher and MISV lower when the data were analysed using method B and C compared to method A due to the criteria for analysis. However, values of TV, CV and MISV for A, B, C and D were relatively similar regardless of the method of analysis.

Comparable findings can be seen in Figure 3.16 and Figure 3.17 which show, respectively, group data for the PD 'asymmetry study' for the more (3.16i) and less (3.16ii) affected hand and PD 'medication study' for patients 'off' (3.17i) and 'on' (3.17ii) medication. More trials were suitable for analysis using methods B and C. In the 'asymmetry' study the mean number of trials using methods A, B and C were, respectively, 10.4 (2.0), 16.0 (3.1) and 16.0 (3.1) whilst in the 'medication' trial the corresponding values were 10.5 (0.6), 16.1 (0.86) and 16.1 (0.86). Relatively similar values were obtained regardless of method of analysis, although methods B and C produced slightly higher CV and lower MISV levels than did method A in all four groups. However, in the more affected hand and 'off' medication state, method D produced slightly higher values for TV, CV and MISV with greater standard deviations around the mean.

3.3.6. Corrections for estimator-bias: comparison between observed and predicted values at lags 2-5.

A further prediction of Wing and Kristofferson's (1973) model is that autocovariance at lag two onwards should be zero. Violations of the model may be deemed to have occurred

if the observed value at lags greater than one are significantly different from zero (see 3.1.6). However, the observed (calculated) autocovariance function is biased in relation to the size of the sample, whereas the theoretically-predicted value (of zero) of the autocovariance function is unbiased (see 3.2.6). As bias in the estimator can be large, especially when the number of response intervals is only thirty (Vorberg and Hambuch, 1978) a calculation for estimator-bias should be performed. I have chosen, like Vorberg and Hambuch (1978) and Wing (1979) to compare the biased observed value with a biased expected (theoretical) value of the estimate.

Figures 3.18, 3.19, 3.20 and 3.21 show data for lags 2-5 for control, PD 'asymmetry', PD 'medication' and HD groups respectively. For each group I have tested at each of lags 2-5, for significant deviations of the estimated autocovariance from the biased expected value; the latter being calculated by inserting obtained estimates from the data for the autocovariance function at lags zero and one into equation 6 (section 3.2.6iii). Each of the figures show the new calculated biased theoretical value (shown by a dotted line) and the biased observed value. Also shown are the 95% confidence intervals (+/- 2 S.E.M.) around the observed values. Significant differences between observed and predicted values were considered to have occurred if the biased predicted value fell outside the confidence intervals.

In Figure 3.18 control data for the first session (**A**), the second session (**B**) and all runs (**C**) are shown. The overall pattern was that covariance was slightly higher at lags 3 and 4, compared to lags 2 and 5 in each session and when the sessions were tallied. The theoretical predicted value fell within the confidence limits at all lags apart from at lags

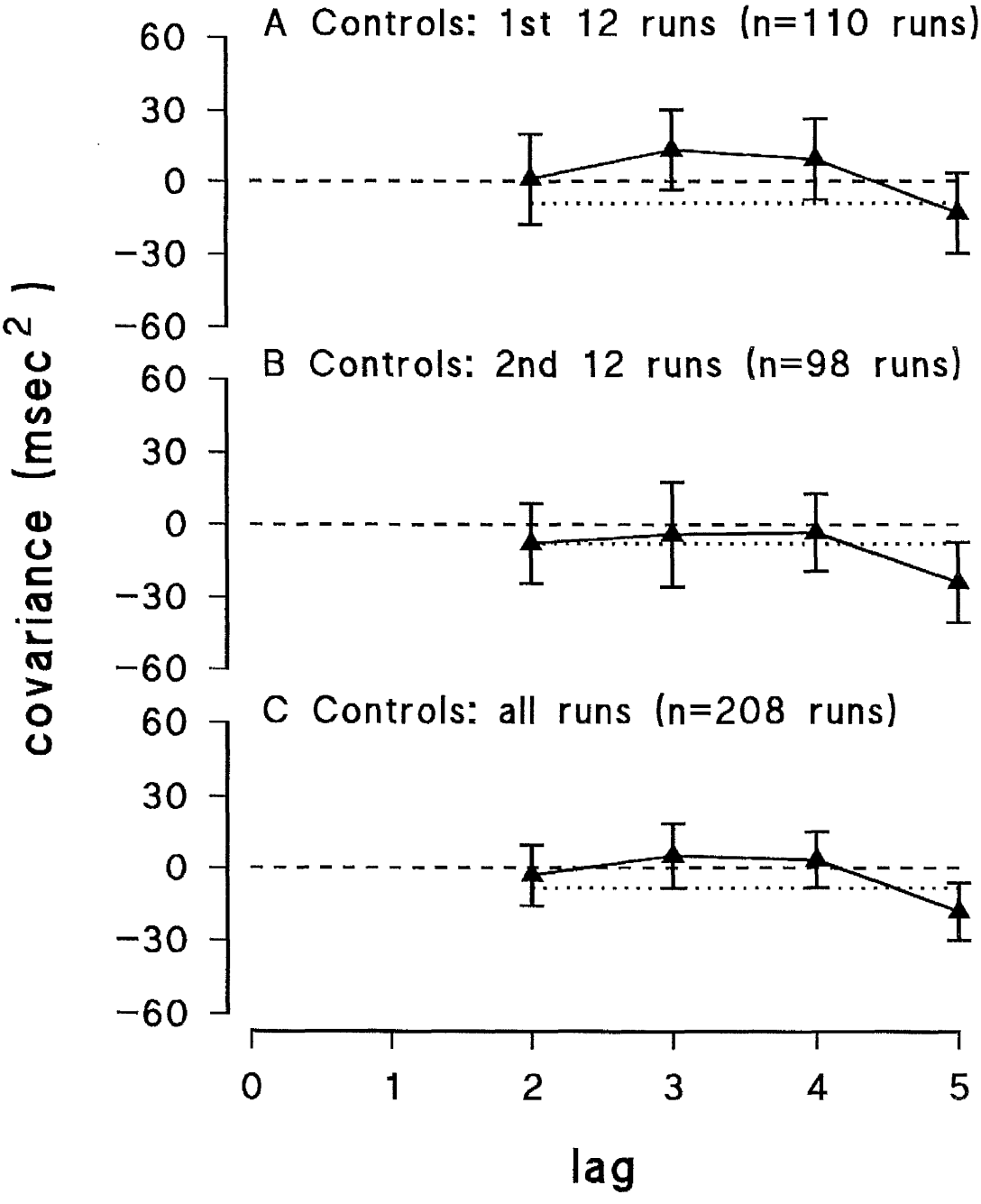

Figure 3.18. Group data pooled across all control subjects for **A** 1st 12 runs, **B** 2nd 12 runs and **C** all runs. Graphs show violations of covariance at lags 2-5 which are predicted to be zero (dashed line; Wing and Kristofferson, 1973; section 3.1.6). Dotted lines represent the predicted value (zero) corrected for estimator-bias (equation 6, section 3.2.6 iii) for values of lag 2-5. The triangles represent the mean observed values (which are *biased*), while the error bars represent +/- 2 SEM (95% confidence intervals). If a predicted value falls outside the 95% confidence interval of the observed value, the predicted value was interpreted as being significantly different to the observed value.

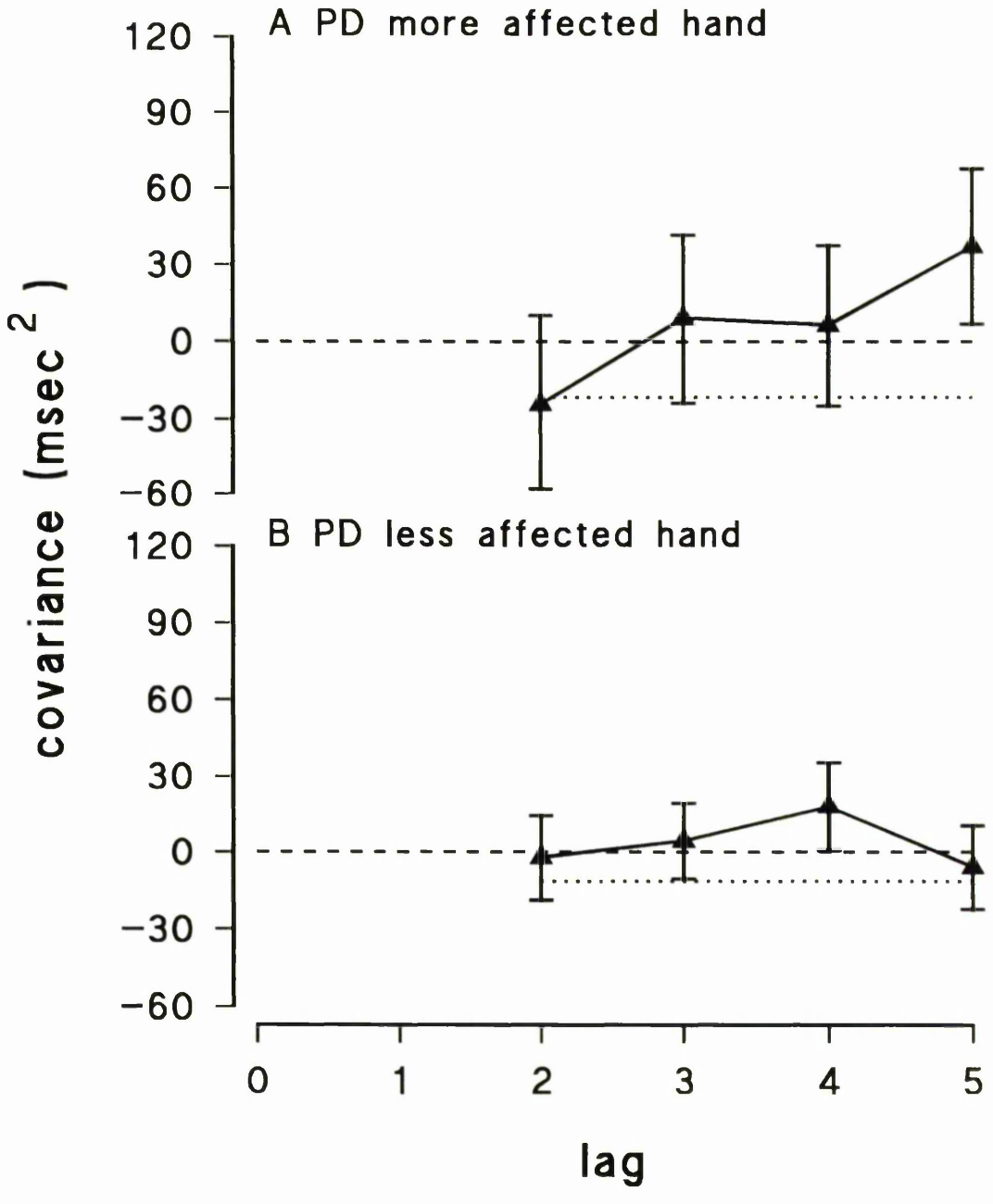

Figure 3.19. Group data pooled across PD patients in the 'asymmetry' study using **A** the more affected hand and **B** the less affected hand. Graphs show violations of covariance at lags 2-5 which are predicted to be zero (dashed line; Wing and Kristofferson, 1973; section 3.1.6). Dotted lines represent the predicted value (zero) corrected for estimator-bias (equation 6, section 3.2.6 iii) for values of lag 2-5. The triangles represent the mean observed values (which are *biased*), while the error bars represent +/- 2 SEM (95% confidence intervals). If a predicted value falls outside the 95% confidence interval of the observed value, the predicted value was interpreted as being significantly different to the observed value.

3 and 4 in the first session. However, the predicted value was not significantly different from the observed values at lags 3 and 4 during the second session. Additionally when the two sessions were combined, the predicted value did not significantly differ from observed values at any lag.

Figure 3.19 shows data from the PD 'asymmetry study' for the more (**A**) and less (**B**) affected hand. For both hands, the observed covariance at lags 3 and 4 was greater, and positive, than at lag 2 (which was negative for both hands). Covariance at lag 5 was greater still in the more affected hand but smaller than at lags 3 and 4 in the less affected hand. However, there were significant deviations between observed and predicated values at lag 5 for the more affected hand and lags 3 and 4 for the less affected hand. Figure 3.20 shows data for the PD 'medication study' for patients when 'off' (**A**) and 'on' (**B**) L-dopa medication. There were significant differences between observed and predicted values of covariance at lags 2, 3 and 5 in the 'off' condition and at lags 2, 4 and 5 in the condition. In all of these cases, positive values of covariance were observed. Therefore, in this patient group, of the eight possible lags for which calculations were performed violations were observed in six cases.

Data for the HD group are shown in Figure 3.21. Although, values of covariance were positive at lags 2, 4 and 5, there were no significant differences between the observed and predicted values.

3.3.7. Analysis of stationarity.

The degree of stationarity (i.e. that intervals produced during a trial do not systematically

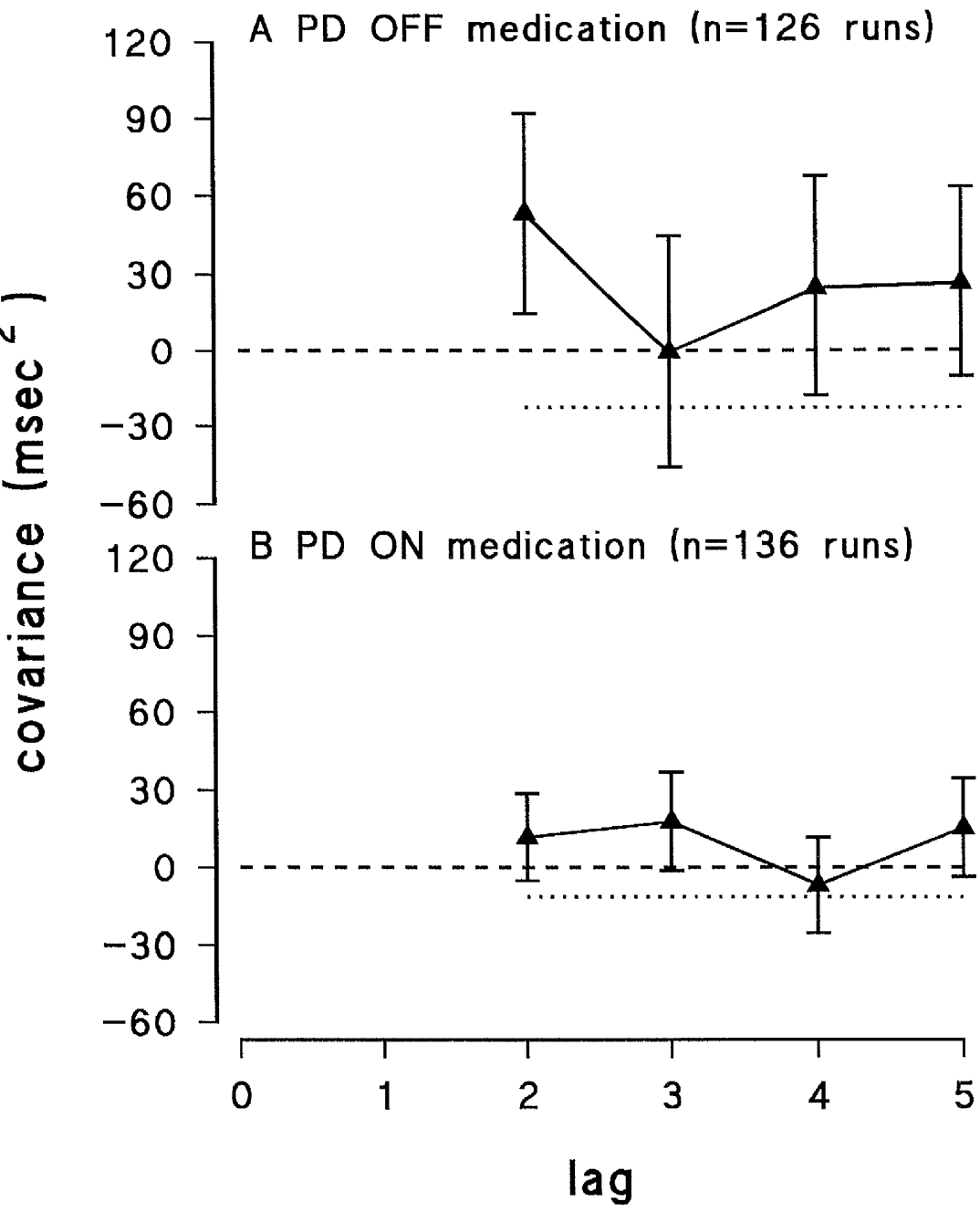

Figure 3.20. Group pooled data across PD patients in the 'medication' study while **A** 'off' medication and **B** 'on' medication. Graphs show violations of covariance at lags 2-5 which are predicted to be zero (dashed line; Wing and Kristofferson, 1973; section 3.1.6). Dotted lines represent the predicted value (zero) corrected for estimator-bias (equation 6, section 3.2.6 iii) for values of lag 2-5. The triangles represent the mean observed values (which are *biased*), while the error bars represent +/- 2 SEM (95% confidence intervals). If a predicted value falls outside the 95% confidence interval of the observed value, the predicted value was interpreted as being significantly different from the observed value.

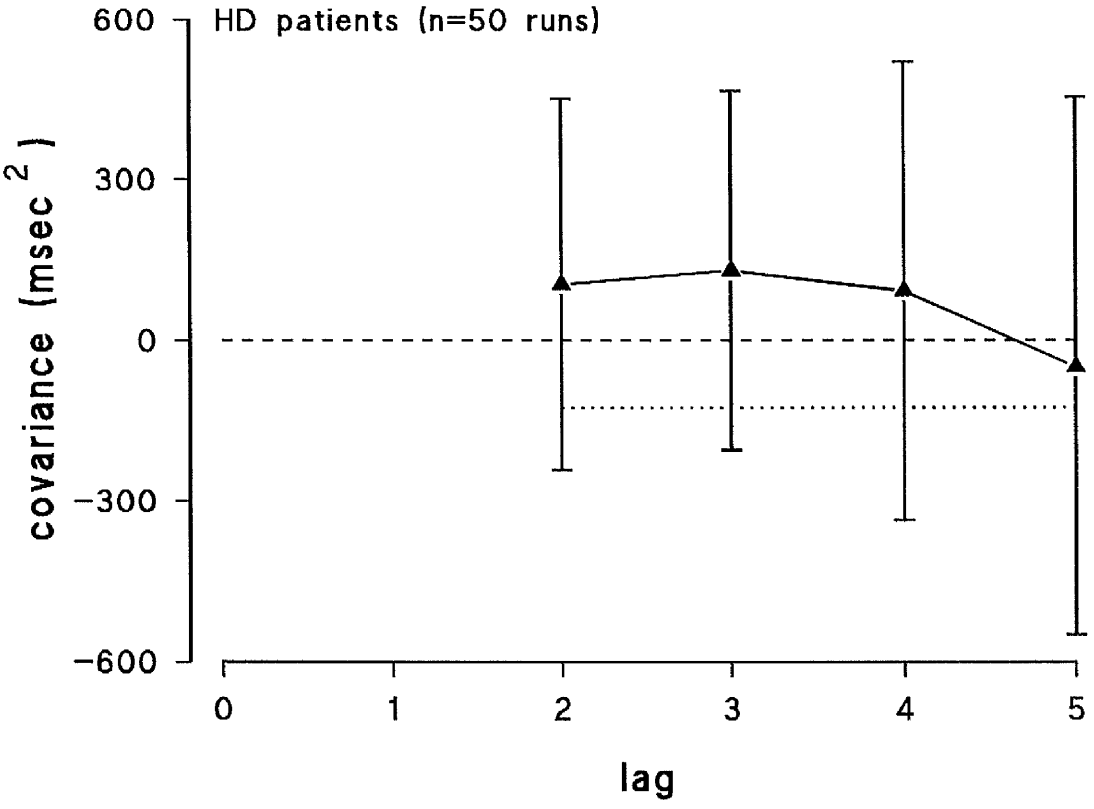

Figure 3.21. Pooled data across the HD patient group. Graphs show violations of covariance at lags 2-5, which are predicted to be zero (dashed line; Wing and Kristofferson, 1973; section 3.1.6). Dotted lines represent the calculated correction for estimator-bias, which is now the *biased* prediction (equation 6, section 3.2.6 iii) for values of lag 2-5. The triangles represent the *biased* mean observed values, while the error bars represent 2 SEM (95% confidence intervals). If a predicted values fall outside the 95% confidence interval of the observed values, then this was interpreted as evidence for the violation of assumptions underlying the model.

change with time, Vorberg and Wing, 1994) has been analysed for data collected from the PD and control groups. Three methods of analysis were employed; firstly, the fitting of regression lines in order to obtain values for the slope, intercept and r^2 for the line, secondly, a comparison of the mean of the first fifteen intervals with the mean of the second fifteen intervals and, thirdly, a comparison of the mean of the first, second and third ten intervals. Table 3.7 shows the results from the analyses in which group pooled data has been partitioned into either those runs in which the regression line was positive (Table 3.7A, i.e. trials in which the intervals were becoming longer with time - subjects were 'slowing down'), negative (Table 3.7B,i.e. trials in which the intervals were becoming shorter - the subjects was 'speeding up') or irrespective of sign of slope (Table 3.7C).

Tables 3.7A and 3.7B show that the percentage of trials which contained either a positive or negative sign for the regression slope varied both between and within the subject groups. In the control groups 23% of the trials within the first twelve runs contained positively-sloped regression lines compared with 53% during the second twelve trials. Therefore, in the second session of experimental trials, the control subjects produced more sequences of IRIs which became slower with time. In the PD groups the percentages were more stable; approximately 40% of all trials produced positively-sloped regression lines. From Tables 3.7A and 3.7B, it can be noted that for control subjects in both the first and second experimental sessions, the mean size of the regression-line slope was approximately 0.4 in the trials containing positive slopes and -0.4 in the trials containing negative slopes. Over thirty intervals this represented a net change of (30 x (-)0.4) 12 msec over the duration of the continuation phase. The magnitude of the slope was higher in all PD

A POSITIVE SLOPES ONLY

Group	%	GM	M1	M2	MA	MB	MC	INT	slope	r^2
1st C	23	549	546	553	544	551	554	542	0.48	0.05
2nd C	53	549	546	552	545	549	553	543	0.37	0.03
PDoff	37	552	544	561	541	553	563	535	1.11	0.10
PDon	43	539	535	543	534	538	544	532	0.45	0.04
PDmr	44	545	538	551	536	544	554	533	0.80	0.09
PDls	40	547	544	551	542	549	552	540	0.49	0.05

B NEGATIVE SLOPES ONLY

Group	%	GM	M1	M2	MA	MB	MC	INT	slope	r^2
1st C	77	545	548	542	549	545	541	552	-0.44	0.05
2nd C	47	548	550	545	552	547	544	554	-0.41	0.04
PDoff	63	532	539	525	542	531	524	548	-0.98	0.11
PDon	57	532	536	527	537	532	526	541	-0.60	0.08
PDmr	56	532	539	525	541	532	523	546	-0.93	0.08
PDls	60	535	540	530	542	535	529	545	-0.64	0.07

C IRRESPECTIVE OF SIGN OF SLOPE

Group	GM	M1	M2	MA	MB	MC	INT	slope	r^2
1st C	546	548	544	548	546	544	550	-0.23	0.05
2nd C	548	548	549	548	548	549	548	0.01	0.04
PDoff	540	541	539	542	539	538	543	-0.21	0.11
PDon	535	535	534	536	535	533	537	-0.14	0.07
PDmr	538	539	537	539	538	537	540	-0.16	0.08
PDls	540	542	539	542	540	538	543	-0.19	0.06

Table 3.7. Group data pooled for the degree of stationarity within the intervals produced in trials. Linear regression was employed and the mean intercept (INT), slope and r^2 values were obtained (*n* numbers identical to Table 3.6). Trials were separated regarding the sign of the slope and group data (1stC/2nd C = first/second 12 runs from control subjects, PDoff/PDon = PD patients either 'off'/'on' medication during the medication trial and PDmr/PDls = more/less affected hand in PD patients during the 'asymmetry' study) for **A** those trials containing positive slopes, **B** those trials containing negative slopes and **C** all trials irrespective of sign of slope are shown. Also shown is dat for the mean IRI (GM), the mean IRI for the first and second 15 intervals (M1 and M2, respectively) and for the first, second and third 10 intervals (M1, M2 and M3, respectively).

groups, with the largest mean slope being 1.11 for positively-sloped trials in the PD 'off' group. However, this only represented a (30 x 1.11) 33.3 msec change over the duration of the trial and accounted for only 37% of the trials in this group. The mean magnitude of the slope was higher in both the PD 'off' and the PD more affected hand groups when compared with the PD 'on' and PD less affected hand group, respectively. In Tables 3.7A-C, it can be seen that throughout subject groups and regardless of the sign of the regression line slope, any change in IRI over time is relatively constant for the pooled group data. That is the difference between the mean IRI for the first and second ten intervals (MA and MB, in Table 3.7) is similar to the difference in mean IRI between the second and third ten intervals (MB and MC).

The r^2 values represent the degree to which the regression line accounts for the variability within the IRIs. For example, in the control group first session, 5% (0.05) of the variability can be accounted for by the regression line. This gives an estimate of the 'goodness of fit' and validity of the regression line. In this case, the regression line did not account for 95% of the variability in the IRIs. The PD'off' group produced data which contained the highest value of r^2, however, this only accounted for 11% (0.11) of the variability.

CHAPTER 3.4: DISCUSSION.

During sequences of finger movements, produced after an initial synchronisation phase and during a non-cued continuation phase, variability around the mean IRI was decomposed into that attributable to a hypothetical central 'clock' and that attributable to a hypothetical 'motor-implementation' system, as described by Wing and Kristofferson (1973) in their theoretical model for the control of repetitive timed movements, for various groups of PD patients, HD patients and control subjects.

In PD patients with symmetrical clinical signs, TV, CV and MISV were significantly higher when using the more affected hand compared with corresponding values observed in either the less affected hand or control subjects. Also, in the PD 'medication' study, TV, CV and MISV were also significantly higher when the patient was 'off' medication, compared to that observed in either the 'on' medication state or control subjects. In the 'on' state there was a small increase in TV, due to CV and not MISV, when compared with that produced by control subjects. Similarly, in data which were obtained in a longitudinal study of one PD patient with asymmetrical clinical signs, a decrease in TV immediately after the onset of L-dopa therapy was observed when using both the more and less affected hands; a large decrease in the more affected hand being attributable to CV and MISV, while a smaller decrease in the less affected hand being attributable to a decrease in CV alone. In HD patients, TV, CV and MISV were extremely large when compared with control subjects: the mean values for these variables were between 7 and 10 times larger than those observed in either the PD or the control groups.

Extended analysis of the data has produced results which question the applicability of using Wing and Kristofferson's (1973) model in studying neurological disorders. The basic predictions of the model are that covariance should be large and positive at lag zero, relatively small and negative at lag one and zero for lags higher than one. However, when data for lags 2-5 were transformed to account for estimator-bias (using methods similar to those used by Wing, 1979), both PD groups produced covariance values which differed significantly from the predicted value. Similarly, approximately 30% of all trials contained positive lag one autocovariance values. The data were analysed using three other methods, including those employed by Ivry *et al* (1988), Ivry and Keele (1989) and Pastor *et al* (1992b) which dealt with such violations in different ways. However, when data were analysed using the four different methods for both PD groups and control subjects, comparison of the results found there to be little difference in the patterns of variance produced both within and between subject groups.

