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1. Cunnington, R., Iansek, R., Johnson, K.A., Bradshaw, J.L. Movement-related potentials in Parkinson's Disease. *Brain,* 1997, 120, 1339-1353.
2. Johnson, K.A., Cunnington, R., Bradshaw, J.L., Phillips, J., Iansek, R., Rogers, M. Bimanual Coordination in Parkinson's disease. *Brain,* 1998, 121, 734-753.
3. Johnson. K.A., Bennett., J.E., Georgiou, N., Bradshaw, J.L., Chiu, E., Cunnington, R., Iansek, R. Bimanual co-ordination in Huntington's disease. *Experimental Brain Research,* 2000, 134, 483-489.
4. Johnson, K.A., Bennett, J.E., Cunnington, R., Georgiou, N., Phillips, J.G., Iansek, R. Chiu, E., Bradshaw, J.L. Bimanual co-ordination in Parkinson's and Huntington's disease. *Perception and Cognition for Action, 2000,* Proceedings from the III Annual Perception for Action Conference, pp.139-148.
5. Bradshaw, J.L. and Johnson, K.A. Circuits for action and inaction: the frontostriatal system and neurodevelopmental disorders in preparation for action. In E.Ihsen and P.Maruff (eds.), *Proceedings for the Fourth Annual Perception for Action Conference*, in press.
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Published Extended Abstracts

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Published Abstracts

2. Johnson, K.A., Bennett, J.E., Cunnington, R., Bradshaw, J.L. Bimanual co-ordination in Parkinson's disease and Huntington's disease: Comparisons and contrasts. *Movement Disorders,* 1998, 13,2.
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Movement Preparation and Execution in Huntington's and Parkinson's diseases.

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Summary

Huntington's and Parkinson's diseases are two distinct models of basal ganglia dysfunction, which share the clinical symptom of bradykinesia. Through a comparison of these two diseases, further information was obtained about the role of the medial motor circuit and other systems in the preparation and execution of voluntary, sequential movement. Previous movement-related potential and behavioural experiments on Parkinson's disease had provided valuable information about the neurological underpinnings of bradykinesia. Rather little research had been undertaken on Huntington's disease. The majority of experiments in this thesis focused on Huntington's disease. With the experimental design reflecting previous work on Parkinson's disease, comparisons were made between the two disease groups. For the first time, the movement-related potential was recorded and described in a group of Huntington's disease patients. In a similar fashion to the Parkinson's disease patients, the huntingtonian pre-movement cortical activity was significantly reduced in comparison with that of the control group, both in the presence and absence of an external cue. The provision of a strategy significantly improved the pre-movement activity in the Huntington's disease group, and the component of the pre-movement activity relating to movement preparation was found to be deficient, in comparison with that of the control group. The pre-movement cortical activity of the Huntington's disease group was recorded over a period of time, to document the neurodegenerative changes. Through the use of behavioural measures, the Huntington's disease group was further differentiated from the Parkinson's disease group by the lack of a beneficial effect of the provision of an external auditory timing cue, and by the lack of a sequencing effect on upper limb sequential movement. Finally, the effect of anti-parkinsonian medication on a sequential bimanual co-ordination task was measured on patients with Parkinson's disease. From these experiments, it was shown that Huntington's disease patients presented particular deficits in the preparation of movement. It was speculated that the two groups of patients might make use of different alternative parallel circuits, as compensation for the deficient medial motor circuit, resulting, in both syndromes, in less efficient movement preparation and in bradykinesia.

Publications

Work reported in this thesis has been published and presented as follows.

Published Full Paper

1. Johnson. K.A., Cunnington. R., Iansek. R., Bradshaw. J.L., Georgiou. N., Chiu. E. Movement related potentials in Huntington's disease – movement preparation and execution. *Experimental Brain Research,* in press.

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Conference Presentations

1. Johnson, K.A., Cunnington, R., Iansek, R., Chiu, E., Georgiou, N., Bradshaw, J.L. *Movement preparation and execution in Huntington's disease – a movement related potential study.* Paper presented at the Experimental Psychology Conference, Macquarie University, Sydney, 1999.
2. Johnson, K., Cunnington, R., Iansek, R., Bradshaw, J.L., Georgiou, N., Chiu, E. *Attentional strategies and movement related potentials in Huntington's disease. Paper presented at the* Fifth Biennial Motor Control and Human Skill Research Workshop, Gold Coast, Australia, 2000.
3. Johnson, K.A., Cunnington, R., Iansek, R., Bradshaw, J.L., Georgiou, N., Chiu, E. *Movement related potentials in Huntington's disease.* Poster presented at the Sixth International Congress of Parkinson's Disease and Movement Disorders, Barcelona, Spain, 2000.

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2. Johnson. K.A., Cunnington., R., Iansek. R., Bradshaw. J.L., Chiu. E. The effect of an attentional strategy on MRPs recorded from Huntington's disease patients.
3. Johnson. K.A., Cunnington., R., Iansek. R., Bradshaw. J.L., Chiu. E. The interaction between external and internal cueing and attentional strategies in Huntington's disease.
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5. Johnson. K.A., Cunnington., R., Iansek. R., Bradshaw. J.L., Chiu. E. Sequential motor control in Huntington's disease.

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2. Johnson, K.A., Cunnington, R., Bradshaw, J.L., Phillips, J.G., Iansek, R., Rogers, M.A. *The role of the basal ganglia in co-ordination bimanual movements.* Poster presented at the Fourth Biennial Motor Control and Human Skill Research Workshop, Perth, Australia, 1997.

3. Johnson, K.A., Bennett, J.E., Cunnington, R., Georgiou, N., Phillips, J.G., Iansek, R., Chiu, E., Bradshaw, J.L. *Bimanual co-ordination in Parkinson's and Huntington's diseases.* Paper presented at the Third Annual Perception for Action Conference, La Trobe University, Bundoora,Victoria, Australia, 1998.

4. Johnson, K.A., Bennett, J.E., Cunnington, R., Bradshaw, J.L. *Bimanual co-ordination in Parkinson's disease and Huntington's disease: comparisons and contrasts.* Poster presented at the Fifth International Congress of Parkinson's Disease and Movement Disorders, New York, NY, USA, 1998.

Declaration

I declare that, to the best of my knowledge, this thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other institution, and contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

..... [redacted] ..... Date 3/4/01

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Abbreviations

BDI – Beck Depression Inventory

CAG - cytosine/adenine/guanine

CM - centromedian nucleus

CMA – Cingulate motor area

CRT – Choice reaction time

DLPFC – dorsolateral prefrontal cortex

DT – Down Time

EEG – Electroencephalography

EMG – Electromyography

FMRI – functional magnetic resonance imaging

GABA – gamma-aminobutyric acid

GPe – globus pallidus externa

GPi - Globus pallidus interna

L-DOPA – levodopa

LED – light emitting diode

M1 – Primary motor cortex

MAS – Mood Assessment Scale

MRP – Movement related potential

MPTP - 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MT - Movement time

n/a – not available

PET – Positron emission tomography

rCBF – Regional cerebral blood flow

RT – Reaction time

SMA – Supplementary motor area

SNr – substantia nigra pars reticulata

SRT – Simple reaction time

STN – subthalamic nucleus

STMS – Short Test of Mental Status

UHDRS – Unified Huntington's Disease Rating Scale

VAmc - nucleus ventralis anterior pars magnocellularis

VApc - Parvocellular portion of the ventral anterior nucleus or nucleus ventralis anterior pars principalis

VLc - nucleus ventralis lateralis pars caudalis of the thalamus

VLo - Centralis lateralis pars oralis of the thalamus

VPLo - Ventral posterolateral nucleus

Xenon-SPECT – Single photon emission computed tomography

Chapter One - General Introduction

The performance of fluid and purposeful sequential movement is reliant upon the successful combination of preparation and execution processes. The medial motor circuit, including the basal ganglia and the supplementary motor area (SMA), is involved in the preparation and execution of voluntary, sequential movement. Huntington's and Parkinson's diseases, as two models of basal ganglia dysfunction, were used in this thesis to understand further the role of the medial motor circuit, and especially the SMA, in the production of voluntary, sequential upper limb movements.

Despite the anatomical and physiological differences between the two disease groups, bradykinesia is an important symptom of both Huntington's and Parkinson's diseases. Parkinson's disease has been well studied as a model of basal ganglia dysfunction. Electrophysiological and behavioural experimental work on Huntington's disease is scarce. The opportunity to develop a better understanding of the neurological underpinnings of the bradykinesia in these two diseases is provided through comparison and contrast. Most of the experiments in this thesis focused on Huntington's disease. The results of these experiments were then compared and contrasted with the well-established findings from previous literature on Parkinson's disease. The similarities and differences between the two groups allowed for speculation about the role of the medial motor circuit in movement control, and possible alternative pathways used in the two disease groups.

This general introduction provides a review of the areas of the brain involved in motor control, focusing on the medial motor circuit and in particular the SMA and the basal ganglia. The anatomy, physiology and movement dysfunction of Parkinson's and Huntington's diseases are also reviewed. These two diseases are compared and contrasted, and the aims and research outline of the thesis are explained.

There are inherent difficulties in using lesion models to understand normal function. Using a lesion model limits the ability to theorize about the functioning of the basal ganglia and other areas of the motor loop (Brooks, 1996). The deficits observed in a lesion model may not be caused by the dysfunction in the basal ganglia, but by secondary side effects of other areas compensating for the loss of original function (Rothwell, 2000). With this caution in mind, however, the employment of Parkinson's

and Huntington's diseases as models of basal ganglia dysfunction has been useful in understanding the movement preparation role of the basal ganglia and supplementary motor area within the motor circuit.

Motor control and the motor circuit

It has been hypothesized that there are five segregated circuits within the cortex, basal ganglia and thalamus, based on anterograde and retrograde labeling studies of primates (Alexander *et al.*, 1990; Alexander *et al.*, 1986). Of particular interest to this thesis is the function of the motor circuit in terms of the preparation and execution of movement. The putamen of the basal ganglia receives topographic projections from the primary motor cortex, the arcuate premotor area, the SMA and the somatosensory cortex (Künzle, 1975; Schell and Strick, 1984). The putamen projects topographically to the globus pallidus externa (GPe), globus pallidus interna (GPi) and substantia nigra pars reticulata (SNr), which then sends projections to thalamic nuclei, including the nucleus ventralis lateralis pars oralis (VLo), nucleus ventralis anterior pars parvocellularis (lateral VApc), nucleus ventralis anterior pars magnocellularis (lateral VAmc) and the centromedian nucleus (CM) (Alexander and Crutcher, 1990a). The motor circuit is then closed by projections from VLo and lateral VAmc to the SMA, from lateral VApc and VLo to premotor cortex, and from VLo and CM to motor cortex (Alexander and Crutcher, 1990a). Greater detail of the proposed direct and indirect circuits within the basal ganglia is provided below. Primate studies suggest the motor circuit is functionally specific throughout the circuit, and each part of the circuit is somatotopically organized. The different areas of the motor circuit appear to respond in specific ways to externally and internally derived cues for movement. They also appear to play different roles in the preparation and execution of movement. In broad terms, the roles of some of the areas of the motor circuit and other related areas are provided below.

Primary Motor Cortex

The primary motor cortex (M1) is involved in the execution of complex finger (and other) movements, and may play an important role in spatiotemporal planning of muscle responses (Böecker *et al.*, 1998; Chen *et al.*, 1997; Gerloff *et al.*, 1998a). Activity of M1 does not seem to be associated particularly with externally or internally cued

movements (Mushiake *et al.*, 1991). M1 activity is modality unspecific; activity is the same both for auditory and visual external cueing (Jahanshahi *et al.*, 1995; Tanji and Shima, 1996).

Parietal Cortex

The parietal cortex directly projects to the motor cortex (Jones *et al.*, 1978; Wise *et al.*, 1997). This area is thought of as an integrative system which processes spatial aspects of movement (Böecker *et al.*, 1998), and is involved in imagining movement (Stephan *et al.*, 1995), tracking targets and saccadic eye movements (Böecker *et al.*, 1998). Regional cerebral blood flow (rCBF) in this area correlates highly with the complexity of the sequential task (Böecker *et al.*, 1998), which suggests that subconscious internal visualization of finger movements in space may be occurring as sequences become increasingly complex. The parietal motor area may be involved in spatial processing or motor sensory integration of movement (Bartenstein *et al.*, 1997). As the complexity or choice of a movement increases, so does the activation of this region (Böecker *et al.*, 1998; Deiber *et al.*, 1991). There is debate in the literature as to whether this area is overactive in Parkinson's disease. It has been shown to become overactive, especially during the performance of longer sequences of movement (Catalan *et al.*, 1999), but during single joystick movements no over-activity has been found (Haslinger *et al.*, 2001). In Huntington's disease this area is hyperactive during the performance of sequential finger movements (Bartenstein *et al.*, 1997). For both diseases, this area may be possibly acting as a compensatory mechanism for basal ganglion dysfunction (Catalan *et al.*, 1999).

Cerebellum

Many roles have been assigned to the cerebellum. Of interest to this thesis is the likelihood that the cerebellum may be involved in the initiation and planning of externally cued movements (Jueptner *et al.*, 1996; Jueptner and Weiller, 1998) and that it may be involved in the timing of motor performance (Mauk *et al.*, 2000). The cerebellum may be used as an alternative pathway in Parkinson's disease (Azulay *et al.*, 1999; Bloxham *et al.*, 1984). Little is known of the functioning of the cerebellum in Huntington's disease.

Thalamus

The thalamus may function as a kind of 'relay station', receiving major projections from the basal ganglia and the cerebellum, and projecting outputs to the SMA, premotor and motor cortices. Different anatomically segregated portions of the thalamus may be differentially involved in the control of externally and internally triggered movements. Cerebellar outputs in primates terminate in the oral portion of the ventral posterolateral nucleus (VPLo) and Area X of the thalamus. VPLo and Area X may play a role in the execution and initiation, respectively, of movements that are externally cued (van Donkelaar *et al.*, 2000). Outputs from the GPi terminate in the VLo and the parvocellular portion of the VApc (Nakano *et al.*, 1996; van Donkelaar *et al.*, 2000). SMA-proper receives major thalamic afferents from the VApc. VApc may play a role in the execution of movements based on internal cues (van Donkelaar *et al.*, 2000).

Cingulate Motor Area

The cingulate motor area (CMA) may be divided into the rostral CMA, the caudal CMA and the dorsal CMA (Roland and Zilles, 1996), based on electrophysiological and connectivity studies. The CMA receives inputs from the cingulate cortex connecting several limbic sources (Devinsky *et al.*, 1995) and from the thalamus (Picard and Strick, 1996). The CMA projects to the primary motor cortex, the parietal lobe and the prefrontal cortex (Picard and Strick, 1996). It may be involved in mnemonic processes and coding of motivational states associated with particular actions (Roland and Zilles, 1996) and sustaining attention for forthcoming movements (Jueptner *et al.*, 1997). The CMA is also activated during the preparation and performance of complex sequential movements (Ball *et al.*, 1999; Catalan *et al.*, 1999).

Lateral Premotor Cortex

The lateral premotor area is believed to be involved in a similar way to the SMA in the preparation of movement, but receives striatal input from anatomically and functionally different areas than does the SMA (Hoover and Strick, 1993). This area receives inputs from both the cerebellum and basal ganglia (Matelli *et al.*, 1989; Schell and Strick, 1984) and also receives strong cortical sensory input (Jones *et al.*, 1978). There are direct anatomical connections between the lateral premotor cortex, the superior parietal

cortex and M1 (Petrides and Pandya, 1984). It has been placed within the lateral motor circuit, which incorporates the cerebellum, parietal and lateral premotor cortices.

The lateral premotor area may be involved more in preparing movements which are externally rather than internally cued (Halsband and Passingham, 1985; Jones *et al.*, 1978; Lu *et al.*, 1994; Mushiake *et al.*, 1991; Okano, 1992; Petrides and Pandya, 1984). This is known via positron emission tomography (PET) studies, lesion studies, depth electrode studies and single cell studies (Deiber *et al.*, 1991; Halsband and Passingham, 1982; Passingham, 1988; Sasaki and Gemba, 1986; Wise and Kurata, 1989). For instance, bilateral cooling of the lateral premotor area disrupts cued reaction time tasks (Sasaki and Gemba, 1986) but does not affect internally generated movements (Halsband and Passingham, 1985).

Of particular interest is the finding that the lateral premotor area shows most impairment in Huntington's patients (Bartenstein *et al.*, 1997). This area is bilaterally *enhanced* in Parkinson's disease patients relative to controls, during both sequential and single movements, which are externally cued (Haslinger *et al.*, 2001; Samuel *et al.*, 1997).

Supplementary Motor Area (medial premotor cortex)

> *"The SMA...may play a significant role in preparation for and execution of sequential motor actions, particularly those arising from internal intent as opposed to those driven by external stimuli" (Marsden et al., 1996) p.485*

Anatomy of the SMA

The SMA is part of Brodmann's area 6 located on the mesial surface of the hemisphere anterior to the foot area of the primary motor cortex and dorsal to the cingulate sulcus (Watson *et al.*, 1986).

Projections to SMA

The SMA receives its major subcortical input from the VLo of the thalamus, which receives major connections from the GPi of the basal ganglia (Hoover and Strick, 1993; Middleton and Strick, 1997; Tokuno *et al.*, 1992). It also receives input from thalamic Area X and nucleus ventralis lateralis pars caudalis (VLc) of the thalamus, which relay

information from the cerebellum (Wiesendanger and Wiesendanger, 1985b). The SMA also receives afferent projections from primary and secondary somatosensory cortex, primary motor cortex and posterior parietal association cortex (Jones *et al.*, 1978).

Projections from SMA

The SMA outputs bilaterally to the primary motor cortices, to the contralateral SMA, and lateral premotor area (Inase *et al.*, 1996). Subcortically, it outputs bilaterally to the striatum, the red nucleus, medullary reticular formation, ipsilaterally to the ventral lateral and centrum medianum nuclei of the thalamus, to the pontine nuclei and to the cerebellum, closing the motor loop (Damasio and Van Hoesen, 1980; Künzel, 1978).

Two distinct areas of the SMA

> *"The pre-SMA seems to be responsible for so-called high-level motor functions, whereas the SMA-proper is more closely related to movement execution."*
> (Nakano *et al.*, 1996) p.22.

The SMA is formed by two distinct cytoarchitectonic areas with a functional difference - rostral {pre-SMA (F6)} and caudal {SMA-proper (F3)} (Matsuzaka *et al.*, 1992; Nakano *et al.*, 1996). Cytoarchitectonic, histochemical and intracortical microstimulation studies support the distinction between pre-SMA and SMA-proper (Luppino *et al.*, 1993; Luppino *et al.*, 1991; Matelli *et al.*, 1991; Matsuzaka *et al.*, 1992; Rizzolatti *et al.*, 1996; Zilles *et al.*, 1996).

The pre-SMA is interconnected with the prefrontal cortex and other non-primary motor cortical areas, whereas the SMA-proper has more direct access to motor effectors (Picard and Strick, 1996). In humans there may be a functional subdivision between SMA-proper and pre-SMA at the level of the ventral anterior commissure line (Passingham, 1996).

Pre-SMA (rostral SMA)

The pre-SMA is located rostral to the genu in area 6aβ (Matelli *et al.*, 1991). It projects to the SMA-proper, the anterior cingulate cortex (area 24), the dorsolateral prefrontal cortex (DLPFC), anterior lateral premotor cortices and posterior parietal areas, including parietal area 7 (Luppino *et al.*, 1993).

The pre-SMA receives thalamic input from Area X and VApc, with a lesser projection from VLc, and receives input from the prefrontal cortex (Wiesendanger and Wiesendanger, 1985b).

The pre-SMA may play a greater role in higher-order motor preparation than execution (Deiber *et al.*, 1991; Luppino *et al.*, 1993; Playford *et al.*, 1992). Indeed, the pre-SMA appears to be preferentially activated during simulated movements (Tyszka *et al.*, 1994). Böecker *et al.* (1998) found increases in rCBF in pre-SMA, which correlated with task complexity. This suggested a role for the pre-SMA other than determining basic parameters of movement execution (Böecker *et al.*, 1998). Enhanced pre-SMA activity was found during preparation and control of pre-learned movement sequences (Halsband *et al.*, 1994; Picard and Strick, 1996).

Data gathered from single unit recordings in monkeys (Halsband *et al.*, 1994; Matsuzaka *et al.*, 1992; Tanji, 1994; Tanji and Shima, 1994), PET studies (Jenkins *et al.*, 2000) and subdural electrode studies (Ikeda *et al.*, 1999) have suggested that the pre-SMA may be more concerned with self-selection and planning of internally generated movements. Activation of this area (but not SMA-proper) occurred when subjects were allowed to choose the direction of joy-stick movements, which were externally cued, in comparison with a fixed movement which was also externally cued. When the role of external and internal cueing was investigated, it was found that activation was more extensive for self-initiated than for visually-triggered movements (Deiber *et al.*, 1999; Deiber *et al.*, 1996).

SMA-proper (caudal SMA)

The SMA-proper is located caudal to the level of the genu of the arcuate sulcus in area 6aα (Dum and Strick, 1991). SMA-proper receives its main thalamic projections from VLo, with some additional contributions from VLc (Wiesendanger and Wiesendanger, 1985b). The SMA-proper is linked with M1, posterior premotor and cingulate areas (F2, F4, area 24d) and several areas in the superior parietal lobule, cingulate area 23, opercular parietal areas and the granular insula (Luppino *et al.*, 1993; Nakano *et al.*, 1996).

The SMA-proper is somatotopically organised, and may be involved more in motor execution than in motor preparation (Jenkins *et al.*, 2000; Luppino *et al.*, 1993;

Matsuzaka *et al.*, 1992). The SMA-proper is activated during execution, as measured by rCBF studies (Grafton *et al.*, 1996; Stephan *et al.*, 1995), or actions not requiring any decision making, such as simple repetitive actions (Colebatch *et al.*, 1991). Böecker *et al.* (1998) found increases in rCBF in pre-SMA which correlated with complexity of a motor sequence, whereas SMA-proper activation was not modulated by task complexity, suggesting a role in motor execution (Böecker *et al.*, 1998). If movement execution is graded according to frequency or force, there are correlations with rCBF in SMA-proper and contralateral M1, but not in pre-SMA (Blinkenberg *et al.*, 1996; Dettmers *et al.*, 1995; Jenkins *et al.*, 1997; Sadato *et al.*, 1996).

The SMA-proper may be involved more with complex, sequential movements than the pre-SMA (Marsden *et al.*, 1996). Sequence-specific neurons may exist in the SMA-proper (Tanji and Shima, 1994). These neurons fire differentially depending on the specific order of similar movements in a sequence. Subdural electrode recordings suggest the SMA-proper is one of the main generators of pre-movement activity preceding self-paced, voluntary movements (Ikeda *et al.*, 1999).

Whilst the difference between the pre-SMA and SMA-proper is acknowledged, due to the methodologies used within the thesis, the functions of the SMA as a whole are discussed.

Physiology of the SMA

The SMA is believed to be involved in the preparation of voluntary motor actions (Marsden *et al.*, 1996; Penfield and Welch, 1951; Yazawa *et al.*, 2000). Its exact role is uncertain, but it may trigger the actual movement via release of inhibition of M1 (Ball *et al.*, 1999). It may be particularly involved in movements that are sequential rather than single, well learnt rather than novel, bilateral rather than unilateral, complex rather than simple, internally rather than externally driven, and involving precise timing of movement. These roles are explored in depth below.