3.4.1. Studies involving patients with PD.

As previously discussed in section 3.1.8., there have been several studies in which repetitive movements in patients with PD have been analysed using Wing and Kristofferson's (1973) model. If it is accepted that the use of the model in the study of neurological disorders is valid, different conclusions from those drawn by previous workers can be drawn from the present findings. However, due to the inconclusive and, sometimes, confusing nature of the past studies, it is thought that within the context of the model the present work has provided more substantial evidence for the nature of timing deficits in PD patients.

Wing *et al* (1984), Wing and Miller (1984) and Ivry and Keele (1989) all reported studies using PD patients with asymmetrical clinical signs. These workers reported an increase in TV when using the more affected hand which was attributable to an increase in CV and not MISV. This was contrary to the present findings in which high values of TV in PD patients when using the more affected hand were attributable to increases in CV *and* MISV; these levels were also significantly higher than levels observed in control subjects. However, Wing *et al* (1984) and Wing and Miller (1984) used only a single patient with asymmetrical signs and reported no statistical analysis of their results. These workers also reported an increase in the mean IRI (longer inter-response intervals) of sequences in PD patients when using the more affected hand. This was contrary to the present findings, in which mean IRI tended (but not statistically significantly) to be lower both when using the more and less affected hands of patients compared with the mean IRI observed in the control subjects: these findings were echoed by results reported in Chapter 2, in which the mean tapping rates for PD patients at both 2 and 3 Hz were higher (and, therefore, the mean IRIs lower) than the tapping rates for either the control subjects, or the target interval (section 2.3.2, Figure 2.7 and Figure 2.8). Ivry and Keele (1989) and Ivry (1986) also reported increases in TV and CV, but not in MISV, when PD patients used the "impaired" as opposed to "unimpaired effector". They stated, categorically, that "there have never been any increases in the motor delay scores in either the Parkinson groups or the few Parkinson patients who had difficulty in the tapping task" (Ivry and Keele, 1989, p. 145). However, only four subjects were used, of which data from one (M.F., Ivry, 1986) had already been reported by Wing *et al* (1984) and Wing and Miller (1984). Again, no statistical analysis for the group data was reported.

Present findings in the 'medication' trial indicate that in the 'off' state PD patients had significantly higher TV, which was attributable to increases in both CV and MISV when compared with either the 'on' state or the first control session. Also, mean IRIs were significantly lower in the PD 'off' group when compared with the first control session and the PD 'on' group when compared with the second control session. However, there was no significant difference in mean IRI between the two medication states; this finding was similar to that reported for mean tapping frequencies in Chapter 2 (see section 2.3.4. and Figure 2.9). However, this was contrary to findings reported by Ivry and Keele (1989), in which no differences in mean IRI, TV, CV or MISV between patients maintained on L-dopa and those abstaining from medication were reported. In their experiments, all seven patients performed two sessions, one week apart, three patients being initially tested 'on', and four 'off'. Due to the nature of PD, neurological signs can fluctuate markedly on a day-to-day basis (Ward, 1991). It was felt that the present protocol for performing an 'on-off' trial was superior to that used by Ivry and Keele (1989), as it was possible that a patient would have felt particularly well (due to the fluctuations seen in clinical signs) on the day when performing the experiment during the 'off' stage and particularly unwell on the day when performing the experiment 'on' medication. In such a situation, it may not be surprising to observe little difference in performance between the two sessions. In the present study, all patients were tested twice on the *same* day after 12-15 hours abstinence from medication, before and after ingestion of a single dose.

The advantage in using a protocol such as that used by Ivry and Keele (1989) was that, unlike the protocol used in the present work, the 'off' stage was not always performed before the 'on' stage, minimising any 'order' effects. In the present protocol, a decrease

in variability seen when patients performed when 'on' compared to 'off' medication, may have been due to a practice effect. However, the control subjects also performed two, similarly-spaced experimental sessions. In comparing the 'off' medication session with the first control session, and the 'on' medication session with the second control session, I have attempted to balance the results for any practice effect. Also, Figure 3.9B shows a comparison between the difference in TV between 'off' and 'on' and between the difference in TV between the first and second control sessions; there was a significantly larger difference in the patient group when compared with the difference in the control group which could not be explained by practice alone.

Therefore, for the findings in the PD group studies, the basal ganglia were implicated in both the 'central clock' or 'timekeeper' and the 'motor-implementation system' hypothesised in Wing and Kristofferson's (1973) model. Increases in both CV and MISV were observed in the performance with both the more affected hand in the 'asymmetry' trial and 'off' state in the 'medication' trial when compared with the performance of either control subjects, and the less affected hand or the 'on' state, respectively. However, the medication trial provided evidence for the possibility of the basal ganglia playing a more subtle role the function of the 'central clock'. In the 'on' state, there was a tendency for an increase in TV, due to an increase in CV alone. This difference was statistically significant ($p=0.0209$, Mann-Whitney, see Figure 3.10A) when the results were compared with the second session of control subjects.

More evidence for the involvement of the basal ganglia in clock function was obtained during the longitudinal study in which a PD patient was tested monthly over a fifteen-

month period, before and during the prescription of daily L-dopa medication. Immediately after the onset of medication, TV, CV and MISV were all reduced in the more affected hand. TV in the less affected hand was also reduced after the onset of medication, but this seemed to be attributable to a decrease in CV alone. Keele and Ivry (1987) reported results from a 'longitudinal' study, in which a patient was tested over several weeks, the first occasion being prior to any daily medication being prescribed. They found that CV declined over the first three sessions after the onset of medication, but MISV remained constant. The decrease in CV and not MISV in the less affected hand of the patient after medication onset in the present longitudinal study may be interpreted as evidence for the involvement of the basal ganglia in clock function which was observed before the onset of detectable clinical signs in that effector. However, due to the very nature of the longitudinal study (that is, only one subject, a lack of suitable controls and any statistical analysis), any conclusions must remain tentative.

Data from the longitudinal study provide further evidence for the effect of practice. Peters (1976) reported a practice effect during a simple repetitive finger movement task. Keele and Ivry (1987) reported that they had "*never* found there to be much benefit on the tapping task from practice after the first couple of trials" (p. 208). However, during the pre-medication phase of the longitudinal study, M.N. produced response sequences in which the mean IRI scores became closer to 550 msec (the target interval) as the sessions progressed. This may be explained by the effect of practice; the clock program which produced intervals of 550 msec having become more entrained. In the group studies, control subjects show a small but clear reduction in TV in the second experimental session when compared to the first session and this was due to a reduction in CV (and not MISV).

Practice is more likely to decrease random variation in the 'clock' as opposed to decreasing random variation in the 'motor-implementation' system.

Therefore, increases in both CV and MISV may be informative regarding the causes of poor performance in motor timing tasks in PD patients, whilst smaller increases in CV alone in patients in whom clinical signs are difficult to detect, may represent a more fundamental involvement of the basal ganglia in motor timing. However, increases in TV may have been due to the clinical signs observed in PD patients which are manifest as motor disorders. Therefore, the present experimental findings might simply have been due to clinical signs such as muscular rigidity, bradykinesia or tremor exerting an influence on performance, especially in the form of an increase in MISV. An effect due to bradykinesia seems unlikely for two reasons; firstly, a target interval of 550 msec was chosen specifically to minimise the effects of bradykinesia. Work described in Chapter 2 had shown that PD patients were capable of producing series of responses at 2 Hz (500 msec) in which no detectable effects of bradykinesia were noted (on average, patients produced shorter intervals than the target interval, and, therefore tapped too quickly). Secondly, the reciprocal tapping data in the present work showed that PD patients were able to produce tapping speeds in a more complex movement which were much faster than would be required in tapping at 550 msec.

Tremor might have influenced production of accurate IRIs. However, any trials containing an interval of more than $\pm$50% of the 550 msec (i.e. less than 275 msec or greater than 825 msec) target interval were rejected. This happened infrequently and usually during the initial 'familiarisation' trials. If tremor was driving tapping performance it may be

surmised that intervals of less than 250 msec would be produced because classical parkinsonian tremor has a frequency of between 4-6 Hz. In the longitudinal study, the patient who produced consistently higher levels of TV, CV and MISV using the more rather than less affected hand during the course of the experimental period, had *no* (which could be detected by a neurologist) tremor either at rest or during voluntary movements. However, tremor may result from the discharge of neural oscillators (Alberts, 1972; Lee & Stein, 1981) and these oscillations may have interfered with oscillators which were used in the timing of movements (see Keele and Ivry, 1987) at a more central level. Therefore, tremor may have had a more fundamental influence on performance. In future experiments an attempt to correlate tremor (and other clinical signs) with levels of CV and MISV may provide a further insight into the influence of tremor. However, in experiments documented in Chapter 2, similar correlations provided little indication that 'tapping performance' was related to clinical signs.

3.4.2. Motor timing in HD patients.

To date, the timing of repetitive movements in HD patients has never been analysed using Wing and Kristofferson's (1973) model. The present work produced two main findings; firstly, HD patients produce mean IRIs which were shorter than both the target interval and those produced by control subjects, and secondly, extremely high levels of TV were associated with the mean IRIs which were attributable to significantly high levels of both CV and MISV when compared to those produced by control subjects.

The first finding is in agreement with observations reported in Chapter 2 in which findings suggested that HD patients produced mean tapping frequencies which were slightly higher

at target frequencies of 1 and 2 Hz (1000 and 500 msec, see Figure 2.12A) during the non-cued phase. Nagasaki *et al* (1981) also reported instances of increased tapping frequencies in HD patients in cued-phases of their experiments (in the form of 'hastening') but whether this finding was observed (by Nagasaki *et al*, 1981) in the non-cued phase is unclear.

The second main finding was that extremely high levels of TV, attributable to high levels of CV and MISV, were observed in the performance of HD patients when compared to that of control subjects, again implicating the basal ganglia in both clock and motor-implementation function. It may not seem surprising that the latter function is affected in patients with HD, a disorder in which sufferers characteristically exhibit abnormal movements. The degree to which these abnormal movements directly affected tapping performance in the present experiments is less clear. Rigidity and bradykinesia can in some cases affect single finger movements (Hefter *et al*, 1987; Thompson *et al*, 1988) in HD patients. However, Table 2.3 shows that when assessed by an independent neurologist, none of the HD patients exhibited any clinical signs of rigidity or tremor and only one patient exhibited detectable bradykinesia. Four of the five patients had difficulty performing a rapid finger-thumb test in which the patient touched the thumb on each of the fingers of that hand. Patient performance was unlikely to have been affected by bradykinesia as mean IRIs produced were shorter than required (that is, similar to PD patients, HD patients tapped too quickly rather than too slowly). Involuntary choreiform movements might have influenced motor timing. However, in agreement with Hayden (1981), in those patients who exhibited choreiform movements, undertaking of a task (in this case the experimental task) typically reduced the degree of involuntary movement for

the duration of the task. Due to the nature of the involuntary movements, any chorea-like jerks tended to result in a 'missed' tap and therefore the subject produced an interval of 825 msec or longer; such trials being discarded. However, the high values of MISV seen in patients with HD may be partly attributable to the mechanisms underlying the choreiform movements.

When compared with control subjects, HD patients also produced high CV. However, it was discussed in section 2.4.6., that an impairment of cortical function common in HD may be evident in perceptual-motor tests (Girotti *et al*, 1988). It may be possible that an increase in TV was partly due to a cognitive defect in which the motor program was not accessed or assimilated correctly in cortical rather than striatal regions. Bradshaw *et al* (1992) reported experiments in which HD patients performed sequential button pressing tasks. They concluded that in HD, impaired motor programming was indicated by patients' difficulty in initiating movements in the absence of external visual cues, and by their problems in utilising advance information to control movement. The authors inferred that the basal ganglia "have a role in the activation and spatial representation of movement". Heindel *et al* (1988) suggested that patients with HD have problems generating the programs for movement. However, like Bradshaw *et al* (1992), the authors did not discuss the possibility of cortical, in addition to striatal, involvement.

3.4.3. Violations of the predictions underlying Wing and Kristofferson's (1973) model; how applicable is the model in the study of neurological disorders?

During collection of the data, numerous trials contained violations of the predictions underlying Wing and Kristofferson's (1973) model. There were two main types of

violations. Firstly, a percentage of all trials contained, on calculation, a statistical structure such that the value of the lag-one autocovariance function was positive. The model explicitly predicts that autocovariance at lag one should be negative (as explained in sections 3.1.6.and 3.1.7). However, it was found that in the PD and control groups between 22.9 and 34.4% of all trials contained a statistical structure such that lag-one autocovariance was positive. Only in the HD group was the percentage considerably lower (5.7%). Two questions arise: how does one deal with trials containing such violations and when does the regularity with which trials contain violations become so serious as to question the integrity of the model?

In the past, several papers in which data have been analysed using the model make mention of the problem of positive lag-one autocovariance. Ivry and Keele (1989) typically attributed the problem to one of sampling using only small numbers of trials. However, different workers have used different methods of dealing with such violations; none seem entirely satisfactory. The choice of method for dealing with trials containing violations would have affected the final interpretation. I have analysed the data in four ways (see 3.3.5.), three of which have been described by other workers. Ivry *et al* (1988) simply took the average of all trials regardless of violations. This method seems undesirable as, by definition, it involves the distortion the estimates for CV (overestimated) and MISV (underestimated). Ivry and Keele (1989) used a method in which all variance was attributed to the clock in trials containing violations at lag-one, and MISV was set to zero. Again, using this method will overestimate CV high and underestimate MISV. In studies of PD patients, Ivry and Keele (1989) found increases in only CV, and not MISV, in the more "impaired effector". In the present findings in which only trials containing no

violations were used, it was found that both CV *and* MISV were significantly higher in the more affected hand of patients with asymmetrical PD. Pastor *et al* (1992b) chose to analyse only a single trial for each subject, i.e. the first trial which contained no such violations. Although, unlike the methods used by Ivry *et al* (1988) and Ivry and Keele (1989), using this method escapes the problem of underestimation of MISV, it contains numerous sampling and statistical problems (see section 3.1.8). The way in which I chose to deal with trials containing violations at lag-one was to discard any such trials, and take the average of a the remaining 'non-violating' trials. The validity of such a method may be questioned as, because methods which overestimate CV (Ivry *et al*, 1988; Ivry and Keele, 1989) have been used in the past, my method, in comparison, may be deemed to overestimate MISV. However, such a method provides a data set which is free from violations of the prediction of the lag-one autocovariance function and therefore within the context of the model, allows satisfactory inferences to be made.

When the present data set was analysed using each of the four methods described above, surprisingly little difference was seen in the mean group data for PD patients and control subjects. However, the various disadvantages associated with each of the three methods employed by other workers were apparent. Using the methods of Ivry *et al* (1988) and Ivry and Keele (1989) (methods B and C, respectively, in section 3.3.5), calculated values for CV were consistently higher and the estimates for MISV consistently lower than those calculated using my method. In addition, the standard deviation around the mean estimates using the method employed by Pastor *et al* (1992b) (method D, in section 3.3.5) tended to be larger than for the other methods, which exemplified the statistical sampling problem associated with this method in which only one trial was analysed.

Although there were no notable differences in TV, CV or MISV when the data set was analysed using the four different methods, this should not detract from the importance of the choice of method used to deal with trials containing violations at lag-one. This lack of difference in the outcome using the methods of analysis, was due to the large experimental effects. However, previous workers (Wing *et al*, 1984; Wing and Miller, 1984; Ivry *et al*, 1988, Ivry and Keele, 1989; Pastor *et al*, 1992b) reported experiments using either fewer numbers of PD patients and/or little or no statistical analysis. In these cases, it may have been that the choice of method used was important in defining the overall pattern of the findings.

Another prediction of the model is that autocovariance at lags higher than one (2-5) will be zero. The present data set contained violations of this prediction. It was found that when data from all trials (containing no violations at lag-one) were pooled for each group, there were significant differences between the observed and expected values in many cases. There was a significant difference between the predicted value of 'zero' and the observed value at lags 3 and 4 in the first session of the control subjects, at lag 5 using the more affected hand and lags 3 and 4 using the less affected hand of PD patients in the 'asymmetry' trial, and at lags 2, 4 and 5 in the 'off' phase and 2, 3 and 5 in the 'on' phase in PD patients on the 'medication' trial.

The observed values were compared against 'zero' (the prediction of the model). However, in order to account for estimator-bias, a new predicted value (corrected for estimator-bias) was calculated following the methods employed by Vorberg and Hambuch (1978). As explained in section 3.2.6., the observed values of the auto-covariance function are biased

(as they are only a sample of the population of probably infinite size) and this bias can be large for $n=30$ intervals. To account for this bias, a correction is needed; one can either 'unbias' the observed value and compare this value with the unbiased predicted value of zero, or, 'bias' into the predicted value and compare this value with the biased observed value. I chose to do the latter, using the method employed by Vorberg and Hambuch (1978).

In the PD patient group, especially, violations of the prediction of zero covariance at lags 2-5 occurred. Unfortunately, unlike the problem of trials containing violations at lag-one, none of the previous workers testing PD patients have provided similar analyses or even discussed this problem. Therefore, the degree to which published data contains violations of the predictions underlying Wing and Kristofferson's (1973) model is unknown.

Two questions arise from these findings: firstly, is there any explanation for the degree of violation both at lag-one and at lags 2-5 which are common in the present data set? Secondly, what implications do these violations have for the applicability of using Wing and Kristofferson's (1973) model in the study of patients with PD?

One reason for the regularity with which trials contain violations of the predictions of the model is non-stationarity of the data; that is, a series of intervals contains drift or trend (see section 3.26.iv). Not only does calculation of the autocovariance function require the data to be stationary (Anderson, 1971), but it has been shown (Vorberg and Wing, 1994) that any trend will be associated with higher levels of positive autocovariance at *all* lags. In the data set, violations at lags 2-5 were usually due to the observed values being

positive. Calculations by Vorberg and Wing (1994) have demonstrated that if trend is introduced into a set of thirty intervals in the form of a 1 msec change per interval (e.g. a linear increase from 300 to 330 msec interval duration), the 'true' value for the lag-one autocovariance function at lag-one is raised from -25 to 44.75, therefore becoming positive and violating the prediction of the model (Vorberg and Wing, 1994, p.19).

The present data set has been analysed in order to discover the degree to which trials contained linear trend. Table 3.6 shows that although trend existed, any drift tended not to be large. The largest trend was observed in the PD 'off' medication group. Linear regression of the pooled data for those runs which contained a positive slope, produced a mean slope of 1.11 indicated a net change of 33.3 msec over thirty response interval. This change was similar to that used by Vorberg and Wing (1994) in the above calculation. In their example, this trend rendered all lags autocovariance function more positive than the 'true' value. However, the interval duration in their example was 300 msec and not the 550 msec used in the present experiments. Therefore, in comparison, a net 'drift' of 33.3 msec in the present data was not as substantial and amounted to the most severe linear trend observed in all the experimental groups. In addition, the present trend analysis was performed only on those trials whose intervals contained negative (and non-violating) lag-one autocovariance. A lack of either definite slopes or substantial r^2 values, when data from other subject groups had been analysed using linear regression techniques, suggested that linear trend could not account for the statistical structure.

However, it is possible that trend may have caused distortions of the 'true' autocovariance values. Additional analysis of the present data set may further reduce the effect of linear

trend. One possibility may be to perform an analysis using Wing and Kristofferson's (1973) model on the residuals of a linear regression of the response intervals for each trial, a procedure used by Ivry and Keele (1989). However, they found that such analysis did not change the tenor of their conclusions. Vorberg and Wing (1994) stated that "guarding against non-stationarity is of utmost importance, as acvf (autocovariance function) may be totally misleading otherwise". They went on to recommend experimental measures necessary to minimise the effects of trend including "providing a synchronisation phase, trial-to-trial knowledge of results possibly with pre-training" (Vorberg and Wing, 1994, p. 19). In the experimental protocol, all subjects were provided with a synchronisation phase, were given immediate feedback in the form of mean IRI and S.D., and were provided with a short training period prior to data collection. However, as stated by Vorberg and Wing (1994) whether the same would be true for "more complex kinds of trend remains an open problem".

The implications of the violations of the predictions of the model at both lags 1-5 for the applicability of using Wing and Kristofferson's (1973) model in the study of not only PD, but other neurological disorders remain unclear. If the frequency with which trials contain violations of the predictions underlying the model is not simply due to trend, then it may be that the assumptions underlying the model are violated. There could be some degree of dependence between the two processes or between two successive clock intervals or two successive motor delay intervals described by the model. If this were the case, then one could either refine the model to incorporate a degree of feedback, or, produce a statistical model for the control of motor timing which would explain a higher proportion of the experimental observations. Wing (1977b) performed a set of experiments, the results of

which forced him to refine the model. In experiments in which subjects were fed back a brief auditory signal of their own response event, the auditory feedback delay associated with the response was perturbed by a small amount at random. The results forced Wing to refine the model to incorporate a certain degree of compensatory feedback. However, how PD patients utilise this compensatory feedback, and the degree to which the model would need to be redefined to incorporate their performance is unknown and would require further experimentation.

3.4.4. Conclusions.

If the validity of the using Wing and Kristofferson's (1973) model in the study of motor timing is accepted, then the present work provides additional evidence for the involvement of the basal ganglia in a central 'timekeeper' or clock and a 'motor-implementation' system. The present work shows increases in variability associated with mean inter-response intervals, attributable to an increase in variability of both a 'clock' and a 'motor-implementation system', in both PD and HD patients when compared to that produced by control subjects. An increase in MISV is not completely unexpected as both HD and PD are movements disorders in which symptoms are usually exhibited in the form of motor deficits. The increase in MISV noted in PD patients is contrary to the findings of other workers.

The increase in CV may be potentially more interesting than the increase in MISV in understanding the role of the basal ganglia in motor timing. Similar inferences about the role of the basal ganglia in clock function were drawn in Chapter 2 in which an involvement of the basal ganglia in some form of timing function was suggested as an

explanation for the decrease in accuracy of performance on cessation of auditory cues, compared to that in the presence of the cues, commonly seen in PD patients. If the model is valid, then aspects of the current experimental findings provide more (albeit indirect) evidence for such involvement.

Wing and Kristofferson's (1973) model is problematic when used to study neurological disorders in order to 'map' the internal 'clock' onto structures within the CNS. However, the problem of violations (of the prediction of the model) is soluble. If the violations are due to drift in the response intervals, then further analysis may provide intervals which are stationary. If the violations are intrinsic to the tapping performance, then the model may need to be redefined to predict sequences which would more closely resemble the observed response sequences.

A more fundamental problem of Wing and Kristofferson's (1973) model is the lack of flexibility in the outcomes. By the nature of the model, experimental outcomes are limited: in comparing two groups of subjects, either CV and/or MISV will either increase or decrease. Therefore, experiments in which tapping performance was tested in patients with various neurological disorders (HD, PD in the present study, and cerebellar disease, Ivry and Keele, 1989) have furtively identified various structures within the brain in which the 'internal clock' may reside. The use of the model produces results which are not particularly selective and does not provide any further insight into the nature of the relationship between the clock and the desired structure. The lack of flexibility in the outcomes arises partially from the fact that only one variable is measured, namely the inter-response interval. Obviously, during a non-cued continuation phase this is the only

task-related variable which can be measured.

However, during the synchronisation phase in which subjects attempt to synchronise their finger tapping movements with a sequence of auditory cues, not only can one measure IRIs but one can measure the degree with which the subjects' responses are synchronous with the metronome intervals (synchronisation error). This may allow more complex biological models to be created which would explain tapping performance during a synchronisation phase. As such, a model would have to incorporate the statistical structure of the response intervals and synchronisation error intervals. A comparison between PD patients and control subjects on such a task may produce a model which provides the opportunity for more detailed inferences about the role of the basal ganglia in the control of motor timing to be made. Intuitively, it seems highly unlikely that motor timing is controlled by only two processes (as hypothesised by Wing and Kristofferson, 1973) and not, as would seem more likely, by a large number of sub-processes. The independence assumption (in which the two processes central to Wing and Kristofferson's model are deemed to be independent from feedback) would seem to be unjustified, and as mentioned, Wing (1979) has modified the model to incorporate a level of feedback.

Therefore, the next set of experiments were designed to study the nature of deficits of motor timing in PD patients during the synchronisation (cued) phase of finger tapping tasks. In discussion of the experimental findings presented in Chapter 2, it has already been observed that mean tapping frequencies were less accurate in PD patients when compared with either the target frequency or control subjects. However, I am now interested not only in response intervals, but also in the degree of asynchrony between

response and metronome intervals. Hary and Moore (1985, 1987a) produced various models which described hypothetical strategies employed by trained musicians whilst performing synchronisation experiments. The aim of the next set of experiments was to not only to quantify and characterise response, synchronisation error and delay (defined as the time between one metronome event and the *next* response interval associated with next metronome event) intervals during the synchronisation phase, but to provide a foundation by which such statistical models may be created to explain *how* PD patients perform a motor timing task.

CHAPTER 4: THE STUDY OF MOTOR TIMING DURING THE SYNCHRONISATION PHASE USING TIME SERIES ANALYSIS.

CHAPTER 4.1. INTRODUCTION.

4.1.1. Asynchrony of repetitive finger movements and metronome pulses during the 'synchronisation' phase.

The production of motor responses in synchrony with a metronome sequence (that is, the synchronisation phase quoted in previous chapters) is referred to as *temporal tracking* (see Bartlett and Bartlett, 1959; Michon, 1967). A detailed study of the performance of temporal tracking in PD patients may provide further insight into the source of deficits in motor timing reported in previous chapters. Results reported in Chapter 2 suggested that PD patients were less able than control subjects to produce accurate mean tapping frequencies during the synchronisation phase. The deficit seen in PD patients may have been due to subjects' inherent inability to produce accurately-timed, regular response intervals and/or an inability to synchronise responses to the auditory cues (metronome). If subjects were to synchronise their responses to the metronome events then, by definition, they would produce accurate response intervals and, therefore, accurate mean tapping frequencies. Asynchrony between metronome and response events may be due to deficits in the perception of simultaneity (Michon, 1968; Shaffer, 1982). Deficiencies in the estimation of temporal parameters may be interpreted as a deficit in timing as opposed to inaccuracies arising from the motor system.

Also reported in Chapter 2 was a further decrease (when compared to the performance of control subjects) in the accuracy of mean tapping frequency production on the removal of the metronome events (uncued response period - continuation phase) in the PD group, which was manifest as an exacerbation of their performance observed during the

synchronisation phase (see 2.3.2). In Chapter 3, an increase in variability in an internal timing system (as well as in the 'motor-implementation' system) was observed in PD patients during the continuation phase when compared to control subjects (if the use of Wing and Kristofferson's (1973) model is valid in the study of basal ganglia disorders). It may be hypothesised that a similar strategy is used to produce a tapping sequence during both the synchronisation and continuation phases, and that this strategy is more unstable during the latter phase because no feedback of performance can be derived from the metronome. Therefore, instability in the timing mechanism observed during the continuation phase may also be manifest during the synchronisation phase.

Therefore, it is pertinent to study the performance of PD patients and control subjects in detail during the synchronisation phase in order to determine the degree to which responses are asynchronous with respect to the metronome events. One of the initial aims of the experiments reported in this chapter was to identify and quantify the asynchrony or *error* interval (E_i), defined as the interval (in msec) between a response event and the associated metronome event. By definition, the value was negative if the response preceded the metronome (that is, the subjects anticipated the metronome) and positive if the response succeeded the metronome.

A small number of workers have all reported that trained musicians anticipate (produce negative error intervals) during synchronisation tapping tasks. Michon (1967) reported anticipatory response sequences, while Hary and Moore (1985) reported that, on average, the trained musicians in their experiments anticipated the metronome by 20 msec and this anticipation was "sometimes as large as 60 msec" (the metronome sequence, which

contained a step function, see 4.1.3, had a mean interval of 700 msec). In experiments performed by Hary and Moore (1987a), five musicians synchronised finger tapping to a sequence of random metronome intervals which had a normal distribution (mean 704 msec, S.D. 12 msec) and produced anticipatory error intervals of 24 (2.7) msec, mean (S.D.), ranging from 5 to 90 msec. Contrary to these findings, Schulze (1992) found that his trained musicians produced positive error intervals when tested at various metronome intervals. One subject produced error intervals with a mean of +27 msec when attempting to synchronise responses to a series of metronome intervals with a mean of 200 msec. The same subject produced mean error intervals of only +5 msec when the metronome interval was 600 msec. However, this discrepancy may have been due to an "unfortunate choice in the type of metronome sound" (Schulze, 1992) used in the experiment. What is clear is that the degree of asynchrony during the synchronisation phase has not been studied in PD patients or age-matched (non-musician) controls, which may be enlightening in the explanation of previously reported discrepancies in motor timing.

4.1.2. Synchronisation strategies employed in temporal tracking.

There are various types of model with which workers have designed with an aim to explain synchronisation strategies (Michon, 1967; Michon and Van der Valk, 1967; Fraisse and Voillaume, 1971; Voillaume, 1971; Hary and Moore, 1985, 1987a, 1987b). Underlying all the models is the assumption that the ability to execute a sequence of synchronised motor acts requires the subject to predict not only the future timing of an external event, but also to predict the timing of his/her response event. A synchronisation task also requires a subject to estimate the temporal association between the metronome and response sequences, that is, the degree of asynchrony between the two sequences.

Therefore, temporal tracking strategies entail two essential components. The first component is a 'resetting' event, which acts to reset a cycle process to time zero. The second component, a 'reference' interval, is a period which is started by the reset event and which culminates in the discrete event of the response (Hary and Moore, 1987a). The reference interval may include both motor and non-motor delays and is modified so that the response event 'coincides' with the metronome event. Models of synchronisation strategies must contain these two components.

A method of testing the validity of various models was introduced by Michon (1967) who was the first to study the cross-correlation functions between response and metronome intervals. To assess the relationships between metronome, response, error and *delay* intervals, D_j, (defined as the time between one metronome event and the *next* response event, see 4.2.4. and Figure 4.3), serial correlograms were calculated. A serial correlogram is a set of either auto- or cross-correlations calculated from auto- and cross-covariance functions at different lags (see 4.2.4, equations 2-7).

Hary and Moore (1985, 1987a, 1987b) have conducted elegant studies of the synchronisation strategies used by trained musicians. They assumed that a subject's performance was characterised by the correlograms. According to them, the various correlograms exhibited the subject's "systematic utilisation of an underlying, but presumably unconscious, strategy in following the instructions to tap on the beat". They postulated that a subject, presented with repeated and identical metronome sequences, will never generate identical response sequences. However, if that subject is utilising a consistent 'set of rules' when performing the synchronisation task, generated response

sequences will have similar and characteristic statistical relations (i.e. set of auto- and cross-correlations) from one sequence to the next (Hary and Moore, 1985). Hary and Moore, therefore, assumed that the set of rules followed by subject in a set of trials produces response intervals with similar correlations with the metronome sequence, rather than exact reproductions of the response sequence. They supposed that these rules collectively constituted a 'strategy'.

Four models of synchronisation will be discussed here. The two most obvious strategies are; firstly, that subjects time each interval from their preceding response, (the *response-reset* strategy, Fraisse and Voillaume, 1971) and, secondly, the next response interval is timed starting from the last metronome event (the *metronome-reset* strategy, Voillaume, 1971). Hary and Moore (1985) also put forward the *error-correction* model, in which the magnitude of the asynchrony, or error, interval has some influence on the timing of the next response. A more refined version of this model, the *mixed-reset* model, was discussed by Hary and Moore (1987a) according to which subjects use both response and metronome events randomly as resets with additional feedback from the synchronisation error.

4.1.3. Analytical methods of validation of strategies used in temporal tracking.

In assessing the validity of various synchronisation strategies, Hary and Moore (1985, 1987a and 1987b) presented results in which a number of correlograms (from lags -30 to 30, see 4.2.4) depicting metronome intervals cross-correlated with response, error and delay intervals were shown. The authors were then able to study the degree to which the subject's response sequence interacted with the metronome. However, it was obvious that if a metronome sequence containing regular intervals was used, correlograms could not

be calculated (for explanation see equation 2, 4.2.4). Therefore, Hary and Moore used metronome sequences which either contained a *step* function (Hary and Moore, 1985) or comprised *random* intervals (Hary and Moore, 1987a) with respect to a mean interval of 700 msec. The latter method had been first used by Michon (1967) and both sequences were designed to contain variability (around a mean) which was low enough to be undetected by the subject (see also Ten Hoopen and Reuver, 1967; Franek *et al*, 1988).

During a trial containing a step function, subjects synchronised their movements to a metronome sequence which contained a series of 30 intervals of 705 msec followed by a series of 30 intervals of 695 msec, which was alternated for a total of 240 intervals. Hary and Moore (1985) used this step function because the serial auto-correlogram of the metronome sequence had a characteristic shape which was relatively simple to trace (this pattern was identical to that found in auto-correlograms of metronome sequences containing step functions in the present work, see Figure 4.12A in 4.3.3). The authors proposed that any interval variable which contained a step (of duration 30 intervals) similar to that of the metronome produced similar auto-correlograms, unless the magnitude of the step was obscured by the subjects' variability. Moreover, cross-correlating the dependent variable sequence with the metronome sequence would maximise the possibility of observing the characteristic metronome shape in the other interval sequences by enhancing periodicities common to both interval sequences.

When Hary and Moore (1985) calculated serial cross-correlograms between metronome and response, error and delay interval sequences they found that all correlograms reflected the basic shape of the metronome serial auto-correlogram at "some phase or polarity".

However, an intrinsic problem in using metronome sequences containing a step function was that any correlations observed may have been due to trivial algebraic relationships arising from the definitions of the variables, rather than to a functional interaction between the subject and the metronome.

Hary and Moore (1985) argued that structural definitions implicit in the step function, and observed in cross-correlograms between the metronome and subject-generated variables, were unlikely to explain their data. However, Hary and Moore (1987a) refined their experiments to use metronome sequences which consisted of randomly-generated (taken from a Gaussian distribution) intervals with respect to a mean (S.D.) interval of 704 (12) msec. The serial auto-correlogram of the random metronome sequences used by Hary and Moore (1987a) contained no significant correlations or characteristic shape (as was also the case for the auto-correlograms calculated for metronome sequences containing randomly-generated intervals observed in the present work, see Figure 4.12B in 4.3.3). Hary and Moore (1987a) postulated that because the metronome interval correlogram lacked any structure, the presence of a temporal microstructure in a subject-generated sequence could not reflect the intrinsic structure of the metronome sequence, but rather the underlying synchronisation strategy or "the causal, functional and dynamic dependency of the tap intervals on the metronome" (Hary and Moore, 1987a).

In order to analyse the validity of a set of rules which constituted a hypothetical strategy, Hary and Moore (1985, 1987a and 1987b) used a computer to implement those rules and to produce a series of responses to the metronome events. Metronome event sequences were taken directly from data files. The computer-generated sequence of response intervals

was then processed in exactly the same manner as the experimental data. The resulting correlograms were then compared with the correlograms obtained from real data. When Hary and Moore (1985, 1987a) detected obvious discrepancies between the real data and computer-generated simulated data, they attempted to determine whether the differences were due to "a poor choice of strategy-parameters" or whether the failure was an integral part of the model. If discrepancies between real and simulated correlograms were due to "fundamentally erroneous" assumptions about the strategy, then the hypothesis underlying that strategy was rejected.

In this way, Hary and Moore (1985) were able to reject the *metronome-reset* strategy in experiments in which trained musicians were asked to synchronise their movements to a metronome containing the aforementioned step function. In the metronome-reset strategy, at the time of a metronome event the subject 'resets' his (internal) time to zero, and thereby starts a new timing cycle which will incorporate a predetermined interval ("the central delay") and a peripheral motor delay before the execution of the response. According to this strategy, the response execution was related to the previous metronome event. Hary and Moore (1985) predicted, therefore, that subjects using this strategy would be indifferent to their error interval. No attempt was made to change performance (i.e. manifest as the subject modifying the duration of the delay interval) according to the size and/or sign of the error interval. Computer-simulated data, using the rules incorporated in this strategy, produced cross-correlograms between metronome and delay intervals with very low correlation. However, the authors found that data obtained from trained musicians contained definite interactions between metronome and delay intervals in the serial cross-correlograms. Hary and Moore (1985) concluded that the lack of correlation

between metronome and delay intervals predicted by the computer simulation was clearly different from the observed relations between these intervals and therefore could not "be rectified without revising the underlying (metronome-reset) strategy".

Within previously hypothesised tracking strategies the subjects' own responses were identified as the exclusive resetting events (Fraisse and Voillaume, 1971; Michon, 1967 and Voillaume, 1971). In this *response-reset* strategy the cyclic process is initiated and terminated by the response itself, with the subject establishing the duration of the intervals between responses. However, Hary and Moore (1987b) have shown that if the response-reset strategy proceeds without correction; error intervals from previous cycles would accumulate and the variance of the error intervals would increase monotonically with time. Also, if the subject effectively ignores the reference time provided by the metronome, the probability that the error interval would eventually exceed the metronome interval would increase asymptotically to one. Even relatively accurate subjects would "wander" and as a result of an inability to reproduce intervals with absolute precision would produce unbounded error intervals. Such instability, manifest by a drifting of the time of the response in relation to that of the metronome beat, was not observed empirically in data produced by Hary and Moore (1985, 1987a and 1987b).

From data obtained from musicians performing temporal tracking tasks to metronome sequences containing step functions, Hary and Moore (1985) provided evidence that their subjects used an *error-correction* model. In using this strategy, subjects would estimate the synchronisation error and use the estimate to modify the internal delay time following the resetting event, before executing the response. Note that this internal delay is different

from the delay interval in that the latter contains additional time constraints due to peripheral motor delays.

A prediction of such a model is a degree of correlation between metronome and delay intervals as the subjects would use the error intervals to modify the delay intervals. Evidence for the model was provided by data (Hary and Moore, 1985) in which the delay interval underwent cyclical changes of the same period as the step function of the metronome. There were significant correlations between metronome and delay intervals and the cross-correlograms observed contained high levels of correlation in a cyclical manner which were similar to those seen in auto-correlograms of the metronome intervals, characterised by the step function.

The error-correction model was redefined by Hary and Moore (1987a). In experiments involving musicians tracking metronome sequences of random intervals (intervals were generated from a Gaussian distribution around a mean of 704 msec and a standard deviation of 12 msec). They predicted that stable metronome-reset strategies with (or without) error-correction would not produce negative first-order correlations between the metronome and delay intervals. However, a negative correlation at lag-one (first order) was seen in their data between metronome and delay intervals. Hary and Moore (1987a) assumed in the case of the metronome-reset strategy, that a metronome interval larger than the mean would delay the mean time of the next response. This delay in the response would be equal (on average) to the change in metronome interval if the subject were oblivious to the change. However, if the subject responded to the increase in metronome interval with an increase in the internal reference interval, then the delay in the response

would be larger. Both situations would lead to non-negative correlations between metronome and delay intervals.

Hary and Moore (1987a) considered the further possibility of a *mixed-reset* strategy in which both response and metronome events may be used as resets with random switching between the two classes of reset events. In this model a switch would connect either the metronome or the response to a resetting "junction". At this junction the switch would allow a given decision rule to use the time of either the metronome or response as a reference for the next response. A feedback loop connecting the error interval to the internal reference interval would serve as a pathway by which the experience of the subject would appear to modify his behaviour. When data were simulated using the rules governing the mixed-reset model, Hary and Moore (1987a) found close resemblances between the real and computer-generated data. They found that both observed and simulated data contained positive first-order correlations in the auto-correlograms of the delay intervals and negative first-order correlations in the cross-correlograms of the metronome and delay intervals.

However, it should be noted that the various pieces of evidence for and against the different synchronisation strategies put forward by Hary and Moore (1985, 1987a and 1987b) only apply to the temporal tracking performance of trained musicians. Models which have been rejected by Hary and Moore may be applicable not only to PD patients, but to age-matched (non-musical) control subjects; conversely, these subject groups may not use strategies which Hary and Moore have suggested are used by musicians.

In the work presented in this chapter there were two main aims:

1. comprehensive characterisation the various temporal parameters, namely, response, error and delay intervals produced by PD patients and age-matched, non-musical control subjects. Subjects performed temporal tracking of three kinds of metronome sequence; a sequence of regular (700 msec) intervals, a sequence containing a step function and a sequence containing random intervals drawn from a Gaussian distribution. The latter two sequences were similar to those used by Hary and Moore (1985 and 1987a, respectively).

2. to calculate serial auto- and cross-correlograms between metronome and subject-generated response intervals in order to make initial predictions about the synchronisation strategies used by PD patients and control subjects.

CHAPTER 4.2: METHODS.

4.2.1. Subjects.

Six male PD patients aged 61.5 (8.2) years, mean (S.D.), range 49-70 and six age-matched male control subjects, age 63.7 (8.5) years, range 50-76 were studied. As in previous studies, all subjects participated with informed consent and the protocols were approved by the local ethics committee.

The average duration of the patients' disease at time of testing was 7.3 (1.6) years. Patients underwent a clinical assessment, performed by a neurologist, immediately prior to the experimental session. All patients were taking daily medication at the time of testing and performed the experiments whilst 'on' their normal medication regime. Details of medication are given in Table 4.1. The mean clinical grading score for patients was 8.2 (2.4) scored on the Webster (1968) disability rating scale. All subjects were right-handed and were tested for handedness using a simple questionnaire to derive the L.Q.)Laterality Quotient). Subjects were also tested for cognitive function using the 'Mini-Mental State' test (Folstein *et al*, 1975). An independent assessment of speed and accuracy of movement was tested using a Reciprocal Aimed Tapping test (Wing *et al*, 1984; see 3.2.1.i), all subjects being tested both before and after the main experimental session. Further clinical details are shown in Table 4.1.

4.2.2. Apparatus.

A CED 1401*plus* interface (Cambridge Electronic Design) was used to monitor and store subjects' responses and to generate and monitor the auditory cues and to store the times

Init.	Age (yrs)	Duration (yrs)	MMS	Clinical grading	Treatment
JS	58	9	30	9 (I)	LD;Am
GM	67	8	30	9 (II)	LD;Se
TC	70	5	29	11 (II)	LD;AC
TH	68	9	30	9 (II)	LD;Se
MK	49	6	30	4 (I)	LD;Se
DR	57	7	30	7 (I)	LD;Se

Table 4.1. Clinical details of the six male PD patients tested. The clinical grading represent the Webster (1968) disability rating and, in parentheses, the Hoehn & Yahr (1967) staging (for details refer to 1.2.2). Abbreviations:- Init = initials; yrs = years; duration = duration of illness since initial diagnosis; MMS = mini-mental score (Folstein *et al*, 1975); LD = L-dopa; AC = anticholinergic; Se = selegiline and Am = amantidine.

of their occurrence, in conjunction with 'Spike 2' (Version 4.61) applications software (Cambridge Electronic Design). The auditory 'clicks' (0.2 msec duration, easily audible) served as metronome sounds and were presented through headphones (Amplivox) to the subjects. The metronome clicks were mixed (using an electronic mixer) with white noise (produced by a white noise generator, Wavetek). The white noise was constant at 70 dB (sound pressure level) and was used to minimise background noise. The experimental set-up is shown in Figure 4.1.

Subjects produced responses using a tapping box identical to that used in the previous chapter (see Figure 3.3). The box was held by the subjects such that the index finger was positioned over a foam pad on the box. An infra-red beam was positioned 6 mm above the box surface and the time at which the beam was broken was recorded on the computer with 0.1 msec accuracy via an amplitude analyser (Frederick Haer) and the CED 1401.

4.2.3. Experimental task.

Subjects were seated comfortably with their right arm resting on a table, adjacent to the tapping box. Subjects were provided with headphones, through which were presented audible clicks serving as metronome sounds. Subjects adjusted the sound level of the metronome to their own satisfaction and were required to produce finger taps by making flexion-extension movements of the metacarpophalangeal joint of the index finger. Subjects were given a few minutes to familiarise themselves with the apparatus and were then instructed to "tap on, not before or after, the beat".

Three types of metronome sequences were presented to the subjects. During 'regular'

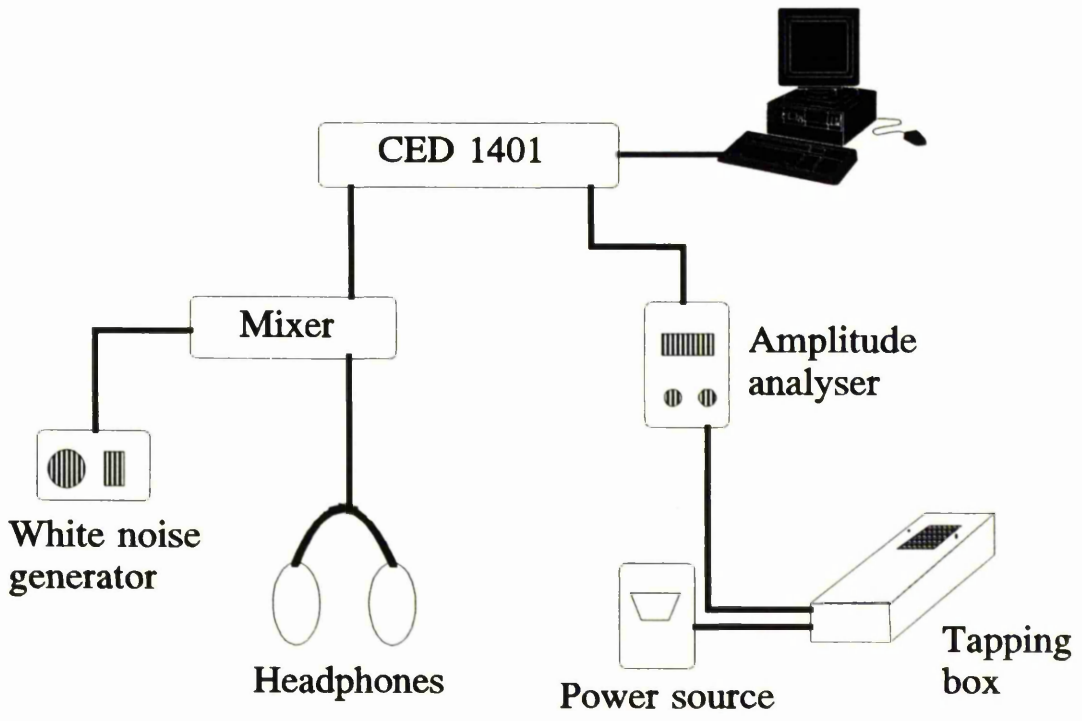

Figure 4.1. Auditory 'clicks' were generated by the CED 1401 interface and monitored and stored on a PC using the 'Spike 2' applications software package (Cambridge Electronic Design). The clicks were mixed with white noise before being presented to the subjects through headphones. Subjects' finger taps were detected by breaking the beam passing across two infra-red detectors on the tapping box, and stored on the PC via an amplitude analyser and the CED 1401 using Spike 2 software.

sequences, subjects were presented with 141 metronome pulses, in which the interval between two successive metronome pulses was 700 msec, to produce 140 intervals. During 'step' sequences, fifty intervals of 705 msec, followed by 30 intervals of 695 msec, 30 intervals of 705 msec and 30 intervals of 695 msec were presented to the subjects. During 'random' sequences, 140 random intervals drawn from a Gaussian distribution with a mean (S.D.) of 701.5 (8.9) msec were presented to the subjects. During both the step and random sequences, the deviations from the mean interval were considered to be smaller than the natural variability of the subjects and below levels of variance which would have been perceived by the subjects. Subjects were not informed about the three metronome sequences and in no case did a subject report noticing any differences between these sequences.

The three types of metronome sequences are shown in Figure 4.2. All subjects performed 18 trials, consisting of six of each sequence presented in a pseudo-random order, and were free to utilise visual, proprioceptive, tactile and any other form of feedback to produce synchronised responses. After each run, subjects were provided with verbal information about their performance and encouraged to produce more synchronous responses. Rest periods of approximately one minute were introduced between each trial and a break of approximately 30 minutes was taken after the first nine trials had been completed.

The first twenty metronome events with their associated response taps were discarded from the data on each run, leaving 121 metronome and response events i.e. 120 intervals. This ensured that any initial transition or adaption phase during which subjects acquired the basic metronome period would be excluded from each run. The duration of a single run

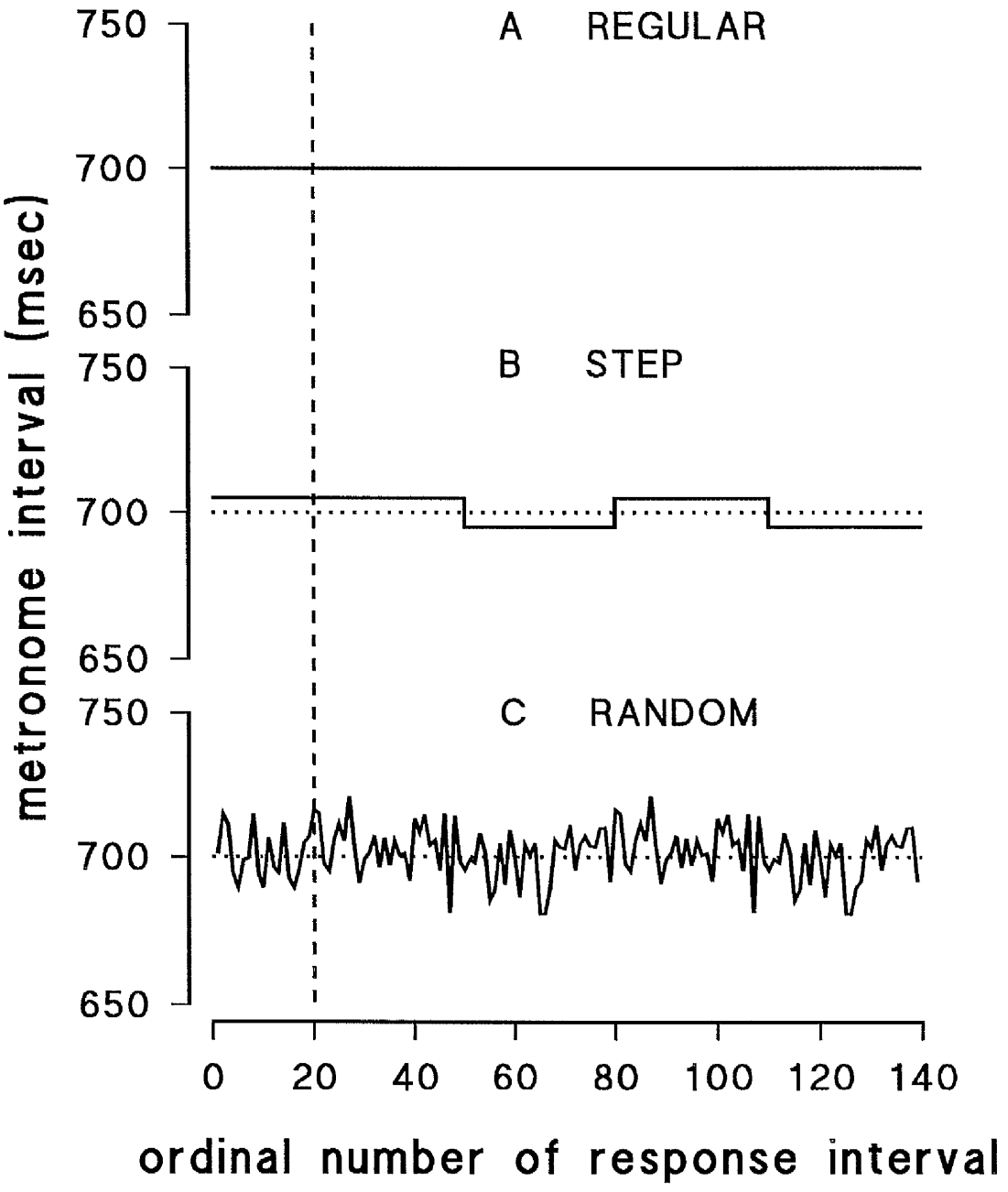

Figure 4.2. The three metronome sequences used. **A**, represents a series of regular 700 msec intervals. **B**, represents steps of 30 intervals, of either 705 or 695 msec duration while **C**, represents random intervals with a mean (S.D.) of 701.5 (8.9) msec. In each case 140 intervals were presented, but the first 20 intervals (prior to the dashed line) were discarded. The mean interval of 700 msec is shown as a dotted line.

contained enough intervals for statistical characterisation but was not long enough to produce fatigue in subjects. In addition, any run containing obvious errors, for example, long intervals produced by the subject missing breaking the infra-red beam, or short intervals associated with 'bounce', was omitted from the subsequent analysis. Therefore, 18 error-free runs (six of each metronome sequence) were collected.

At the beginning and end of the main experimental session, all subjects performed two further runs (one at the beginning and one at the end) in which 140 regular metronome intervals of 600 msec were presented. Performance on these trials provided information about i) the effects of bradykinesia on the ability to produce response intervals at 600 and 700 msec and ii) the effects of fatigue during the testing session.

4.2.4. Data analysis and statistics.

The following variables, which were all time intervals (measured in msec) were calculated; *Mj*, the *j*th metronome interval, *Rj*, the *j*th response (or tap) interval, *Ej*, the *j*th error interval and *Dj*, the *j*th delay interval. The error interval was defined as the elapsed time between the occurrence of a metronome event and that of the associated response event and, by convention, was negative when the response preceded the metronome. The delay interval was defined as the elapsed time between the occurrence of one metronome event and the *next* response event (which was associated with the *next* metronome event). The definition and derivation of each variable are shown in Figure 4.3. The relationships between D_j, R_j and E_j are expressed as;

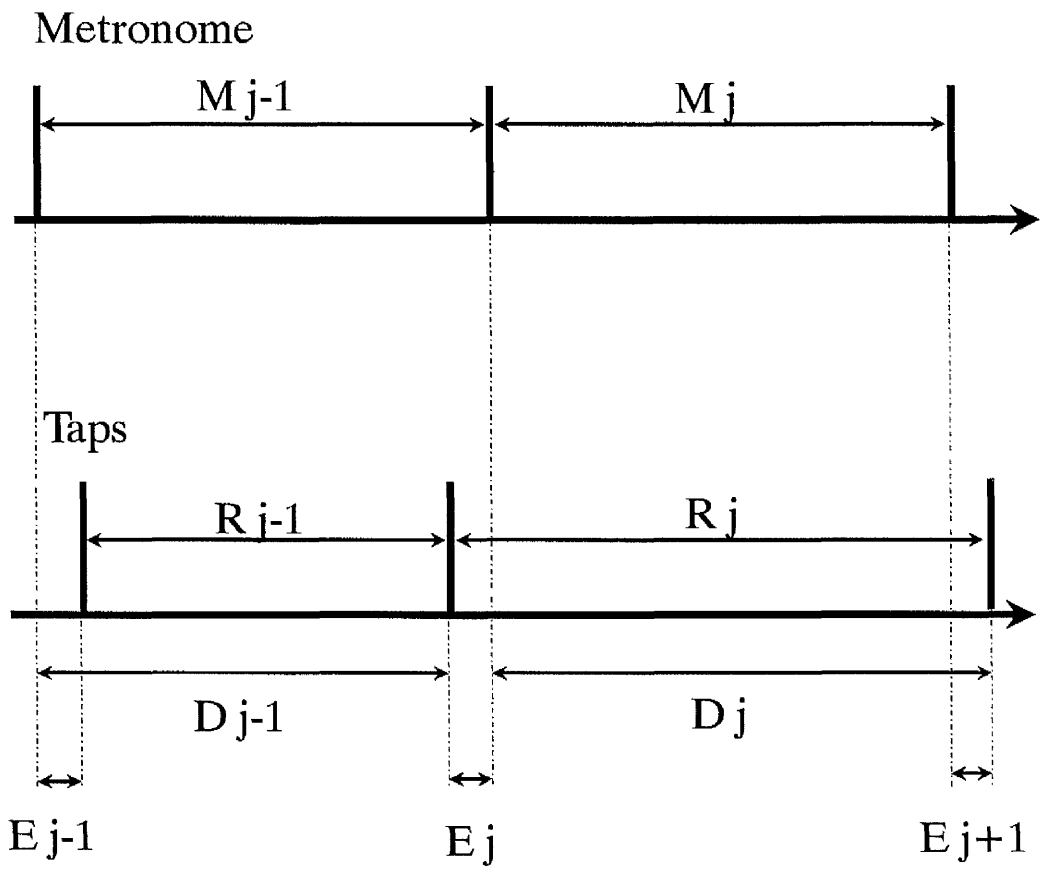

Figure 4.3. Graphic representation of the variables and their notation. Two *metronome intervals* (M_{j-1} and M_j) and two *response intervals* (R_{j-1} and R_j) are shown. E_j represents the *error interval* defined as the time between the response and metronome events associated with the opening of the response and metronome intervals (R_j and M_j, respectively). D_j represents the *delay interval* defined as the time difference between the metronome event opening M_j and the response event closing R_j. All variables were measured and calculated in msec.

$$D_j = R_j + E_j$$

(equation 1)

The four variables were calculated for the last 120 metronome and response intervals in each run (for each run) in each of the three metronome series and for the trials at 600 msec in both PD and control groups. Descriptive statistics were calculated separately for the mean and S.D. (over six trials), for *R*, *E* and *D* in each metronome series and in each subject group. Again, preliminary descriptive statistics indicated that the data-sets violate the assumption of homogeneity of variance used for normally-distributed data-sets, therefore precluding the use conventional parametric methods. Non-parametric inferential statistics were employed, using Wilcoxon's signed ranks, matched pairs test and the Mann-Whitney U test for intra- and inter-group analyses, respectively.