Preparation of movement

The SMA is involved in the preparation of voluntary movement. Neuronal recordings in monkeys indicate increased activity in pre-SMA during preparatory periods before actual well-learned task performance (Matsuzaka *et al.*, 1992; Tanji, 1994; Tanji *et al.*,

1988). Movement related potentials recorded during epilepsy surgery from subdural electrodes have shown bilateral SMA activity prior to movement (Ikeda *et al.*, 1992; Neshige *et al.*, 1988). Specific SMA neurons may fire selectively for direction of movement (Tanji and Kurata, 1985; Tanji and Shima, 1994), timing of movement and the appropriate force of movement (Riehle *et al.*, 1994; Tanji and Shima, 1994). The number of SMA neurons firing increases with increased force requirements (Dettmers *et al.*, 1995).

Complex sequential movement and the SMA

The SMA is active during the performance of complex sequential movements (Jenkins *et al.*, 1994; Roland *et al.*, 1980). Stimulation of the SMA results in complex upper limb movements, in comparison with stimulation of primary motor cortex which results in localized movements (Förster, 1936; Penfield and Welch, 1951). Blood flow increases within the SMA during the performance of sequential, well-learned movement (Catalan *et al.*, 1998; Orgogozo and Larsen, 1979; Shibasaki *et al.*, 1993). In comparison, single repetitive movement involves increased blood flow in the primary sensory hand area (Colebatch *et al.*, 1991; Deiber *et al.*, 1991; Fox *et al.*, 1985; Roland *et al.*, 1980). Functional magnetic resonance imaging (fMRI) studies show that the SMA-proper is more extensively activated for sequential than for fixed movements (Deiber *et al.*, 1999). Xenon-Single Photon Emission Computed Tomography (SPECT) functional imaging work demonstrates SMA activation during the execution of a sequence of different isolated finger movements, but not during fast repetitive (non-sequential) flexions of the same fingers (Roland *et al.*, 1980).

Single cell studies indicate that the SMA responds in advance of a remembered sequence of movements, or in the midst of a sequence, and that sequence specific neurons respond to one particular movement sequence and not another (Mushiake *et al.*, 1991; Tanji and Shima, 1994; Tanji and Shima, 1996). Mushiake and Strick (1995) found that neurons in dorsal GPi, which project to the SMA, were involved in the processing of sequential movements (Mushiake and Strick, 1995). Set-related neurons are common in SMA and premotor cortex (Kurata and Wise, 1988); sequence specific neurons are common in SMA only (Mushiake *et al.*, 1991). SMA neurons begin firing prior to the initiation of complex movements (Brinkman and Porter, 1979).

Lesions of the SMA result in deficits in the performance of complex sequential movements (Brinkman, 1984; Dick *et al.*, 1986). The behavioural results of lesions of SMA indicate its involvement in higher control of sequential movements and motor subroutines (Freund, 1987).

Movement related potential (MRP) studies show greater pre-movement negative cortical activity prior to complex sequential rather than single movements (Lang *et al.*, 1989; Simonetta *et al.*, 1991). Highest early negative readiness potentials are recorded from over the vertex, when movements are sequential or bimanual (Benecke *et al.*, 1985; Kitamura *et al.*, 1993; Lang *et al.*, 1989).

Well-learnt movement and the SMA

The SMA is thought to be more highly activated during the performance of well-learnt motor sequences than during the acquisition of new motor skills (Grafton *et al.*, 1992b). The SMA is more activated during the performance of well-learnt key-presses than during the learning of a new sequence of key-presses. In contrast, the lateral premotor area is more highly activated during the learning of the new sequence (Jenkins *et al.*, 1994). Pianists playing a well-learnt piece of music, which is of course a highly automatic task, show increased activation of the SMA-proper. If the pianists play an unfamiliar piece the pre-SMA is activated (Sergent *et al.*, 1992). Practice may have an effect on the level of SMA activation in humans (Picard and Strick, 1996).

Bimanual co-ordination and the SMA

The SMA may play an important role in the co-ordination of bimanual movements. Studies from a variety of methodologies support this claim. Anatomical studies suggest there are strong interhemispheric connections between the two SMAs (Rouiller *et al.*, 1994) and strong bilateral connections to the basal ganglia (Stephan *et al.*, 1999). Each SMA connects to the ipsilateral and contralateral primary motor areas (DeVito and Smith, 1959; Muakkassa and Strick, 1979). This suggests the SMA is ideally connected to play a role in bimanual co-ordination.

Neuronal activity in SMA is associated with contralateral and ipsilateral movements (Brinkman and Porter, 1979; Tanji *et al.*, 1988). Bilateral activation of each SMA is found, even for unilateral movements (Deecke, 1987; Roland *et al.*, 1980). Unilateral

SMA electrical stimulation elicits bimanual complex reactions (Fried *et al.*, 1991; Penfield and Welch, 1951).

Lesion studies have also implicated the SMA in bilateral movement control. Unilateral SMA lesions in monkeys result in poorer performance of tasks requiring bimanual co-ordination (Brinkman, 1981; Brinkman, 1984; Wiesendanger *et al.*, 1996). Lesions of unilateral SMA in humans results in difficulties performing alternating movements of both hands (Dick *et al.*, 1986; Freund and Hummelsheim, 1985; Laplane *et al.*, 1977).

Patients with SMA damage may present with mirror movements (mirror symmetrical movements of the two hands) (Chan and Ross, 1988; Luria, 1966). Damage to the SMA and corpus callosum may result in the alien hand syndrome, where one hand performs unintended movements (Feinberg *et al.*, 1992; Gasquoine, 1993; Goldberg *et al.*, 1981; McNabb *et al.*, 1988; Trojano *et al.*, 1993). Parkinson's disease patients, with disrupted SMA activity, show difficulties in bimanual co-ordination (Horstink *et al.*, 1990). MRP studies have shown greater cortical activity, possibly reflecting the SMA, for bilateral compared with unilateral movements (Uhl *et al.*, 1996; Uhl *et al.*, 1993).

Internally generated movement and the SMA

Both the lateral premotor area and the SMA are involved in externally and internally cued movement (Tanji, 1996); however, as discussed above, the degree of involvement appears to differ (Praamstra *et al.*, 1996). Studies from PET scanning (Deiber *et al.*, 1991; Jahanshahi *et al.*, 1995; Playford *et al.*, 1992; Remy *et al.*, 1994; Wessel *et al.*, 1997), fMRI (Böecker *et al.*, 1994; Deiber *et al.*, 1999), and MRP studies (Cunnington *et al.*, 1995; Gerloff *et al.*, 1998b; Jahanshahi *et al.*, 1995; Papa *et al.*, 1991) indicate the SMA is more involved in internally cued movements, and the lateral premotor area more involved in externally cued movements.

More SMA neurons appear to fire approximately 2 seconds before internally generated movements than for externally cued movements (Halsband *et al.*, 1994). In the lateral premotor area, more neurons will fire 2 seconds before externally cued than for self-initiated movements (Mushiake *et al.*, 1990; Mushiake *et al.*, 1991; Okano and Tanji, 1987; Romo and Schultz, 1987). Bilateral cooling of the SMA leads to a reduction in performance of tasks requiring internal preparatory processes (Tanji *et al.*, 1985), but to

unimpaired performance of tasks which require a reaction to external stimuli (Schmidt *et al.*, 1992).

Precise timing plans and the SMA

The SMA may be involved in sub-movement timing of predictable movements (Deecke *et al.*, 1985; Deecke *et al.*, 1987; Gerloff *et al.*, 1997), but not unpredictably timed movements (Cunnington *et al.*, 1995; Halsband *et al.*, 1993; Lang *et al.*, 1990). For example, pre-movement cortical activity is greater when musicians tap different rhythms with each hand, compared with simultaneous tapping of the same rhythm in each hand (Lang *et al.*, 1990). When the timing of a movement is predictable, pre-movement cortical activity is greater than when the movement is non-predictable. This is regardless of whether the direction of movement is predictable or unpredictable (Cunnington *et al.*, 1995). MRP studies have shown that when the timing of the external cue is predictable, pre-movement negativity begins earlier than when the cue cannot be anticipated (Kutas and Donchin, 1980; Thickbroom *et al.*, 1985). Subdural electrode recordings made during epilepsy surgery indicate that the SMA-proper has a specific temporal pattern with respect to self-paced movement and is involved in motor preparation earlier than the primary sensorimotor area (S1-M1) (Ohara *et al.*, 2000).

Basal Ganglia

> *"The basal ganglia play a primary role in both movement preparation and execution. This role could possibly be to optimize the pattern of muscular activity employed by a limb to reach its target once a motor decision has been taken." (Brooks, 1996) p.440.*

The functions of the basal ganglia are still to be determined fully, but are believed to be involved in modulating and facilitating motor and cognitive programs (Parent, 1990; Young and Penney, 1998). The basal ganglia are activated during most motor tasks (Böecker *et al.*, 1998).

Anatomy of the basal ganglia

The basal ganglia consist of a group of structures located beneath the outer cortical layers of the cerebral hemispheres. These consist of the caudate nucleus, the putamen (together known as the striatum) and the external and internal divisions of the globus

pallidus (Nicholls *et al.*, 1992). The substantia nigra and the subthalamic nucleus have both afferent and efferent connections to the basal ganglia, so although they are mid-brain structures, they are a functional part of the basal ganglia.

Projections to the basal ganglia

The striatum receives multiple afferent projections from the cerebral cortex, substantia nigra, thalamus, dorsal raphe nucleus, locus ceruleus, pallidum, subthalamic nucleus (STN), pedunculopontine nucleus and other subcortical afferents as well as the hippocampus and the amygdala (Nakano *et al.*, 2000; Parent and Cicchetti, 1998).

Anatomically, there is a projection from dorsolateral prefrontal cortex and the pre-SMA to the anterior striatum, which are known to be involved in trial-by-error learning and learning of sequential tasks, respectively. The middle-posterior striatum receives inputs from premotor areas including the SMA (Hoover and Strick, 1993), which are involved in initiation and performance of internally driven sequences.

Projections from the basal ganglia

The GPi and the SNr are the major output regions of the basal ganglia. Their influence is inhibitory in nature, via gamma-aminobutyric acid (GABA)-ergic inhibition on the excitatory premotor neurons of the ventral tier thalamic nuclei (Parent and Cicchetti, 1998). The GPi and the SNr each contain multiple output channels, each of which project to distinct cortical areas in the frontal lobe (Middleton and Strick, 1997).

The GPi together with the SNr may act as the motor output region of the basal ganglia and this area outputs to the VLo, via GABAergic inhibitory connections (Parent, 1990; Young and Penney, 1998). The output nucleus of the basal ganglia is the GPi which projects to the ventral thalamic nuclei (Albin *et al.*, 1989). The VLo sends excitatory outputs to the SMA. The GPi also outputs to the brainstem, and the noncholinergic portion of the pedunculopontine nucleus. The substantia nigra reticulata also outputs to the superior colliculis and mesopontine tegmentum (Obeso *et al.*, 1997).

The basal ganglia project to both lateral and medial motor areas, but predominantly to SMA (Alexander and Crutcher, 1990b; Ceballos-Baumann and Brooks, 1997; Künzle, 1975; Matelli *et al.*, 1989; Middleton and Strick, 1997; Wiesendanger and Wiesendanger, 1985a).

Indirect and Direct circuits theory of basal ganglia anatomy

One current theory of basal ganglia function posits that the basal ganglia may be separated anatomically and functionally into two pathways - the 'direct' and the indirect' pathway, both of which send projections from the putamen to the GPi (Albin *et al.*, 1989; Alexander and Crutcher, 1990a; DeLong, 1990) (see Figure 1.1).

The direct pathway might monosynaptically project from the putamen to inhibit the GPi (see far left diagram of Figure 1.1). It is GABAergic and co-localised with Substance P and Dynorphin. The direct pathway may facilitate movements by disinhibiting specific thalamic neurons from tonic inhibition received from the substantia nigra and GPi (Young and Penney, 1998). The thalamus is able to then provide excitatory feedback to the cortex.

The indirect pathway leads from GABA/Enkephalinergic putaminal neurons and projects to the GPe (see far left diagram of Figure 1.1). From the GPe there are two inhibitory projections - one to the sensoriomotor region of the subthalamic nucleus and one to the GPi (Obeso *et al.*, 1997). The GPe is inhibited, so the subthalamic nucleus is disinhibited. The subthalamic nucleus is then believed to send an excitatory projection to the GPi and the substantia nigra reticulata (Shink *et al.*, 1996), which inhibits the thalamus. The indirect pathway may inhibit the thalamic neurons that would otherwise facilitate unwanted movement, thereby suppressing unwanted movement (Young and Penney, 1998).

According to this theory, in Parkinson's disease the loss of cells in the substantia nigra compacta would lead to an increased inhibition of the thalamus, and reduced output to the SMA, resulting in difficulties selecting and maintaining motor programs (see middle diagram of Figure 1.1) (Young and Penney, 1998). This is analagous to reducing the activity of the direct pathway, and subsequently the motor loop (note the thinner direct pathway arrow in Figure 1.1). Larger than normal activity in the indirect pathway occurs, resulting in over-activity of STN and GPi neurons (note the thicker indirect pathway arrow in Figure 1.1). Motor deficits in Parkinson's disease, such as akinesia, bradykinesia and hypometria, are thought to result from abnormally large GPi inhibition of thalamocortical neurons influencing the frontal lobes (Contreras-Vidal, 1999; DeLong and Wichmann, 1993; Lozano *et al.*, 1995).

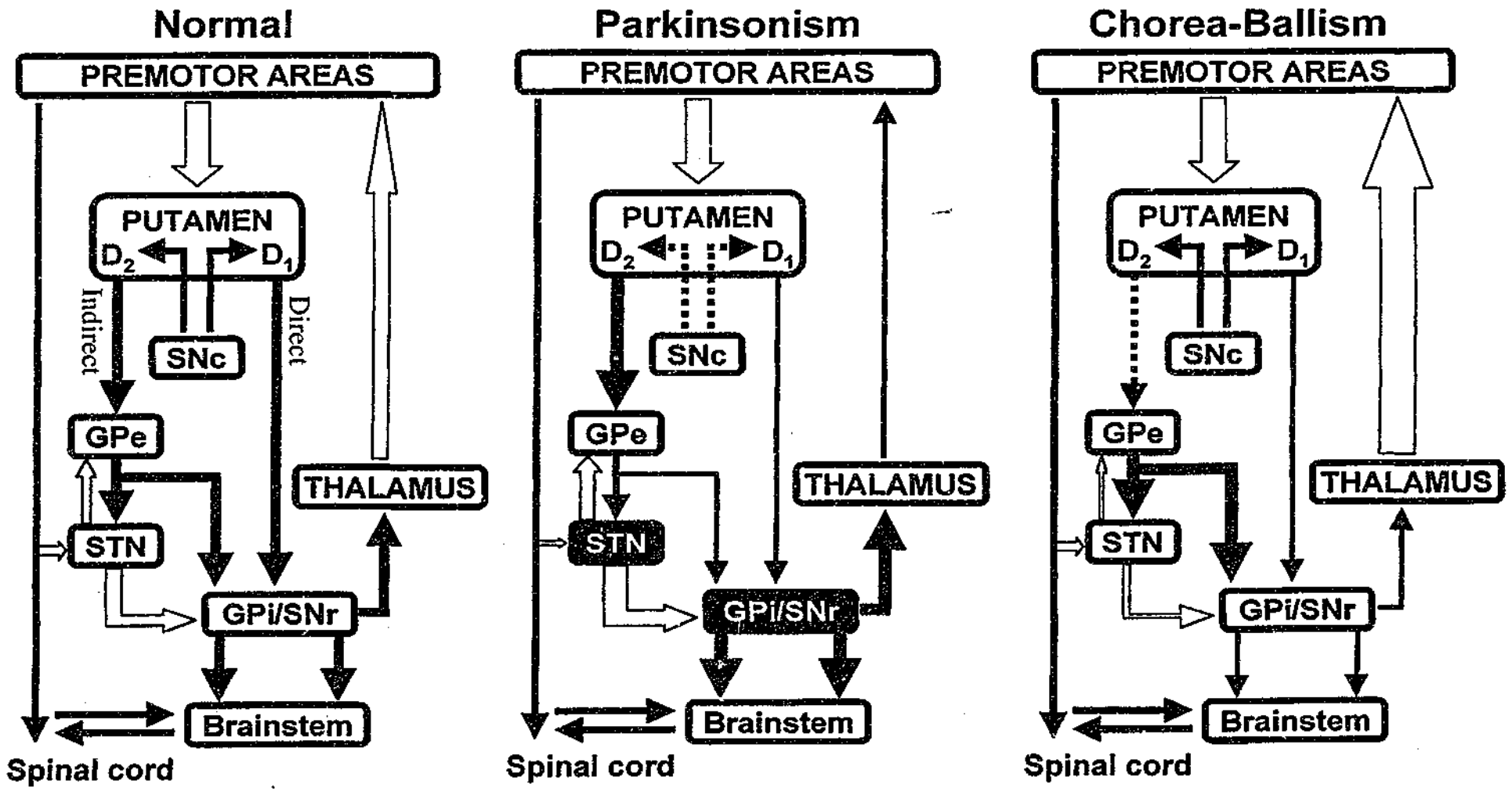


Figure 1.1: The direct and indirect pathways through the basal ganglia in normal healthy people (left), parkinsonism (middle) and huntingtonian chorea or ballism (right). D_1, D_2 = dopamine D_1 and D_2 receptors; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticulata; GPe = globus pallidus externa; GPi = globus pallidus interna; STN = subthalamic nucleus. [Adapted from Obeso, J.A. & Rogriguez, M.C. (1997). Basal ganglia pathology: A critical review. In J.A.Obeso, M.R. DeLong, C. Ohye, & C.D.Marsden (Eds.), *The basal ganglia and new surgical approaches for Parkinson's disease: Advances in neurology* (Vol.74, pp.3-16). Philadelphia: Lippencroft-Raven, and reproduced from Bradshaw, J.L. (2001). *Developmental disorders of the frontostriatal system.* East Sussex: Psychology Press.]

Huntington's disease may affect the indirect pathway and motor loop (see the far right diagram and note the thin indirect pathway arrow in Figure 1.1). It affects the striatal inhibitory GABA- and enkephalin-containing neurons, which project to the GPe. This loss might produce over-activity in the GPe neurons, excessively inhibiting subthalamic neurons, resulting in less stimulation of the GPi and disinhibition of the thalamus, disturbing its output to the SMA (note the thicker arrow from the thalamus). This might result in an inability to suppress inappropriate movements, and may explain the motor incoordination, uncontrollable choreiform movements, dysarthria and dysphagia typical of Huntington's disease (Berardelli *et al.*, 1999; Hedreen and Folstein, 1995; Macmillan and Quarrell, 1996; Penney *et al.*, 1990). Striatal projections to the SNr and the GPe are affected early in the course of the disease, before the striatal pathway to the GPi is affected (Penney *et al.*, 1990). Loss of striatal projections to SNr might lead to abnormal saccade generation. This theory is supported by results which suggest that chorea may be ameliorated by dopamine-depleting agents and dopamine receptor-blocking agents, which would counteract excessive dopaminergic activity in the neostriatum (Hedreen and Folstein, 1995). Loss of chorea and onset of dystonia later in the disease may reflect disruptions to the direct pathway (note thinner direct pathway arrow in Figure 1.1) (Macmillan and Quarrell, 1996). Loss of inhibitory GABA and substance P neurons to the GPi and SNr may result in increased inhibition of the thalamus. This may cause the parkinsonism and dystonia found later in the course of Huntington's disease (Hallett, 1980; Penney *et al.*, 1990; Phillips *et al.*, 1996; Thompson *et al.*, 1988; Young and Penney, 1998).

There are a number of problems with the internal/external model of basal ganglia function. Anatomical studies do not necessarily support the hypothesis of two circuits within the basal ganglia. For example, the model predicts a segregation of striatal output pathways, yet anatomical evidence suggests there is a collateralisation of axons (Inase *et al.*, 1996). Clinical studies do not necessarily support the two circuits theory either. This model suggests that lesions that decrease GPi activity should result in reversal of cardinal signs of Parkinson's disease. Surgery such as pallidotomy, and thalamotomy, however, do not show effects on motor function (Samuel *et al.*, 1998; Sutton *et al.*, 1995), or only show modest improvements during the 'off' state (Lozano *et al.*, 1995).

The internal/external model of basal ganglia function, however, does provide an anatomical explanation of the symptoms of Parkinson's and Huntington's diseases, which is useful for a comparison of the two diseases.

Physiology of the basal ganglia

The physiological role of the basal ganglia has been the subject of much research; however, the exact role this area plays in movement control is quite unclear. The basal ganglia appear to be activated when a movement is performed or planned (Brooks, 1996). This activation is independent of whether the movement needs to be timed, or directed, or is being learnt (Brooks, 1996). The basal ganglia may facilitate movement by "optimizing the pattern of muscular activity used to reach the goal state, whether the movement be self-initiated or cued" (Brooks, 1996, p.438).

The basal ganglia may be involved in the learning, selection, planning, initiation and execution of willed actions (Contreras-Vidal, 1999). It may act as a gate, phasically suppressing and releasing tonic inhibition of thalamic pathways. The basal ganglia may filter and suppress unwanted movements (Ceballos-Baumann and Brooks, 1997).

The phasic neuronal discharge associated with the extra-cellular recordings of the globus pallidus appeared to show a pattern of predicting the end of a movement 'hold' period or the initiation of the next movement in a sequence. This discharge may cue the termination of pre-movement cortical activity in the SMA (Brotchie *et al.*, 1991).

The basal ganglia may facilitate and optimise sequential motor performance, mediating this process through interaction with premotor cortex via thalamocortical projections (Böecker *et al.*, 1998). The basal ganglia may focus motor patterns by inhibiting unwanted movements (Böecker *et al.*, 1998; Marsden and Obeso, 1994) and act to facilitate sequential motor actions by sending signals to the SMA after each step of the movement sequence (Brotchie *et al.*, 1991). For example, this may occur when a subpopulation of pallidal cells is fired in response to the degree of automaticity and predictability of the wrist movement. A separate group of cells is fired biphasically at onset and cessation of electromyographic (EMG) activity, which may be providing cues to the SMA, allowing it to switch to the next movement in a programmed sequence (Brotchie *et al.*, 1991). The pallidal discharge from the basal ganglia is temporally related to subcomponents of the motor sequence, and may be setting up the correct

motor program. Injection of a GABA agonist into the pallidum leads to both tonic and phasic cocontraction of wrist flexors and extensors during movement (Mink and Thach, 1991). Böecker *et al.* (1998) suggests that "the pallidum may act to focus and filter desired motor patterns during movement, optimising them and inhibiting unwanted movements" (Böecker *et al.*, 1998, p.1078). The basal ganglia may focus motor patterns by inhibiting unwanted movements and facilitating sequential motor actions by sending signals to the SMA after each step of a sequence (Böecker *et al.*, 1998; Brotchie *et al.*, 1991).

Two disorders of the basal ganglia were used in this thesis as models to further elucidate the functioning of the medial motor circuit in motor control.

Parkinson's Disease

Parkinson's disease is a progressive degenerative disorder, with symptoms including rigidity, shuffling gait, a stooped posture, generalised slowness and stiffness of movement, loss of facial expression, episodic freezing of movement, a tendency to fall, dysarthria and hypophonia, micrographia, resting tremor, bradyphrenia, and depression (Iansek *et al.*, 1997; Joseph, 1996).

Parkinson's disease - anatomy and physiology

Parkinson's disease targets the nigrostriatal and mesofrontal dopaminergic projections, with additional loss of cells in the noradrenergic, serotonergic and cholinergic fibers (Brooks, 1996). The striatum and pallidum are left intact. Up to 80-85% of the dopamine neurones in the substantia nigra and 80% of striatal dopamine are lost (Joseph, 1996; McRitchie *et al.*, 1996).

In Parkinson's disease the loss of cells in the substantia nigra compacta may lead to an increased inhibition of the thalamus and reduced output to the SMA, resulting in difficulties selecting and maintaining motor programs (Young and Penney, 1998). This is analagous to reducing the activity of the direct pathway and subsequently the motor loop.

PET studies indicate that during internally generated movements, the SMA is significantly under-activated in Parkinson's disease compared with normals (Jahanshahi *et al.*, 1995; Jenkins *et al.*, 1992; Owen *et al.*, 1998; Playford *et al.*, 1992;

Rascol *et al.*, 1994). Recent fMRI studies have also shown reduced activity in the mesial premotor and prefrontal areas in patients with Parkinson's disease (Haslinger *et al.*, 2001; Sabatini *et al.*, 2000). This activity is increased following treatment with the dopamine agonist apomorphine (Jenkins *et al.*, 1992) or levodopa (L-DOPA) (Haslinger *et al.*, 2001; Rascol *et al.*, 1994).

The cerebellar-parieto-lateral premotor loop and the primary motor area are overactive during sequential and single movements in Parkinson's disease (Hanakawa *et al.*, 1999; Haslinger *et al.*, 2001; Rascol *et al.*, 1997; Sabatini *et al.*, 2000; Samuel *et al.*, 1997). The over-activity of the cerebellar-parieto-lateral premotor loop has been postulated as a compensatory mechanism for decreased medial premotor activity due to cell loss in the basal ganglia (Haslinger *et al.*, 2001). After administration of L-DOPA, the over-activation of the lateral premotor area, primary motor and parietal cortices is relatively normalised, whilst activity in the SMA is significantly improved (Haslinger *et al.*, 2001).

Parkinson's disease - movement dysfunction

Parkinson's disease patients are slower than controls to initiate and execute sequential movements (Agostino *et al.*, 1998; Jones *et al.*, 1994; Pastor *et al.*, 1992b; Stelmach *et al.*, 1987). Movement times progressively slow as the sequence continues (Agostino *et al.*, 1992; Georgiou *et al.*, 1994) especially if a button must be released before a light cues which next button to press in a sequence (Rogers *et al.*, 1997). Switching between two different tasks as part of a movement sequence is slower in Parkinson's disease than in controls (Benecke *et al.*, 1987; Harrington and Haaland, 1991) and pauses between sub-movements are longer in the disease group (Weiss *et al.*, 1997). This slowing of movement, or bradykinesia, of Parkinson's disease may reflect impaired output from the putamen via the thalamus to the SMA (Jahanshahi *et al.*, 1995).

This bradykinesia of Parkinson's disease may be improved with the provision of external cues. Parkinson's disease patients show a reliance on external cues to guide movements (Connor and Abbs, 1991; Flowers, 1978b; Freeman *et al.*, 1993; Georgiou *et al.*, 1993; Ho *et al.*, 1999; Jackson *et al.*, 1995; Kritikos *et al.*, 1995; Oliveira *et al.*, 1997; Praamstra *et al.*, 1998; Rogers *et al.*, 1997). Patients may have trouble using an

internal representation of action and anticipating the next movement in a sequence, and so use external cues to guide movement (Flowers, 1978a).

During self-initiated movement, the movement related potential in Parkinson's disease is often (but not always) significantly lower than that of the control group (Barrett *et al.*, 1986; Deecke and Kornhuber, 1978; Dick *et al.*, 1987; Dick *et al.*, 1989; Feve *et al.*, 1992; Jahanshahi *et al.*, 1995; Shibasaki *et al.*, 1978; Simpson and Khuraibet, 1987; Tarkka *et al.*, 1990). With altered output from the basal ganglia to the SMA, Parkinson's disease patients show a reduced amplitude MRP, compared with controls, when they perform an internally determined (non-cued) sequential tapping task (Cunnington *et al.*, 1995), indicating reduced SMA and primary motor functioning. Interestingly, they show an absence of a MRP if the sequential task is externally determined (cued). This indicates that in order to produce a movement, the Parkinson's disease patients may be using an alternative pathway.

Dysdiadochokinesia is one clinical feature of Parkinson's disease. Such deficits of Parkinson's disease patients in performing bimanual co-ordinated movements have been tested experimentally. Most studies have found that there was a deficit in the ability of these patients to perform movements simultaneously or sequentially (Alberts *et al.*, 1998; Benecke *et al.*, 1986; Benecke *et al.*, 1987; Horne, 1973; Horstink *et al.*, 1990; Johnson *et al.*, 1998; Lazarus and Stelmach, 1992; Schwab *et al.*, 1954; Shimizu *et al.*, 1987: Talland and Schwab, 1964). Three studies, however, have found no disturbance in the ability of Parkinson's disease patients to perform co-ordinated bimanual movements (Brown *et al.*, 1993; Cohen, 1970; Stelmach and Worringham, 1988). Brown and Jahanshahi (1998) even found an improvement in the visually guided pegboard task, when it was performed simultaneously with a tapping task, compared with the pegboard performed unimanually. The relative ability to perform bimanual tasks by patients with Parkinson's disease is therefore equivocal. The effect of anti-parkinsonian medication on bimanual co-ordination in Parkinson's disease is unknown.

In summary, Parkinson's disease is associated with a slowness of movement for unimanual and bimanual movements, especially down a sequence, and with a unique responsiveness to external cues. The cortical preparatory activity in Parkinson's disease is reduced in amplitude.

Huntington's Disease

Huntington's disease is an autosomal dominant, neurodegenerative disease with a mean age of onset of 40 years. It is characterised by motor, psychiatric and cognitive disturbances. Death occurs between 12 and 15 years after the onset of symptoms. The prevalence of Huntington's disease is approximately 5-10/100,000, and is found the world over (Vonsattel and DiFiglia, 1998).

Huntington's disease produces cognitive and psychiatric changes, in particular cognitive deterioration, affective and psychiatric symptoms with personality changes, memory loss, and depression (Bradshaw and Mattingley, 1995; Rosenblatt and Leroi, 2000). Huntington's disease patients show a progressive cognitive decline which correlates with progression of neuronal degeneration throughout the striatum (Lawrence *et al.*, 1996).

Patients with Huntington's disease show a variable number (between 40 and 86 copies) of cytosine/adenine/guanine (CAG) motifs in a protein-coding part of the *huntingtin* gene (IT15), found on chromosome 4p16.3 (Huntington's Disease Collaborative Research Group, 1993). Unaffected individuals have between 9 and 33 copies of the CAG trinucleotide, which are stably transmitted. Repeat lengths of between 34 and 39 are not stably transmitted and may not be 100% penetrable (Penney and Young, 1998). The CAG trinucleotide encodes the amino acid glutamine. The huntingtin protein encoded by the Huntington's disease gene contains a polyglutamine tract of varying length near the N-terminal of the protein, and when it reaches 38 glutamine residues in length it becomes toxic (Bates, 2000). Polyglutamine aggregates are found within and outside nuclei, primarily in the cortex, but also throughout the body, although the pathology is apparently restricted to the brain (DiFiglia *et al.*, 1997; Vonsattel and DiFiglia, 1998). The relationship between the aggregation of the polyglutamine protein and the death of cells in the disease is unknown (Bates, 2000).

DiFiglia and colleagues recently reported that a cleaved N-terminal product of the protein aggregates in neuronal intranuclear inclusions in the Huntington's disease cortex and striatum, but not in other areas of the brain (DiFiglia *et al.*, 1997). It is possible that the cleavage and accumulation of the huntingtin fragment is associated with the pathogenesis in Huntington's disease (Sapp *et al.*, 1999). Cortical degeneration may be independent of neuronal loss in the striatum. Intraneuronal nuclear inclusions, N-

terminal mutant huntingtin, and ubiquitin in dystrophic neurites have been found in the cortex of Huntington's disease patients, and degeneration of corticofugal axons may be an early feature of the disease. Nuclear inclusions formed by N-terminal mutant huntingtin are more prevalent in the cortex than the striatum (Sapp *et al.*, 1999).

Recent work investigated the role of the huntingtin protein, via regulation of individual gene activity in a mouse model of Huntington's disease (via tetracycline-controlled transcriptional activation) (Yamamoto *et al.*, 2000). These mice expressed a mutated huntingtin protein fragment, and demonstrated the neuropathology and progressive motor dysfunction typical of Huntington's disease in humans. The researchers blocked the expression of the mutant protein, which led to a disappearance of the neuronal inclusions and motor dysfunction. It was concluded that the continuous expression of the protein was required to maintain the symptoms of the disease and that suppressing expression of the gene could reverse the symptoms in the mouse model (Yamamoto *et al.*, 2000). This research offers exciting future prospects of genetic therapy for people with the Huntington's disease gene.

Huntington's disease - anatomy and physiology

The process and anatomy of cell loss in Huntington's disease is poorly understood (Mansuy and Bujard, 2000). The basal ganglia are most prominently affected by the disease, with neuronal loss and astrocytosis occurring in the caudate, the putamen and the globus pallidus (Myers *et al.*, 1991; Vonsattel *et al.*, 1985). The thalamus, subthalamic nucleus, substantia nigra, cerebellum, cortex, hypothalamus, hippocampus, and brain stem also suffer some cell loss (Macmillan and Quarrell, 1996; Vonsattel *et al.*, 1985).

This disease results in the selective degeneration of the GABAergic output neurons of the striatum projecting to the striatum and substantia nigra (Faull *et al.*, 1996; Kowall *et al.*, 1987). This selective loss of GABAergic neurons in Huntington's disease is accompanied by a substantial increase in the number of $GABA_A$ receptors in the globus pallidus (Faull *et al.*, 1996) and substantia nigra (Penney and Young, 1982). This increase in $GABA_A$ receptors in the globus pallidus occurs in the very early stages of the disease, i.e. grade 0 cases where it is not possible to detect changes in striatum (Faull *et al.*, 1996). This $GABA_A$ receptor has four subunit classes with 14 different

subtypes (Nicholson and Faull, 1996). Nicholson and Faull (1996) used post-mortem human brain tissue from seven subjects (aged between 65-94), including four normal and three Huntington's disease patients. They found no detectable signal in the putamen for any of the $GABA_A$ receptor subtypes studied. This correlated with the loss of striatal projection neurons characteristic of Huntington's disease. There was also an increase in the level of mRNA expression of two subtypes (α_1, γ_2) in the globus pallidus (Nicholson and Faull, 1996). Excitotoxic mechanisms may be involved in the neurodegenerative process possibly via quinolinic acid (Kowall *et al.*, 1987). Quinolinic acid lesions in rats produce an increase in $GABA_A$ receptors in the globus pallidus (Faull *et al.*, 1996).

Huntington's disease is associated with loss of medium-sized GABAergic spiny efferent neurons and interneurons in the striatum, but with spared somatostatin/neuropeptide Y aspiny interneurons (Dawbarn *et al.*, 1985; Ferrante *et al.*, 1985; Graveland *et al.*, 1985; Kowall *et al.*, 1987). The loss of striatal neurons leads to a loss of excitatory projections from the STN to the GPi, and reduced inhibitory input to the thalamus, leading to increased thalamocortical activity (DeLong, 1990).

Brain-imaging techniques typically show bilateral atrophy of the striatum, and, as the disease progresses, there is greater global cortical atrophy, beginning in the frontal regions. In vivo MRI studies have shown reduced striatal volumes (Aylward *et al.*, 1994; Aylward *et al.*, 1996). SPECT and PET studies have indicated decreased striatal D_2 receptor binding (Antonini *et al.*, 1996; Ichise *et al.*, 1993; Weeks *et al.*, 1996) and reduced striatal glucose consumption (Antonini *et al.*, 1996; Grafton *et al.*, 1992a; Kuwert *et al.*, 1993). Post-mortem studies suggest there is a preferential loss of striatal neurons projecting to the external segment of the globus pallidus (Albin *et al.*, 1992; Albin *et al.*, 1990).

One current model of Huntington's disease suggests that the D2-bearing indirect circuit via the GPe and STN to GPi is targeted preferentially, compared with the direct striatal output pathway to the GPi, which is rich with D1 receptors (Albin, 1995; Hedreen and Folstein, 1995). Other researchers, however, have found no evidence for preferential neuronal loss in the indirect pathway in Huntington's disease (Ferrante *et al.*, 1994), but evidence for parallel reductions in both D1 and D2 binding via PET methodology (Ginovart *et al.*, 1997; Turjanski *et al.*, 1995).

At rest, the Huntington's patients show decreased regional cerebral blood flow in the bilateral caudate, putamen and the anterior cingulate (Bartenstein *et al.*, 1997) and bilateral frontoparietal areas (Weeks *et al.*, 1997). [^{18}F] fluorodeoxyglucose-PET measures indicate that glucose metabolism is reduced in the caudate and lentiform nucleus in the early stages of the disease (Kuhl *et al.*, 1982; Kuwert *et al.*, 1990) and the frontal cortex is similarly affected as the disease progresses (Kuwert *et al.*, 1993; Leenders *et al.*, 1986).

Whilst performing externally cued, sequential movements, $H_2{}^{15}O$ rCBF PET studies (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997) have indicated that Huntington's disease patients show *impaired* bilateral activation in SMA, M1, CMA, precuneus, the lateral premotor cortices, dorsolateral prefrontal and orbitofrontal cortices. This represents under-activation of all the frontal lobe areas that receive basal ganglia outputs of the motor loop.

The lateral premotor areas show most impairment in the Huntington's disease patients (Bartenstein *et al.*, 1997). This area is believed to be involved, in a similar way to the SMA, in the preparation of movement. It, however, receives striatal input from anatomically and functionally different areas than the SMA (Hoover and Strick, 1993) and may be more involved in preparing movements which are externally than internally cued (Halsband and Passingham, 1985). Indeed, this area is bilaterally enhanced in Parkinson's disease patients relative to controls, during unimanual, externally cued finger sequencing tasks (Samuel *et al.*, 1997). Huntington's disease patients show enhanced activation of the parietal cortex and the posterior cingulate, and patients who perform the sequential finger tapping task well, show increased activation on the left parietal cortex (Bartenstein *et al.*, 1997). The parietal cortex is involved in spatial processing and may be used as an alternative pathway to the dysfunctional basal ganglia, in both Huntington's and Parkinson's diseases. This suggests that external cueing will not benefit Huntington's disease patients. No brain activation studies have been performed which compare the effects of internally and externally cued movement in Huntington's disease.

Huntington's disease - movement dysfunction

The most characteristic movement dysfunction in Huntington's disease is the involuntary hyperkinetic dance-like movement of chorea, defined by Berardelli *et al.* (1999) as "the random flow of muscle activity from one part of the body to another" p.399. Chorea may abate in the more advanced stages of the disease, when akinetic and bradykinetic movements become clearer. Chorea appears to be quite a separate phenomenon from bradykinesia in Huntington's disease. Involuntary movements such as chorea do not correlate with voluntary movement parameters in Huntington's disease (Phillips *et al.*, 1994) and may not be as useful as voluntary movement parameters, such as bradykinesia, in describing the advancement of the disease (Bradshaw *et al.*, 1992). Chorea can be partially suppressed during voluntary movements (Hefter *et al.*, 1987). Suppression of chorea with drugs does not improve bradykinesia.

Huntingtonian voluntary movement is characterised by difficulties in co-ordination, movement initiation and execution (Hefter *et al.*, 1987). Bradykinesia is a dysfunction present from the early stages of the disease. It is attributed to functional and structural abnormalities in the basal ganglia and cortical motor areas (Berardelli *et al.*, 1999; Currá *et al.*, 2000; Herz, 1931; Thompson *et al.*, 1988). Bradykinesia as a movement dysfunction in Huntington's disease is a very common finding. Huntington's disease patients are slower than normals in executing repetitive finger movements (Garnett *et al.*, 1984; Hefter *et al.*, 1987). Saccades are slow, and there may be inappropriate intrusion of saccades during smooth eye pursuits (Hefter *et al.*, 1987). This bradykinesia is not specifically associated with either the acceleration or deceleration phases of movement, and so is not believed to be specifically linked to problems with initial movement force (acceleration phase) or to excessive reliance upon terminal visual guidance (deceleration phase) (Phillips *et al.*, 1996).

Although slower than controls, Huntington's disease patients are able to perform simple, unimanual voluntary movements. Their performance of more complex, multi-joint tasks involving sequential movements appears to be more severely impaired (Johnson *et al.*, 2000). They avoid performing sequential movements, preferring to perform individual components of the movement separately. They have profound difficulties in executing sequential hand squeezing-elbow flexing movements (Thompson *et al.*, 1988). Huntington's disease patients are slower in executing

sequential finger tapping (Georgiou *et al.*, 1995), sequential tracing patterns (Agostino *et al.*, 1992) and unimanual zig-zag patterned sequential movement than controls (Currá *et al.*, 2000; Phillips *et al.*, 1996). It is a contentious point in the literature, however, whether the slowness in Huntington's disease during the performance of sequential movements is additive, as in the sequence effect shown in Parkinson's disease.

The effect of external cues on movement performance in Huntington's disease is particularly understudied. There are very few studies that have been designed to investigate specifically the effect of cues on movement. The gait performance of Huntington's disease patients did not improve in the presence of an external cue (Churchyard *et al.*, 2000). A similar result was found with the bimanual co-ordination of Huntington's disease patients, which did not improve with the presence of an external auditory cue (Johnson *et al.*, 2000).

Huntington's disease patients have difficulties performing complex sequential bimanual movements. Dysdiadochokinesia as a symptom presents early in Huntington's disease (Young *et al.*, 1986). Patients are slower than controls at performing (separately) the Purdue pegboard task and repetitive finger tapping bimanually. When the two tasks are combined, with one hand tapping whilst the other places pegs, their tapping performance is significantly worse, but their pegging is not significantly different from controls (Brown *et al.*, 1993). Attentional resources may be applied to the pegboard task, to the detriment of the tapping task. Huntington's disease patients are significantly more variable and less accurate in performing a bimanual circling movement than controls (Johnson *et al.*, 2000).

Voluntary movement in Huntington's disease may be characterised as inefficient and inconsistent (Halsband *et al.*, 1990; Phillips *et al.*, 1996; Weeks *et al.*, 1997). The movements of patients appear to be more variable than normal (Smith *et al.*, 2000). Skilled arm movements often begin normally, but become jerky and irregular before the end of the movement (Smith *et al.*, 2000). This may be due to a disturbance in error correction (Smith *et al.*, 2000). The handwriting of this patient group is slower and more variable than that of normal people, implying that the preparation rather than the production of writing is affected (Phillips *et al.*, 1994). Huntington's disease patients are less consistent in the stroke duration and length of movement production than controls (Phillips *et al.*, 1994). They do not require any more sub-movements than

controls to perform the movement, but there are more changes in velocity, indicating problems in movement force efficiency, resulting in bradykinesia. Indeed, in one study, the Huntington's disease group was 42% less efficient than the control group (Phillips *et al.*, 1994).

Huntington's disease is associated with a deficit in the building up of EMG activity, resulting in prolonged bursts from the agonist and antagonist muscles (Thompson *et al.*, 1988) and prolonged contraction before peak force (Hefter *et al.*, 1987). There may be inappropriate motor unit selection (Bylsma *et al.*, 1990) leading to an interference with co-ordination (Bradshaw *et al.*, 1992), although the coactivation pattern of agonist and antagonist muscles is conserved (Hefter *et al.*, 1987). The EMG pattern in Huntington's disease is quite different from that seen in Parkinson's disease. In Parkinson's disease the first burst in the agonist is small but of normal duration. In Huntington's disease the EMG pattern is highly variable and prolonged (Thompson *et al.*, 1988).

The amplitude-contraction relationship is altered depending on the state of the disease progression. Normally, the time taken for contraction of a muscle remains constant, irrespective of the amplitude of the force of contraction, because there is a linear rate of rise of tension with increasing amplitude. This adjustment allows for co-ordinated movements, and is lost in Huntington's disease. In a milder state of the disease, the contraction time may be prolonged, but is still independent of amplitude. Later, as the disease progresses, the rate of rise of tension is reduced (decreased amplitude) so that as the amplitude increases, so does the time to peak contraction (Hefter *et al.*, 1987). There may be impairment in the firing rate modulation of the motor neurons, as is required for normal contractions of muscles.

Reaction time is prolonged for single finger movements (Girotti *et al.*, 1988; Hefter *et al.*, 1987). Huntington's disease patients do not seem to be able to utilise advance information to speed up simple reaction time; they show a similar reaction time with simple and choice paradigms. This may be because of an inability to prepare or preprogram movement properly (Jahanshahi *et al.*, 1993).

Akinesia, or the loss of voluntary movement, has also been reported in Huntington's disease (Bradshaw *et al.*, 1992; Girotti *et al.*, 1988; Herz, 1931), especially at the end-stages of the disease.

In summary, Huntington's disease movement is characterised by involuntary and voluntary movement deficits. Deficits in voluntary movement involve co-ordination, movement preparation and execution. Huntingtonian movement is bradykinetic, and complex sequential movements are particularly deficient. Execution of movement is inefficient and variable, and appears to be associated with deficits in EMG activity. The preparation of movement also appears to be affected, although this proposition is based on behavioural measures only. Unlike Parkinson's disease, there have been no studies performed on cortical preparatory activity in Huntington's disease.

Aims and Research Outline

Both Huntington's and Parkinson's diseases present deficits with the production of unimanual and bimanual sequential movements. This suggests that the common feature of bradykinesia is a result of impaired output from the pallidocortical projections activating the premotor cortex and SMA.

Movement related potentials have been recorded successfully in patients with Parkinson's disease, enabling a better understanding of the nature of the movement deficits in that disease and of normal motor control. These MRP studies have also provided a neuro-functional underpinning for rehabilitation in that disease. To date, no MRP studies have been performed with Huntington's disease patients.

There are possible cue and sequence effects in Huntington's disease, as in Parkinson's disease, but the literature is equivocal. Further investigation is needed to elucidate these issues. A clearer understanding of the nature of deficits in Huntington's disease will enable a better understanding of the functions of the medial motor circuit in normal motor control and may certainly help in rehabilitation. Further work is also needed to understand the effect of anti-parkinsonian medication on bimanual co-ordination in Parkinson's disease.

The following eight chapters describe a set of experiments that were designed to provide further information about the preparation and execution of sequential movement in Huntington's and Parkinson's diseases. The first five experimental chapters attempted to clarify the cortical preparatory activity of Huntington's disease and the effect of the provision of external cues and attentional strategies on this activity (Chapters Two, Three and Four). By using imagined movement, the components

relating to movement preparation and execution in Huntington's disease were disclosed (Chapter Five) and a prospective study on neurodegeneration in Huntington's disease was initiated (Chapter Six). The following two experimental chapters provided information on the behavioural response of Huntington's disease patients to the provision of external cues (Chapter Seven) and the generation of sequential movements (Chapter Eight). The penultimate chapter of the thesis investigated the effect of anti-parkinsonian medication on the performance of bimanual movements in Parkinson's disease (Chapter Nine). Chapter Ten drew the main findings of each experimental chapter together into a final discussion on the preparation and execution processes of sequential movement in Huntington's and Parkinson's diseases.

Movement Related Potentials Studies

Movement related potentials (MRPs) reflect changes in cortical activity related to the preparation and execution of voluntary movement (Deecke and Lang, 1996). Two components comprise the MRP: the early component has a slowly increasing negative shift which starts one to two seconds before movement onset, is bilaterally symmetrical across the scalp and is maximal at the vertex (recorded at electrode position Cz). The late component consists of a rapidly increasing negative potential, beginning within 500 ms of movement. This cortical activity returns to a baseline level following the movement (Deecke *et al.*, 1998).