4.2.5. Extended pilot study: The relationship between observed and subjective synchronisation error.

Two PD patients (JS and GM, see Table 4.1), mean age 62.5 years, and two control subjects, mean age 62.0 years, underwent an extended protocol on a separate occasion, in order to provide an estimate of the differences between the objective synchronisation error (OSE) and the subjective synchronisation error interval (SSE) as perceived by the patient. The protocol was two-fold. Firstly, in protocol A, subjects were asked to synchronise their finger movements to a short train of regularly-spaced metronome intervals (interval duration, 700 msec). A total of ten different metronome sequences was presented, containing between 11-20 metronome events. The subjects were informed that the trials contained between 11-20 metronome events, but had no prior knowledge as to

the length of a particular trial. The sequences were presented in a pseudo-random order so that the subjects performed one trial at each of the ten different trial lengths. After each trial, the subject was immediately required to give an estimate of the degree of synchrony of his *last* response with the *last* metronome event. This was done by the subject placing a mark on a rating scale. On the rating scale, a horizontal line represented time. Two vertical lines indicated the exact time of occurrence of the last *two* metronome beats, and the subject was informed that he was to think of the distance between the two vertical lines as directly representing, in a linear fashion, the temporal interval between two successive metronome beats. The subject was required to draw a vertical line through the horizontal line, using the indicated time of the last two beats as a temporal reference, corresponding to the instant at which he thought he tapped. A diagram of the rating scale is shown in Figure 4.4. The distance between the two vertical lines which represented the last two metronome events was 70 mm, therefore 1 mm represented 10 msec. The distance (in front or behind) between the subjects' mark and the last metronome was used as a subjective estimate of the synchronisation error. Immediately after marking the subjective rating scale, subjects were asked to mark a confidence rating scale. This scale was a horizontal line 10 cm in length, in which the left end represented "0% confidence" and the right end "100% confidence". Subjects were asked to place a mark through the line which represented their confidence in the subjective synchronisation rating (for example, if the subjects marked at around -100 msec on the subjective rating scale, but conceded that it was "a guess" then a low percentage on the confidence rating would be marked).

In the second section of the protocol, protocol B, the patients were required to produce synchronised responses to a train of regularly-spaced metronome beats (interval duration,

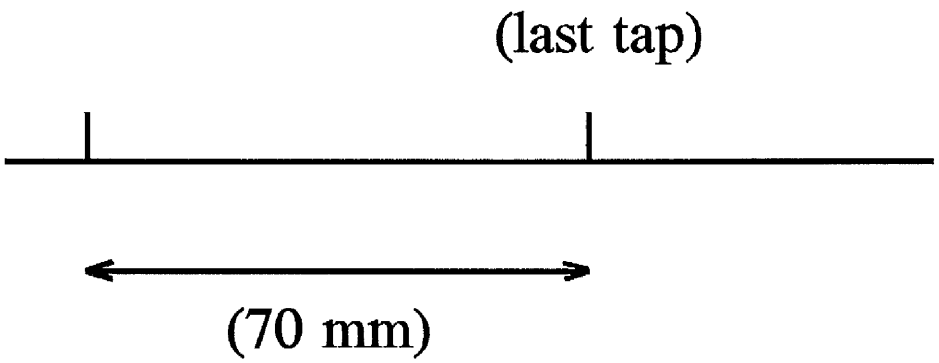

Figure 4.4. Diagrammatic representation of the rating scale employed in order to assess the relationship between observed and subjective synchronisation error. The horizontal line represents time and the two vertical lines indicate the exact time of occurrence of the last two metronome beats. The subjects were informed that they were to think of the distance between the two vertical lines as directly representing, in a linear fashion, the temporal interval between two successive metronome beats.The subject was then required to draw a line through the horizontal line at the point where they thought they tapped. Note that neither the arrow nor the bracketed characters were present on the rating scale used during the experiment.

700 msec) similar to those described in section 4.2.3. However, at a certain point during the trial the metronome events were abruptly terminated and the patient was asked to assess the synchrony of his last response in the form of a SSE rating, with regards to the last metronome event on the rating scale described above and a confidence rating. The point at which the trial was stopped was when the *experimenter* considered that the synchronisation error interval, at that instant, fell into one of three categories - 'small', 'medium' or 'large'. A total of fifteen trials were presented which incorporated five of each of these categories.

4.2.6. Characterisation of the temporal statistical relations between intervals: production of serial auto- and cross-correlograms.

Further analysis was performed in order to assess the temporal relationships between the four variables (*M, R, E* and *D*) using the data collected in the protocol described in section 4.2.3. Serial correlograms were calculated in order to determine the extent to which the interval variables were sequentially correlated with themselves and with one another. A serial correlogram is a sequence of correlation coefficients (each with a value between ± 1) arranged for graphical display according to an index, or lag (variable k) which indicates the number of intervals separating the two variables being correlated. For example, the correlation coefficient between adjacent intervals had an index of k (lag) = 1, and that between sequential interval pairs *separated by one interval* (for example, the first and third, or second and fourth intervals) had an index of k =2. Values of k ranging from -30 to +30 were calculated, using expressions provided by Hary and Moore (1985, 1987a). Auto-correlograms, in which interval values were correlated with themselves and cross-correlograms in which the value of a variable (for example, the error interval) was

correlated with another variable (for example, the metronome interval) were calculated.

Auto- and cross-correlograms were produced by the calculation of auto- and cross-correlation functions at each lag, from auto- and cross-covariance functions, respectively. The expressions used for the calculation of these function were;

$$C_x(k)=\sum_{j=1}^{N-k}\frac{(X_j-\mu_x)(X_{j+k}-\mu_x)}{N-k}$$

[k=0, 1,..., 30] (equation 2)

$$\mu_x=\sum_{j=1}^{N-k}\frac{X_j}{N}$$

(equation 3)

$$r_x(k)=\frac{C_x(k)}{C_x(0)}$$

(equation 4)

$$C_{xy}(k)=\sum_{j=1}^{N-k}\frac{(X_j-\mu_x)(Y_{j+k}-\mu_y)}{(N-k)}$$

[k=0, 1,..., 30] (equation 5a)

$$C_{xy}(k)=\sum_{j=1+k}^{N}\frac{(X_j-\mu_x)(Y_{j+k}-\mu_y)}{(N+k)}$$

[k=-1, -2,..., -30] (equation 5b)

$$r_{xy}(k) = \frac{C_{xy}(k)}{\sqrt{C_x(0)C_y(0)}}$$

(equation 6)

$$CI(k) = \frac{2}{\sqrt{(N-k)}}$$

(equation 7)

where k is the event lag, $C_x(k)$ is the sample autocovariance function, $r_x(k)$ is the sample autocorrelation coefficient function, $C_{xy}(k)$ is the sample cross-covariance function, and $r_{xy}(k)$ is the sample cross-correlation coefficient function. μ is the sample mean and $C(0)$ is the sample variance for the population of N time intervals in the time series X_j and Y_j. $CI(k)$ is the approximate 95% confidence interval around the calculated values of the autocorrelogram.

CHAPTER 4.3: RESULTS.

4.3.1. Characterisation of the statistical structure of temporal tracking performance in PD patients and control subjects.

Figure 4.5. compares the subject-generated response parameters (R, E and D) produced by one PD patient (Figure 4.5A) and one control subject (Figure 4.5B), each during a *single* trial, when attempting to synchronise their responses with a metronome sequence of 120 intervals, in which the intervals had been drawn randomly from a Gaussian distribution. It can be seen in both examples that the deviations from the mean interval (701.5 msec) introduced into the random metronome sequence were smaller than the natural variability of the response intervals observed in both the patient and control subject. Figure 4.5A shows that the PD patient produced response intervals which were similar to the metronome sequence throughout the trial in that they did not deviate significantly from the mean metronome intervals. However, in this trial, the patients' error and delay intervals were less accurate. An accurate performance would have produced delay intervals similar to the response (and metronome) intervals and error intervals close to zero (i.e. the response being in synchrony with metronome). The patient produced negative error intervals, that is, produced responses in anticipation (or advance) of the metronome events. The patient also produced a cyclical pattern of error intervals, so that some intervals exceeded -375 msec (cycle 'trough') while others were close to zero (-7 msec, cycle 'peak'). The cyclical component, in this example, had a frequency of approximately forty response intervals. As a consequence, the delay intervals also contained a cyclical element; the magnitude of the delay intervals varying between 324 and 714 msec.

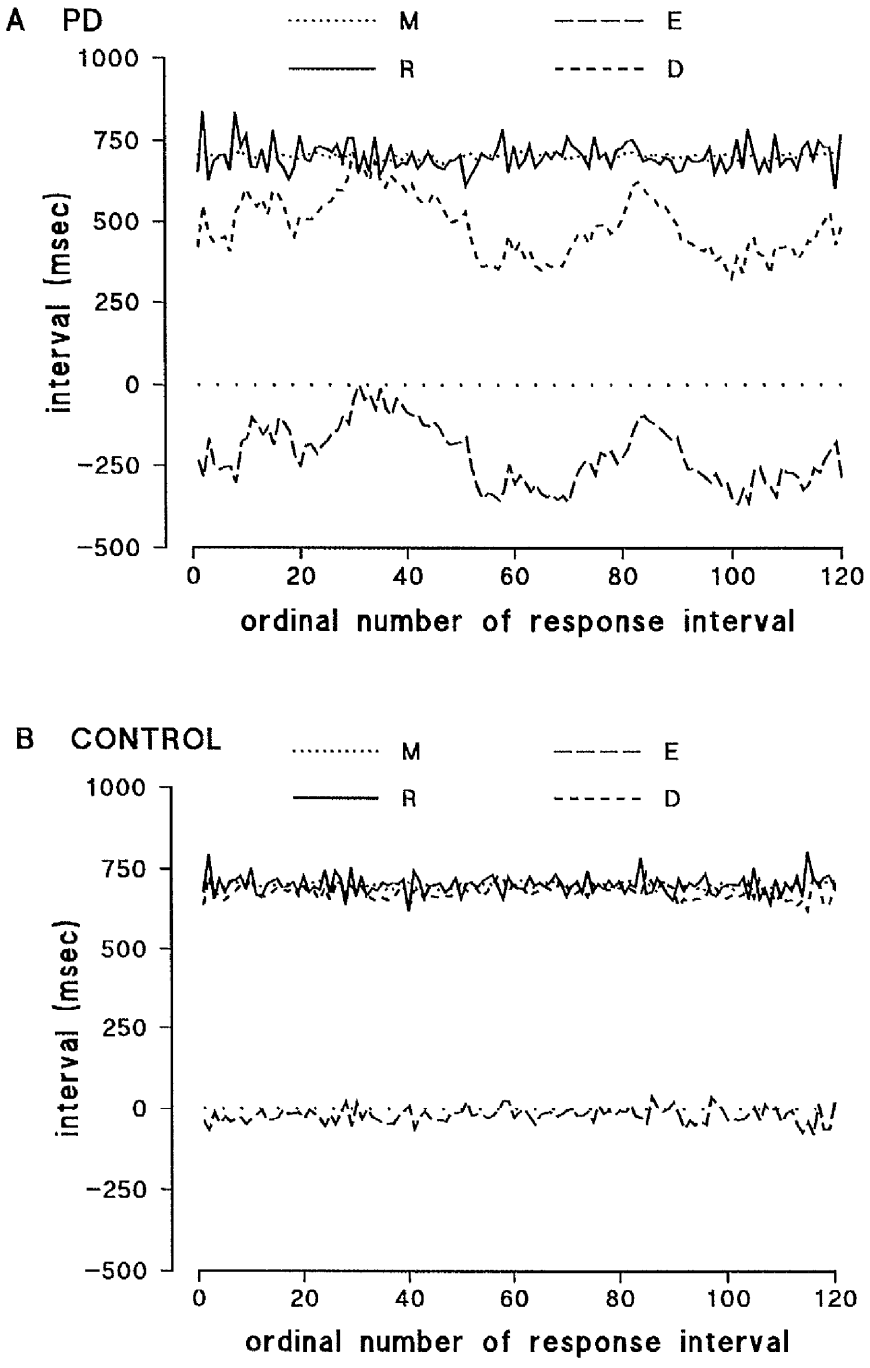

Figure 4.5. Temporal tracking performance during a single trial for one PD patient **(A)** and one control subject **(B)** when attempting to synchronise their response intervals (R) with the random metronome intervals (M). Each point represents the designated parameter at that point during the time course of the trial. Error (E) and delay (D) intervals are also represented. An accurate performance would have produced values of R and D close to those of M and values of E close to zero.

Figure 4.5B shows a single trial in a control subject; the performance in this trial was more synchronous. The subject's response intervals were similar to those of the metronome sequence and the error intervals were, by comparison with the patient's performance, smaller ranging from -78 to 38 msec and did not seem to contain a cyclical component. Therefore, the control subject's performance was more synchronous than that of the patient and at certain points in the trial responses occurred after the metronome. As a consequence the control subject produced, on average, delay intervals which were closer to the magnitude of the response intervals (range 625 to 742 msec).

For each of the three types of metronome sequences data were pooled for each subject and then descriptive and inferential statistics were performed on the group data. It was apparent that the mean response intervals over a single trial would be close to 700 msec (the mean metronome interval except for the random series in which the mean was 701.5) as subjects always produced the same number of response events as metronome events. The degree of *variability* around the subjects' mean interval was considered to be of more interest than the mean intervals in documenting temporal tracking performance. Figure 4.6 shows the mean (S.D.) group data for variability in the form of standard deviation around the mean response intervals for both control and PD groups. Both groups produce standard deviations around the mean response intervals of between 30 and 40 msec. However, although there was a tendency for the *control* group to produce higher levels of variability, this was not significant for either the regular, step or random metronome sequences (p=0.6594, 0.8032 and 0.5560, respectively, Mann-Whitney).

Comparisons were made between the synchronisation error intervals produced by the

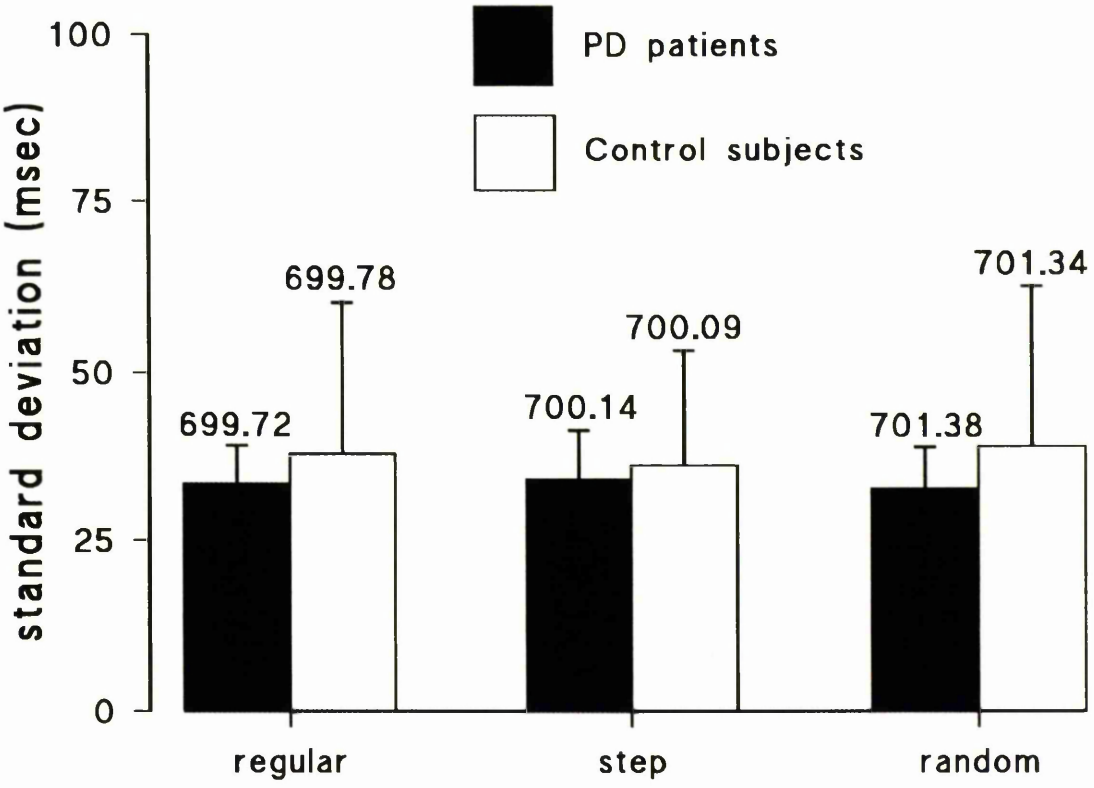

Figure 4.6. Mean (S.D.) group data for the standard deviation around the mean response intervals produced by control and patient groups while tracking three types of metronome sequence (regular, step and random). The numbers represent the group mean (in msec) for the response intervals, the mean metronome intervals being 700 msec for the regular and step function, and 701.5 msec for the random metronome sequence. There was no significant difference in the standard deviation associated with the mean response interval between control and patient groups while tracking either a regular, step or random metronome sequence (p=0.6594, 0.8032 and 0.5660, respectively, Mann-Whitney).

control and patient groups. Figure 4.7A shows the mean (S.D.) group data for the error intervals of both groups. Both groups produced negative error intervals (anticipatory response intervals). The negative error intervals were significantly larger in the patient group when compared with the control group, when tracking regular, step and random metronome sequences (p=0.0098, 0.0159 and 0.0144, respectively, Mann-Whitney). Figure 4.7B shows the mean (S.D.) group data for the standard deviation associated with the mean error interval for both groups of subjects, for the three types of metronome sequences. While tracking each metronome type, the patients produced higher levels of standard deviation (variability) than those produced by the control subjects but the differences were not statistically significant (p=0.2220, 0.0852 and 0.2713, for tracking regular, step and random metronome sequences, respectively, Mann-Whitney).

Similar comparisons were made between the mean delay intervals produced by the control and patient groups. Figure 4.8A shows the mean (S.D.) group data for delay intervals of both groups of subjects. The delay intervals were consistently higher in the control group, reflected by the consistently less negative error intervals (see above), when compared with those seen in the patient group. There was a significant difference between the mean delay intervals produced by the control and patient groups when tracking either regular, step or random metronome sequences (p=0.0099, 0.0158 and 0.0144, respectively, Mann-Whitney). Figure 4.8B shows the mean (S.D.) group data for the standard deviation associated with the mean delay intervals produced by both groups of subjects, for the three types of metronome sequences. Again, the patient group consistently produced higher levels of standard deviation than those produced by the control group. However, these differences were not statistically significant (p=0.2199, 0.0865 and 0.1873, for tracking

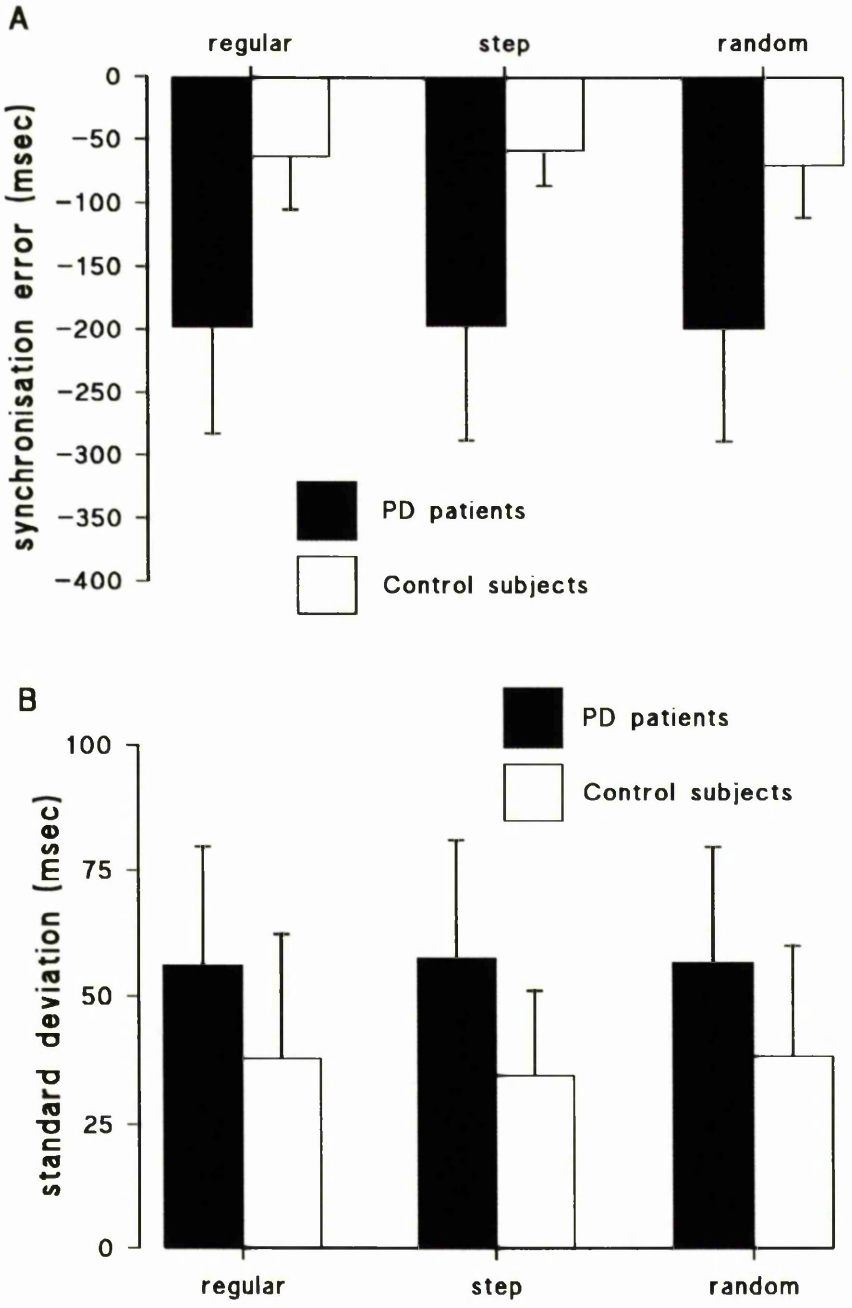

Figure 4.7. Mean (S.D.) group data for the mean error interval **(A)** and the standard deviation associated with the mean error interval **(B)** for control and patient groups while tracking three types of metronome sequence. Both groups produced negative mean error intervals which were significantly higher in the patient group when compared with the control group (p=0.0098, 0.0159 and 0.0144, for tracking regular, step and random metronome sequences, respectively, Mann-Whitney). Although the standard deviation associated with the mean error interval was consistently higher in the patient group when compared with that observed in the control group, no significant differences were found.

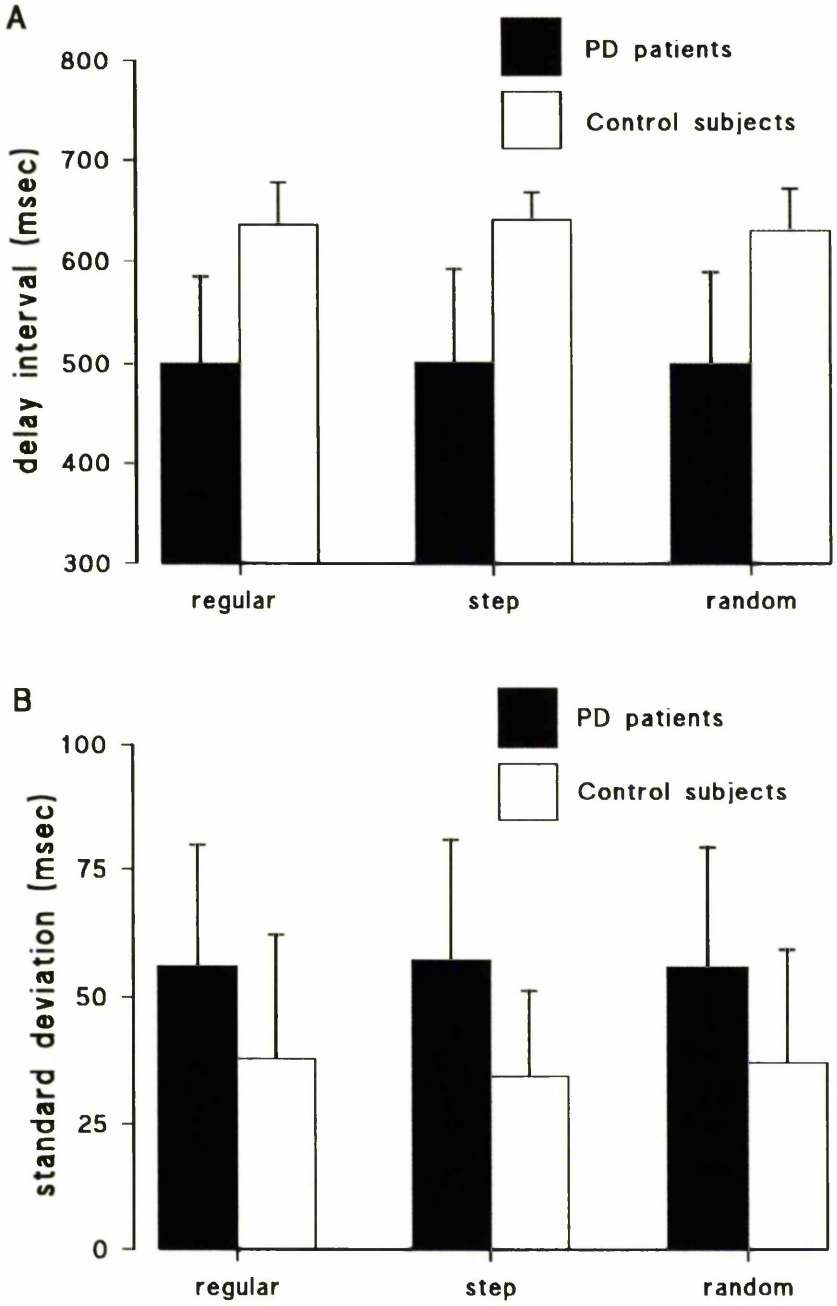

Figure 4.8. Mean (S.D.) group data for the mean delay interval **(A)** and the standard deviation associated with the mean delay interval **(B)** for control and patient groups while tracking three types of metronome sequence. Mean delay intervals were significantly higher in the control group when compared with those produced by the patient group (p=0.0099, 0.0158 and 0.0144, for tracking regular, step and random metronome sequences, respectively, Mann-Whitney). Although the standard deviations associated with the mean delay intervals were consistently higher in the patient group when compared with those observed in the control group, no significant differences were found.

regular, step and random metronome sequences, respectively, Mann-Whitney).