The SMA, M1 and the CMA probably all contribute to the potential, either in sequence or simultaneously (Ball *et al.*, 1999; Ikeda *et al.*, 1993; Yazawa *et al.*, 1998). The late component of the MRP reflects cortical activity associated with the execution of movement, most likely from the contralateral M1. This component of the potential appears to follow the somatotopic organisation of M1 (Cheyne *et al.*, 1991; Deecke *et al.*, 1998). M1 neurons appear to become more active around the time of execution (Tanji and Shima, 1994). The early component of the MRP reflects cortical activity associated with movement preparation, and the source of this activity comes from the SMA, M1 and probably the CMA. This is supported by data from intracranial recordings from within premotor and sensorimotor areas, which show that both the SMA and M1 contribute to early-stage pre-movement activity (Ikeda *et al.*, 1992; Ikeda *et al.*, 1999; Neshige *et al.*, 1988; Rektor *et al.*, 1994; Yazawa *et al.*, 1998). Single-cell recordings indicate that neurons in the SMA, M1, somatosensory and parietal areas show increased set activity, related to preparation prior to movement, often several seconds before movement onset (Alexander and Crutcher, 1990b; Crutcher and Alexander, 1990; Kurata and Tanji, 1985; Mushiake *et al.*, 1991; Okano and Tanji, 1987; Romo and Schultz, 1992; Tanji and Kurata, 1985; Tanji and Shima, 1994; Wise and Kurata, 1989). Local cerebral blood flow studies have provided evidence of SMA involvement in the preparation for movement (Deiber *et al.*, 1991; Fox *et al.*, 1985). High-resolution EEG and fMRI results indicate that the anterior CMA, the pre-SMA, and the inferior parietal lobe become active before M1 and the SMA proper, prior to self-paced movement (Ball *et al.*, 1999).

Experiments with Parkinson's disease patients also suggest a role for the SMA in the early component of the MRP. With a loss of dopaminergic neurons of the substantia nigra pars compacta, the output of the basal ganglia to the SMA is severely disrupted, as shown in cerebral blood flow studies (Jahanshahi *et al.*, 1995; Playford *et al.*, 1992). A significant reduction in amplitude of the early MRP is found in Parkinson's disease compared with control participants (Cunnington *et al.*, 1995; Dick *et al.*, 1989; Simpson and Khuraibet, 1987). Impaired MRP amplitudes in Parkinson's disease may reflect impairment in the SMA contribution to motor preparatory activity.

Huntington's disease is also associated with cell loss in the basal ganglia and SMA function is negatively affected (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997). The precise nature of the impact of Huntington's disease on SMA activity and consequently motor control is, however, unknown. Furthermore, no studies have investigated MRPs in Huntington's disease.

Chapter Two – MRPs in Huntington's disease – self-initiated and externally cued movements

Huntington's disease is associated with neuronal loss and astrocytosis of areas that form part of the motor loop (Alexander *et al.*, 1990). Cell loss occurs predominantly in the caudate, putamen and globus pallidus, but also occurs in the subthalamic nucleus, substantia nigra, thalamus and cortex (Macmillan and Quarrell, 1996; Vonsattel *et al.*, 1985). Subsequent to cell loss in these motor areas, Huntington's disease patients present bradykinetic deficits in sequential movements (Agostino *et al.*, 1992; Currá *et al.*, 2000; Johnson *et al.*, 2000; Phillips *et al.*, 1995; Thompson *et al.*, 1988; Young *et al.*, 1986). Levels of bradykinesia in Huntington's disease negatively correlate with metabolic activity in the putamen and caudate (Penney and Young, 1998).

Movement related potentials (MRPs) reflect changes in cortical activity preceding voluntary movement (Deecke *et al.*, 1969), including contributions from the supplementary motor area (SMA) and primary motor cortex (Ikeda *et al.*, 1993; Yazawa *et al.*, 2000). The SMA is active during the preparation for movement (Alexander and Crutcher, 1990b; Ohara *et al.*, 2000) and so contributes to the MRP (Ikeda and Shibasaki, 1992; Ikeda *et al.*, 1999).

With altered output from the basal ganglia to the motor loop (Ceballos-Baumann and Brooks, 1997; DeLong and Wichmann, 1993; Young and Penney, 1998) Parkinson's disease patients show a reduction in activity of the SMA (Jenkins *et al.*, 1992; Owen *et al.*, 1998; Playford *et al.*, 1992). Pre-movement cortical activity recorded from the scalp surface of people with Parkinson's disease is reduced in amplitude (Dick *et al.*, 1989; Praamstra *et al.*, 1996). This indicates that reduced MRP amplitudes in Parkinson's disease reflect impairment in the SMA contribution to motor preparatory activity. This may underlie the parkinsonian akinesia and bradykinesia (Jenkins *et al.*, 2000).

The SMA appears to be preferentially involved in internally determined movement (Mushiake *et al.*, 1990; Tanji and Shima, 1994) although it is active also during externally cued movements (Okano and Tanji, 1987). MRPs recorded during internally determined (non-cued) voluntary movements show increased activity compared with MRPs recorded from externally determined (cued) movements (Cunnington *et al.*, 1995; Praamstra *et al.*, 1995). Cunnington *et al.* (1995) found that during internally cued

movements, Parkinson's disease patients produced pre-movement cortical activity that was significantly reduced in amplitude compared with a control group, indicating impaired SMA activity. During externally cued movement, Parkinson's disease patients showed no pre-movement activity, suggesting movement was prepared via other pathways. The lateral premotor area has been suggested as an alternative, externally modulated pathway (Passingham, 1988; Samuel *et al.*, 1997).

With the cell loss noted above, output from the basal ganglia to the motor loop may be impaired in Huntington's disease (Weeks *et al.*, 1997). Activation of the SMA is known to be impaired in this disease (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997). The MRPs recorded from cued and non-cued conditions have not been reported from a Huntington's disease group. This experiment compared the MRPs recorded during externally and internally determined voluntary movements in Huntington's disease and matched controls. This was done to understand further cortical activity related to movement preparation and the bradykinesia found in Huntington's disease. To investigate whether the internal preparation of movement would lead to an increase in pre-movement brain activity, comparisons of the MRPs between and within the Huntington's disease and control groups for the cued and non-cued conditions were performed. It was expected that the Huntington's disease group would show deficits, especially in movement preparation in comparison with the control group, particularly when the movement was externally cued.

METHOD

Participants

Four female and ten male Huntington's disease patients, aged 31 - 63 years, with a mean age of 50.5 (Standard Deviation 9.9) years, and four female and ten male control participants, aged 31- 64 (mean age 50.4, SD 9.3 years) were tested. All participants were right handed (Patterson and Bradshaw, 1975).

The diagnosis of Huntington's disease was confirmed by CAG repeat lengths (Gusella *et al.*, 1997) for five of the participants, and their CAG repeat lengths varied from 42-44. The other nine Huntington's disease participants had family histories of the disease and a psychiatrist confirmed their diagnoses.

Twelve of the Huntington's disease patients were assessed on the Unified Huntington's Disease Rating Scale (Total Motor Score) (UHDRS) (Huntington Disease Group, 1996) and scored between 3 and 68 (mean UHDRS score 31.50, SD 22.13). On the Shoulson and Yahn rating scale (Shoulson and Fahn, 1979) all patients scored between 0 and 2.5. The duration of disease of the group varied between one and sixteen years (mean duration of disease 6.00, SD 4.56 years).

All participants were screened for histories of stroke, serious head injury and other neurological disturbances. They were also screened for dementia using the Short Test of Mental Status (STMS) (Kokmen *et al.*, 1987). Their depression levels were assessed using the Mood Assessment Scale (MAS) (Yesavage *et al.*, 1983). The Huntington's disease group (mean MAS score 9.00, SD 5.38, n = 14) was significantly more depressed than the control group (mean MAS score 3.42, SD 3.78, n = 12), [$F(1,24) = 9.071$, $p < 0.05$].

Participants were not withdrawn from their medication. Clinical data are shown in Table 2.1. Informed consent was obtained from each participant in accord with the Helsinki declaration, and all experimental work was carried out under the approval of local ethical committees.

Procedure

Participants performed a right-handed, sequential, choice, button-pressing task along a tapping board. This consisted of two parallel rows of ten buttons, with two centered start buttons and one centered end button (see Figure 2.1). Buttons were 12 mm in diameter, and were spaced 30 mm apart both within and between rows. Adjacent buttons on the board were therefore calculated to subtend a visual angle of approximately 3° from the participants' average viewpoint 500-600 mm from the board. The button heads were raised 21 mm above the board and were spring loaded so that each button had to be moved a total of 16 mm to be fully depressed and returned automatically to its raised position after being released (Cunnington, 1997).

Hall effect sensors detected the depression of the buttons. High-energy magnets (rare earth neodymium) were fitted in the base of each button. Hall effect sensors, which detected the strength of magnetic flux, were fitted to the board below each button. When a button was pressed, the magnet within the button was brought closer to the

Table 2.1: Clinical data for Huntington's disease patients.

Participant	Age (years)	Sex	Duration of disease (years)	STMS	MAS	Medication	Dose (mg/day)	UHDRS motor subscale	Triplet repeat score
1	60	M	8	37	0	-	-	31	42
2	55	M	8	31	8	Tetrabenazine	75	48	43
3	63	F	8	33	15	-	-	44	
4	38	M	4	30	11	Carbamazepine Thioridazine	300 35	56	
5	58	M	16	35	7	-	-	55	**
6	53	F	14	33	10	-	-	n/a	
7	57	M	5	36	4	-	-	3	
8	44	M	3	35	11	-	-	19	44
9	47	M	1	36	4	Sertraline hydrochloride	100	15	42
10	31	F	2	33	15	-	-	n/a	
11	47	M	3	36	0	-	-	11	43
12	44	M	7	*	16	-	-	68	
13	40	M	1	32	11	-	-	24	
14	61	F	4	34	14	-	-	4	

Notes: Dashes indicate that the participant was not taking medication.
STMS – Short Test of Mental Status
MAS – Mood Assessment Scale
UHDRS – Unified Huntington's Disease Rating Scale
* English was this participant's second language
** HD participant had two family members with confirmed CAG lengths above 40.

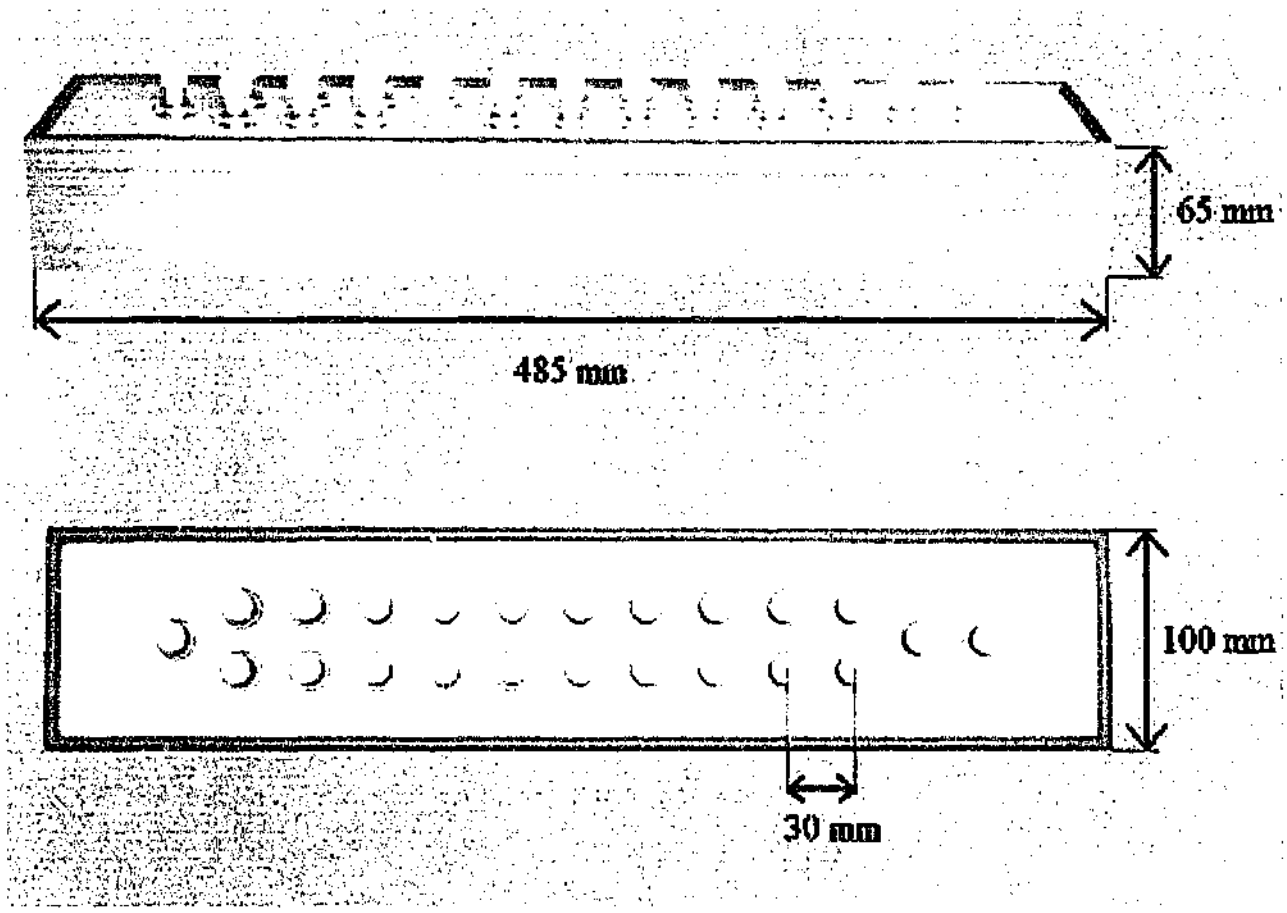


Figure 2.1: The tapping board used for the experimental tasks. Dimensions of various components are marked.

sensor, thereby increasing the magnetic flux detected. When the magnetic flux exceeded a threshold level, a change in state was signalled by a Schmitt trigger. Magnets and sensors for each button were calibrated and matched so that the trigger signal, indicating depression or release of a button, always occurred when the button moved past the point 3 mm from its fully depressed position. Light-emitting diodes were also fitted within a perspex ring of 18 mm diameter at each button's base. These could be illuminated and extinguished according to pre-arranged spatial and temporal patterns to provide both movement position and timing cues. A laptop computer controlled the presentation of light cues, recorded inter-button movement duration times, and detected any errors. Errors were recorded when a button was pressed out of sequence, or when a button was accidentally double-pressed (Cunnington, 1997).

Participants were required to press buttons on the tapping board along a particular pathway, which was used for both conditions (see Figure 2.2). The same procedure was used as per Cunnington *et al.* (1995). All participants were tested in two conditions, which differed only by the presence or absence of external cues to guide movement. The movement required for both conditions was exactly the same. Participants always moved from right to left along the board, at a rate of one movement every 4 s. After sufficient practice on the tapping board, all participants first completed the cued condition, followed by the non-cued condition. No instruction was given regarding anticipation of the light cue.

Cued condition

Participants were asked to press, as quickly as possible, the next button in the sequence once the light extinguished under the button they were presently pressing. The pathway on the tapping board was fully illuminated and lights underneath the buttons were sequentially extinguished four seconds after the release of each previously depressed button in the pathway. The external cues gave information regarding both the spatial and temporal requirements of the movement.

Non-cued condition

Participants were asked to time themselves to hold down each button for at least four seconds before moving, as quickly as possible, to the next button in the sequence. The pathway was not illuminated and no cues were given as to movement timing or location.

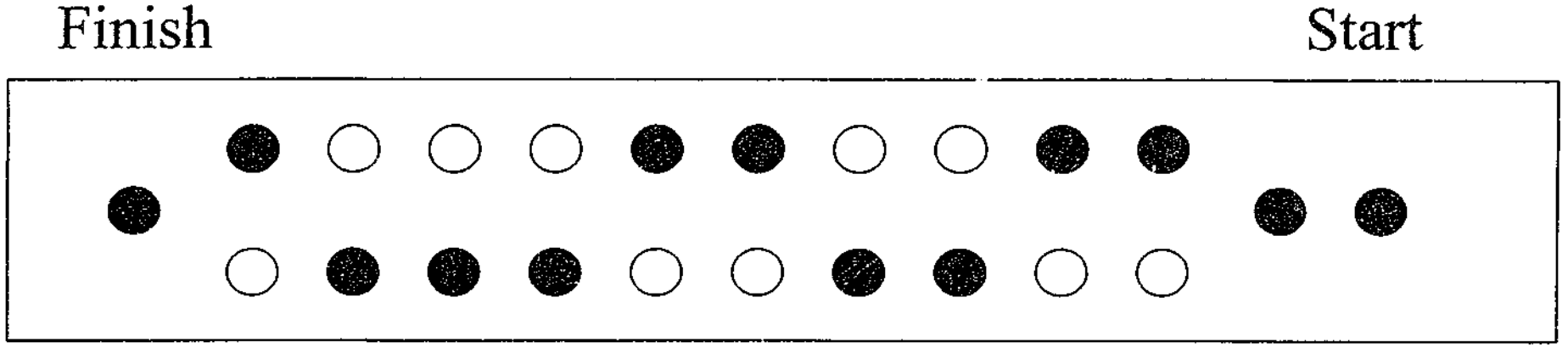


Figure 2.2: The tapping board. The circles on the board represent the buttons, and the shaded circles represent the illuminated buttons that the participants pressed. All participants used their right index fingers to press the buttons, and moved from right to left along the board.

Movement responses needed to be internally generated. The participants thus internally determined the spatial and temporal requirements of the movement.

Movement-related potentials were recorded using an Amlab workstation (AMLAB International, Sydney, Australia) which performed digital off-line processing and averaging of EEG activity. The EEG was recorded from silver/silver chloride surface electrodes, with recording electrodes placed at positions Cz, C3 and C4 (10-20 system), referenced bilaterally to electrodes over both mastoids, and with a ground electrode on the forehead. Electrode impedances were always kept below 5 kΩ.

The EEG was amplified using isolated AC amplifiers with a long time constant (gain 20 000 V/V, time constant 25 000 ms), digitized at 100 Hz, and filtered at 20 Hz (low-pass). The EEG potentials were averaged over 4-s sweeps time-locked to the extinction of light cues on the tapping board, over the period from 3 s before the cue to 1 s after it.

The release of buttons on the tapping board triggered a signal, conveyed via the laptop computer, to the AMLAB workstation, where a square pulse of 100 ms duration was produced in response to the signal. This square pulse was used to trigger the averaging of activity time-locked to each button-release.

An artifact-rejection system disabled the averager for any sweeps in which the recorded EEG potential deviated by >150 μV peak-to-peak. Consequently, sweeps containing artifacts from vertical eye movements, blinks and large EMG responses from neck and jaw muscles were rejected from the mean. At least 100 sweeps were averaged in each condition for each participant. Averaged potentials were calibrated to μV units and corrected to a baseline calculated as the average potential over the first 1000 ms of the trace.

Horizontal eye movements associated with the task were minimized since the distance between consecutive buttons on the board subtended a visual angle of <1.5°, and no contribution of electrooculographic activity to MRPs for the same movement execution task had previously been found in either control participants or patients (Cunnington *et al.*, 1995).

Characteristics of average potentials for each participant in each condition were quantified by the following measures.

Early Slope

Linear regression was used to calculate the average slope of the potential over the period from 1500 to 500 ms prior to movement onset. This is a measure of neural activity relating to the early component of the MRP.

Movement Time

This is the time from the release of one button on the tapping board to the depression of the next button.

All measures were analyzed by two-way ANOVA (Group by Cue), and t-tests where appropriate.

RESULTS

Mean MRPs for the Huntington's disease patients and the controls for the cued and non-cued conditions are shown in Figures 2.3 and 2.4. Qualitatively, the mean MRPs of the control group for the cued and non-cued conditions showed increasing negative pre-movement activity. The greatest activity was always recorded at electrode site Cz. Therefore the quantitative statistics were confined to the recordings from site Cz. The Huntington's disease group, in comparison, showed very reduced pre-movement activity for both the non-cued and cued conditions.

Quantitatively, the control group produced an increase in pre-movement activity, with an early slope which significantly differed from zero for both the cued (mean 4.52, SD 2.56 μV/s), [$t(13) = 6.614$, $p < 0.05$], and non-cued (mean 4.28, SD 2.00 μV/s), [$t(13) = 7.983$, $p < 0.05$] conditions. The Huntington's disease group produced an increase in pre-movement activity, with an early slope significantly differing from zero for the non-cued condition (mean 1.58, SD 2.65 μV/s), [$t(13) = 2.233$, $p < 0.05$], but failed to produce increasing pre-movement activity for the cued condition (mean –0.54, SD 2.59 μV/s), [$t(13) = 0.776$, $p > 0.05$].

The early slope of the control group, irrespective of cue condition (mean 4.02, SD 2.07 μV/s), was significantly greater than the early slope of the Huntington's disease group for the two conditions (mean 0.52, SD 0.53 μV/s), [$F(1,26) = 38.522$, $p < 0.001$]. There was no main effect of cue, and no interaction between cue and group.

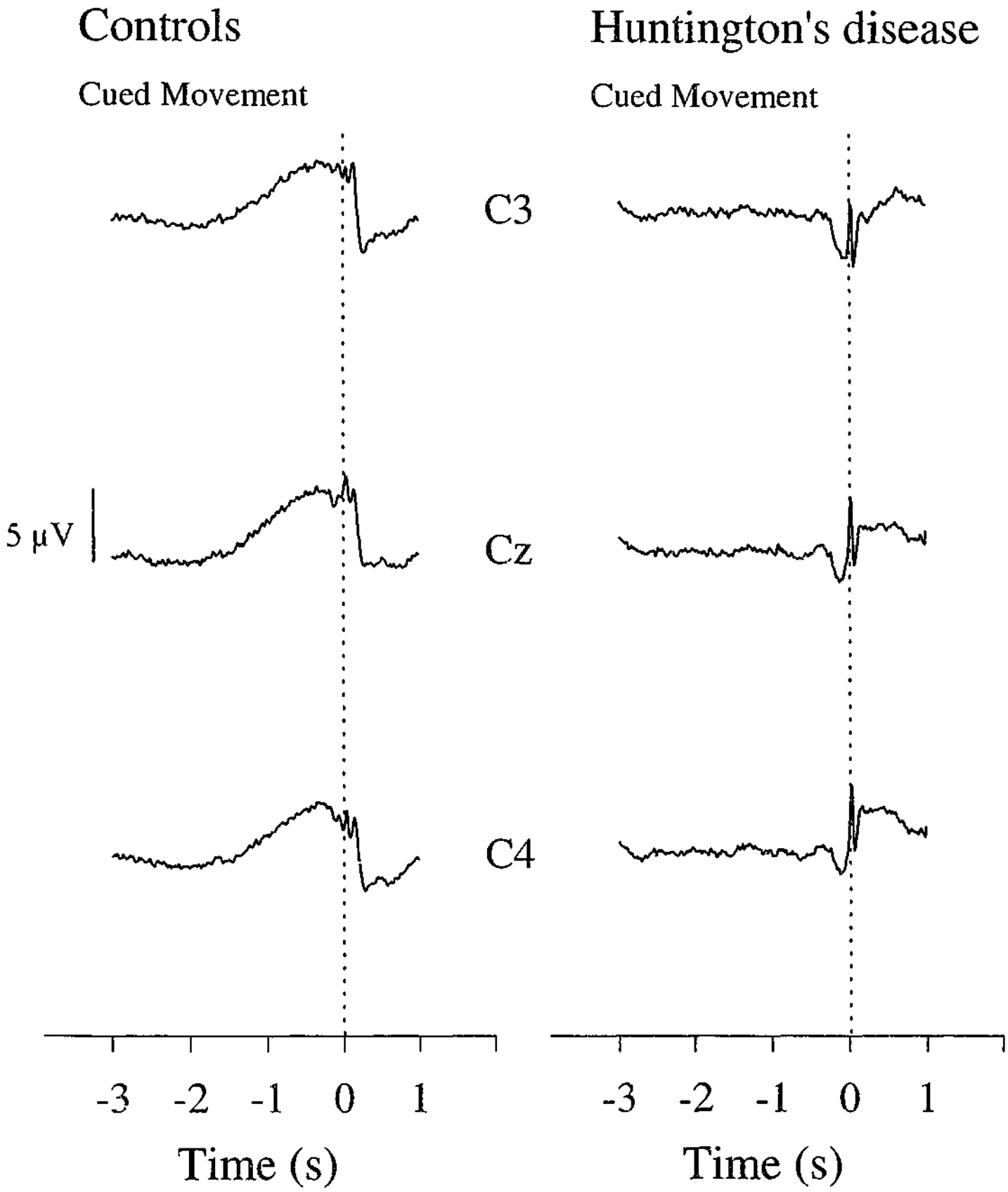


Figure 2.3: Grand average MRPs for control and Huntington's disease participants in the presence of external cues, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

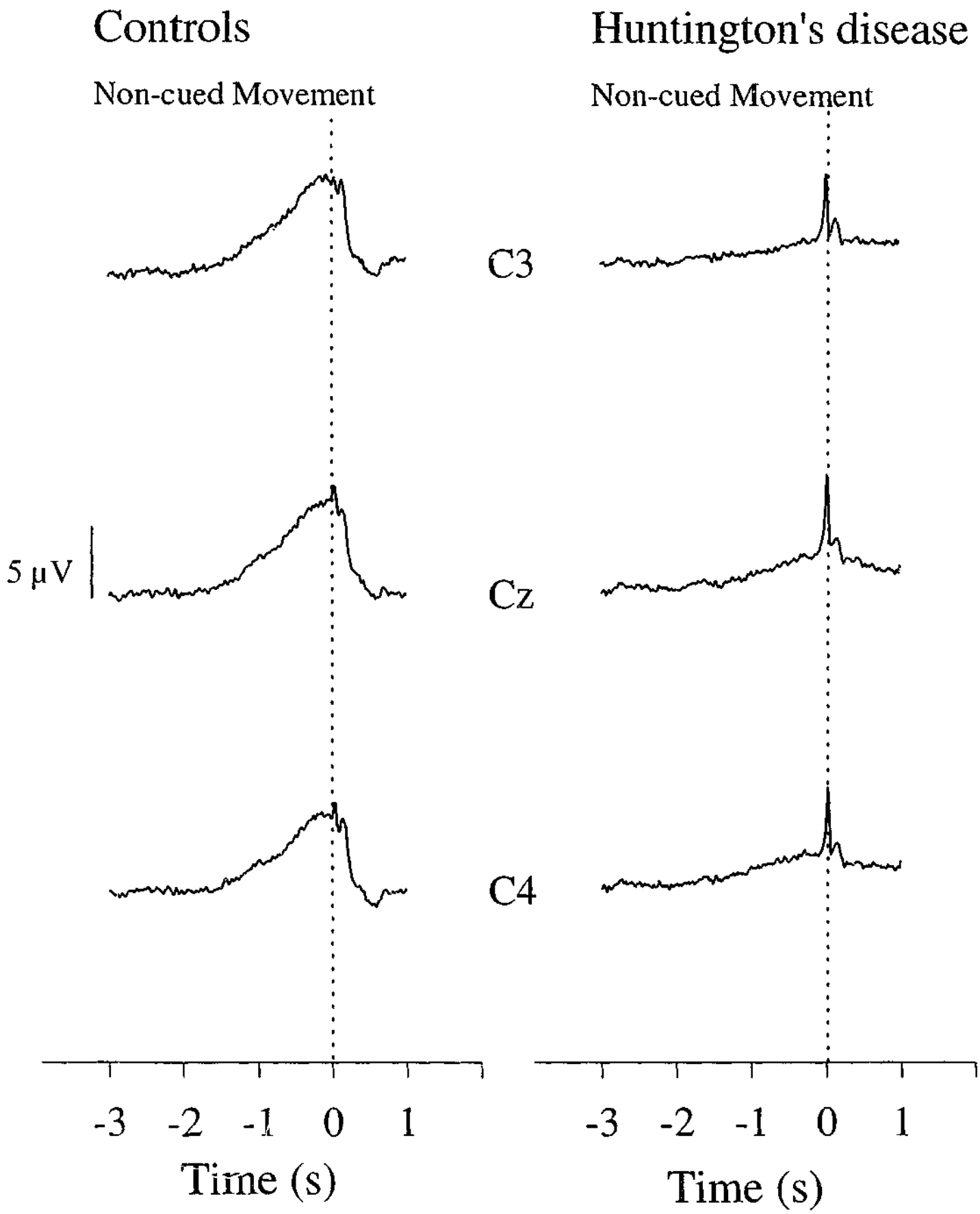


Figure 2.4: Grand average MRPs for control and Huntington's disease participants in the absence of external cues, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

The control group (mean 333, SD 180 ms) was significantly faster than the Huntington's disease group (mean 500, SD 206 ms) in how quickly the group moved from one button to the next within the sequence, [$F(1,26) = 6.416$, $p < 0.018$]. In the presence of the cue (mean 370, SD 167 ms), the Movement Time of both groups was significantly faster than in the absence of the cue (mean 463, SD 240 ms), [$F(1,16) = 9.671$, $p < 0.005$].

DISCUSSION

The Huntington's disease group produced pre-movement cortical activity that was significantly reduced in comparison with the control group, for both the cued and non-cued conditions. For both groups, the presence or the absence of the external cue had no effect on the pre-movement cortical activity. When examining the early MRP amplitudes for the Huntington's disease group in more detail, rising pre-movement activity was recorded from the Huntington's disease group without cues. With an external cue provided, however, the Huntington's disease group showed no significant level of pre-movement preparatory activity.

The SMA is believed to be particularly involved in the preparation of internally cued movement (Jenkins *et al.*, 2000; Wessel *et al.*, 1997). Huntington's disease patients showed a reduced level of activity in the pre-movement potential during the non-cued condition, a result which mirrored that of the Parkinson's disease patients (Cunnington *et al.*, 1995). This result indicates an impairment in the SMA contribution to motor preparatory activity in Huntington's disease, a finding which concurs with recent PET studies (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997).

Interestingly, the Cunnington *et al.* (1995) study found a significant main effect of cue, such that in the absence of the external cue the pre-movement activity was significantly greater than in the presence of the cue, for both the control and the Parkinson's disease groups (Cunnington *et al.*, 1995). That result was not found in this experiment. Prior MRP studies of normals have also shown increasing activity prior to the movement, during the cued movement condition (Jahanshahi *et al.*, 1995). The control group may have internally modelled the movement intuitively in the cued condition, producing an increase in activity. This concept is explored in Chapters Three and Four. In contrast with the control group, no significant amount of pre-movement activity was recorded

from the Huntington's disease group, as was also the case with Parkinson's disease (Cunnington *et al.*, 1995) for the same task. The movement preparation may have been made in areas other than those believed to be recorded in the MRP (Deiber *et al.*, 1991; Ohara *et al.*, 2000; Okano and Tanji, 1987).

It is known that external cueing particularly helps Parkinson's disease movement performance, and this knowledge has been used to develop rehabilitation strategies (Iansek, 1999). It is unclear as to why these spatial and timing cues should benefit movement. It may be that Parkinson's disease patients rely on external cues as a compensatory mechanism to bypass the dysfunctional basal ganglia motor pathway and so utilise the lateral premotor area (Deiber *et al.*, 1991; Mushiake *et al.*, 1991).

The lateral premotor area is believed to be involved in a similar way to the SMA in the preparation of movement, but to receive striatal input from anatomically and functionally different areas than the SMA (Hoover and Strick, 1993). It may participate more in preparing movements that are externally rather than internally cued, e.g. (Halsband *et al.*, 1993; Halsband and Passingham, 1985; Mushiake *et al.*, 1991; Okano, 1992). This area is activated to a greater degree in Parkinson's disease patients than in controls, during unimanual finger sequencing tasks that are externally cued (Samuel *et al.*, 1997), and may be used in a compensatory manner (Praamstra *et al.*, 1996). In contrast, the lateral premotor areas show considerable impairment in Huntington's disease (Bartenstein *et al.*, 1997).

An area that may become important in Huntington's disease is the parietal motor area. This area may be involved in spatial aspects or motor-sensory integration of movement tasks (Bradshaw and Mattingley, 1995). Neurons in this area selectively respond to rotation of upper limb joints (Bartenstein *et al.*, 1997). As the complexity or choice of a movement increases, so does the activation of this region (Böecker *et al.*, 1998; Deiber *et al.*, 1991). In Huntington's disease these areas are hyperactive (Bartenstein *et al.*, 1997), suggesting possible recruitment of additional areas. Research utilizing externally and internally cued movement, with whole brain scanning, would further elucidate these issues in Huntington's disease.

In conclusion, this study has shown for the first time the MRP produced by Huntington's disease patients in the presence and absence of external cues. These results suggest a reduction in movement preparatory activity in Huntington's disease in

both the presence and absence of external cueing. This possibly reflects impairment in SMA activity, as is the case in Parkinson's disease. Areas other than the SMA may have been involved in movement preparation in this disease, leading to compromised preparation of movement.

Chapter Three - The effect of an attentional strategy on MRPs recorded from participants with Huntington's disease

Many researchers have documented the reliance upon external cues for improved motor performance by patients with Parkinson's disease. Of particular interest is the recent observation that such performance significantly improves in the absence of external cues but with attention directed to the task. Selective attention appears to be relatively spared in Parkinson's disease (Lee *et al.*, 1999), and has been used as an effective strategy for rehabilitation in a number of motor contexts.

Morris and colleagues demonstrated that stride length, cadence, double-limb-support duration and velocity of patients with Parkinson's disease significantly improved when patients were asked to concentrate on walking to a normal footstep pattern, without the aid of external cues (Morris *et al.*, 1996). This improvement was as considerable as when patients walked over floor markers set out at normal footstep lengths. However, when a secondary task was introduced, so that whilst walking with the rehabilitation strategy in mind, the patients also recited sentences of increasing levels of complexity, gait performance declined to the hypokinetic gait typical of the disease. Thus when attention was shifted away from the primary task of walking, parkinsonian performance reappeared.

Directed attention also improves handwriting in Parkinson's disease. Micrographia improved when attention was drawn to the task by asking patients to write in a larger font size (Oliveira *et al.*, 1997). Directed attention also improved speech volume in Parkinson's disease. If attention was drawn to the hypophonic nature of parkinsonian speech, via experimenter instruction, people with Parkinson's disease were able to modulate reading volume in a fashion similar to controls (Ho *et al.*, 1999).

External cues may draw attention to the task (Morris *et al.*, 1996; Cunnington *et al.*, 1999). Attention may improve movement production through the use of conscious control mechanisms, if more automatic control systems are affected by disease (Marsden and Obeso, 1994). The parkinsonian improvement seen in response to external cues may be due to attention being drawn to the task parameters required to complete the task normally, rather than to any specific quality of the cue itself.

Parkinson's disease patients may be more adept than controls in using visual information to facilitate movement initiation (Praamstra *et al.*, 1998).

Of particular interest is the finding that when an attentional strategy, to prepare and model the movement in advance, is provided to Parkinson's disease patients, the cortical preparatory activity recorded prior to the movement significantly increases (Cunnington *et al.*, 1999).

It is unknown whether the provision of an attentional strategy will improve the motor performance of people with Huntington's disease on tasks that would normally be under automatic control. Huntington's disease patients perform automatic movements in a bradykinetic fashion, somewhat similar to patients with Parkinson's disease. The provision of an appropriate strategy could greatly benefit these patients. Of concern, however, is the greater cortical atrophy associated with this disease (Sprengelmeyer *et al.*, 1995; Vonsattel and DiFiglia, 1998). Huntington's disease patients show attentional impairments in cognitive tasks that require sequential, automatic processing, which may be attributed to striatal damage (Lawrence *et al.*, 1998). They also show impairments in internally cueing shifts in attention to particular aspects of a task, in the absence of external information (Georgiou *et al.*, 1997). From previous studies on attentional impairments associated with the disease, however, it appears that Huntington's disease patients should be able to shift their attention (Filoteo *et al.*, 1995), and indeed utilise an attentional strategy.

Sprengelmeyer *et al.*, (1995) asked participants to press a switch whenever a particular target appeared on the screen, amongst various stimuli (Sprengelmeyer *et al.*, 1995). In one condition, an auditory cue warned when a stimulus was due to appear, in another the stimulus appeared without warning. The Huntington's disease patients were impaired in their reaction time when there was no warning prior to the stimulus. They were able, however, to shift their attention in response to the auditory cue, subsequently improving reaction time. Georgiou *et al.* (1997) investigated the use of vision as a mechanism of directing attention to a stimulus-response button-pressing task. Huntington's disease patients reacted more quickly when a vibrotactile stimulus occurred on the visually attended hand (Georgiou *et al.*, 1997). Both of these studies indicate that Huntington's disease patients are able to utilise attention and external information to improve their movements.

This experiment investigated the effects of an attentional strategy upon the cortical activity relating to the preparation of movement in Huntington's disease, in the presence of an external cue. It is unknown if patients with Huntington's disease can utilise an attentional strategy, and what effect this strategy would have on the pre-movement cortical activity.

METHOD

Participants

Twelve Huntington's disease patients (11 male, 1 female), aged 37 - 62 years (mean age 52.5, SD 8.5 years) and twelve control participants (10 male, two female), aged 37- 66 years (mean age 52.6, SD 8.9 years), were tested. All were right-handed (Patterson and Bradshaw, 1975).

The diagnosis of Huntington's disease was confirmed by CAG repeat length (Huntington's Disease Collaborative Research Group, 1993) for 5 of the participants, whose CAG repeat lengths varied from 42-44. One other Huntington's disease participant had two family members with CAG lengths above 40. The other Huntington's disease participants had family histories of Huntington's disease; a psychiatrist confirmed diagnosis.

The Huntington's disease patients were assessed on the UHDRS (Huntington Disease Group, 1996), and scored between 3 and 56 (mean UHDRS score 26.83, SD 18.42). On the Shoulson and Fahn rating scale (Shoulson and Fahn, 1979), all patients scored between 0 and 2.5. The duration of disease of the Huntington's disease group varied between one and sixteen years, (mean duration of disease 5.58, SD 4.12 years).

Participants were screened for dementia using the STMS (Kokmen *et al.*, 1987) and their depression levels were assessed using the MAS (Yesavage *et al.*, 1983). The Huntington's disease group (mean MAS score 7.67, SD 5.55) did not significantly differ from the control group (mean MAS score 3.67, SD 3.92).

Participants were not withdrawn from their medication. Clinical data are shown in Table 3.1. Informed consent was obtained from each participant in accord with the Helsinki declaration and all experimental work was carried out under the approval of

Table 3.1: Clinical data for Huntington's disease patients.

Participant	Age (years)	Sex	Duration of disease (years)	STMS	MAS	Medication	Dose (mg/day)	UHDRS motor subscale	Triplet repeat score
1	60	M	8	37	0	-	-	31	42
2	54	M	8	31	8	Tetrabenazine	75	48	43
3	37	M	4	30	11	Carbamazepine Thioridazine	300 35	56	
4	58	M	16	35	7	-	-	55	**
5	57	M	5	36	4	-	-	3	
6	44	M	3	35	11	-	-	19	44
7	47	M	1	36	4	Sertraline hydrochloride	100	15	42
8	47	M	3	36	0	-	-	11	43
9	40	M	1	32	11	-	-	24	
10	55	M	8	36	18	-	-	34	
11	61	F	4	34	14	-	-	4	
12	62	M	6	33	4	-	-	22	

Notes: Dashes indicate that the participant was not taking medication.
STMS – Short Test of Mental Status
MAS – Mood Assessment Scale
UHDRS – Unified Huntington's Disease Rating Scale
** HD participant had two family members with confirmed CAG lengths above 40.

the Kingston Centre Research and Ethics Committees and the Monash University Standing Committee on Ethics in Research on Humans.

Procedure

Participants performed a right-handed, sequential, choice, button-pressing task using the tapping board, as described in Chapter Two. The same ten-button pathway was used for both conditions of the experiment (see Figure 2.2). The pathway on the tapping board was fully illuminated and lights underneath the buttons were extinguished four seconds after the release of the previous button in the pathway.

All participants were tested in two conditions, in a repeated-measures design. The movement required for both conditions was exactly the same; the only difference was the instruction given by the experimenter.

Strategy condition

Participants were asked to press, as quickly as possible, the next button in the sequence once the light went out under the button they were presently pressing. The participants were also asked to anticipate the extinction of the LED light by timing four seconds, and to prepare for the next movement. The exact instructions were: "The light will go off 4 seconds after your previous movement. Try to time the interval yourself and try to anticipate when the light will go off so that when the light goes off you are ready to move".

No strategy condition

Participants were asked to press, as quickly as possible, the next button in the sequence once the light went out under the button they were presently pressing. No instruction was given regarding anticipation of the light going out, nor about preparing the next movement. The exact instructions were: "Hold down each button until the light underneath goes off, then move as quickly as possible to press the next button in the sequence."

Testing in each condition was counterbalanced. Half the participants in each group were tested in the strategy condition first and a time delay was introduced before testing in the no-strategy condition, to prevent carry-over effects. Of the six controls who were tested in the strategy condition first, a mean delay of 136 (SD 83) days was introduced

before the no strategy condition: for the six Huntington's disease participants, there was a mean delay of 150 (SD 75) days. There was no significant difference with respect to the number of days delay between the two groups, $t(10) = 0.304$, $p > 0.05$. For the other half of the participant pool, the no-strategy condition was followed by the strategy condition, within the same testing session.

The methodology involved in recording the MRPs was described in Chapter Two. Characteristics of average potentials and subtracted functional components for each participant in each condition were quantified by the following measures.

Early Slope

The average slope of the potential, over the period from 1500 to 500 ms prior to movement onset, was calculated using linear regression. This is a measure of neural activity relating to the early component of the MRP.

Movement Time

This is a measure of the time taken to move from the release of one button to the depression of the next button in the sequence.

All measures were analyzed by ANOVA (mixed factorial with unweighted means), *t* tests and post-hoc tests where appropriate.

RESULTS

Mean MRPs for the Huntington's disease patients and the controls, for the strategy and non-strategy conditions, recorded at electrode sites Cz, C3 and C4, are shown in Figures 3.1, 3.2 and 3.3. Qualitatively, the Huntington's disease group's mean MRP for the strategy condition showed increasingly negative pre-movement activity, which was in contrast with the very reduced pre-movement activity recorded from the non-strategy condition. The difference between the two conditions for the control group was not great. The greatest activity was always recorded at electrode site Cz. Therefore the quantitative statistics were confined to the recordings from site Cz. Single sample *t*-tests were used to indicate whether the pre-movement preparatory activity, recorded from electrode Cz, significantly differed from zero. The control group's mean MRPs for the strategy (mean 5.90, SD 2.78 μV/s) [$t(11) = 7.341$, $p < 0.001$] and non-strategy (mean 3.40, SD 1.83 μV/s) [$t(11) = 6.426$, $p < 0.00$] conditions showed significantly

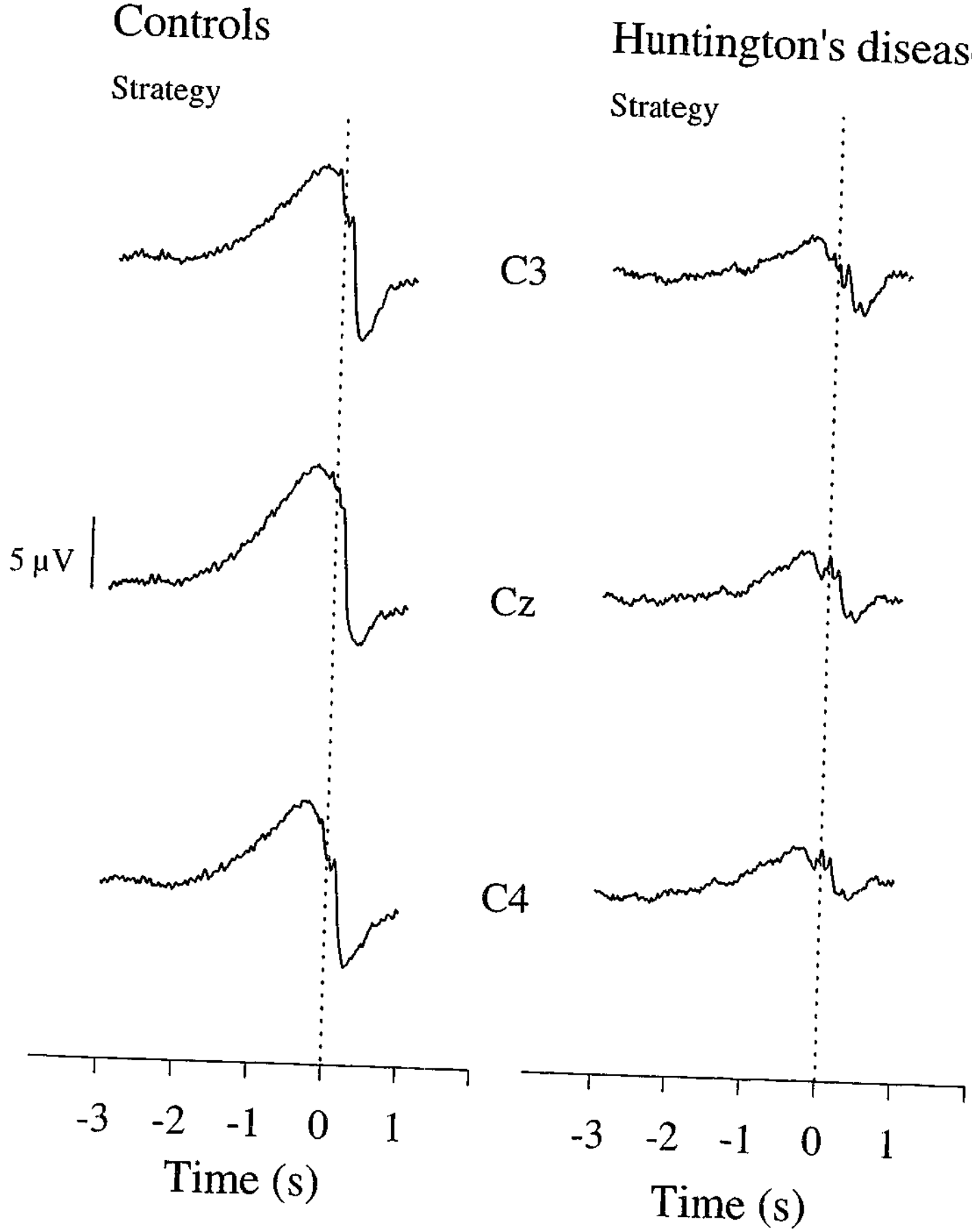


Figure 3.1: Grand average MRPs for control and Huntington's disease participants in the presence of a strategy, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