All subjects produced a further two trials, one before and one after the main experimental session. In these two trials metronome sequences of 600 msec regular intervals were presented to the subjects. Comparisons of temporal tracking performance before and after were made for both subject groups in order to i) assess the effects of bradykinesia on the ability to produce response intervals at the shorter metronome intervals and ii) assess the effects of fatigue on performance.

Figure 4.9 shows mean (S.D.) group data for the standard deviation around the mean response intervals for both control and PD groups, in trials in which a regular metronome sequence (600 msec interval) was presented both immediately prior to and immediately after the main experimental session. Both patient and control groups were able to produce mean response intervals close to the metronome interval in the trials performed before (599.92 and 600.20 msec, respectively) and after (600.15 and 599.90 msec, respectively) the main experimental session.

There was no significant difference in the standard deviation associated with the mean response interval between trials performed before and after the main experimental session in the control group (p=0.7890, Wilcoxon). In the patient group, there was a tendency for the standard deviation to be higher in the trial performed after the main experimental session compared to that performed before, but this difference was not significant (p=0.0890, Wilcoxon).

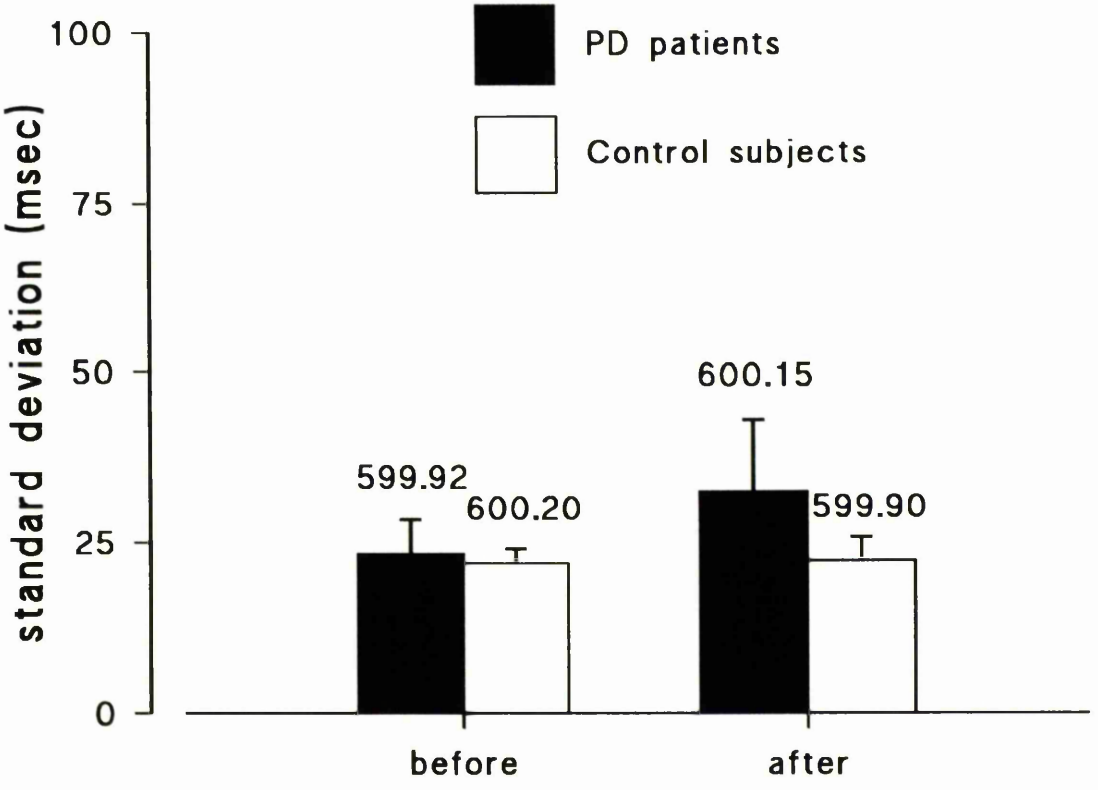

Figure 4.9. Mean (S.D.) group data for the standard deviation around the mean response intervals produced by control and patient groups while tracking regular metronome sequences of 600 msec interval which were presented either before or after the main experimental session. The numbers represent the group mean (in msec) for the response intervals. There was no significant difference between the performance in trials presented before or after the main experimental session either in control or patient groups ($p=0.7890$ and 0.0890, respectively, Wilcoxon).

4.3.2. The relationship between observed synchronisation error (OSE) and subjective synchronisation error (SSE) in PD patients and control subjects.

Two PD patients and two control subjects used in the above experimental protocol also performed an extended protocol in which the OSE of the response event associated with the last metronome event of a sequence was compared with the subject's SSE, which was measured using the subjective rating scale shown in Figure 4.4. Figure 4.10 shows the relationship between SSE and OSE for the two control subjects (Figure 4.10A) and the two PD patients (Figure 4.10B). Data of the two control subjects were pooled, and data of the two PD patients were pooled separately (see section 4.2.5). Figure 4.10 presents a scatter-plot in which the OSE for each trial was plotted against the SSE for that trial.

Figure 4.10 again demonstrates the difference in OSE produced by patients when compared to those produced by control subjects; the range of OSEs for the control subjects was between -150 and +80 msec whilst the range for the patients was between -390 and -15 msec. There was also a wider range of values associated of SSE associated with the PD group; a range of -180 to +150 msec, compared with a range of -110 msec to +100 msec seen in the control subjects. What was more relevant was the relationship between OSE and SSE. Using linear regression, the regression line for both control subjects and PD patients was calculated and shown in Figure 4.10 as a solid line. It can be seen in Figure 4.10A that for control subjects, the regression line had a positive slope (0.419, r value of 0.268). This meant that as the OSE became more positive, the SSE also became more positive. This relationship bordered on being statistically significant (p=0.0781, Spearman's Rank correlation). However, in the PD group, there seemed to be little relationship between OSE and SSE. The slope of the regression line was very close to zero

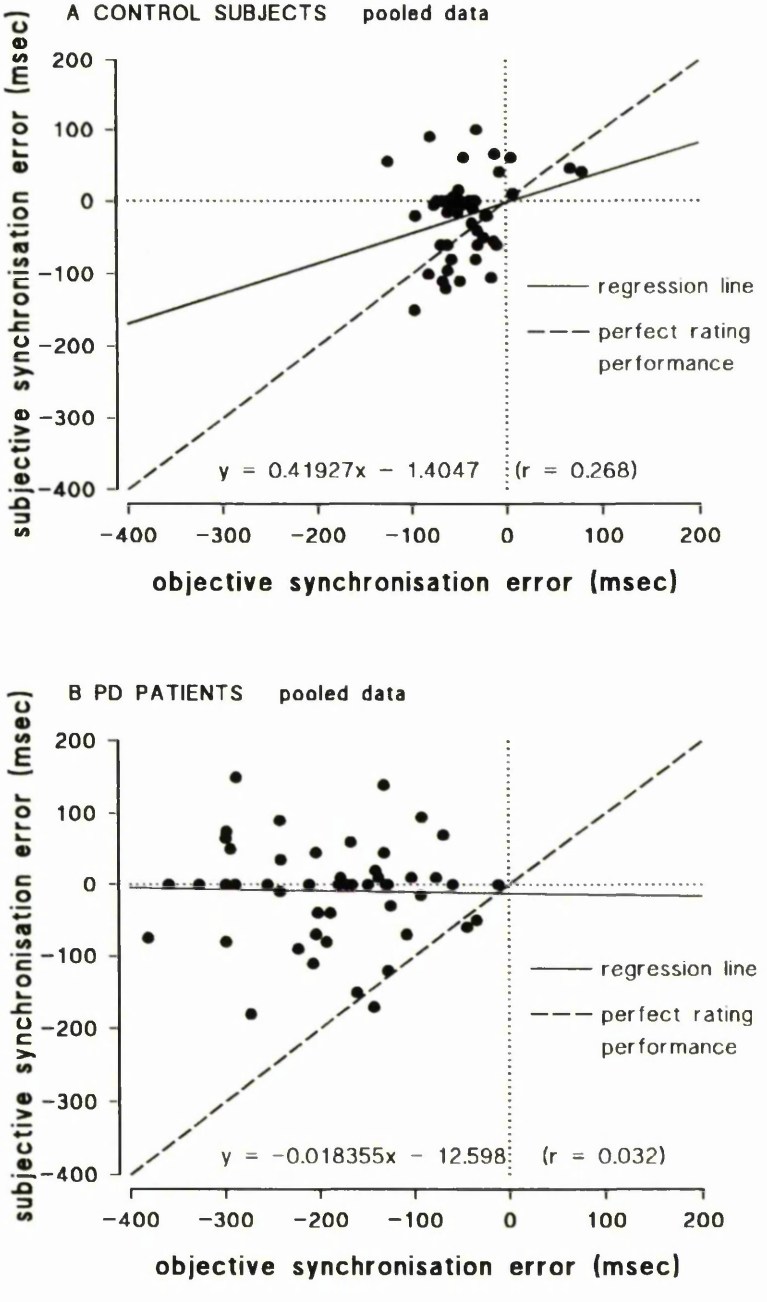

Figure 4.10. The relationship between observed synchronisation error (OSE) and subjective synchronisation error (SSE) in two control subjects **(A)** and two PD patients **(B)**. The solid lines represent the regression line (the equation being that which describes the regression line) calculated using linear regression, while the dashed line represents a perfect rating performance. In the control group the regression line had a positive slope (0.419, r value of 0.268) which represented a relationship which bordered on statistical significance (p=0.0781, Spearman's Rank correlation) whilst in the patient group the regression line slope was close to zero (-0.018, r value of 0.032) and any relationship between OSE and SSE was not statistically significant (p=0.842, Spearman's Rank correlation).

(-0.018, r value of 0.032) and this represented a 'relationship' which was not statistically significant (p=0.842, Spearman's Rank correlation). There seemed to be little or no relationship between OSE and SSE in the patient group; as OSE became more positive there was no systematic increase in the positive sign of the SSE.

Immediately after completing the subjective rating scale for each trial, subjects also completed a confidence rating scale (see section 4.2.5) in which a rating for their confidence in the accuracy of the previous SSE score was ascertained. Figure 4.11 represents the relationship between SSE and confidence rating in control subjects (Figure 4.11A) and PD patients (Figure 4.11B). Again linear regression was used to produce a regression line (represented as a solid line in Figure 4.11).

Figure 4.11A shows that the relationship between SSE and confidence rating in control subjects produced a negatively-sloped regression line (slope of -0.0928, r value of 0.620), indicating that as SSE ratings became more positive, control subjects became less confident in the accuracy of their SSE ratings. This relationship, however, was not statistically significant (p=0.861, Spearman's Rank correlation). An different situation seemed to occur in PD patients; Figure 4.11B shows that the relationship between SSE and confidence rating produced a positively-sloped (0.0916, r value of 0.507) regression line and the relationship was statistically significant (p=0.039, Spearman's Rank correlation). Therefore it seemed that patients' SSE ratings became more positive, they became more confident about the accuracy of the SSE ratings.

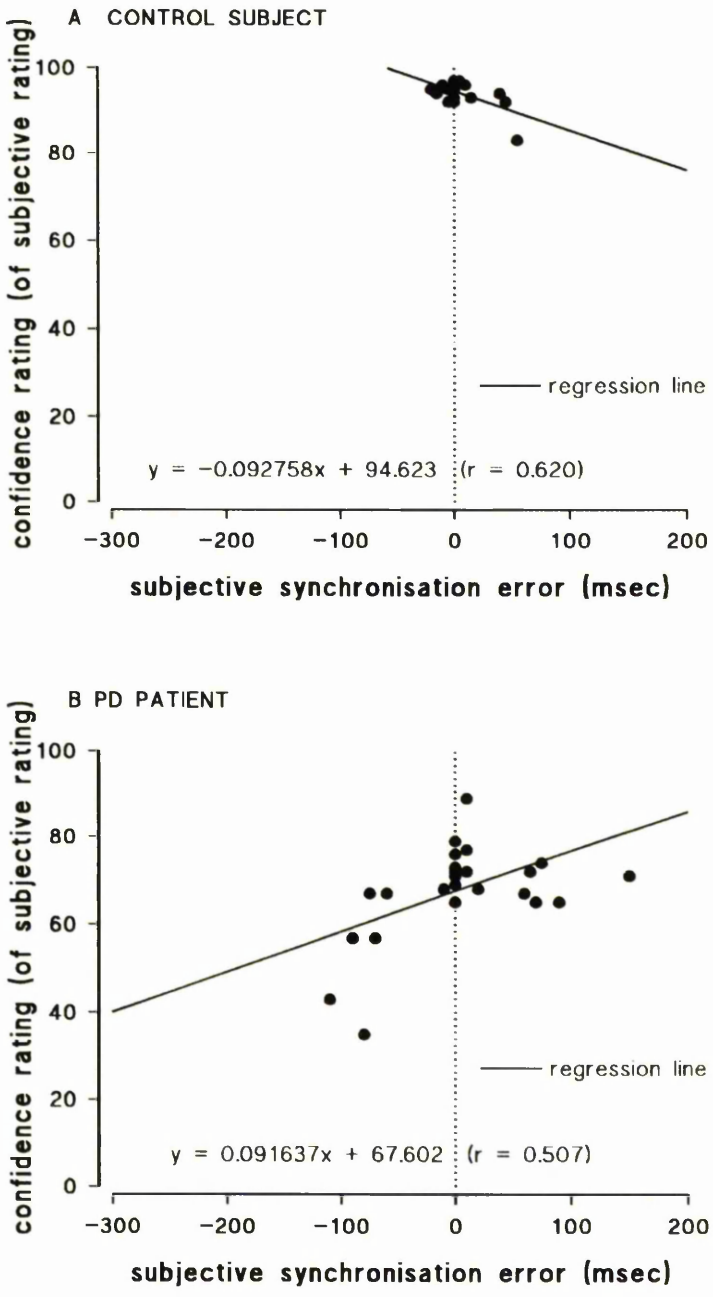

Figure 4.11. The relationship between SSE and a confidence rating for SSE in two control subjects **(A)** and two PD patients **(B)**. The solid line represents the regression line (the equation being that which describes the regression line) calculated using linear regression. In the control group the regression line had a negative slope (-0.093, r value of 0.620) which represented a relationship which was not statistically significant (p=0.861, Spearman's Rank correlation) whilst in the patient group the regression line slope was positive (0.092, r value of 0.507) and this represented a statistically significant relationship (p=0.039, Spearman's Rank correlation) between SSE and confidence rating.

4.3.3. Examples of the temporal statistical relationship between intervals using serial auto- and cross-correlograms.

This section serves to provide examples of serial auto- and cross-correlograms calculated using equations shown in section 4.2.6 and described in section 4.1.3, for sequences of metronome, response error and delay intervals. The examples used will provide an initial insight into differences in the strategies used by patients and control subjects in performing temporal tracking tasks. As each trial produced numerous auto- and cross-correlograms, only a selection will be shown. The examples shown will be of similar to correlograms shown in work published on temporal tracking in musicians using metronome sequences incorporating a step function (Hary and Moore, 1985) and using a metronome sequence of random intervals (Hary and Moore, 1987a).

Figure 4.12 shows the auto-correlogram for the metronome, R_xM, for the metronome sequence containing a step function (Figure 4.12A) and the metronome sequence containing random intervals (Figure 4.12B) as described in section 4.2.3. In each example, the auto-correlogram has been calculated from lags -30 to +30, similar to those calculated by Hary and Moore (1985, 1987a). Figure 4.12A shows a similar types of auto-correlogram for the metronome as those shown by Hary and Moore (1985, Figure 2a, p.75). The serial auto-correlogram in the present work had a characteristic shape which represented the step function in which the metronome intervals alternated between 695 and 705 msec every thirty intervals. Hary and Moore (1985) deduced that if subjects were (subconsciously) responding to the step change, then auto-correlograms for subject-generated intervals or cross-correlograms of subject-generated intervals with metronome intervals would produce correlograms with a similar structure.

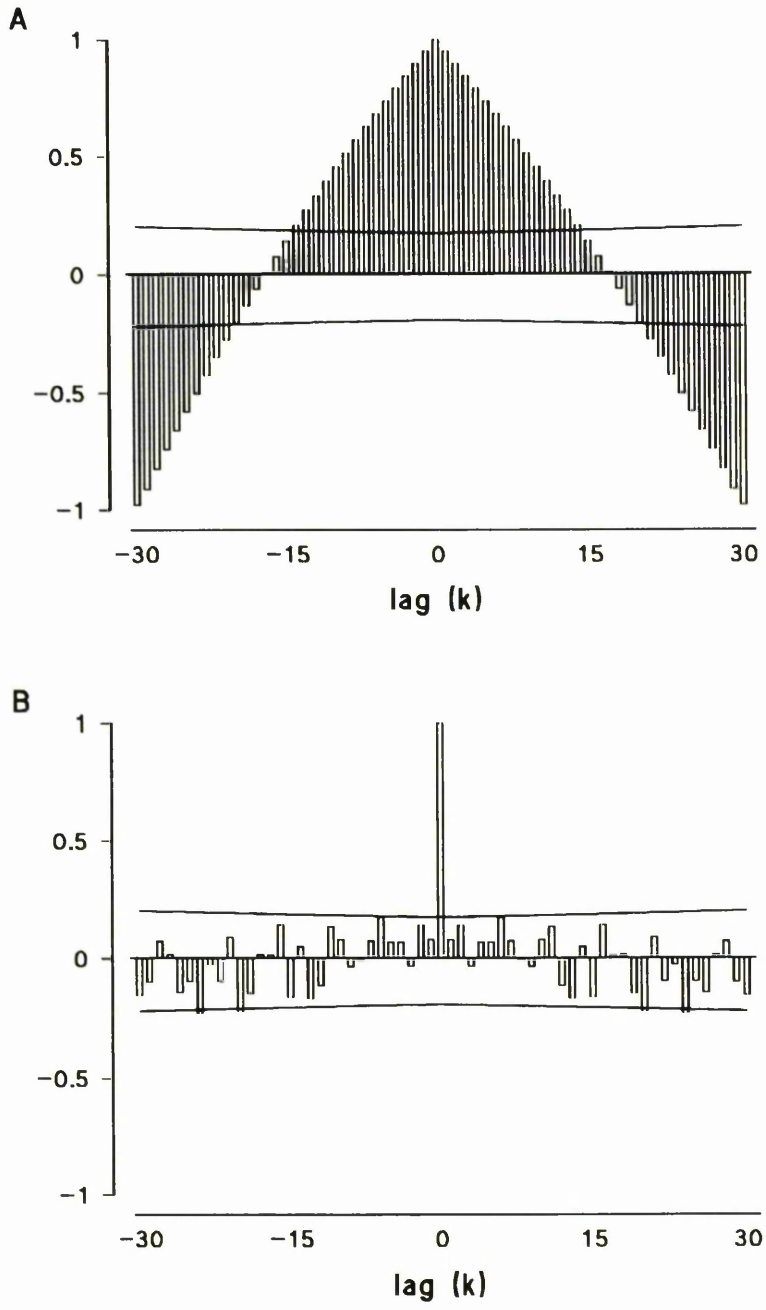

Figure 4.12. Serial auto-correlograms of an interval sequence of the metronome (R_xM) with **(A)** interval duration changing from 695 msec to 705 msec every 30 intervals (step function) and **(B)** interval duration containing random fluctuations around a mean (S.D.) of 701.5 (8.9) msec. The serial auto-correlograms were calculated using equation 4 (section 4.2.6) and the lines represent the 95% confidence intervals of the correlation coefficients (equation 7, section 4.2.6). The serial auto-correlogram shown in **A** was similar to that shown by Hary and Moore (1985, Figure 2a, p. 75), whilst that the serial auto-correlogram shown in **B** was similar to shown by Hary and Moore (1987a, Figure 2d, p. 308).

Figure 4.12B shows a serial auto-correlogram, as shown by Hary and Moore (1987a, Figure 2d, p.308) in which the random and independent variation in the metronome interval sequence ensured the absence of any significant correlation between intervals (apart from at lag zero). This produced a serial auto-correlogram for the random metronome sequence which contained an almost 'impulse-like' structure. The present analysis is based on the theory of Hary and Moore (1987a) that the presence of any temporal structure in the subject-generated intervals, which would be revealed in the serial auto- and cross-correlograms would not be derived from any intrinsic structure in the metronome sequence itself (as the random metronome sequence contains no structure, Figure 4.12B, unlike the step metronome sequence, Figure 4.12A), but would be due to a consequence of the underlying synchronisation strategy used by the subject.

Figures 4.13, 4.14, 4.15 and 4.16 all show examples of serial auto- and cross-correlograms calculated from data obtained from temporal tracking studies in PD patients and age-matched (non-musician) control subjects described in section 4.2.3. The figures are of a similar format to those shown by Hary and Moore (1985, 1987a) so that initial comparisons could be made.

Figures 4.13 and 4.14 show correlograms calculated from data obtained during a single run, which was deemed typical of the performance of a control subject and a PD patient, respectively, in which subjects tracked a metronome sequence containing a step function. The auto-correlogram for the metronome had a characteristic shape and was shown in Figure 4.12A. The format of Figures 4.13 and 4.14 was similar to that used by Hary and Moore (1985, Figure 2b-d, p. 75) in that three serial correlograms were shown;

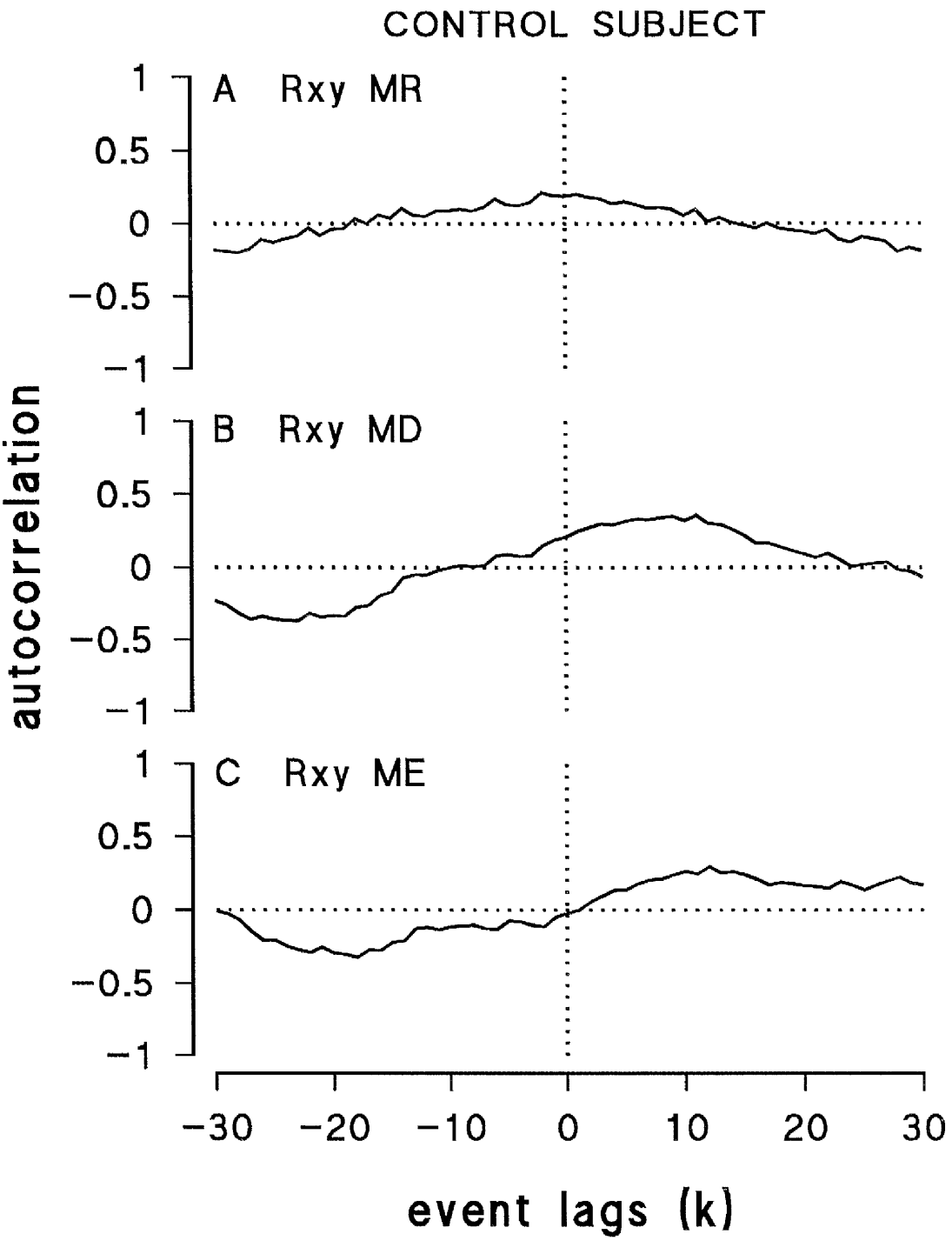

Figure 4.13. Serial cross-correlograms between the metronome interval and **A** the response interval ($R_{xy}MR$), **B** the delay interval ($R_{xy}MD$) and **C** the error interval ($R_{xy}ME$) for a single trial performed by a control subject while tracking a metronome sequence containing a step function. This represents a format similar to that used by Hary and Moore (1985, Figure 2b-d, p. 75).