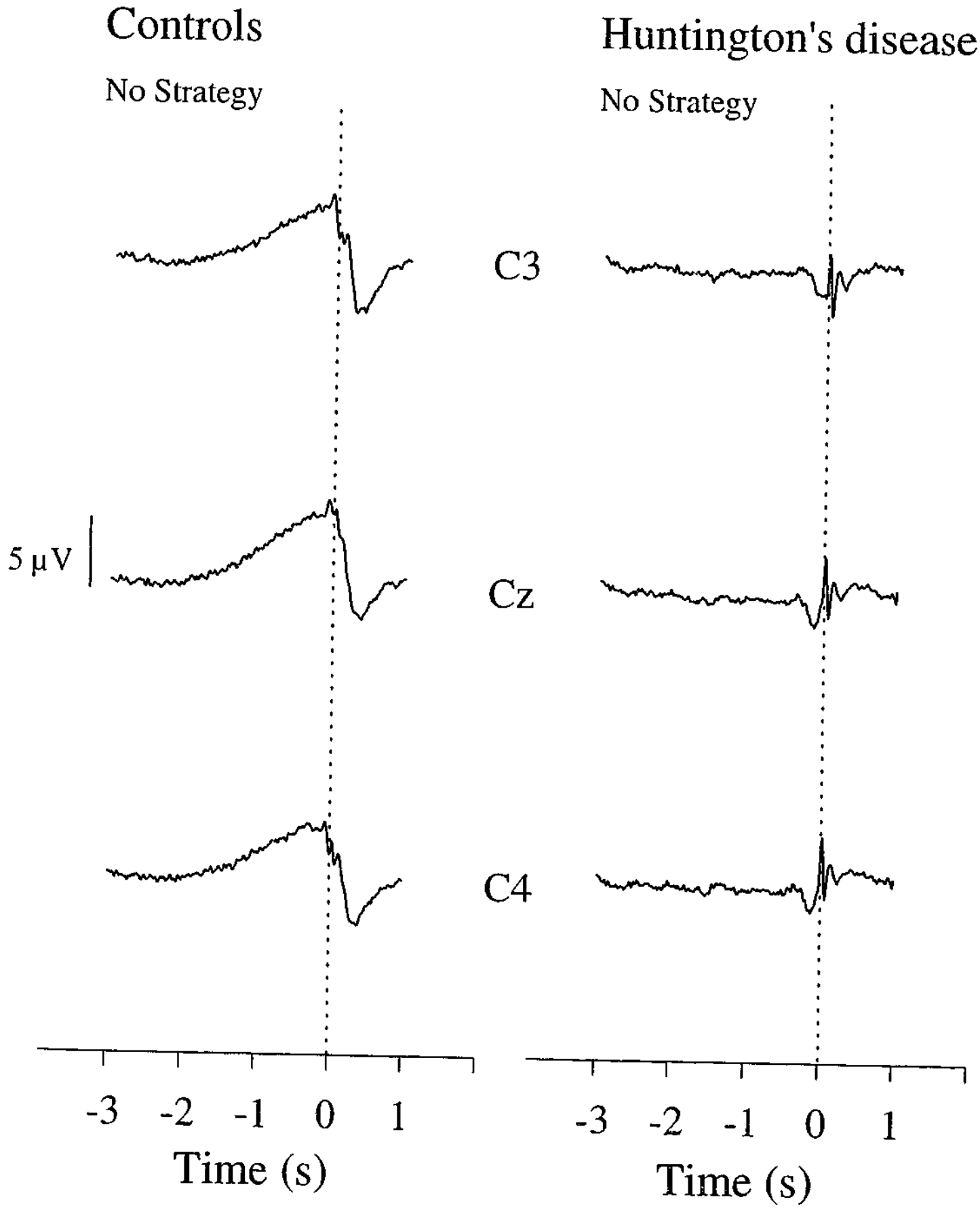


Figure 3.2: Grand average MRPs for control and Huntington's disease participants in the absence of a strategy, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

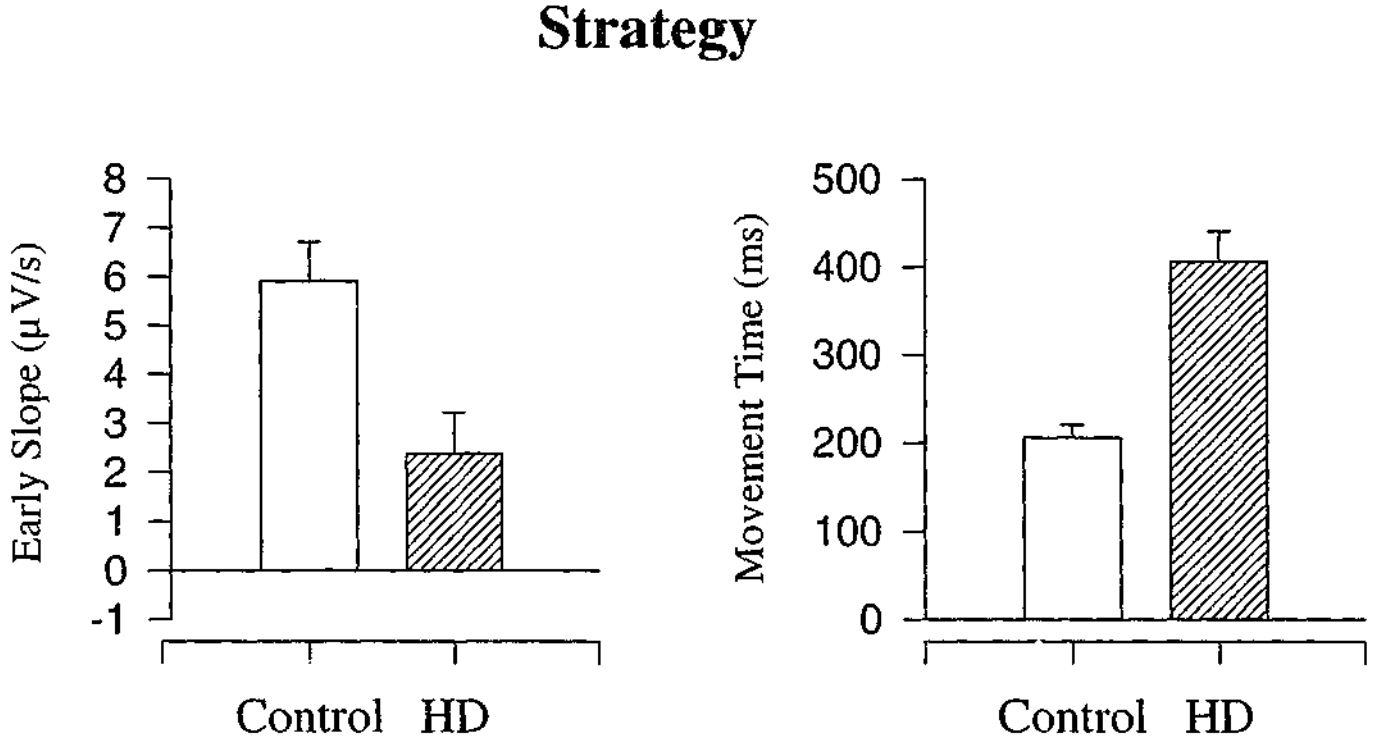


Figure 3.3: Means and standard errors of the Early Slope and Movement Time of the control and Huntington's disease participants, in the presence and absence of the strategy.

increasing pre-movement activity prior to movement. The Huntington's disease group clearly showed increasing pre-movement activity before movement for the strategy condition (mean 2.37, SD 2.89 μV/s) [$t(11) = 2.844$, $p < 0.016$], but no level of pre-movement preparatory activity for the non-strategy condition (mean –0.11, SD 1.71μV/s) [$t(11) = -0.222$, $p > 0.05$].

The control group (mean 4.65, SD 2.63 μV/s) produced a significantly greater early slope at position Cz than the Huntington's disease group (mean 1.13, SD 2.65 μV/s), [$F(1,22) = 24.968$, $p < 0.001$]. For both groups, the use of an anticipatory strategy had a significant effect on the pre-movement preparatory activity. With the use of the strategy, the early slope was significantly greater (mean 4.14, SD 3.31 μV/s) than when no strategy was employed (mean 1.64, SD 2.49 μV/s), [$F(1,22) = 14.188$, $p < 0.001$]. When either group was given an anticipatory strategy there was a significant improvement in the pre-movement preparatory activity. There was no significant interaction between group and usage of strategy.

The strategy did not have a significant effect on Movement Time, for either group, and there were no interactions between group and usage of strategy, although the control group (mean 230, SD 76 ms) moved significantly faster than the Huntington's disease group (mean 404, SD 104 ms) from one button to the next in the sequence, [$F(1,22) = 26.528$, $p < 0.001$], see Figure 3.3.

The severity of Huntington's disease, as rated by the UHDRS, correlated with the Movement Time in the no strategy condition [$r(10) = 0.653$, $p < 0.041$], indicating that the more severe the effects of the disease on an individual, the slower their Movement Time. When the strategy was provided, there was no correlation between the UHDRS and Movement Time.

The possible carry-over effects of the order of the conditions performed by each participant were analyzed by listing Order as a between-subjects factor in three-way ANOVAs. There were no effects involving Order, for Early Slope or Movement Time.

DISCUSSION

Without the attentional strategy the Huntington's disease patients failed to produce a rising pre-movement potential, a finding which concurred with the cued results of Chapter Two. Interestingly, with the attentional strategy, there was a significant

increase in the pre-movement activity of the Huntington's disease group. The only difference between the two conditions was the slight alteration in instructions by the experimenter for the strategy condition - "Anticipate the extinction of the LED light and prepare for the next movement."

The data from the Huntington's disease group contrasted with those of the control group. Like the Huntington's disease group, the attentional strategy also led to a significant increase in pre-movement activity of the control group. Without the attentional strategy, however, the control group still produced a rising pre-movement potential, in accord with the cued results of Chapter Two.

The results of the control group, in comparison with the Huntington's disease group, raise some interesting issues. In the non-strategy (cued) condition, the increase in pre-movement activity suggested that the control group was internally preparing the movement, possibly engaging areas such as the SMA. When the strategy was given, there was a significant increase in the pre-movement activity for the control group. This control group was able to utilise the strategy, possibly additionally modelling the movement internally, and subsequently increasing pre-movement preparatory activity. The control data from this experiment is in contrast with the control data for the Parkinson's disease study (Cunnington *et al.*, 1999), where there was no difference between the strategy and no strategy conditions in the early slope of the pre-movement potential. With an average age of 67.3 years, the control group for the Parkinson's disease group was approximately 15 years older than the control group for this study. The effect of age and the ability to utilise a strategy to significantly improve the pre-movement cortical activity is unknown, and should be investigated further.

The pre-movement activity recorded from the Huntington's disease group in the non-strategy condition was negligible, and there appeared to be little inherent modelling of the required movement. The medial motor system was possibly bypassed, in favor of some other system, to produce the desired movement. When the attentional strategy was given, a rising pre-movement potential was recorded in the Huntington's disease group, even though the movement was externally cued. Similar processes appeared to be operating for both the control and the Huntington's disease groups, as both groups were able to make use of the strategy. This process appears to be intact in Huntington's disease, at least in the early to middle stages of the disease.

The attentional strategy was successful in increasing the cortical activity related to the preparation of movement in Huntington's disease. The strategy may have put the task under attentional control, which previously might have been under deficient automatic control. For instance, metronome pacing may draw attention to the timing required of a task; the visual light cue may draw attention to spatial aspects. Such findings have potentially important implications for developing possible rehabilitation techniques in Huntington's disease.

The presence of the strategy had no effect on the Movement Time for either group. This result is not surprising, as the instructions for both conditions were to move as quickly as possible. As expected, the control group was significantly faster than the Huntington's disease group in how quickly they moved from one button to the next on the sequential pathway.

In this experiment, movements were always externally cued. The interaction between the provision of external cues and attentional strategies has not been investigated systematically, in either Parkinson's disease or in Huntington's disease. This was the basis of Chapter Four.

Chapter Four - The interaction between external and internal cueing and an attentional strategy on MRPs in Huntington's disease

Control participants may pre-attentively model voluntary movement (Morris *et al.*, 1996), preparing and anticipating the up-coming movement in a top-down process, facilitating speed and accuracy. This process may occur during both cued and non-cued conditions.

Pre-movement potential studies have shown that cortical preparatory activity is greatest for *non-cued, predictably* timed movements (Cunnington *et al.*, 1995; Jahanshahi *et al.*, 1995). The SMA, as one generator of the pre-movement potential, is believed to be particularly involved in sub-movement timing of predictable (Deecke *et al.*, 1985; Gerloff *et al.*, 1997), in comparison with unpredictably timed movements (Cunnington *et al.*, 1995; Halsband *et al.*, 1993; Lang *et al.*, 1990). It is also thought to be especially involved in non-cued movements, relative to those cued (Gerloff *et al.*, 1997; Tanji and Shima, 1994). The absence of the cue will force the individual to self-time and spatially self-guide the movement. The individual may internally model the movement via top-down processing, and prepare the movement in advance, possibly via the medial motor circuit with involvement from the CMA (Ball *et al.*, 1999).

Control participants also show pre-movement activity prior to externally *cued, predictably* timed movements (Cunnington *et al.*, 1995). In the presence of the cue, the individual may simply be reacting to the stimulus, which may invoke bottom-up processing. As the condition involves predictable timing however, the individual may, in a similar fashion to the non-cued condition, be internally modelling and automatically timing the movement as well as relying on the external cue. During the cued condition, pre-movement activity is often reduced, in comparison with the non-cued condition (Cunnington *et al.*, 1995), although the size of the difference is debatable (Jahanshahi *et al.*, 1995; Praamstra *et al.*, 1998). This may indicate that the medial motor system is involved in the preparation of that movement but is joined by other systems in parallel, such as the cerebellum-lateral premotor system (Mauk *et al.*, 2000).

The cortical activity recorded during cued and non-cued predictably timed conditions is significantly reduced in both Parkinson's and Huntington's disease patients, suggesting

that these patients do not intuitively model the movement (Cunnington *et al.*, 1995; Chapter Two). Parkinson's disease patients may be less likely than control participants to adopt a pre-programming strategy (Berger *et al.*, 1999; Jahanshahi *et al.*, 1992). It is unknown, but is thought to be unlikely, whether Huntington's disease patients intuitively adopt pre-programming strategies. During non-cued conditions, these patient groups will be forced to self-time and spatially self-direct the movement, potentially invoking the dysfunctional medial motor circuit, consequently resulting in reduced pre-movement cortical activity (Cunnington *et al.*, 1995; Chapter Two).

During cued conditions, the Parkinson's and Huntington's disease patients may be responding to the cue in a bottom-up, reactive fashion with no anticipation of the forthcoming movement (Praamstra *et al.*, 1996). Parkinson's disease patients appear to have trouble using an internal representation of action, and to have trouble anticipating or predicting the next movement in a sequence, and so use external cues to guide movement (Flowers, 1978a). Subsequently, in a cued, predictably timed condition, there is no or reduced pre-movement activity recorded from the Parkinson's disease group (Cunnington *et al.*, 1995; Praamstra *et al.*, 1998). Other pathways, such as the lateral premotor area may be involved in the preparation of the movement (Samuel *et al.*, 1997).

Huntington's disease patients do not appear to rely on external cues to guide movement to the same extent as Parkinson's disease patients (Churchyard *et al.*, 2000; Johnson *et al.*, 2000), possibly because of damage to the lateral premotor area (Bartenstein *et al.*, 1997). It is unclear how the Huntington's disease patients prepare their movements in the presence of external cues, but the parietal motor area may instead be involved in the preparation of movement (Johnson *et al.*, 2000). The Huntington's disease patients, like the Parkinson's disease group, produced no pre-movement activity during the cued condition in Chapter Two.

When a strategy is introduced to attend consciously to anticipating the cue and generate a response internally, there is a significant improvement in the pre-movement potential in Parkinson's (Cunnington *et al.*, 1999) and Huntington's (Chapter Three) diseases, in the presence of the external cue. As Cunnington *et al.* (1999) argues, the presence of the external cue may not of itself be so important in improving motor performance in Parkinson's disease, but it may instead be the underlying cognitive strategy used by the

patients which is the critical difference (Cunnington *et al.*, 1999). The strategy may invoke more conscious cortical control mechanisms, possibly alleviating the burden from the dysfunctional basal ganglia motor pathway; this cortical activity would still contribute to the pre-movement potential. Control participants may inherently use an internal model of movement (the strategy) regardless of the presence or absence of the external cue. The Parkinson's and the Huntington's disease patients may need the external cue to facilitate usage of the strategy. This point, however, has not been tested experimentally.

If the Huntington's disease group is asked to generate internally a movement response using the cognitive strategy, it is unclear what effect the presence or absence of the external cue will have on the pre-movement activity. In a comparison of the presence or absence of the external cue, the strategy would be altered to state: "concentrate on preparing the response". The external cue may provoke better concentration and enhance usage of the strategy, leading to an improved pre-movement potential. The absence of the external cue may invoke the medial motor system, also leading to an improved pre-movement potential in comparison with the non-strategy conditions. Thus Chapter Four asked whether the external cue facilitates usage of the strategy.

Patients with Huntington's disease were tested under four conditions, covering the presence and absence of the external cue and the cognitive strategy. The four conditions were:

Condition 1 With a strategy and with external light cues

Condition 2 With no strategy and with external light cues

Condition 3 With no strategy and no external light cues

Condition 4 With a strategy and no external light cues

METHOD

Participants

Nine Huntington's disease patients (7 male, 2 female), aged 44 - 63 years (mean age 54.5, SD 6.9 years), and nine control participants (7 male, 2 female), aged 39- 59 years (mean age 51.1, SD 6.8), were tested. All were right-handed (Patterson and Bradshaw, 1975).

The diagnosis of Huntington's disease was confirmed by CAG repeat length (Huntington's Disease Collaborative Research Group, 1993) for 5 of the participants, and their CAG repeat lengths varied from 42-44. One other Huntington's disease participant had two family members with CAG lengths above 40. The remaining Huntington's disease participants had family histories of the disease, were assessed and a psychiatrist confirmed diagnosis.

The Huntington's disease patients were assessed on the UHDRS (Huntington Disease Group, 1996), and scored between 3 and 55 (mean UHDRS score 25.56, SD 19.62). On the Shoulson and Fahn rating scale (Shoulson and Fahn, 1979), all patients scored between 0 and 2.5. The duration of disease of the Huntington's disease group varied between one and sixteen years, (mean duration of disease 6.22, SD 4.47 years).

Participants were screened for dementia using the STMS (Kokmen *et al.*, 1987). Depression levels were assessed using the MAS (Yesavage *et al.*, 1983), and did not vary between the two groups.

Participants were not withdrawn from their medication. Clinical data are shown in Table 4.1. Informed consent was obtained from each participant in accord with the Helsinki declaration, and all experimental work was carried out under the approval of the Kingston Centre Research and Ethics Committees and the Monash University Standing Committee on Ethics in Research on Humans.

Procedure

Participants performed a right-handed, sequential, choice, button-pressing task using the tapping board, as described in Chapter 2. The same ten-button pathway was used for all four conditions of the experiment (Figure 2.2). The four conditions varied only by the presence or absence of the strategy or the external light cue. In the cued conditions (Conditions 1 and 2), the pathway on the tapping board was fully illuminated and lights underneath the buttons were extinguished four seconds after the release of the previous button in the pathway. In the non-cued conditions (Conditions 3 and 4), the pathway was not illuminated and no cues were given as to movement timing. The movement required for all four conditions was exactly the same; the only difference was the instruction given by the experimenter, and the presence or absence of the external light cue.

Table 4.1: Clinical data for Huntington's disease patients.

Chapter Four

Participant	Age (years)	Sex	Duration of disease (years)	STMS	MAS	Medication	Dose (mg/day)	UHDRS motor subscale	Triplet repeat score
1	60	M	8	37	0	-	-	31	42
2	54	M	8	31	8	Tetrabenazine	75	48	43
3	58	M	16	35	7	-	-	55	**
4	57	M	5	36	4	-	-	3	
5	44	M	3	35	11	-	-	19	44
6	47	M	1	36	4	Sertraline	100	15	42
7	47	M	3	36	0	-	-	11	43
8	61	F	4	34	14	-	-	4	
9	63	F	8	33	15	-	-	44	

Notes: Dashes indicate that the participant was not taking medication.
STMS – Short Test of Mental Status
MAS – Mood Assessment Scale
UHDRS – Unified Huntington's Disease Rating Scale
** HD participant had two family members with confirmed CAG lengths above 40.

The instructions for the four conditions were as follows:

Condition 1 (With a strategy and with external light cues) – Participants were asked to press, as quickly as possible, the next button in the sequence once the light extinguished under the button they were presently pressing. The participants were asked also to anticipate the extinction of the LED light by timing four seconds and to prepare for the next movement. The exact instructions were: "The light will go off 4 seconds after your previous movement. Try to time the interval yourself and try to anticipate when the light will go off so that when the light goes off you are ready to move".

Condition 2 (With no strategy and with external light cues) – Participants were asked to press, as quickly as possible, the next button in the sequence once the light extinguished under the button they were presently pressing. No instruction was given regarding anticipation of the light going out, nor about preparing the next movement. The exact instructions were: "Hold down each button until the light underneath goes off, then move as quickly as possible to press the next button in the sequence."

Condition 3 (With no strategy and no external light cues) – Participants were asked to press, as quickly as possible, the next button in the sequence, and to time themselves to hold down each button for at least four seconds before moving to the next button in the pathway. No instruction was given regarding anticipation of the light going out, nor about preparing the next movement. The exact instructions were: "Hold down each button for at least four seconds, then move as quickly as possible to press the next button in the sequence."

Condition 4 (With a strategy and no external light cues) – Participants were asked to press, as quickly as possible, the next button in the sequence, and to time themselves to hold down each button for at least four seconds before moving to the next button in the pathway. The participants were also asked to prepare in advance the next movement. The exact instructions were: "Hold down each button for at least four seconds, then move as quickly as possible to press the next button in the sequence. Try to time the interval yourself and prepare in advance the next movement."

The strategy conditions were always tested after the non-strategy conditions, to prevent carry-over effects, and the cued conditions were always tested before the non-cued conditions. As many of the participants were involved in the previous strategy experiments, a time delay was introduced before testing for the new experiment, to

prevent order effects. Six Huntington's disease participants (mean 111, SD 75, range: 12-166 days) and five control participants (mean 144, SD 60, range: 63-280 days) had been exposed to the strategy before testing for this experiment.

The methodology involved in recording the MRPs was described in Chapter Two. Characteristics of average potentials and subtracted functional components for each participant in each condition were quantified by the following measures.

Early Slope

The average slope of the potential, over the period from 1500 to 500 ms prior to movement onset, was calculated using linear regression. This is a measure of neural activity relating to the early component of the MRP.

Movement Time

This is a measure of the time taken to move from the release of one button to the depression of the next button in the sequence.

All measures were analysed by three-way ANOVA (mixed factorial with unweighted means) [Group by Cue by Strategy], and *t* tests where appropriate.

RESULTS

Mean MRPs for the Huntington's disease patients and the controls, for each of the four conditions, recorded at electrode sites Cz, C3 and C4, are shown in Figures 4.1 to 4.4. Qualitatively, the control group appeared to produce greater pre-movement cortical activity than the Huntington's disease group under every condition. The pre-movement activity for the control group was greatest in the condition with the strategy and external cues (condition 1), and did not appear to vary greatly between the other conditions. The Huntington's disease group showed greater pre-movement activity during the two strategy conditions (conditions 1 and 4) compared with the non-strategy conditions (conditions 2 and 3). The greatest activity was always recorded at electrode site Cz. Therefore the quantitative statistics were confined to the recordings from site Cz. Single sample t-tests were used to indicate whether the pre-movement preparatory activity, recorded from electrode Cz, significantly differed from zero. The only pre-movement activity which did not significantly differ from zero was recorded from the

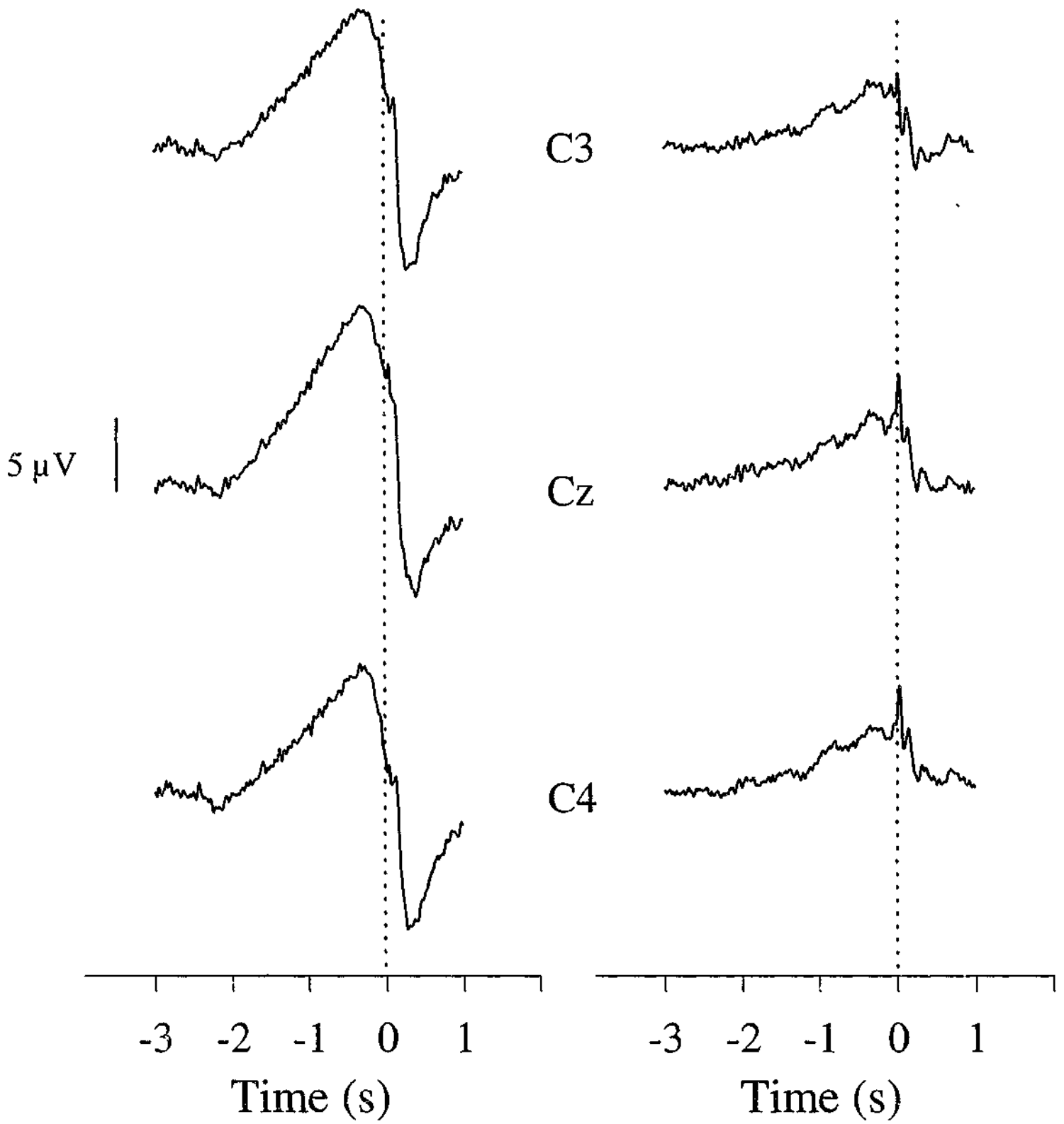


Figure 4.1: Grand average MRPs for control and Huntington's disease participants in the presence of a strategy and external cues, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

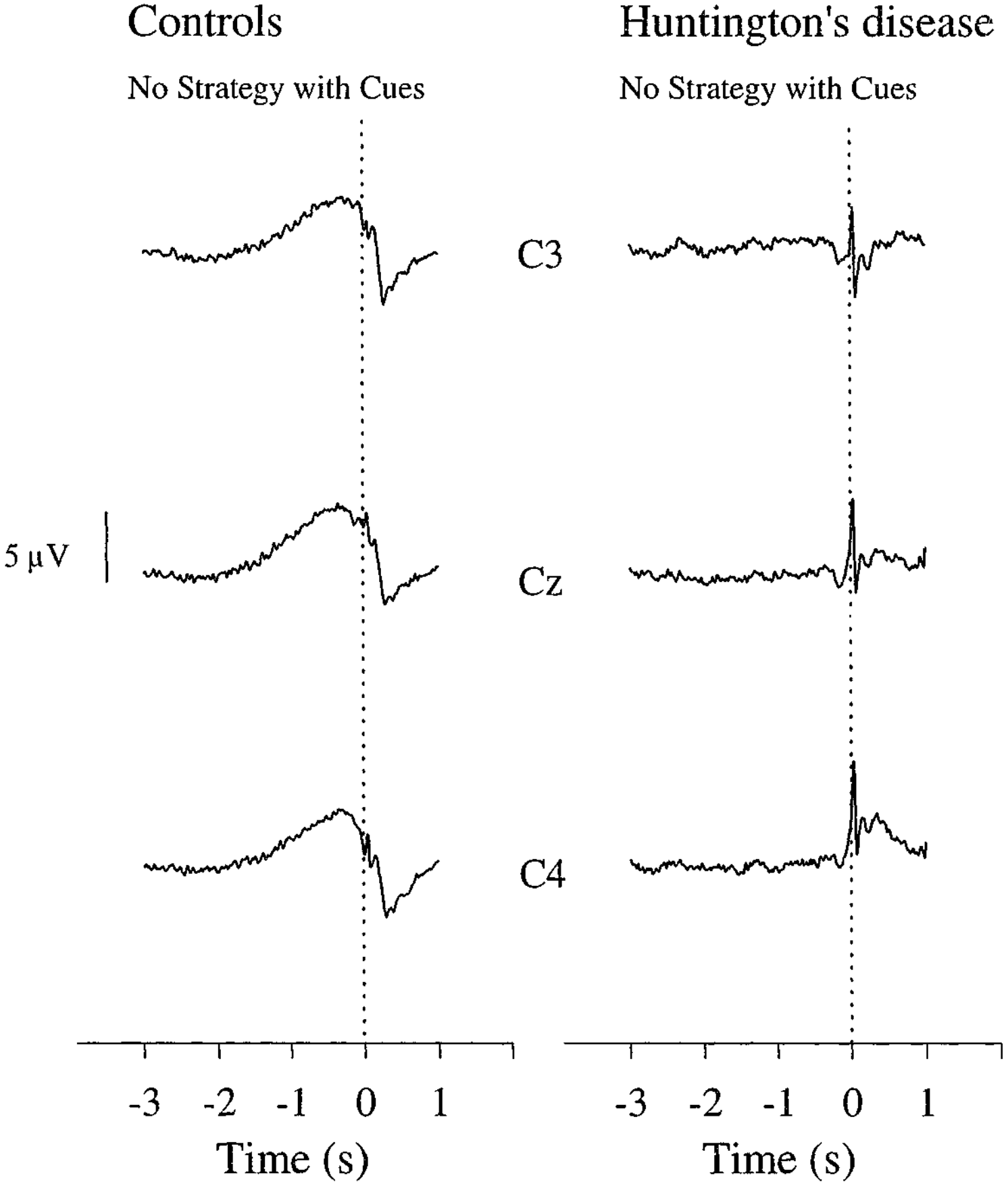


Figure 4.2: Grand average MRPs for control and Huntington's disease participants in the absence of a strategy, in the presence of external cues, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

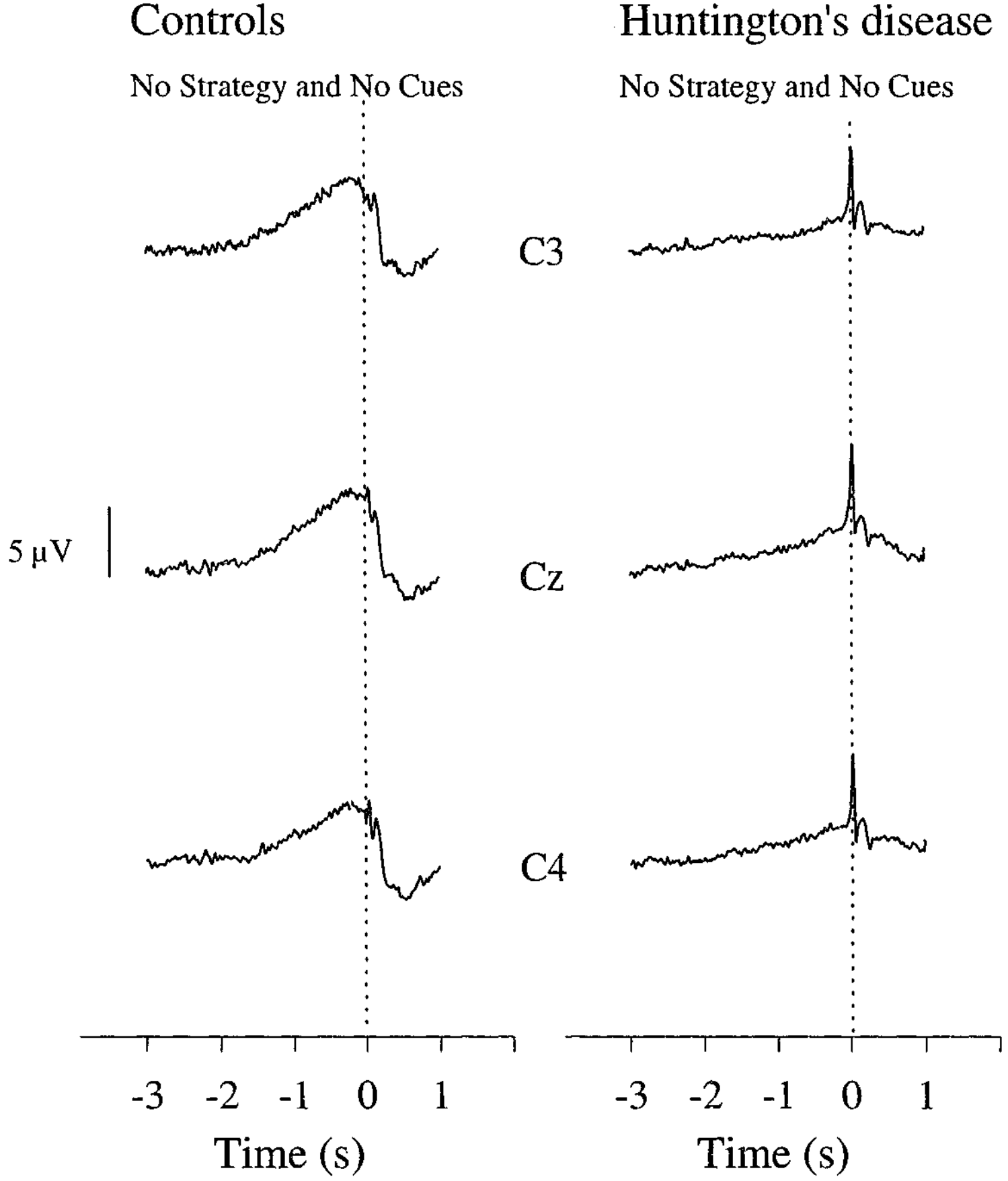


Figure 4.3: Grand average MRPs for control and Huntington's disease participants in the absence of a strategy, in the absence of external cues, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

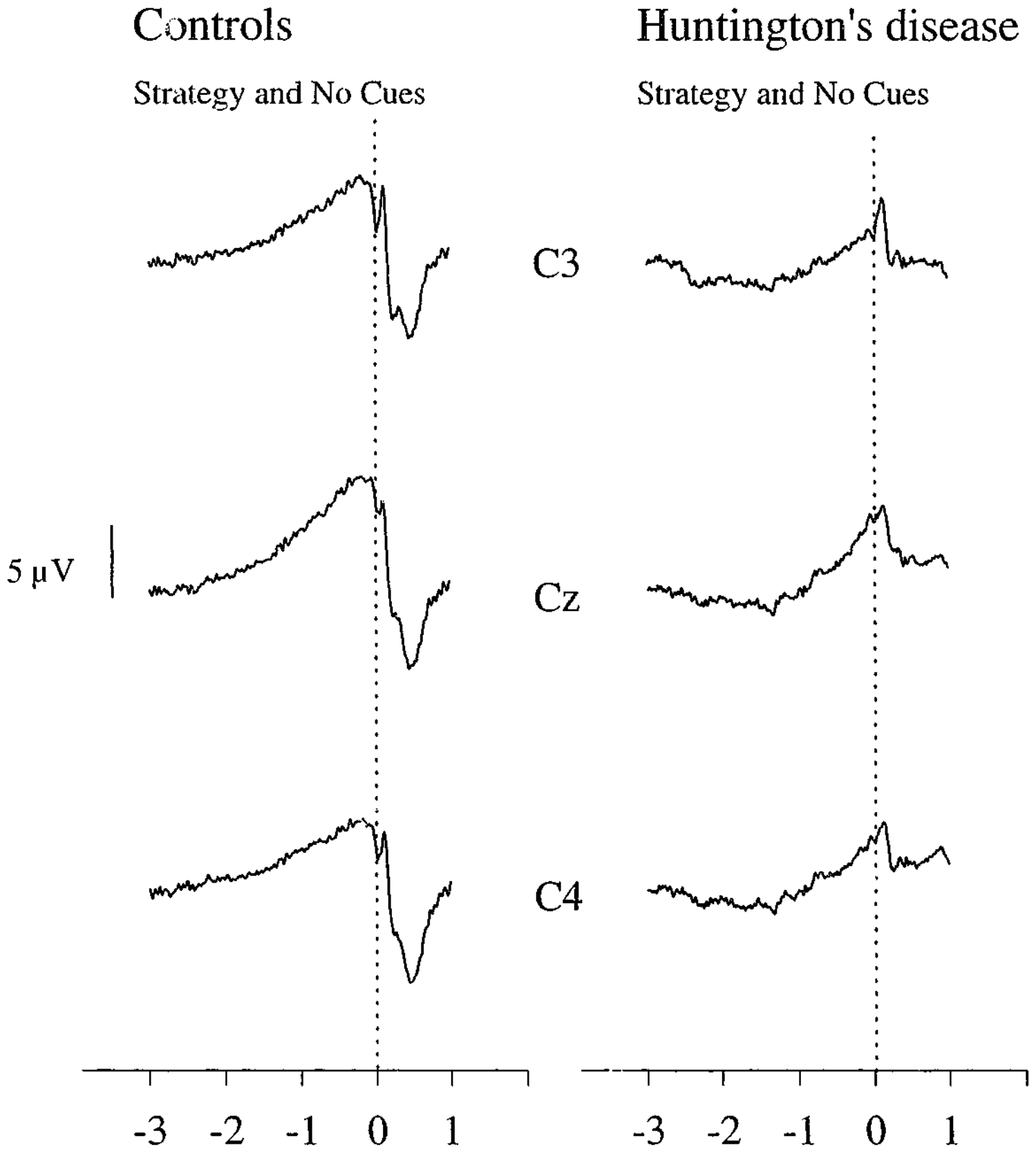


Figure 4.4: Grand average MRPs for control and Huntington's disease participants in the presence of a strategy, in the absence of external cues, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

Huntington's disease group, in the second condition (no strategy and externally cued), [$t(8) = 0.644$, $p > 0.05$].

The control group (mean 4.87, SD 3.04 μV/s) produced a significantly greater early slope at position Cz than the Huntington's disease group, analysed across all four conditions (mean 1.76, SD 2.54 μV/s), [$F(1,16) = 22.470$, $p < 0.001$], see Figure 4.5.

There was a significantly greater early slope in the presence of the strategy (mean 4.39, SD 3.6 μV/s), in comparison with the absence of the strategy (mean 2.24, SD 2.29 μV/s), analysed across all four conditions, for both groups, [$F(1,16) = 8.834$, $p < 0.009$].

There was a significant Group by Cue by Strategy three-way interaction, [$F(1,16) = 5.920$, $p < 0.027$], which was broken down by Group. There was no interaction between Cue and Strategy for the Huntington's disease group, nor was there a Cue main effect. The Cue did not have an effect on any of the four conditions for this group. There was a strong trend in the predicted direction for a Strategy main effect. In the presence of the strategy the early slope of the pre-movement potential (mean 2.75, SD 3.01μV/s) was almost significantly different from the early slope in the absence of the strategy (mean 0.76, SD 1.47 μV/s), [$F(1,8) = 4.342$, $p > 0.071$]. This effect was probably not significant because of a lack of power due to the low number of available participants. This condition was in fact significant in the study reported in Chapter Three. The significance of the three-way interaction was driven by the difference in the early slope between the conditions for the control group, which produced a significant Cue by Strategy interaction, [$F(1,8) = 10.473$, $p < 0.012$], (see Figure 4.6). In the presence of the external cue, there was a significant difference between the early slopes recorded during the strategy (mean 7.67, SD 3.62 μV/s) and the no strategy (mean 3.89, SD 2.03 μV/s) conditions, for the control group [$F(1,8) = 8.070$, $p < 0.022$]. In the absence of the external cue, the early slopes recorded during the strategy (mean 4.39, SD 2.56 μV/s) and no strategy (mean 3.53, SD 2.12 μV/s) conditions were not significantly different, [$F(1,8) = 0.731$, $p > 0.05$].

The control group (mean 281, SD 122 ms) was significantly faster than the Huntington's disease group (mean 486, SD 221 ms) in how quickly they moved from one button to the next within the movement sequence, [$F(1,16) = 6.796$, $p < 0.019$]. For both groups, the movement with the cue (mean 358, SD 179 ms) was significantly faster than the non-cued movement (mean 410, SD 227 ms), [$F(1,16) = 8.965$, $p < 0.009$].

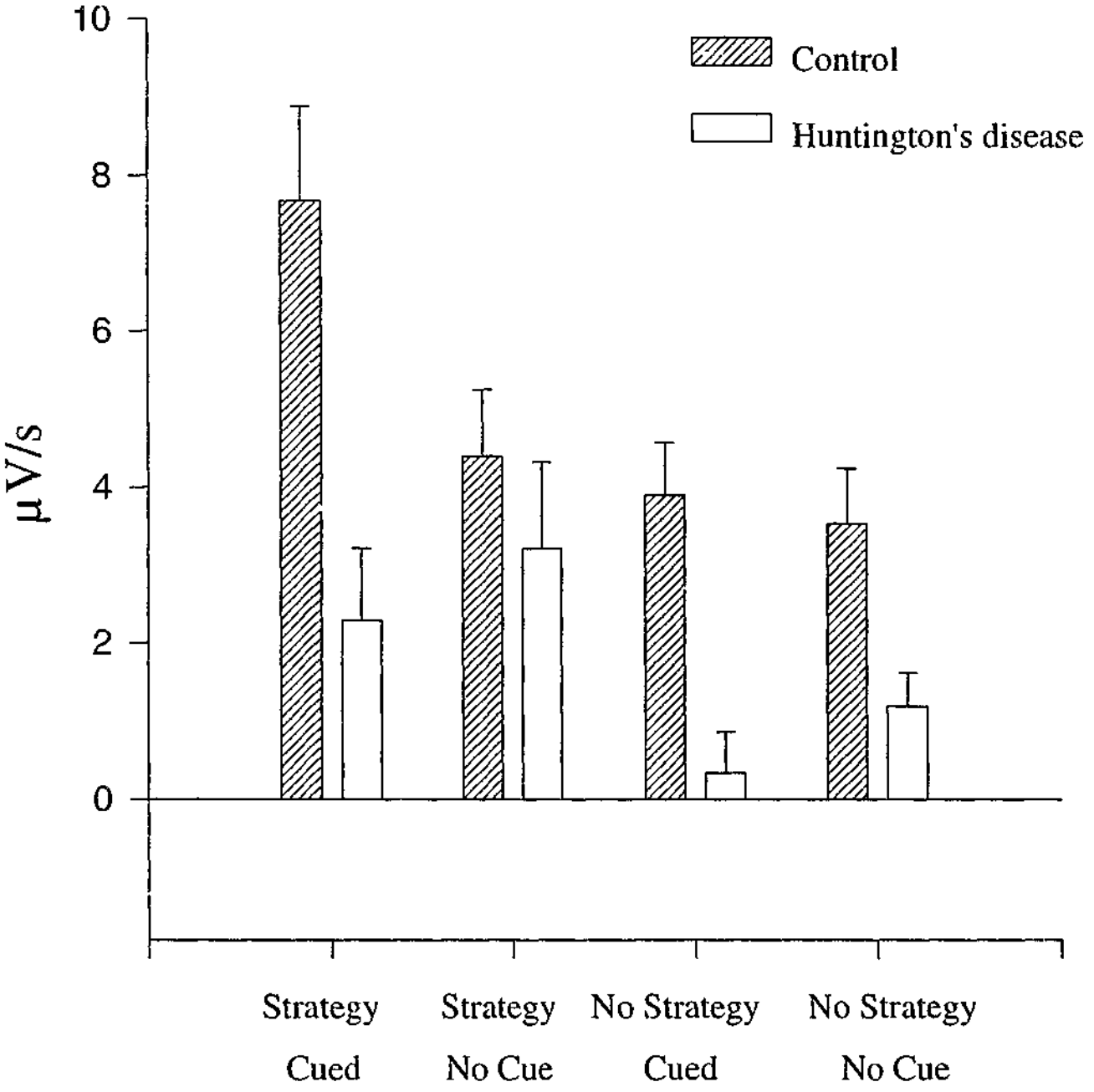


Figure 4.5: Means and standard errors of the Early Slope of the control and Huntington's disease participants, in the presence and absence of the strategy and the external cues.