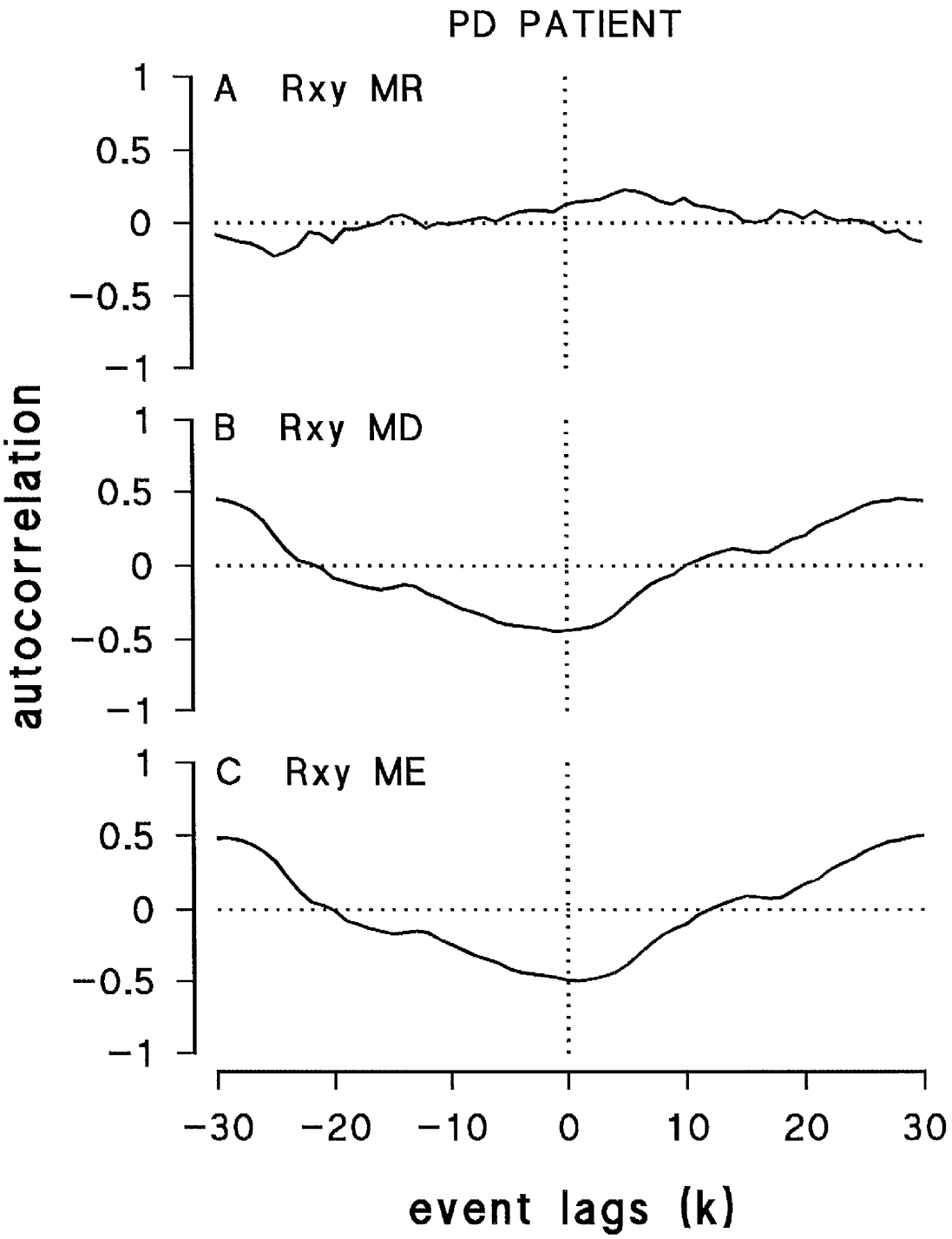

Figure 4.14. Serial cross-correlograms between the metronome interval and **A** the response interval ($R_{xy}MR$), **B** the delay interval ($R_{xy}MD$) and **C** the error interval ($R_{xy}ME$) for a single trial performed by a PD patient while tracking a metronome sequence containing a step function. This represents a format similar to that used by Hary and Moore (1985, Figure 2b-d, p. 75).

cross-correlograms for metronome and response ($R_{xy}MR$), delay ($R_{xy}MD$) and error ($R_{xy}ME$) intervals. The serial cross-correlograms shown in Figures 4.13 and 4.14 all reflected the basic shape of the metronome serial auto-correlogram (shown in Figure 4.12A) at some phase or polarity. This indicated that each of the three variables (R, E and D) were (in some way) correlated with the metronome period.

In the examples shown, there were differences in the correlograms produced by subject and patient groups. In the $R_{xy}MR$, the lag at which the peak value for positive correlation was observed was -2 for the control subject and +5 for the PD patient. The maximum values for negative and positive correlation were higher in the PD patients compared to those for control subjects, for both $R_{xy}MD$ (-0.435 at lag 0 and 0.453 at lag 28 for the patients and -0.366 at lag -23 and 0.355 at lag 11 for control subjects) and $R_{xy}ME$ (-0.497 at lag 1 and 0.494 at lag 29 for PD patients and -0.319 at lag -18 and 0.293 at lag 12 for control subjects).

Figures 4.15 and 4.16 show correlograms again calculated from a single run in which the performance typified that of either a control subject (Figure 4.15) or a PD patient (Figure 4.16), during trials in which subjects tracked a metronome sequence which contained random intervals. The auto-correlogram for the metronome had no temporal structure and was shown in Figure 4.12B. The format of Figures 4.13 and 4.14 was similar to that used by Hary and Moore (1987a, Figure 2a-c, p. 308). In these examples three correlograms were shown; an auto-correlogram for the delay interval (R_xD), and cross-correlograms for metronome and response ($R_{xy}MR$) and metronome and delay ($R_{xy}MD$) intervals. Due to the lack of structure within the metronome sequence, Hary and Moore (1987a) presumed that

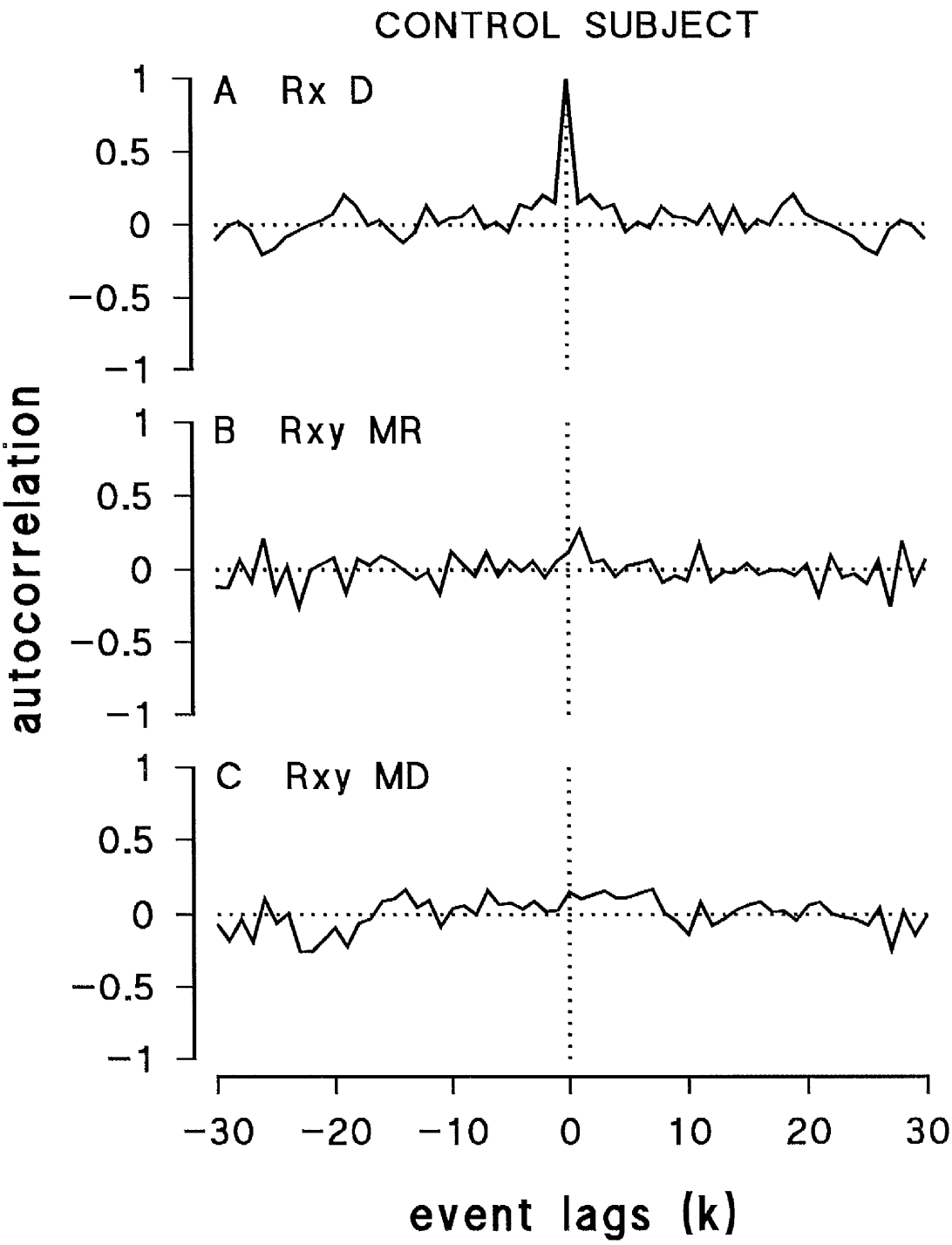

Figure 4.15. **A** Serial auto-correlograms for the delay interval (R_xD) and cross-correlograms between the metronome interval and **B** the response interval ($R_{xy}MR$) and **C** the delay interval ($R_{xy}MD$) for a single trial performed by a control subject while tracking a metronome sequence containing random intervals. This represents a format similar to that used by Hary and Moore (1987, Figure 2a-c, p. 308).

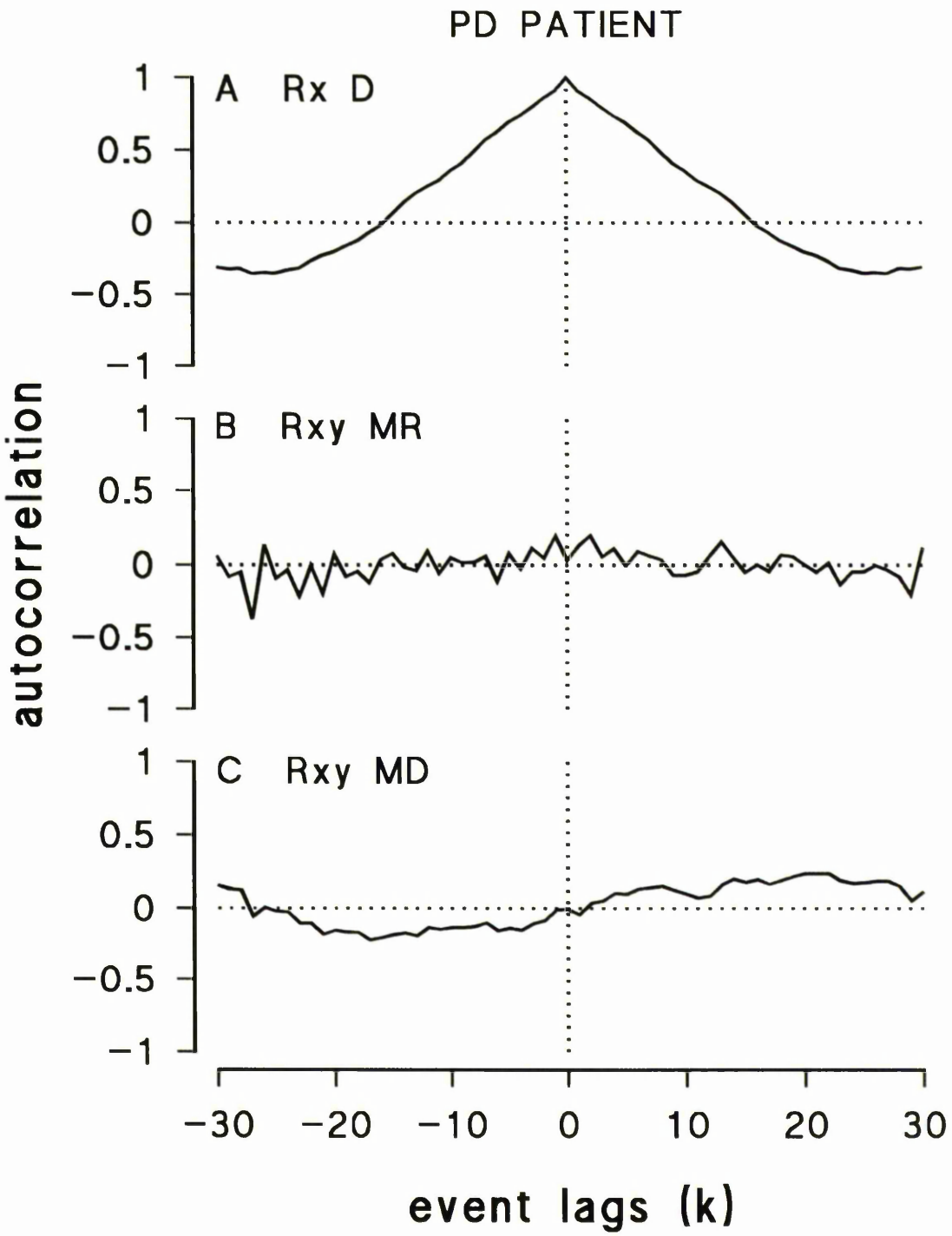

Figure 4.16. **A** Serial auto-correlograms for the delay interval (R_xD) and cross-correlograms between the metronome interval and **B** the response interval ($R_{xy}MR$) and **C** the delay interval ($R_{xy}MD$) for a single trial performed by a PD patient while tracking a metronome sequence containing random intervals. This represents a format similar to that used by Hary and Moore (1987, Figure 2a-c, p. 308).

any micro-structure within the subject-generated intervals must be due to an underlying synchronisation strategy.

There were differences between the correlograms produced by the PD patients and the control subjects in the examples shown. In the R_xD, a positive correlation was associated with lags around zero. However, this correlation was only positive between lags -5 and +5 for the control subject but in the case of the PD patient, positive correlations occurred between lags -16 and +16. There seemed to be little pattern in the $R_{xy}MR$ in the example shown for either the control or the PD patient or in $R_{xy}MD$ for the control subject. However, for the PD patient, $R_{xy}MD$ seemed to contain a structure which may have been due to an underlying synchronisation strategy, as the random metronome interval contained no structure. All the example correlograms shown for both the patient and the control subject were typical of correlograms in many trials obtained from both groups.

CHAPTER 4.4: DISCUSSION.

Sequences of finger tapping movements, synchronised with 120 metronome intervals were analysed for a group of male PD patients and a group of male age-matched (non-musician) control subjects. Initial analysis attempted to characterise response, error and delay intervals in the performance of the two groups, while extended analysis attempted to produce an initial insight into the strategies which may have been employed by subjects, using serial auto- and cross-correlograms. The relationship between objective synchronisation error (OSE) and subjective synchronisation error (SSE) was investigated for the last response of a sequence in two of the patients and two of the control subjects.

Neither the mean response intervals nor the variability around the mean response intervals produced by PD patients were significantly different to those produced by the control subjects. However, there was a significant increase in the mean error interval and decrease in the mean delay intervals produced by PD patients during each of the three metronome sequence types, when compared to those produced by control subjects. Findings indicated that while control subjects had some degree of awareness about the size of their OSE in the form of a positive correlation (which bordered on statistical significance) between OSE and SSE, PD patients seemed to be unaware, at a conscious level, of their SSE. There was no correlation between OSE and SSE in the patient group.

Serial correlograms provided evidence that all subjects responded to the changes of metronome interval during the step sequences. Initial data from trial sequences of random metronome intervals suggested that, in the examples used which were representative of the

performance of the two subject groups, PD patients and control subjects may have used different synchronisation strategies.

4.4.1. Characterisation of subject-generated intervals during a simple temporal tracking task.

The mean response interval and the standard deviation associated with the mean response interval produced by the patient group were not significantly different from those produced by control subjects. This may seem surprising in that findings in Chapter 2 suggested that a percentage of patients produced a 'hastened' response at the target intervals closest to 700 msec (1000 and 500 msec, 1 and 2 Hz). However, due to the nature of analysis it was necessary for each trial to contain 121 responses to coincide with the 121 metronome events; therefore the similarity in mean response intervals produced by the subject groups was simply an artefact of the experimental design. Additional responses would have created difficulty in the calculation of error and delay intervals for that response. Any trial in which a subject produced more than 121 responses ('hastening') or less than 121 responses (due to, for example, bradykinesia) would have been rejected, as the temporal variables would have been incalculable. To minimise this problem, the six patients used in the present study were all only mildly affected by PD (see Table 4.1) and were known to be able to reproduce trials which contained the desired number of responses. This factor may have been contributory to patients producing similar levels of variability around the mean response interval to those produced by control subjects.

One of the most interesting and novel findings of the present work was the significant difference in mean error and mean delay interval between control and patient group for

each of the metronome sequence types. Control subjects tended to anticipate the metronome by producing responses approximately 60-70 msec before the metronome event (that is, they produced negative error intervals) while PD patients anticipated the metronome events by approximately 200 msec. Hary and Moore (1985, 1987a) found that in similar tasks trained musicians tended to anticipate the metronome by 20-25 msec. Their findings are relatively comparable to the present work as they were based on sequences of 140 metronome intervals of which only the last 120 were analysed, and sequences contained similar step and random functions to those used in the present work. Therefore, it seemed that the trained musicians were more synchronous with the metronome events than the present non-musical control subjects who, in turn, were more synchronous than the PD patients. As a consequence of the mathematical relationship between the error and delay variables (see equation 1, section 4.2.4), delay intervals were significantly lower in PD patients than those produced by the control subjects for each metronome sequence type. The difference in error and delay intervals between patient and control groups was unlikely to be due to bradykinesia, as patients were able to produce response intervals of a shorter duration (600 msec), both immediately before and after the main experimental session. The variability associated with the response intervals did not differ significantly between either the two sessions in the patient group, or between the two subject groups.

However, not only were the patients less synchronous but their error (and delay) intervals typically contained a low frequency, cyclical component which was not apparent in the control subjects' performance (see Figure 4.5). It seemed as if the patients error intervals 'drifted', within 30 intervals, from being relatively synchronous to being grossly asynchronous. In such trials, patients then seemed to drift back to an error interval which

was more synchronous and this gave the impression of the error intervals having a cyclical component. A similar pattern was seen in the delay intervals. This cyclical component, common in the patient data, may have been the reason for the tendency for levels of variability associated with both error and delay intervals to be higher in the patient group compared with the control group (see Figures 4.7B and 4.8B). However, these difference were not statistically significant. The cyclical component must have been an integral factor in the way patients perform the task; it was noted that during such a trial patients still produced relatively accurate response intervals although the associated error intervals contained differing degrees of asynchrony. The production of a model to explain temporal tracking in PD patients would have to incorporate this low frequency cyclical component.

4.4.2. Objective versus subjective synchronisation error: is there a relationship?

Two theories may have explained the reason for the increase in negative error interval for the patient group when compared to that of the control subjects. Firstly, patients may have been consciously aware that they anticipated the metronome events, but could not physically improve their performance. Secondly, patients may have been consciously unaware of any asynchrony, and so felt no improvement was necessary. The findings of the experiments described in section 4.3.2., in which SSE was compared with OSE, strongly suggest the latter theory would explain patient performance.

In the two control subjects studied there was a relationship which bordered on the statistically significant, in the form of a positive correlation between OSE and SSE. If this relationship is indicative of performance of non-musical control subjects (and more subjects would need to be tested) there is a suggestion that control subjects were (to some

degree) consciously aware of the magnitude of an error interval when a trial was suddenly terminated. However, no such relationship was observed between the OSE and SSE in the two PD patients. Again, if this finding was indicative of the patient 'population', it suggested that the patients were consciously unaware of their synchronisation errors, and demonstrated deficits in the perception of simultaneity. Patients unawareness was compounded by the finding that their confidence in the SSE was greater as their SSE became more positive; the two PD patients never produced a positive OSE.

Keele *et al* (1985) tested not only motor timing (using similar finger tapping tests) but also tested timing perception in a group of neurologically-intact subjects by asking subjects to judge the duration between brief perceptual events. They found that there was a correlation between low variability in motor timing and relatively good acuity in the judgement of duration of perceptual events. Ivry and Keele (1989) tested the ability to judge the duration of two perceptual events in PD patients. They found no perceptual deficit in PD patients when compared to results obtained from control subjects. However, in the same groups of subjects they also found no differences in motor timing between the patient and control group, using Wing and Kristofferson's model to analyse the data (discussed in section 3.1.8). Pastor *et al* (1992a), who also tested time estimation in PD patients concluded that the latter unusual finding of Ivry and Keele "necessitates cautious interpretation of these (perception of time) results". Pastor *et al* (1992a) showed that patients with PD underestimated the duration of a time interval in a verbal time estimation task and showed overproduction of time intervals when required to reproduce a short time sample. These findings led Pastor *et al* (1992a) to suggest that "time estimation, i.e. the 'internal clock', is abnormally slow in PD". Artieda *et al* (1992) observed that temporal discrimination

thresholds were elevated in PD patients, indicating the "existence of an abnormality of timing mechanisms" in these patients.

However, Ivry and Keele (1989) and Pastor *et al* (1992a) simply tested the estimation and reproduction of, in essence, a single interval (two time points). In the present work subjects were being asked to provide an estimation of the accuracy of an ongoing motor task, without any knowledge of the duration of the task. Therefore, the present work provided preliminary evidence in a small PD patient group, for sensory deficits in the perception of timing of a sequence of voluntary movements with a sequence of external cues; that is, a deficiency in sensorimotor integration of proprioceptive, tactile and kinaesthetic feedback from the effector with the auditory stimulus from the metronome events.

The present work provides initial evidence to suggest a deficit in the perception of simultaneity which is an example of an inherent abnormality of perceptual, rather than motor, timing in PD patients. Further evidence which indicated that timing deficits in PD patients were not simply limited to motor timing was provided by Obeso *et al* (1987). They reported a deficit in temporal somaesthetic discrimination in PD patients, who showed prolonged time intervals required for paired electrical stimuli to be perceived as separate in time.

"...the senses and intellect being uninjured" is a phrase often quoted from the original description of PD (Parkinson, 1817). However, although PD is primarily a motor disorder there is clinical and experimental evidence to suggest that some sensory abnormality

occurs. Patients commonly report improvements in gait when traversing patterned or lined floors which provide sensory cues (Ward, 1991). Similarly, experimental evidence such as the findings reported in Chapter 2, in which PD patients' performance deteriorated in the absence of external cues, and work by Brown and Marsden (1988) and Jones *et al* (1992) has shown that external sensory cues could improve PD patients' performance in various tasks, suggesting sensory deficits in PD. Flowers (1978) reported that external sensory cues improved patients' performance in visual tracking experiments, which provided further evidence for changes in the sensory domain profoundly influencing motor performance. Anatomically, the striatum is richly innervated both by widespread areas of the overlying cerebral cortex and by various thalamic nuclei; this predicts a heavy in-flow of sensory information into the basal ganglia (Alexander and Crutcher, 1990).

Therefore, it may be possible that patients' performance on the present task is affected by deficits in sensorimotor integration. Marsden (1982) reported that although kinaesthetic function was normal in PD patients, abnormalities of proprioceptive feedback may be apparent. Moore (1987) also reported evidence for decreased corollary discharge in PD patients.

Although PD patients produced relatively accurate response intervals in the present experimental task, their error intervals showed the performance to be grossly asynchronous. The patients did not seem to be consciously aware of the asynchrony. If conscious awareness of subjects' response intervals with respect to the metronome events is fundamental in the underlying synchronisation strategy, then further experiments may expose the deficit in sensory feedback which causes the lack of correlation between OSE

and SSE. However, it may be the case that 'monitoring' of the response and metronome sequence may be processed at a subconscious level.

4.4.3. Initial predictions about synchronisation strategies used by PD patients and non-musical control subjects.

The auto- and cross-correlograms shown in Figures 4.13-4.16 were obtained from response sequences from a control subject and a PD patient during a single trial. However, the correlograms were typical of those produced both in other trials performed by those subjects and in trials performed by other control subjects and patients. Figures 4.13 and 4.14 show that in these examples both control subjects and patients responded to the step function, as the subject-generated correlograms contained patterns which were characteristic of statistical structure of the metronomic step function. However, the subjects were not consciously aware of the step function and both Hary and Moore's (1985) and the present experiments had been designed so that the step (10 msec) was "small enough to avoid detection by the subject".

As the present experimental protocol was almost identical to that used by Hary and Moore (in that a metronome sequence with an identical step function was used, Hary and Moore, 1985, and a metronome sequence containing random intervals was used, Hary and Moore, 1987a), initial predictions about the possible synchronisation strategies employed, in the examples shown, for both the PD patient and the control subject, were made using similar logic. Hary and Moore (1985, 1987a) presumed that if a subject, presented with repeated metronome sequences employed a consistent strategy, then similar and characteristic relations (i.e. sets of correlations) would be observed from one trial to another. Hary and

Moore produced hypothetical models of synchronisation strategies (see 4.1.3), and programmed a computer to implement those rules and produce a series of hypothetical 'taps'. The computer-generated sequence was processed in the same manner as a subject-generated sequence and the resultant correlograms compared. Discrepancies between subject-generated and computer-generated data resulted, ultimately, in the rejection of the hypothetical synchronisation strategy for that subject group.

Hary and Moore (1985), using this process, rejected the metronome-reset strategy (see 4.1.3) as an explanation of the performance of trained musicians. Such a model predicts minimal correlation between the metronome and delay intervals. The authors found there to be definite interactions between the metronome and delay intervals in the serial correlograms obtained from response sequences produced by the musicians. Similarly, in the examples shown in Figure 4.13B and Figure 4.14B, which were typical of correlograms produced by other subjects, there seemed to be a definite interaction between the metronome and delay intervals observed in the serial correlograms obtained from sequences produced by (non-musical) control subjects and PD patients, respectively. Using, the criteria provided by Hary and Moore (1985, 1987a), this provided initial evidence against the use of a metronome-reset strategy by both control subjects and PD patients while performing the temporal tracking task.

Hary and Moore (1987a) also considered that trained musicians may have used a mixed-reset strategy (see 4.1.3). In such a strategy, both the response and metronome events may be used as the reset event. A feedback loop connecting the error interval to an internal reference interval would serve as a pathway by which a subject's experience could modify

his behaviour. The mixed-reset strategy model predicts positive correlations between delay intervals at small lags (k approximately -3 to 3), and a negative first-order correlation between the metronome and delay intervals. The similarity between computer-generated and data obtained from trained musicians whilst tracking a metronome sequence containing randomly-fluctuating intervals caused Hary and Moore (1987a) to conclude that their subjects may have adopted a mixed-reset strategy. However, in trials using random metronome intervals, the correlograms obtained from response sequences produced by a non-musical control subject presented positive correlations between delay intervals at lags -5 to 5 (Figure 4.15A) but there was no first-order negative correlation between delay and metronome intervals (Figure 4.15C). In correlograms obtained from response sequences produced by a PD patient, there were significant positive correlations between delay intervals at lags -16 to 16 (Figure 4.16A), not predicted by the mixed-reset strategy. In addition, the cross-correlogram of metronome and delay intervals produced by the patient did not contain a significant negative first-order correlation (Figure 4.16C). However, the correlogram did contain a gradual change in polarity, again not predicted by the mixed-reset strategy which may have been indicative of the cyclical component observed in the delay intervals produced by patients (see Figure 4.4B and section 4.3.1). Again, using the criteria of Hary and Moore (1985, 1987a) the mixed-reset strategy would have to be rejected for both the control subject and the PD patient.

Therefore, it would seem that both the metronome-reset and mixed-reset synchronisation strategies (described by Hary and Moore, 1985; 1987a) are unlikely to be employed by either the non-musical control subject or the PD patient. The performance in the two trials used as examples in section 4.3.3 were typical of trials produced by that subject group

(n=6). There were differences in the serial correlograms obtained from response sequences produced by control subjects and PD patients (see 4.3.3). These differences indicated that different strategies may have been employed by the PD patient in performing the temporal tracking task, compared to those employed by the control subject. What is required is a model (or models) for a synchronisation strategy which produces similar computer-generated response sequences and serial correlograms as those seen in the subject-generated data.

CHAPTER 5: GENERAL DISCUSSION.

5.1. Is there a deficit of timing in patients with basal ganglia disorders?

Clinical and anecdotal evidence demonstrates that patients with PD (and to a lesser extent, HD) have difficulty walking, speaking and writing, and thereby implicates the basal ganglia in the control of repetitive movements (Kanazawa, 1986). Given that such movements involve a timing component, the question fundamental to the present work was what role do the basal ganglia have in the control of motor timing? Are the problems associated with the aforementioned movements simply due to motor deficits manifest in the clinical signs of rigidity, bradykinesia and tremor, or, is there an underlying deficit of *timing* in patients with basal ganglia disorders?

Work presented in this thesis provided evidence for a deficit of motor timing in both PD and HD patients. Work described in Chapter 2 suggested that the ability of PD patients accurately to produce mean tapping frequencies changed with target frequency. This change of performance was unlikely to have been due to the effector system, as different target frequencies produced selective changes in performance even though the same arm and finger were used throughout, and especially at lower target frequencies at which bradykinesia was unlikely to have been a factor. Therefore, any change in performance was more likely to have been due to inaccuracies of motor timing. In addition, there was no correlation between any of the clinical motor signs and an index (see section 2.3.3) of tapping performance. Work described in Chapter 3 showed that variability attributable to a hypothetical clock (as theorised by Wing and Kristofferson, 1973), as well as that attributable to a hypothetical motor-implementation system, was significantly higher in both PD and HD patients when compared with control values. An increase in clock variability alone was observed in patients 'on' medication (during the 'medication' trial)

compared to that observed in control subjects, and a decrease in clock variability in a hemi-parkinsonian patient, tested regularly over a fifteen-month period, using the less affected hand after the onset of daily medication (see section 3.3.3), suggested that deficits in motor timing may have been present when the classical neurological signs were less apparent. Chapter 4 described preliminary work which suggested deficits in both the ability of PD patients to synchronise responses with sequences of metronome pulses and in their conscious perception of any asynchrony. Although PD and HD patients possess generalised motor deficits which may impede the production of sequences of movements, the present findings support the existence of a specific deficit of motor timing in human basal ganglia disorders.

5.2. What role do the basal ganglia have in the 'timing circuits' within the CNS?

If the basal ganglia, as suggested, are involved in motor timing, the next question to be answered is *how* are they involved? Different structures within the brain have been implicated in timing. The existence of an internal timekeeper in the inferior parietal lobe has been proposed by Tanaka *et al* (1987) following a detailed study of a patient with pure word deafness. On the other hand, circadian rhythmicity of drinking, sleep and temperature depends on the integrity of the hypothalamic suprachiasmatic nuclei (Stephan and Nuñez, 1977). Therefore, on the basis of the limited anatomical knowledge available at present, it is likely that the brain may possess several linked timekeeping centres (Keele and Ivry, 1987).

Workers have begun to examine the concept of an internal clock regulating motor timing by analysing patients with timing disorders. The present study has provided evidence for

a clock disorder in patients with PD (along with the findings of Wing *et al*, 1984, Ivry and Keele, 1989 and Pastor *et al*, 1992) based on Wing and Kristofferson's (1973) model of timing. Ivry *et al* (1988) suggested that the lateral region of the cerebellum plays an important role as a timekeeper and the medial region is important in motor-implementation. Lesions in either the basal ganglia or the cerebellum may lead to increased variability in a timekeeping process. The location of the clock was further clouded by results obtained from patients with cortical lesions. Ivry (1986) observed, when response sequences were analysed using Wing and Kristofferson's (1973) model, increases in both clock and motor implementation in patients with lesions in the precentral and motor areas of the frontal cortex.

Keele and Ivry (1987) proposed that to account for the effects of damage to the basal ganglia, cerebellum and cortex on clock function, these three neural systems are either part of a timing loop or part of an integrated circuit in which one neural system plays a primary role in timing. This loop could take the form of a simple circuit linking all three structures and implicating all the different structures within the circuit in the control of timing. For example, the timing of 550 msec intervals would involve setting a pathway through the loop which would require 550 msec to complete the neural circuit. Keele and Ivry (1987) postulated that circuits which timed, for example, 700 msec intervals would presumably involve more synapses or involve slower conducting neurons; this would increase the amount of time taken to complete each circuit. The normal functioning of such a system would be disrupted if damage occurred at any point along the circuit and would explain why lesions in either the cerebellum, cortex or basal ganglia could cause an increase in clock variability. However, anatomically, there is little overlap between the

cortico-basal ganglia (see 1.1.2 and 1.1.3) and the cortico-cerebellar loops, despite the common relay of both subcortical structures in the ventral portion of the thalamus (Parent, 1990). Therefore it seems unlikely that such a simple timing circuit would be continuous.

A second, more complex, form of timing circuit was proposed by Keele and Ivry (1987) in which a structure is connected to the other two structures by two local loops. They assumed that one of the loops determines 'timing information' while the other loop is involved with other, unrelated computations. For example, if the motor cortex had just sent a signal, via the pyramidal tract, which resulted in a motor response, this signal would simultaneously initiate the process needed to determine the next response. A number of different operations could then be evoked including, for example, processes within the cerebellum which may determine the time at which the response could be made and the basal ganglia which may provide some other parameter input. When all of the computational outputs of the various procedures are returned to the motor cortex, the next response would be triggered and the cycle repeated.

This simplified explanation exemplifies the fact that deficits which affect any of the procedures or disrupt the system at any point prior to the triggering of a response will contribute to increased timing variability. Indeed, the affected structures may not play a direct role in timing control, but could induce added noise into the timing circuit, since the different operations could not be implemented until the preceding response has been initiated. In the above explanation, Keele and Ivry (1987) cited the cerebellum as the structure which controlled the timing of the circuit in the more complex timing circuit. As the correlational work of Keele *et al* (1985) suggested that motor timing in a tapping task

and perception-of-time tasks involved a common motor process (see 4.4.2), Keele and Ivry (1987) suggested that if a timing component was restricted to a single neural structure (e.g. the cerebellum), only a select group of patients should be impaired in both tasks. Research by Ivry and Keele (1989) led them to believe that the operation of the internal clock could be localised within the cerebellum. They found that not only did cerebellar patients demonstrate substantial increases in variability attributed to an internal timekeeping process in a tapping task, but were the only patient group (compared to patients with cortical, striatal and peripheral lesions) to show deficits in a task in which the temporal task-demand was primarily perceptual (and not motor). Ivry and Keele (1989) found this perceptual discrimination of time to be normal in PD patients (see 4.4.2) but also, surprisingly, found motor timing variability to be not significantly different from that of control subjects. Work presented in this thesis provided strong evidence to suggest that deficits of motor timing occurred in PD and initial evidence to suggest that the perception of simultaneity (see 4.3.2 and 4.4.2.) *was* deficient in PD, whilst Pastor *et al* (1992) provided evidence of an impairment of the perception of elapsed time between two temporal events in PD patients. Deficits of motor timing have also been observed in HD patients. According to the use of the same logic as Ivry and Keele (1989), this would implicate not only the cerebellum, but also the basal ganglia in a central role in the timing requirements of a motor program.

5.3. What aspects of motor timing do the basal ganglia control?

An important finding in the work described in Chapter 2 was that the ability of PD patients to produce accurate mean tapping frequencies deteriorated following removal of the auditory cues. It may be argued that the synchronisation (cued) phase of tapping tasks

described must have provided a period in which the internal clock became entrained to the target interval, and that this entrainment was stored in 'memory' associated with the clock. The deterioration of performance observed in PD patients after cue removal may have been due to either a impairment of acquisition, storage of retrieval within this 'clock memory', or, ineffective entrainment. Initial findings documented in Chapter 4 suggested deficits in patients' ability to synchronise their responses with the metronome events, and therefore, an impairment in the acquisition of information from their 'clock memory'.

The control of motor timing during the synchronisation of motor acts with external events is influenced by external factors (i.e. the physical aspects of the stimuli), as well as random fluctuations and systematic errors arising from the internal control and executive mechanisms. Mates (1994) considered that the accuracy of synchronisation is influenced by various factors: the confines of the sensory systems (limiting the subject from perceiving the asynchrony), the confines of the motor systems (limiting the subject from correcting sufficiently the perceived asynchrony), and inaccuracy of the corresponding temporal intervals reproduced by an internal time-keeping mechanism in a sequence of responses. Several principal questions then arise. What is the source of the negative synchronisation error observed in the control subjects? What impairment(s) produce the increased magnitude of anticipatory synchronisation error observed in PD patients? Which induced sensory event or events related to brain activity are internally synchronised to provide subjective simultaneity, and which (if any) are defective in PD?

Although Hary and Moore (1985, 1987a) were relatively successful in the production of models of human synchronisation strategies which were tested using computer simulations,

these models could not account for, or did not predict, the negative synchronisation errors commonly observed in the trained musicians used in their experiments and in the non-musical controls and PD patients in the present work. Hary and Moore (1987a) postulated that the CNS may possess a 'critical' node at which the average synchronisation error is, in fact, zero or perceived to be zero even when, in the laboratory frame of reference, it is negative. Mitrani *et al* (1986) suggested that there may be a locus of convergence in the brain for two sensory modalities with different conduction delays, a point at which temporal information about the metronome is compared with information about the response event. The process at this locus might involve several time-consuming sub-processes including detection and identification of the metronome event, detection and identification of the response event (the latter requiring both kinaesthetic and auditory inputs), a decision about the temporal order about the events and a decision about the time order between them. Hary and Moore (1987a) admitted that these were mere speculations. However, findings presented in this thesis (larger synchronisation errors in PD patients and an apparent reduction in conscious awareness of such asynchrony) suggest that further experiments may elucidate the role of basal ganglia, which may serve as such a critical node in the receipt of sensory information.

Mates (1994) suggested that a delay between the stimulus presentation and the temporal availability of its representation in CNS, may consist not only of a simple delay in the neural transmission of sensory information, but also a delay in the assimilation of the incoming sensory information into a form which would stimulate 'perceptual centres' within the brain. Patients with PD may produce larger anticipatory synchronisation errors due to a deficit in the integration of incoming sensory information. For example, on

tapping, sensory information integrated by defective basal ganglia would take a longer amount of time to be made available to other neural structures within the internal clock circuit (temporal central availability of stimulus, Mates, 1994). In such an example, PD patients could respond before the metronome event while perceiving the response to be synchronous. Initial findings suggest that PD patients are consciously unaware of such synchronisation errors.

I suggest that the basal ganglia integrate sensory information, which is provided to the structures within an internal clock circuitry, central to the timing of repetitive movements. What evidence for such a role was provided in the present work? Findings presented in Chapter 2 demonstrated that although the PD patients produced less accurate mean tapping frequencies in the presence of auditory cues when compared with those produced by control subjects, patient performance deteriorated even further following cue removal. As previously suggested, this may have been due to ineffective entrainment of the clock during the synchronisation phase. However, removal of the auditory entrainment information in the form of the desired target interval, reduced the patients ability to produce accurately-timed intervals although tactile, visual and proprioceptive feedback were still available. Further, albeit more indirect, evidence about the role of feedback was presented in Chapter 3. Frequent violations of the predictions of Wing and Kristofferson's (1973) model were observed in response sequences produced by PD patients. One explanation for the incidence of violations was that the independence assumption, fundamental to the model, was not applicable to PD patient performance within the context of Wing and Kristofferson's (1973) model. That is, the hypothetical clock and the hypothetical motor-implementation system were not independent, and the two processes

operated, in some instances, in a closed-loop fashion. One inference would be that the clock received feedback from the motor-implementation system and that the high levels of clock variability observed in patient performance may have been due to deficits of sensorimotor integration in the basal ganglia.

Therefore, one hypothesis may be that during the synchronisation phase, PD patients (due to a diseased basal ganglia) are unable to effectively integrate sensory information (compared with normal subjects) in the form of tactile, visual and proprioceptive feedback from their responses, in order to compare this information with the auditory feedback of the metronome event. Information about the comparison of the timing of response and metronome event would then influence timing centres (e.g. cerebellum) of the internal clock and, in the case of PD patients, would produce less accurate motor timing. It could also be hypothesised that during the continuation phase, without the external auditory cues, the effectiveness of the basal ganglia to provide comparative feedback about the accuracy of response intervals would be further diminished. This would explain the deterioration of performance observed in patients after cue removal and high levels of variability attributable to an internal clock (as hypothesised by Wing and Kristofferson, 1973) observed during the uncued phase.

5.4. Future work.

Initially, further experiments should be performed to investigate the relationship between subjective and objective synchronisation errors, and such experiments would be identical to those described in section 4.2.5 in which only two PD patients and two control subjects were tested. Subsequently, a further set of experiments would provide additional insight

into the degree of asynchrony, between a response and a metronome event, required before the synchronisation error is perceived and corrected. Michon (1967) reported a set of experiments in which subjects produced sequences of finger taps to 'ramp' metronome sequences. Metronome sequences containing ramps comprised of series of intervals which gradually became either faster (for example, first interval of 800 msec, gradually decreasing to 600 msec) or slower, the change in interval being constant. Michon (1967) found that subjects, during sequences of either increasing or decreasing interval, did not produce sets of intervals which gradually became longer or shorter, respectively, but altered their responses intervals in series of 'steps'. Analysis of the width and height of such 'steps', in response sequences produced by PD patients may provide further insight into the size of a 'threshold' of synchronisation error required before error correction and before conscious awareness of such an error.

The methodology outlined in experiments presented in Chapter 4 represents the basis for further work into the role of the basal ganglia in motor timing. Further understanding requires a functional model for the strategy used by PD patients when performing temporal tracking tasks. According to Hary and Moore (1985, 1987a), response sequences in which a similar synchronisation strategy had been employed would produce similar serial correlograms (see section 4.1.3). Chapter 4 provided examples of serial auto- and cross-correlograms produced by PD patients. What is required is a model which predicts the temporal statistical patterns observed in those correlograms. Initial findings presented in Chapter 4, coupled with Hary and Moore's criteria used in determining the validity of a hypothetical synchronisation strategy, provided initial evidence for the rejection of two models as strategies used (in the examples shown) by both PD patients and the non-musical

control subjects. The two models, hypothesised by Hary and Moore, were the metronome-reset strategy (1985), and the mixed-reset strategy, (1987a). An information-processing model is required to simulate synchronisation strategies used by PD patients such that when computer-simulated response sequences were produced, serial correlograms calculated from the sequences similar to those produced by patients were observed. Such a model would provide valuable insight into both the strategy used by PD patients and, after comparison with strategies employed by control subjects, the role of basal ganglia in the control of motor timing.

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Abnormalities of human rhythmic voluntary movement in Parkinson's disease

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Clinical observations that patients with Parkinson's disease (PD) show disturbances of repetitive voluntary movements e.g. festination and freezing of gait, which may be alleviated by external sensory inputs (Ward, 1991) suggest a role for the basal ganglia in the internal guidance of movement. We have tested this hypothesis, with Local Ethical Committee approval, by comparing the ability of nine Parkinsonian and twelve age-matched healthy subjects to synchronize finger tapping, produced by rhythmic wrist movements, with auditory signals of different target frequencies (range 1–5 Hz) and to sustain rhythms following sudden withdrawal of auditory cues.

Healthy subjects were very accurate in duplicating both the regularity and mean rate of auditory signals. The tapping rhythms of PD patients were more variable. In addition, patients tended, on average, to tap too rapidly at the low and too slowly at the high target frequencies. The mean tapping rates of the patient group were significantly greater than those of the controls at targets of 1 and 2 Hz for the non-preferred hand and at 3 Hz for the preferred hand and significantly lower at 5 Hz for the non-preferred hand ($P < 0.05$, t test). The tapping accuracy of almost all of the patients fell outside the normal range at two or more target frequencies, although these abnormalities were usually unilateral, and altered patterns comprised 'hastening' (Nakamura *et al.* 1978), i.e. increased rates at low-intermediate targets, or 'faltering,' i.e. reduced rates at high targets. Removal of auditory cues produced slight deterioration of accuracy in healthy subjects. The impairment in performance was more marked in the PD group. Mean tapping rates increased significantly ($P < 0.05$, paired t test), from already elevated levels, at 1 and 2 Hz targets (both hands) and 3 Hz (preferred hand) and decreased significantly ($P < 0.05$) at 4 Hz (non-preferred hand) and 5 Hz (preferred hand). However, cases of frank 'hastening' and 'faltering', where tapping patterns were most severely disrupted, were relatively less affected by cue suppression indicating an inherent disturbance of rhythm generation in PD. Furthermore, patients showing 'hastening' of tapping reported frequent episodes of festination/freezing of gait suggesting that these phenomena may be related.

Thus, whilst PD patients are less able to synchronize repetitive voluntary movements to external cues than healthy subjects they are generally more reliant upon such cues to maintain rhythms. These findings are consistent with the basal ganglia contributing to the internal guidance of movements.

Supported by the MRC. J.S.F. is in receipt of a SERC studentship.

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COMMUNICATIONS

Deficits of human rhythmic voluntary movements in Huntington's disease

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Experimental and clinical observations that patients with Parkinson's disease (PD) show an increased reliance on external timing cues to set the tempo of repetitive movements (Freeman *et al.* 1993; Ward, 1991) suggest that the basal ganglia are normally involved in the internal cuing and timekeeping of motor activities. To test whether deficits in the motor programming of rhythmic movements are a general feature of basal ganglia dysfunction, we have obtained complementary data from Huntington's disease (HD) patients in whom these centres are affected by a different pattern of neuropathology.

The ability of fourteen HD patients and twelve, age-matched healthy subjects to synchronize finger tapping, produced by rhythmic wrist movements, with auditory signals of different target frequencies (range 1–5 Hz) and to sustain rhythms following the sudden withdrawal of auditory cues was investigated with Local Ethical Committee approval. Healthy subjects were accurately able to duplicate both the mean rate and regularity of cue signals over the 1–5 Hz range. HD patients, however, had significantly reduced mean tapping rates at 3, 4 and 5 Hz target frequencies (Bonferroni-corrected P values, respectively, $< 0{\cdot}05$, $< 0{\cdot}01$ and $< 0{\cdot}01$, Mann–Whitney). In addition, patients' tapping rhythms showed marked irregularity. Whilst maximal tapping frequencies (MTFs) were, on average, abnormally low in the HD group ($P < 0{\cdot}01$, Mann–Whitney), individual patient's mean tapping rates at 3 and 4 Hz targets were significantly less than their MTFs (Bonferroni-corrected P values, respectively, $< 0{\cdot}01$ and $< 0{\cdot}05$, Wilcoxon). Thus, slowness of movement *per se* did not account for depression of patients' mean tapping rates at 3 and 4 Hz targets, although it probably contributed at the 5 Hz target. In neither patient nor control groups did auditory cue suppression elicit significant changes in mean tapping rates.

The inaccuracy of tapping rates found in HD indicates that a definite disturbance of neural rhythm formation is present in the disease and supports the view that the basal ganglia participate in this aspect of motor programming. However, HD patients, unlike parkinsonians, showed no sign of continuously utilizing auditory timing signals to sustain tempo or counteract inherently impaired performance. Thus, in HD, a more profound inability to analyse the temporal parameters of extrinsic inputs and/or intrinsically generated movements may be suspected.

Supported by the MRC. J.S.F. is in receipt of a SERC studentship.

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Journal of Neurology, Neurosurgery, and Psychiatry 1993;**56**:1078–1084

The influence of external timing cues upon the rhythm of voluntary movements in Parkinson's disease

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Abstract

The ability of patients with Parkinson's disease (PD) and healthy subjects to synchronise finger tapping, produced by rhythmic wrist movements, with auditory signals of target frequencies (range 1–5 Hz) and to sustain such rhythms following sudden withdrawal of auditory cues was studied. Healthy subjects were able, in the presence of auditory cues, to duplicate target frequencies accurately over the range investigated both in terms of mean tapping rate and in regularity of tapping. PD patients were less accurate under these conditions and on average tended to tap too rapidly at the lower (1–3 Hz) target frequencies and too slowly at the highest (5 Hz) target frequency. In addition, the variability of their tapping rhythms was generally greater. Healthy subjects were able to sustain tapping rhythms well following suppression of auditory signals. By contrast, withdrawal of external timing cues resulted in marked impairment of the patients' rhythm generation. At lower frequency targets (1–3 Hz) patients' tapping rates increased over rates which were already elevated in the presence of external cues. Conversely, at higher target frequencies (4–5 Hz), the average tapping rate tended to decline further from previously depressed levels. The accuracy of almost all patients fell outside the normal range. Two patterns of tapping errors were found. The first was hastening of tapping which was most evident at intermediate target frequencies. The second was faltering which occurred mainly at the higher target frequencies. These forms of behaviour may result from inherent abnormalities of internal rhythm generation since they occurred both in the presence and absence of external timing signals. Overall, our findings are consistent with the view that the basal ganglia have a role in the internal cueing of repetitive voluntary movements.

(*J Neurol Neurosurg Psychiatry* 1993;**56**:1078–1084)

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Received 19 May 1992
and in revised form
8 January 1993.
Accepted 19 January 1993

A current theory of basal ganglia function attributes these motor centres with a primary role in the internal initiation and timekeeping of movements. This view is, in part, founded on the common clinical observation that many patients with Parkinson's disease (PD) experience difficulty in performing repetitive voluntary movements.[1] An extreme example of this type of movement deficit is the well known "freezing" phenomenon of PD, in which patients exhibit an inability to start or to continue cyclic motor activities such as walking, speech, or handwriting.[2 3 4] In addition, there is much anecdotal evidence that PD freezing may be both triggered and terminated by external sensory inputs. For example, periodic visual inputs from a striped pattern on the floor or a staircase can help PD patients to sustain locomotion. Thus, suppression of freezing by external cues indicates an increased dependence of the rhythm generator upon extrinsic reinforcement for its continued operation. As a corollary, freezing may represent a basic failure of internal rhythm generation by the basal ganglia.

Detailed measurements of the influence of external sensory information on the ability of PD patients accurately to produce rhythmic movements are, therefore, highly relevant in assessing the possible role of the basal ganglia in internal rhythm generation. There is, as yet, a dearth of such quantitative data. Nakamura *et al*[5 6 7 8] have reported abnormalities in the ability of PD patients to perform repetitive finger tapping in response to auditory signals and have proposed that characteristic deficits in rhythm formation exist in this disorder.

In the present experiments we have focused upon a quite different aspect of rhythm formation in PD, namely the reliance of patients on external timing cues to generate and maintain rhythms. To this end, we compared the effects of withdrawal of auditory cues upon finger tapping performance in PD patients and healthy subjects. We also investigated whether abnormal rhythm production in PD was related to the occurrence of freezing in everyday activities and to the co-existence of tremor.

Methods

SUBJECTS

Nine patients (five men, four women) aged 60·8 (6·7) years, mean (SD), and 12 healthy subjects (five men, seven women) aged 63·4 (7·9) years were studied. All subjects participated with informed consent and the protocols were approved by the local ethical committee.

The diagnosis of PD was made by a consultant neurologist on the basis of the classic

triad of tremor, rigidity, and bradykinesis and the absence of any atypical signs or symptoms. Patients were investigated while on their routine therapy, which in all cases included standard levodopa formulations and in some cases additional medication. No distinction was made between the "on" and "off" phases. The average duration of the patients' disease at the time of testing was 6·4 (3·0) years. Patients were assessed for rigidity, bradykinesia, and gait, each scored on four point scales[9] in which 0 = normal or absent and 3 = severely disturbed, immediately before experimental sessions. Rigidity: eight patients were graded 1 and one patient graded 2. Bradykinesia: five patients were graded 1 and four patients were graded 2. Gait: two patients were graded 0, two patients were graded 1, three patients were graded 2, and two patients were graded 3. Four of the patients had an asymmetrical pattern of Parkinsonian signs and of these two were more severely affected on the left side and two on the right. Postural tremor was measured accelerometrically at each wrist. Mean peak frequencies for the left and right wrist were, respectively, 6·0 (1·5) Hz and 6·1 (1·5) Hz with corresponding ranges of 4·3–8·7 Hz and 4·0–8·2 Hz. The incidence of freezing of gait during everyday activities was also scored for individual patients according to a four point scale: 0, never; 1, several times per month; 2, several times per week; 3, daily.

FINGER TAPPING TEST

Subjects sat in a chair with one forearm resting comfortably upon a table placed in front of them. A flexible metal loop was fitted snugly to the index finger just proximal to the terminal interphalangeal joint. The hand was placed palm downwards over a wooden board to which was attached a metal contact plate. Subjects produced tapping of the index finger by making rapid, alternating flexion and extension movements of the wrist. They were instructed to make small but distinct movements, raising the finger about 5 mm above the contact plate between strikes, so as to minimise any effects of bradykinesia in the patients. Each time the metal loop on the index finger struck the contact plate it completed an electrical circuit and generated a brief voltage pulse.

Auditory cues of target tapping frequencies were played through a loudspeaker as sequences of "clicks". These signals were produced by an electronic signal generator feeding into an audioamplifier. Trains of regularly spaced cue pulses at 1, 2, 3, 4, and 5 Hz were used. Blocks of trials in which different target frequency cues were presented were interspersed in a pseudorandom manner.

Two main protocols were employed. In protocol 1, tapping performance was recorded over 30 second periods, throughout each of which an auditory cue signal at a given preselected frequency was presented continuously. Subjects were instructed to tap in rhythm with the auditory "clicks". Such recording periods were separated by gaps of about 1 minute to allow subjects to rest. In protocol 2, tapping performance was again recorded over a series of 30 second periods. However, in this case the auditory cues were presented for only the first 10 seconds, after which the "clicks" were abruptly turned off. Subjects were instructed to tap in rhythm with the cue signal during the initial 10 second phase and then to continue to tap at the same rhythm during the remaining 20 second phase of the trial when the cues were absent. Again, 1 minute recovery periods were allowed between trials. Tapping performance of each hand was tested: protocol 1 was first applied to both hands and then both hands were tested with protocol 2.

DATA ANALYSIS

A computer was used to sample, store, and analyse tapping and tremor data. Voltage pulse trains corresponding to the occurrence of, respectively, finger taps and auditory cue signals were sampled at 100 Hz by separate channels of the A/D. Any tap pulse which followed its predecessor by an interval of <50 ms was rejected to eliminate counting artefactual contacts. Mean (SD) frequencies and plots of instantaneous frequencies (reciprocals of successive intertap intervals) of tapping pulses were calculated for each sampling period. Accelerometric tremor recordings were sampled at 50 Hz by one channel of the A/D and analysed by Fourier transform to determine the power spectrum, peak frequency and overall power.

STATISTICS

Multivariate analyses of variance (MANOVA) were applied to test whether overall differences existed between—firstly, the mean rates and variability of tapping performance of the PD and control groups in the presence of auditory cues, and secondly, the tapping performance within each group in the presence and absence of cues. Unpaired t tests (corrected for unequal variance) and paired t tests were used to identify those signal frequencies at which differences existed between the mean tapping rates, respectively, of the PD and control groups and of individual subjects in the presence and absence of cues. These comparisons each involved five sets of dependent tests. In this situation there is an increased risk of false positives (type I errors) and a compensatory α adjustment procedure (for example, Bonferroni) may be applied. In the present analyses, Bonferroni adjustment dictates that a p value of 0·01 should be interpreted at the $\alpha = 0{\cdot}05$ level of significance. However, many statisticians (see Cohen[10] for review) consider the Bonferroni adjustment to be excessively conservative and that its use leads to an unacceptable loss of power (increase in type II errors—that is, false negatives). Therefore, precise, non-adjusted p values are given throughout the text so that readers can decide significance levels.

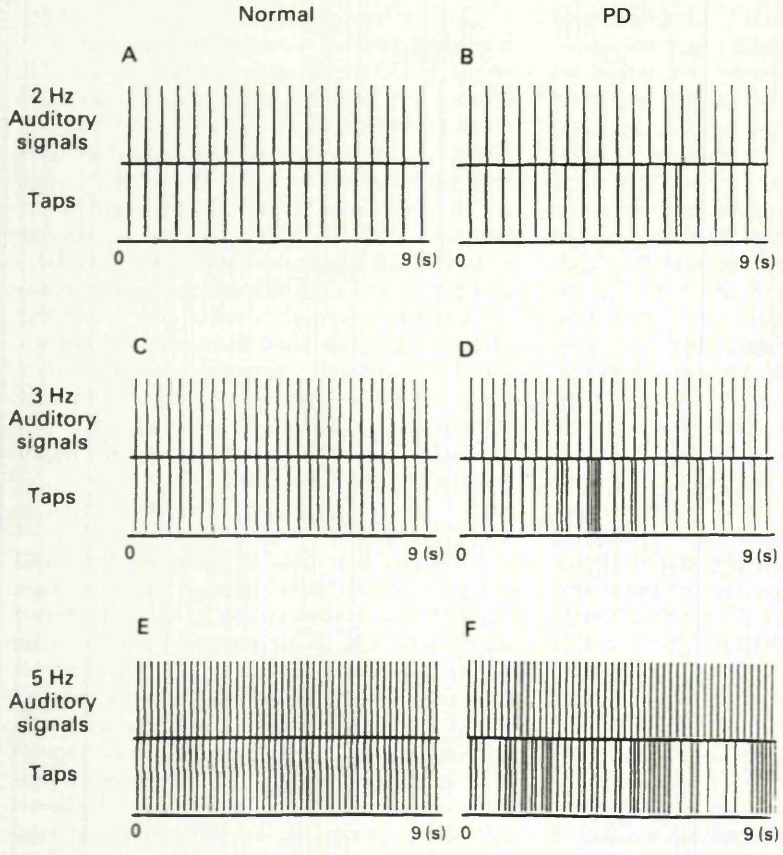

Figure 1 Finger tapping performance of a normal subject and PD patient in the presence of auditory signals of target frequency. Separate series of pulses representing the occurrence of, respectively, auditory signals and finger taps show the relative timing of these two sets of events in 9 second records obtained during 30 second periods of tapping at 2 Hz, 3 Hz, and 5 Hz targets in the normal (A, C, and E) and PD (B, D, and F) subjects.

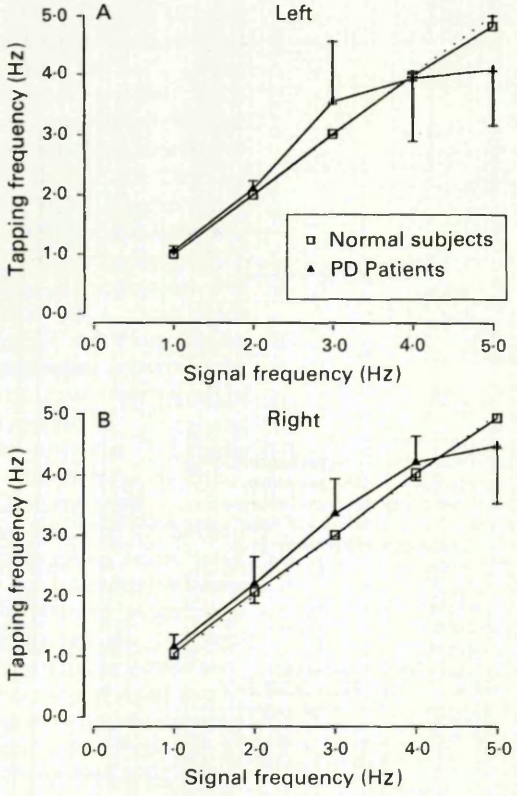

Figure 2 The relationships between finger tapping frequency and the frequency of auditory cue signals in healthy subjects and PD patients. Mean (SD) tapping frequencies are shown. Data for left (non-preferred) hand are plotted in (A) and for the right hand in (B). The dotted line, with unity slope, indicates exact correspondence of tapping and cue frequencies. The mean tapping rates of the PD group, across the range of signal frequencies, differed significantly from those of the control group ($p = 0{\cdot}01$, MANOVA).

Results

EXTERNALLY SIGNALLED RHYTHM GENERATION IN PD AND HEALTHY SUBJECTS

Figure 1 compares the abilities of a healthy subject and a representative PD patient to duplicate the rhythm of sequences of auditory cues, presented at varying frequencies, by making voluntary wrist movements to produce tapping of the index finger.

Segments of recordings made from, respectively, the healthy subject (fig 1A, C, and E) and the PD patient (fig 1B, D, and F) during 2 Hz, 3 Hz and 5 Hz trains of equally spaced auditory "clicks" show characteristic differences in performance. The pattern of pulses produced by the tapping movements of the healthy subject reproduced far more accurately the rhythm of the auditory cues, both regarding mean frequency and regularity, than those of the patient. In particular, the patient tapped too rapidly at lower (1–3 Hz) signal frequencies and too slowly at higher (4–5 Hz) signal frequencies. The lack of consistency in the relative timing of tap and cue pulses in figure 1 suggests that neither the PD patient nor the healthy subject responded directly to each individual "click" in the train of auditory signals at any of the cue frequencies. Interspersed in the patient's tapping pulse trains are occasional very short intervals (about 110–125 ms), corresponding to instantaneous tapping rates of 8–9 Hz, which are not present in the records of the healthy subject. However, equally short intertap intervals appeared in the records of healthy subjects striving to tap at their maximum rate (typically averaging about 6 Hz for a 10 second period), when their rhythm became far more variable. The mechanism responsible for these sporadic, closely spaced pulse pairs is uncertain. However, none had instantaneous frequencies more than about 10 Hz and their occurrence had no definite periodicity.

Plots of group data (fig 2) indicate that PD patients were, in general, less exact than healthy subjects in replicating the cue frequency and in producing an even pace. Results from the left (fig 2A; non-preferred in all subjects tested) and right (fig 2B) hands are illustrated. The relatively larger SD values of the patient group suggest that the tapping performance of the patients, at each signal frequency, was more variable than that of the controls and this was confirmed by statistical analysis ($p = 0{\cdot}01$, MANOVA, note that non-Bonferroni adjusted p values are given throughout, see Methods). The mean tapping rates, considered across the overall range of target frequencies, of the patient and control groups also differed ($p = 0{\cdot}01$, MANOVA). Figure 2 shows that the PD patients as a whole tended to tap more rapidly than healthy subjects at low intermediate signal

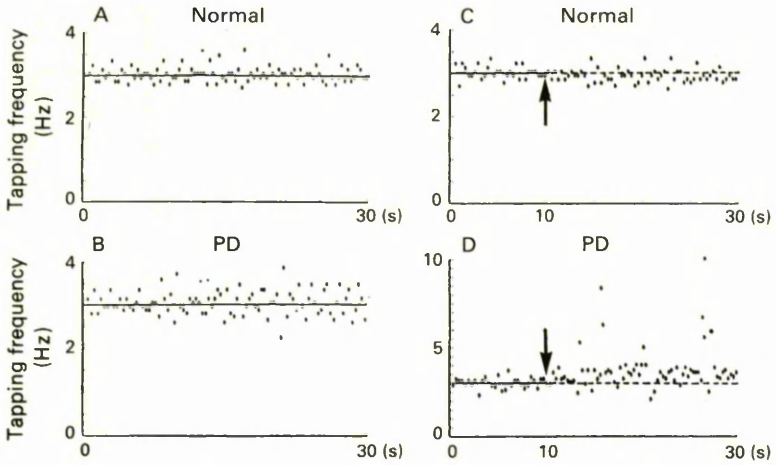

Figure 3 Plots of instantaneous frequency of finger tapping in a healthy subject and PD patient in the continuous presence of 3 Hz auditory signals and following removal of cues. Each point represents the occurrence of a single tap. The height of each point indicates its instantaneous frequency in relation to the immediately preceding tap and was calculated as the reciprocal of the intertap interval. In (A) and (B) the tapping performances of, respectively, the healthy subject and PD patient in the continuous presence of cues are shown. The solid horizontal lines indicate cue frequency. In (C) and (D) the auditory signal was played, respectively, to the healthy subject and patient during the first 10s of each plot. At the times indicated by the arrows the auditory signals were turned off and tapping during the remaining 20s periods was in the absence of auditory cues. The solid horizontal lines in the initial 10 second periods of the records show the frequency of the auditory signals. These levels are continued as dashed lines in the later 20 second periods. The scales of the vertical axes differ in (D) from those in (A) (B) and (C).

frequencies and less rapidly at the highest (5 Hz) frequency investigated. The mean left hand tapping rates of the patient group were higher than those of the control group for cue frequencies of 1 Hz and 2 Hz and lower for the 5 Hz signals (p values, respectively, 0·004, 0·009, and 0·036, *t* test). Essentially similar findings were obtained for right (preferred) hand performance, although only at 3 Hz did the difference approach a significant level ($p = 0·049$). In neither the patient nor control groups were there significant differences between the mean tapping rates of left versus right hands at any of the target frequencies.

Detailed investigation of the behaviour of individual patients revealed that two distinct subclasses of tapping abnormalities contributed to the impaired accuracy, in terms of mean rates, of the PD group as a whole. Abnormal performance was defined as tapping rates which fell, at two or more target frequencies, outside the range of values obtained from healthy subjects. Data for each Parkinsonian hand (18 hands from nine patients) were analysed independently. The first pattern of abnormality, termed hastening, comprised an increase and the second, termed faltering, comprised a reduction in mean tapping frequencies. Instances of hastening (four hands) were most common at 3 Hz and 4 Hz targets while faltering (four hands) was only displayed at the higher (4 Hz and 5 Hz) target frequencies. At the 5 Hz target, some hasteners tapped in excess of the signal frequency. Only one patient showed abnormal performance with both hands and she displayed contrasting patterns on the two sides.

RHYTHM GENERATION IN THE ABSENCE OF EXTERNAL SIGNALS IN PD AND HEALTHY SUBJECTS

Figure 3 presents instantaneous frequency plots of the tapping performance of representative healthy and PD individuals during 30 second periods in which a 3 Hz auditory cue signal was either present throughout (A and B) or removed after 10 seconds (C and D).

The plots obtained during continuous auditory signals show two main features. Firstly, the healthy subject (fig 3A) and PD patient (fig 3B) were both able to establish almost immediately a tapping rhythm approximating to the cue frequency upon onset of the auditory signal. Secondly, in neither case is there any definite sign of a transition in performance such as might result from loss of concentration or tiredness. Comparison of the tapping performance of individual subjects during the first and last 10 second periods of the 30 second tests confirmed that in neither patients nor controls was there a systematic deterioration in accuracy as trials progressed. Similar findings were obtained for all target frequencies.

Figure 3C shows that the tapping performance of the healthy subject was relatively unaffected by withdrawal of the auditory signals. By contrast, the performance of the patient (fig 3D, note different frequency scale) underwent a clear alteration following removal of auditory cues. There was an increase in average tapping frequency and the rhythm became far more irregular. Similar trends were noted for the 3 Hz target frequency in the patient group as a whole (see below). These changes seem certain to have resulted from withdrawal of cue signals, since they did not occur in the presence of auditory cues (fig 3B).

The plots in figure 4 compare the tapping performance of healthy and PD groups in the presence of auditory signals and following their sudden removal once the rhythm had been well established. Results for the left (non preferred) hand are illustrated.

Figure 4 shows that the withdrawal of external cues had a pronounced influence on the performance of the patients (fig 4B) whereas it had little effect on that of the healthy subjects (fig 4A). Statistical analysis confirmed that the mean tapping rates of the PD group, across the whole range of signal frequencies, differed significantly in the presence and absence of cues ($p = 0·01$, MANOVA) while those of the control group did not. Cue suppression resulted in the patients' mean tapping frequencies increasing at the two lowest target frequencies (1 Hz and 2 Hz) and declining at the 4 Hz target (p values, respectively, 0·038, 0·027, and 0·033, paired *t* test). Similar findings were obtained for their right (preferred) hand tapping performance. Withdrawal of cue signals caused increases in mean tapping rates at targets of 1, 2, and 3 Hz and a reduction at 5 Hz (p values, respectively, 0·009, 0·035, 0·028, and 0·047, paired *t* test). In all cases, these changes represented a further reduction in

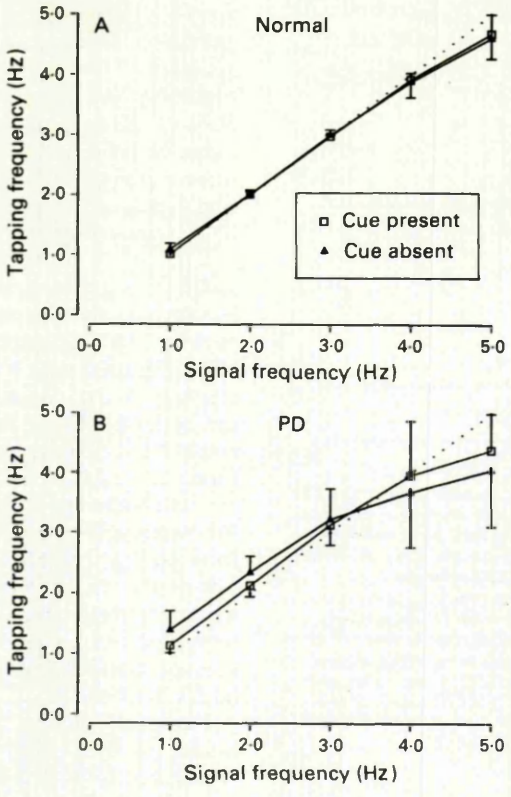

Figure 4 Plots comparing the tapping performance of subjects in the presence and absence of auditory signals for the group of healthy subjects (A) and group of PD patients (B). Mean (SD) values for the left (non-preferred) hand are given. Dotted lines indicate unity slope. The mean tapping rates of the PD group, across the range of signal frequencies, differed significantly in the presence and absence of auditory cues ($p = 0{\cdot}01$, MANOVA). Those of the control group did not.

accuracy. Although these effects of cue suppression, at individual signal frequencies, are often at borderline levels of statistical significance (see Methods), the fact that they were observed bilaterally strongly supports their general validity.

Analysis of the performance of individual patients' hands demonstrated that instances of the two subclasses of abnormal performance, hastening and faltering, were found following cue withdrawal. Hastening was now the predominant pattern (six hands out of 18 possible instances) and was most commonly noted for 2–4 Hz targets while faltering (two hands) was observed at 3–5 Hz targets.

RELATIONS OF ABNORMAL RHYTHM GENERATION IN PD TO TREMOR, BRADYKINESIA, AND FREEZING

Tremor characteristics were compared between PD hands showing different types of tapping abnormalities. PD hands were grouped according to hastening, faltering, or "within normal" behaviour as defined above. Neither the mean peak frequency nor the power of postural tremor differed significantly (t test) between these groups. Individual instances of abnormal tapping performance were noted in the absence of appreciable tremor, while in other instances tapping accuracy was "within normal limits" despite the presence of pronounced, low frequency tremor.

To analyse the relation of abnormal tapping performance to bradykinesia and freezing, patients were categorised as hasteners or falterers depending on whether they displayed exclusively hastening or faltering performance as previously defined. Two patients were excluded: one showed different abnormalities in the two hands and one exhibited an alteration in pattern between the test conditions. There was no evidence of any differences between these two patient categories concerning scores of clinical bradykinesia. However, there was a tendency for the patients in the hastener group to show more frequent freezing episodes. All four of these patients had freezing ratings of 2 or 3, whereas each of the three patients in the falterer group had ratings of 0 or 1.

Discussion

The present findings demonstrate that the ability of PD patients to generate simple, rhythmic voluntary movements is impaired in two distinct respects. First, and in agreement with previous studies,[5 6 7] patients are less able than healthy subjects to synchronise accurately their movements to extrinsic timing cues. Secondly, the patients exhibit a greater reliance on external cues for rhythm formation. Thus, in PD there appears to be a deficit of external guidance co-existing with a probably more fundamental derangement of internal cueing for stereotyped, repetitive voluntary movements.

ABNORMALITIES OF SYNCHRONISATION OF MOVEMENTS TO EXTERNAL CUES IN PD

Our findings generally confirm earlier observations of Nakamura and colleagues[5–7] for finger tapping and of Logigian *et al*,[11] for repetitive isometric contractions of finger muscles that PD patients show two separate types of synchronisation abnormalities. The first is an elevation of tempo as targets exceed 2–3 Hz and the second a depression of tempo at targets approaching 5 Hz.

A straightforward explanation of the latter form of behaviour, since slowness of movement is a common feature of PD, is that patients cannot produce sufficiently rapid movements. We cannot exclude the possibility that an inherent inability of some of our patients to maintain an adequate pace of movement contributed to their synchronisation errors for the 5 Hz target. However, a number of patients with extreme disturbances of rhythm formation, the hasteners, actually achieved mean tapping rates in excess of 5 Hz. Thus, slowness of movement was not a universal limiting factor in the PD group and a more basic synchronisation deficit was probably responsible.

This view is supported by the occurrence in patients' records of sporadic groups of two to three taps at instantaneous frequencies of 8–9 Hz. Such closely spaced taps, which contribute to the irregularity of rhythms in PD, are unlikely to have been produced by individually planned, separate movements. The fact that none occurred at instantaneous rates exceeding about 10 Hz suggests that they were not simply artefactual contacts; if so, rates up to 20 Hz (for 50 ms rejection interval) would be anticipated. Although an interaction between Parkinsonian tremor and

voluntary activity has been reported,[11] the lack of any obvious periodicity in the occurrence of these high frequency bursts argues against such a mechanism having been the sole cause. A clue to their likely origin is provided by the appearance of similar 8–9 Hz pulse pairs in the records of healthy subjects attempting to tap at maximal rate when intertap variability increases dramatically and approaches Parkinsonian levels. Present models[12] of repetitive movement propose that a central neural oscillator sets the tempo of the rhythm. Thus, the increased variability of tapping of healthy subjects at maximal rates may be due to destabilisation of such a neural oscillator. If so, the occurrence of an analagous oscillator instability, but at relatively lower frequencies, may underlie PD patients' difficulties in synthesising sequences of regular and appropriately paced movements.

DEPENDENCE OF PD PATIENTS ON EXTERNAL CUES FOR RHYTHM FORMATION

The main new finding of the present study is that the tapping performance of PD patients deteriorates following withdrawal of external timing cues. Tapping rates increased for low intermediate frequencies and decreased for high target frequencies. These changes correspond to an exaggeration of pre-existing patterns of inaccuracies found in the presence of timing cues.

Models of rhythmic movement generation by the nervous system comprise two conceptually distinct elements, namely an internal timekeeper or oscillator component and an implementation or effector component.[13] Although movement implementation itself is abnormal in PD, inaccuracies of repetitive movement arising from this source are likely to occur equally in both the presence and absence of external timing cues. The increased dependence of PD patients on external timing cues for rhythm formation, therefore, argues strongly in favour of a deficit of internal timekeeping. Since healthy subjects are able to generate motor programmes for ongoing repetitive movements by extrapolating temporal parameters from previous similar movements,[14] this capacity must be assumed to be impaired in PD.

Nakamura *et al*[5–7] have, on quite separate grounds, also proposed a disturbance of internal rhythm formation in PD. These authors placed considerable emphasis on a hastening phenomenon in PD which was characterised by a clear cut transition frequency of 2–3 Hz, at which the tapping rate suddenly jumped to a new plateau level of 5–6 Hz. The latter frequency was thought to represent an intrinsic oscillation occurring within the healthy nervous system which is unmasked in PD. In this respect, however, the present results differ from those of Nakamura *et al.*[5–7] The tapping rhythms of our PD patients very rarely showed an obvious transition frequency or any sign of convergence to a single frequency.

RELATION OF ABNORMALITIES OF RHYTHM GENERATION TO TREMOR, BRADYKINESIA, AND FREEZING IN PD

Tremor is a common feature of PD. It occurs predominantly at frequencies of 4–6 Hz[15] and is believed to result from oscillatory discharge of neurons in the ventrolateral thalamus.[16 17] Logigian *et al*[11] have proposed that in PD the neural oscillators for repetitive voluntary movement and for tremor become synchronised. The general tendency of our patients' tapping frequency to shift towards the PD tremor band is consistent with this "attractor" theory. However, none of the patients showed a dominant frequency in their tapping behaviour such as would be expected if a powerful entrainment occurred. More importantly, the incidence of the different types of abnormal tapping performance (hastening or faltering) among our PD sample correlated with neither the peak frequency nor the power of the recorded postural tremor. In addition, clear instances of tapping deficits were seen in patients lacking appreciable tremor. This echoes the finding of Narabavashi and Nakamura[3] that disturbances of repetitive tapping persist in PD patients following alleviation of tremor (and rigidity and akinesia) by medication or surgical thalamotomy. Therefore, while the tapping performance of our patients was presumably influenced to some extent by coexisting tremor (and its pathological neural generator), the balance of evidence favours a more fundamental disruption of an independent internal oscillator for repetitive voluntary movement.

As discussed earlier, slowness of voluntary movement does not appear to be responsible for inaccuracies of rhythmic tapping movements in PD. Equally, there was no systematic association between the presence of hastening or faltering tapping behaviour and the clinical score of bradykinesia.

Nakamura *et al*[3 6] regarded the hastening phenomenon they observed in rhythmic finger tapping as closely related to PD freezing. A relationship between hastening and freezing is also suggested by the observation that PD patients often show a freeze-release-hasten-freeze cycle gait and speech in which, for example, freezing episodes during walking are immediately preceded by a quickening of pace and shortening of step.[18] In keeping with this notion, we found that all of our PD patients whose sole tapping disorder was an abnormally increased rate reported relatively high incidences of freezing episodes during everyday activities. Therefore, some common pathological processes probably predispose to disturbances of rhythmic hand movements and freezing in PD, although it would be premature to assume a single causative mechanism.

Overall, the present finding that our patients were abnormally dependent upon external timing cues to regulate the tempo of finger tapping indicates that in PD deficits of central programming are not confined to the sequencing of relatively complex movements

(see Refs 19–22) but also apply to the rhythm generation which underlies extremely simple, stereotyped, and repetitive voluntary movements.

The work was supported by the MRC. JSF was in receipt of a SERC Studentship. We wish thank Ms Frances Culshaw for development of computer software and tapping apparatus and Drs RG Lascelles and D Neary for allowing us to study patients under their care.

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Neurological stamp

Luigi Galvani (1737–98)

Luigi Galvani, the anatomist, physician and physiologist who discovered 'animal electricity', came from Bologna. The galvanometer, which was invented by Andre Ampère (1775–1836), was named after Galvani as was the process of covering steel with a layer of zinc (galvanism).

Galvani observed that static electricity that was stored in a Leyden jar caused dissected frogs' legs to twitch. This occurred if they were placed on metal during a thunderstorm. He also noted that when dissected frogs' legs were hung from brass hooks on an iron railing, the muscles contracted when they came into contact with the iron. Galvani concluded that the source of the electricity was in the muscles and nerves of the animals. His findings were later disproved by Alessandro Volta who by 1800 had constructed electric batteries consisting of two different metals in an electrolytic salt solution. Volta established that the source of the electricity in Galvani's experiment had been two different metals with the animals' body fluids acting as the conducting medium. Galvani's observations were, however, the starting point of electrophysiology.

Galvani was honoured with this Italian stamp in 1934 on the occasion of the First International Congress of Electro-Radio-Biology (Stanley Gibbons 423, Scott 330).

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Journal of Physiology (1994) 475.P : 22-23P

Does L-dopa improve the ability of Parkinsonian patients to perform timed repetitive movements?

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A typical feature of patients with Parkinson's Disease (PD) is an impairment of production of appropriately timed repetitive movements. With the approval of the Local Ethics Committee, we have examined the ability of twelve PD patients to synchronize finger tapping with a train (550 ms intervals) of fifteen auditory signals and to sustain the tapping rate for thirty-one taps following cessation of the auditory cues. Patients were tested on two occasions (each involving 11–20 error-free runs), once ('off') after 12–15 h abstinence from normal L-dopa medication and again ('on') 1 h following ingestion of a single normal dose. We employed Wing & Kristofferson's (1973) model of control of motor timing to analyse the response intervals produced during the non-cued tapping phase of those runs ($n = 8$–14) during which the major assumptions underlying the model were not violated. Using the appropriate expressions, we decomposed the total variance (TV) of the inter-tap interval (ITI) on each run into the variance attributable to the hypothetical 'clock' (CV) and that attributable to the hypothetical and independent 'motor-implementation system' (MISV).

Table 1. Group mean (S.D.) values of the ITI, TV, CV and MISV for 'on' and 'off' conditions

	PD 'off'	PD 'on'	*P*
ITI (ms)	538·2 (15·9)	535·1 (13·9)	0·9063
TV (ms^2)	1187·4 (589·7)	526·1 (243·6)	0·0005
CV (ms^2)	698·5 (324·3)	349·8 (150·7)	0·0005
MISV (ms^2)	244·9 (174·0)	88·2 (50·2)	0·0005

Two-tailed exact *P* values were derived from 'on' vs. 'off' comparisons using Wilcoxon's test.

The data (Table 1) show clearly that, contrary to the findings of Ivry & Keele (1989), L-dopa produced a significant decrease in TV which, moreover, was attributable to significant decreases in both CV and MISV. These results suggest that, in so far as the mathematical model is valid and applicable in the study of neurological deficit, the L-dopa-induced reduction in the temporal variability of timed repetitive movements observed in our patients can be attributed to decreased variability in the operations of both an internal 'clock' and a 'motor-implementation system' driven by the clock.

Supported by the MRC. J.S.F. is in receipt of an SERC studentship.

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Asymmetrical performance of timed repetitive movements in patients with asymmetrical Parkinson's disease (PD)

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With the approval of the local ethics committee, we have examined the ability of twelve right-handed PD patients, with bilaterally asymmetrical neurological signs, to synchronize finger tapping with a train (550 ms intervals) of fifteen auditory signals and to sustain the tapping rate for thirty-one taps following cessation of the auditory cues (one run). As indicated by prior independent neurological examination, signs were worse on the right in six patients and, in the remaining six, worse on the left. Ten patients were maintained on L-DOPA, one on amantadine and one was taking no medication. Each subject completed ten runs with the right hand followed by ten runs with the left hand and then, following a period of 45 min, a further two blocks of ten runs, with the order of hands reversed. We employed Wing & Kristofferson's (1973) model of control of motor timing to analyse the response intervals produced during the non-cued tapping phase of those runs ($n = 9$–17) during which the major assumptions underlying the model were not violated. Using the appropriate expressions, we decomposed the total variance (TV) of the inter-tap interval (ITI) on each run into the variance attributable to the hypothetical 'clock' (CV) and that attributable to the hypothetical and independent 'motor-implementation system' (MISV).

Table 1. Group mean (S.D.) values of ITI, TV, CV and MISV for 'worse' and 'better' hand conditions

	Worse hand	Better hand	P
ITI (ms)	535·0 (24·8)	539·9 (17·0)	0·3078
TV (ms^2)	1089·1 (681·6)	550·5 (331·2)	0·0005
CV (ms^2)	663·7 (338·6)	364·4 (214·9)	0·0005
MISV (ms^2)	212·7 (203·6)	93·1 (61·7)	0·0047

Two-tailed exact P values were derived from comparisons of performance between hands using Wilcoxon's test.

The data (Table 1) show clearly that, while there was no significant difference in mean produced ITI between the two hands, mean TV when using the worse hand was significantly higher than when using the better hand. This raised TV was attributable, moreover, to significant increases in both CV and MISV. In so far as the mathematical model is valid and applicable to the study of neurological deficit, these results therefore lend support to our previous findings (Freeman *et al.* 1994) which implied that, in the production of timed repetitive movements, the basal ganglia are involved in the operations of both an internal 'clock' and a 'motor-implementation system' driven by the clock.

Supported by the MRC. J.S.F. was in receipt of an SERC studentship.

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