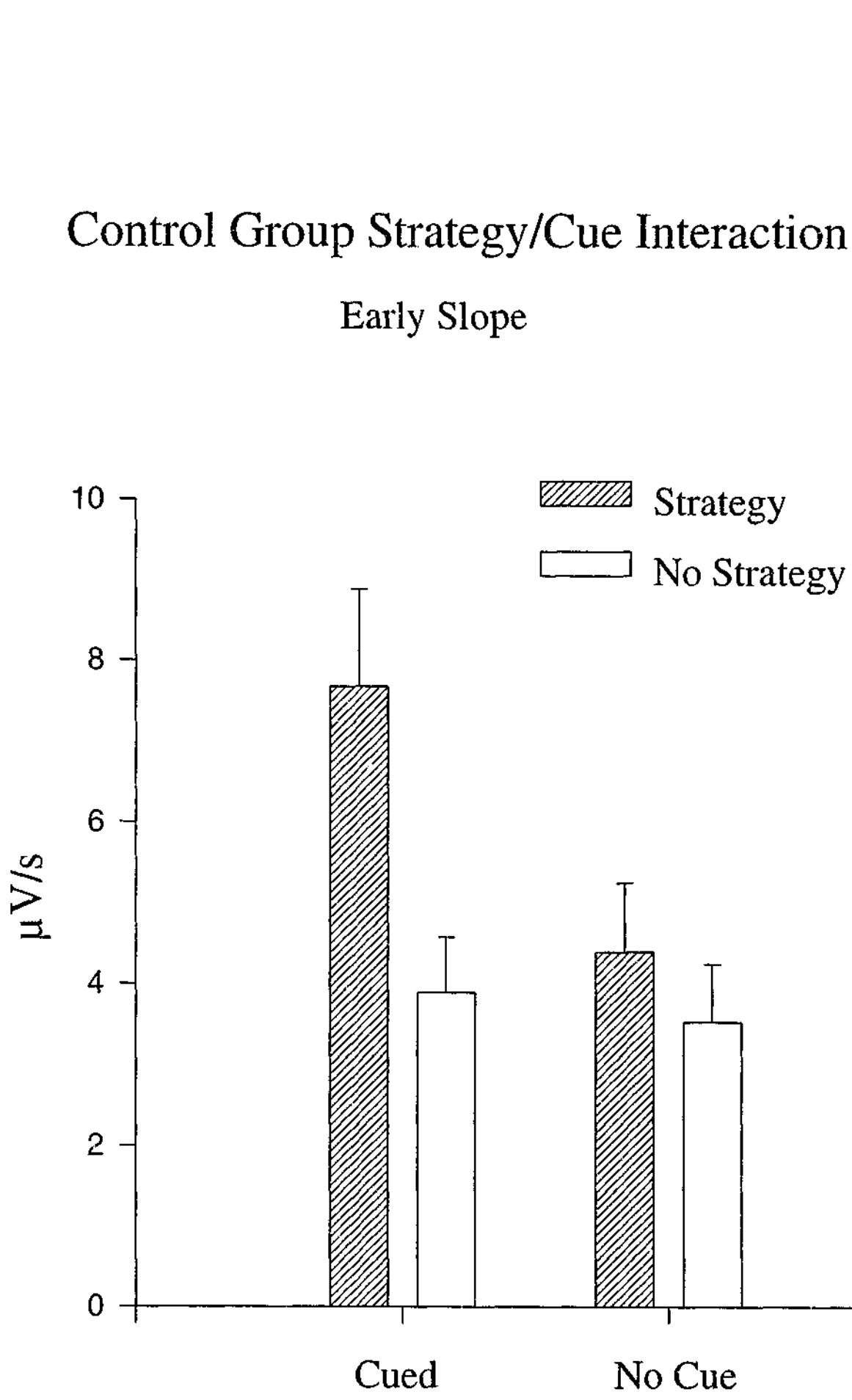


Figure 4.6: Means and standard errors of the Early Slope of the control group, in the presence and absence of the strategy, in the cued and non-cued conditions.

There was no significant effect of strategy for either group, and there were no interactions between group, strategy or cue.

DISCUSSION

The Huntington's disease group produced evidence of greater pre-movement cortical activity in the presence than in the absence of the strategy. This difference between the strategy and non-strategy conditions was not quite significant, but there was a strong trend in this direction. In Chapter Three, this difference was significant, with 12 participants in the Huntington's disease group. With only nine participants available for this experiment, power may have been sub-optimal. Interestingly, again there was no main effect of cue for the Huntington's disease group. This has been a consistent finding from the last two experiments, and concurs with three lines of evidence. First, past experimental literature showed no effect of external cues with Huntington's disease patients (Churchyard *et al.*, 2000; Johnson *et al.*, 2000). Secondly, external cues are not used, or reported as used, as rehabilitative aids in Huntington's disease clinics. Thirdly, the anatomy of cell death and cerebral blood flow suggests that the utilisation of external cues may be difficult, especially via the cerebellum-lateral premotor cortex circuit (Weeks *et al.*, 1997). The Huntington's disease group was able to utilise the strategy, but the presence or absence of the external cue had little effect on the pre-movement cortical activity. This is in direct contrast with the control group.

In the presence of the external cue, the pre-movement cortical activity of the control group using the strategy was significantly greater than when the control group was not instructed to use the strategy. In the absence of the external cue, there was no significant difference in pre-movement activity for the control group between the strategy and non-strategy conditions. The original question for this chapter was whether the external cue facilitated usage of the strategy. It appears that, for normal healthy individuals, in order for the strategy to influence significantly the pre-movement cortical activity, the external cue must be present.

The external cue in conjunction with the strategy may have promoted the concentration or attention of these control participants. This may have facilitated better planning and anticipation, benefiting the pre-movement cortical activity. In Huntington's disease, this effect was lost. For the control group, there may be a parallel combination of the

medial and lateral premotor areas contributing to the pre-movement potential, in the presence of the strategy, to prepare internally the movement (primarily medial), and in the presence of the external cue (primarily lateral). The strategy may also have invoked other areas of the cortex, increasing the cortical activity prior to movement. The anterior attentional network (including the anterior cingulate), and/or the fronto-parietal areas may all be involved in the cognitive attentional strategy. It must be noted, however, that a wider network of anatomical areas may be responsible for carrying out the process of attention (Posner and Petersen, 1990).

The important difference between the two strategy conditions was in the utilisation of the external cue. In condition 1, the strategy was to anticipate the extinction of the LED by timing four seconds and to prepare for the next movement in advance. In condition 4, the participants were to time themselves to hold down each button for at least four seconds before moving to the next button in the pathway, and to prepare in advance the next movement. In both conditions the participant was asked to time internally the four-second interval, possibly invoking activity of the SMA.

The presence of the cue in condition 1 may have reinforced the individual's timing of the four-second interval. This reinforcement was lost in condition 4, without the external cue. Subsequently, there was not the same increase in pre-movement cortical activity. The absence of reinforcement of the four-second timing cue may have deleteriously affected the pre-movement activity. Timing of sub-movements within a sequence has been considered to be a role of both the SMA and the cerebellum. A new experiment could investigate the effect of reinforcement of the timing cue by alternating blocks of conditions 1 and 4 in the one experimental session, and building up separate averages. In this way, reinforcement of the four-second interval would be more readily available for the participant.

The Movement Time data indicated that the control group was faster in their movement from one button to the next within the movement sequence than the Huntington's disease group. For both groups the presence of the cue aided their Movement Time, which was also found in Chapter Two. As demonstrated in Chapter Three, the presence of the strategy did not alter the time taken to move from one button to the next. This was not surprising, as the instructions to participants were to move as quickly as possible.

The contention of this thesis is that the control group may be internally modelling forthcoming movement, regardless of whether the movement is cued or non-cued. This may explain why there is no difference in the pre-movement activity of the control group in the cued and non-cued conditions in Chapter Two, and in other previous studies e.g. (Jahanshahi *et al.*, 1995). By internally modelling the movement, the medial motor system may be involved in movement preparation, as reflected in the pre-movement potential. Certainly during the non-cued condition, where the participant is required to self-time and to self-direct the movement, it is likely that the SMA would be involved in preparation of this predictably timed, sequential movement. During the cued movement condition, the control group's inherent internal modelling and predicting of movement, even (perhaps particularly) at an automatic level, would also involve the SMA. The presence of the cue may also provoke other motor systems, such as the cerebellum-lateral premotor system, to become involved in the movement planning.

When a strategy is introduced to prepare internally the movement, time the four-second interval and, in the cued condition, to anticipate the extinction of the light cue, the SMA may again by involved. The strategy may also invoke more conscious attentional cortical processes, which may be reflected in the pre-movement potential. Although the control participants may inherently model the movement internally without a strategy being suggested to them, with the addition of the strategy the control group showed in Chapter Three and in this experiment, a significant increase in pre-movement cortical activity. This suggests that the control group, with additional conscious control, is able to prepare a movement in advance with greater cortical activity. This was not found in the older Parkinson's disease control group data from Cunnington *et al.* (1999). This suggests two points. This ability to use conscious attentional capacity to help prepare the movement may decrease due to the ageing process. Alternatively, the older control participants may be inherently internally modelling movement to a greater degree than younger controls and might have reached an asymptote before the introduction of a strategy.

In the cued/strategy condition (condition 1), the control participants may be internally preparing the movement, using the external light cue, and consciously attending to the task, to produce a pre-movement potential which is significantly greater in the early

slope than in any of the other conditions. In this condition, the medial and lateral premotor areas may be working in parallel, with the attentional networks, to prepare the movement. In the non-cued/strategy condition (condition 4) it was suggested, in the introduction of this chapter, that the absence of the external cue might invoke the medial motor system, leading to an improved pre-movement potential in comparison with the non-strategy conditions. This was found not to be the case. The main finding of this chapter is that in a normally functioning brain of approximately 50 years of age an external cue must be present in order to facilitate utilisation of the strategy.

It is the contention of this thesis that, in Huntington's disease, movement in the presence of an external cue does not appear to be pre-planned normally, as there is no pre-movement rising potential. In the absence of the external cue, when the movement must be self-timed and self-directed, the pre-movement potential is not significantly different from the externally cued potential, i.e. it is significantly reduced in comparison with the control group (Chapter Two). This suggests that the medial motor system is not being used to the same extent as the control group in planning the movement, which may be due to cell loss in this system.

In Huntington's disease, the strategy was utilised. This suggests that the Huntington's disease group was able to benefit from the more conscious attentional cortical processes, which may be reflected in the pre-movement potential. Unlike the control group however, the presence or absence of the external cue had no effect on the utilisation of the strategy, and subsequently on pre-movement cortical activity. This suggests that another circuit within the brain, possibly incorporating the parietal motor area, may perform the pre-planning of the movement. Further research, with spatial resolution, would help to resolve this issue.

Chapter Five - Movement related potentials in Huntington's disease – movement preparation and execution

An inability to preprogram effective movements may be an important motor deficit in Huntington's disease. Kinematic analyses suggest that Huntington's disease patients are impaired in utilizing advance information to control sequential movements (Bradshaw *et al.*, 1992), to facilitate simple reaction time (Jahanshahi *et al.*, 1993) and are impaired in bimanual co-ordination (Johnson *et al.*, 2000). Patients' movements are slower than those of controls (Hefter *et al.*, 1987) during and when switching between simultaneous and sequential movements (Agostino *et al.*, 1992; Garnett *et al.*, 1984; Thompson *et al.*, 1988). This bradykinesia does not seem to be a product of impaired force production or increased reliance upon terminal visual guidance; it may instead be due to variability associated with internal cues regulating movement (Phillips *et al.*, 1996), or an abnormality in motor programming of sequences (Thompson *et al.*, 1988). Huntington's disease patients may require more ongoing guidance of movements than controls, as reflected in increased movement times (Bradshaw *et al.*, 1992). Inappropriate motor unit selection (Bylsma *et al.*, 1990) may lead to an interference with co-ordination, although the co-ordinated agonist-antagonist pattern is conserved (Hefter *et al.*, 1987). The production of the movement may be intact, but the construction of the motor program may be affected, leading to bradykinesia (Phillips *et al.*, 1994).

If Huntington's disease does lead to disruptions of the motor loop, via basal ganglia and frontal cortex dysfunction, supplementary motor area (SMA) functioning would also be affected. Regional cerebral blood flow studies have implicated the SMA and other frontal structures in the disease process, which may help to explain the kinematic findings. Whilst performing externally cued, sequential movements, Huntington's disease patients show impaired activation in the SMA, striatum, anterior cingulate, sensorimotor cortex, the lateral premotor cortices (Bartenstein *et al.*, 1997), precuneus, dorsolateral prefrontal and orbitofrontal cortices and primary motor area (Weeks *et al.*, 1997). The SMA, in particular, has been associated with the preparation of movements, particularly those which are sequential, complex, bilateral and internally derived, e.g. (Brinkman, 1981; Deiber *et al.*, 1991; Dick *et al.*, 1986; Grafton *et al.*, 1996; Marsden *et al.*, 1996).

Positron emission tomography studies, with their otherwise good spatial resolution, have been unable to differentiate temporally between preparatory and execution deficits involved in Huntington's disease movement. Movement related potentials (MRPs) allow a valuable examination of the temporal aspects of frontal cortical activity involved in movement preparation and execution.

Mental simulation of a motor task appears to activate brain areas involved in movement preparation, such as the SMA, and may also activate, to a small degree, those areas of the brain involved in movement execution (Jeannerod, 1999; Roland *et al.*, 1980; Romero *et al.*, 2000; Roth *et al.*, 1996; Stephan *et al.*, 1995). It is possible to separate the components of the MRP, which relate to movement execution from those relating to movement preparation, by recording cortical activity when participants perform and imagine performing a movement (Cunnington *et al.*, 1996). The MRP recorded from the movement task contains components relating to both preparation and execution. The MRP from the imagined task contains components relating to movement preparation and little if any execution-related activity from the primary motor cortex.

The early-stage components of the MRPs associated with real and imagined movement do not differ in amplitude or temporal characteristics in normal participants (Cunnington *et al.*, 1996), suggesting similar cortical movement preparation processes. During the late-stage component, however, the MRP associated with movement imagery is reduced in amplitude when compared with the MRP associated with actual movement (Cunnington *et al.*, 1997), reflecting reduced movement execution activity of the primary motor cortex.

Parkinson's disease patients, with nigrostriatal hypodopaminergia, produce a MRP with a reduced early slope and peak amplitude (Cunnington *et al.*, 1995), indicating a reduction in the functioning of the SMA and primary motor cortex. Movement execution components, arising predominantly from the primary motor cortex, are relatively unaffected in Parkinson's disease; however the movement preparation components, arising principally from the SMA and motor area, are reduced in amplitude and abnormally prolonged, compared with the controls (Cunnington *et al.*, 1997).

Huntington's disease patients and hemi-Parkinson's disease patients exhibit a similar bradykinesia in their imagined as with their executed movements (Dominey *et al.*, 1995; McLennan *et al.*, 2000). An experimental design, similar to that used in Cunnington *et*

al. (1997) with Parkinson's disease patients, was employed in this present study to investigate the MRPs in Huntington's disease. The aim was to determine the effects of the disorder upon the cortical activity relating to preparation and execution of movement. A prediction of abnormally reduced MRPs was made, based on the bradykinesia and akinesia seen in huntingtonian movement.

METHOD

Participants

One female and nine male Huntington's disease patients, aged 37 - 60 years (mean age 50.7, SD 7.3 years), and two female and eight male control participants, aged 37- 59 (mean age 52.3, SD 7.3 years), were tested. All participants were right-handed (Patterson and Bradshaw, 1975).

The diagnosis of Huntington's disease was confirmed by CAG repeat length (Huntington's Disease Collaborative Research Group, 1993) for five of the participants (Gusella *et al.*, 1997). One other Huntington's disease participant had two family members with confirmed CAG lengths above 40. The remaining four Huntington's disease participants had family histories of Huntington's disease and were diagnosed by a psychiatrist.

On the Shoulson and Fahn rating scale (Shoulson and Fahn, 1979), all patients scored between 0 and 2.5. Nine of the patients were rated on the UHDRS (Huntington Disease Group, 1996), and scored between 3 and 56 (mean UHDRS score 29.33, SD 19.60). The duration of disease varied between one and sixteen years (mean 6.6 years, SD 4.95).

All participants were screened for histories of stroke, serious head injury, other neurological disturbances, and for dementia using the STMS (Kokmen *et al.*, 1987). Depression levels were assessed using the MAS (Yesavage *et al.*, 1983), and did not vary between the two groups.

Each participants' ability to imagine performing upper limb motor actions was assessed using an amended version of the Florida Praxis Imagery Scale (Ochipa *et al.*, 1997), with 32 items (one point per item). This scale asked participants to imagine performing a motor action, and to answer, from two options, which joint caused the action.

"Imagine you are using a pair of scissors. Which joint moves more, your wrist or your finger joints?" is an example (see Appendix). The control group (mean 30.44, SD 1.13) scored significantly higher on the imagery scale than the Huntington's disease group (mean 27.88, SD 1.73), [$t(15) = 3.67$, $p < 0.002$].

Participants were not withdrawn from their medication. Clinical data are shown in Table 5.1. Informed consent was obtained from each participant in accord with the Helsinki declaration, and all experimental work was carried out under the approval of local ethical committees.

Procedure

The same procedure was used as per Cunnington *et al.* (1997). The logic and interpretation of the findings are identical to those employed in the Parkinson's disease study. Participants performed a right-handed, sequential button-pressing task using the tapping board, consisting of two parallel rows of ten buttons, beneath which were LEDs. The LEDs illuminated a ten-button pathway for sequential button pressing, which was used for all tasks of the experiment (Figure 2.2). All the LEDs were initially illuminated, and during the experimental trials the lights progressively extinguished from right to left at a rate of one every four seconds.

The three experimental tasks are discussed below.

Performed Movement

Participants were required to hold down each illuminated button (moving from right to left) until the light underneath was extinguished (always a period of 4 s), then to press the next illuminated button in the sequence as quickly as possible.

Imagined movement

Participants were instructed to focus on the last illuminated button to the right and imagine their finger pressing the button. When the light underneath was extinguished, participants were asked to imagine moving their finger to press the next illuminated button in the sequence, without actually performing the movement.

Table 5.1: Clinical data for Huntington's disease patients.

Chapter Five

Participant	Age (years)	Sex	Duration of disease (years)	STMS	MAS	Imagery	Medication	Dose (mg/day)	UHDRS motor subscale	Triplet repeat score
1	60	M	8	37	0	29	-	-	31	42
2	54	M	8	31	8	n/a	Tetrabenazine	75	48	43
3	52	M	4	29	16	n/a	-	-	26	
4	37	M	4	30	11	28	Carbamazepine Thioridazine	300 35	56	
5	58	M	16	35	7	26	-	-	55	**
6	53	F	14	33	10	27	-	-	n/a	
7	57	M	5	36	4	29	-	-	3	
8	44	M	3	35	11	27	-	-	19	44
9	45	M	1	36	4	26	Sertraline hydrochloride	100	15	42
10	47	M	3	36	0	31	-	-	11	43

Notes: Dashes indicate that the participant was not taking medication.
STMS – Short Test of Mental Status
MAS – Mood Assessment Scale
UHDRS – Unified Huntington's Disease Rating Scale
** HD participant had two family members with confirmed CAG lengths above 40.

Watching lights

Participants simply fixated on the last illuminated button to the right and, when the light underneath was extinguished, they changed fixation to the next illuminated button in the sequence. Participants were instructed not to imagine any finger movement, and only to move their eyes to follow the progressive extinction of lights along the sequence.

For all tasks, participants were explicitly instructed to try to anticipate extinction of the light cue, so that when the cue was given they were ready to respond. The amplitude of the early MRP component is dependent upon the internal generation of responses (Cunnington *et al.*, 1995). Therefore, participants were always and continually instructed to concentrate on anticipating the cue, thereby internally generating responses, even though an external timing cue was provided. The external cue was necessary to provide a constant time point from which MRPs to covert responses could be determined. The tasks were always performed in the above order, with all participants performing the movement task first.

The methodology involved in recording the MRPs was described in Chapter Two. EMG activity associated with upper limb movement was recorded from two silver/silver chloride surface electrodes placed over the biceps brachii muscle of the right arm. Electrode impedances were always kept below 5 kΩ. An AMLAB workstation performed digital off-line processing and averaging of the EMG activity. The EMG was amplified at a gain of 10 000 V/V (time constant 97 ms), digitized at 100 Hz, and filtered at 48 Hz (low pass). The EMG potentials were averaged over 4-s sweeps, time-locked to the extinction of light cues on the tapping board, over the period from 3 s before the cue to 1 s after it.

MRPs for the watching-lights task should involve only extraneous components, such as anticipation of forthcoming cues, horizontal eye movements associated with following the lights along the board, and visual evoked potentials associated with extinguishing of the light cues. A previous study using the same motor-imagery task showed no difference between MRPs for the watching-lights task compared with a fixation task in which no eye movements were made. Therefore, horizontal eye movements between responses were unlikely to contribute to recorded MRPs (Cunnington *et al.*, 1996). In the present study, the effect of any such eye movements was controlled via the watching-lights task, which is physically equivalent to the imagined-movement task.

MRPs for the imagined-movement task should involve additional endogenous components relating to the planning and preparation of the forthcoming response. Therefore, to identify the MRP component relating to movement preparation alone, MRPs for the watching-lights task were subtracted from those for the imagined-movement task. Similarly, MRPs for the performed-movement task would involve additional components relating to movement execution. Therefore, to separate the component relating to movement execution alone, MRPs for the imagined-movement task were subtracted from those for the performed-movement task.

Characteristics of average potentials and subtracted functional components for each participant in each task were quantified by the following measures.

Early Slope

Linear regression was used to calculate the average slope of the potential over the period from 1500 to 500 ms prior to movement onset. This is a measure of neural activity relating to the early component of the MRP.

Peak amplitude

The maximum amplitude of the potential occurs near the time of the cue, and reflects the combined activity of early and late components of the MRP, which overlap around the time of movement onset. The measure of the peak amplitude is arithmetically different from the peak amplitude of group mean MRPs. Peak amplitudes for the individual MRP traces vary slightly in time, and as a consequence are partly averaged out when combined into group mean MRPs. Therefore, this measure of peak amplitude may appear quite different from the peak amplitudes in mean MRPs, since it is measured from individual traces before averaging group data.

Post-peak slope

The average slope of the potential was measured from the time of the peak to 300 ms after the peak. This reflects the rate of decrease in activity associated with the termination of pre-movement activity reflected in the MRP. Measures of the post-peak slope were not analyzed for the experimental tasks of performed movement and imagined movement, since the termination of both pre-movement and execution-related activity overlap following the peak, making interpretation difficult. The post-peak slope

was therefore measured only for the subtracted functional MRP components in which these confounding factors were isolated and removed.

All measures were analyzed by independent samples one-tailed *t* tests.

RESULTS

Mean MRPs for the Huntington's disease patients and the controls, for the movement, imagined movement and watching lights tasks, recorded at Cz, C3 and C4 are shown in Figures 5.1 to 5.3. Qualitatively, the control group's mean MRPs for the movement and imagined movement tasks show rising negative pre-movement activity, peak amplitudes around the time of movement/imagined movement, and steep positive post-movement activity. The Huntington's disease group's mean MRPs also show rising pre-movement activity, which peak at the time of movement, and have a steep post-peak slope. For both the performed and imagined movements the MRP for the Huntington's disease group is reduced in size, compared with the control group. EMG responses for each of the three tasks show activation of the biceps muscle during movement, but no significant muscle activity during the imagined and watching lights tasks. The greatest activity was always recorded at electrode site Cz. Therefore the quantitative statistics were confined to the recordings from site Cz.

Early Slope

For the movement task, the control group (mean 5.40, SD 3.46 μV/s) produced a significantly steeper early slope at Cz than the Huntington's disease group (mean 2.00, SD 2.87 μV/s), [$t(18) = 2.39$, $P < 0.05$] (see Figure 5.4). For the imagined movement task, the control group (mean 3.69, SD 1.89 μV/s) again produced a significandy steeper early slope at Cz than the Huntington's disease group (mean 1.20, SD 1.83 μV/s), [$t(18) = 2.99$, $P < 0.05$]. For the watching lights task, there was no significant difference between the two groups, [$t(18) = 1.44$, $P > 0.05$].

Peak Amplitude

For the movement task, there was no significant difference between the control group (mean 11.46, SD 7.38 μV) and the Huntington's disease group (mean 7.65, SD 6.88 μV), [$t(18) = 1.20$, $P > 0.05$], (see Figure 5.4). For the imagined movement task, however, there was a significant difference between the control group (mean 8.07, SD

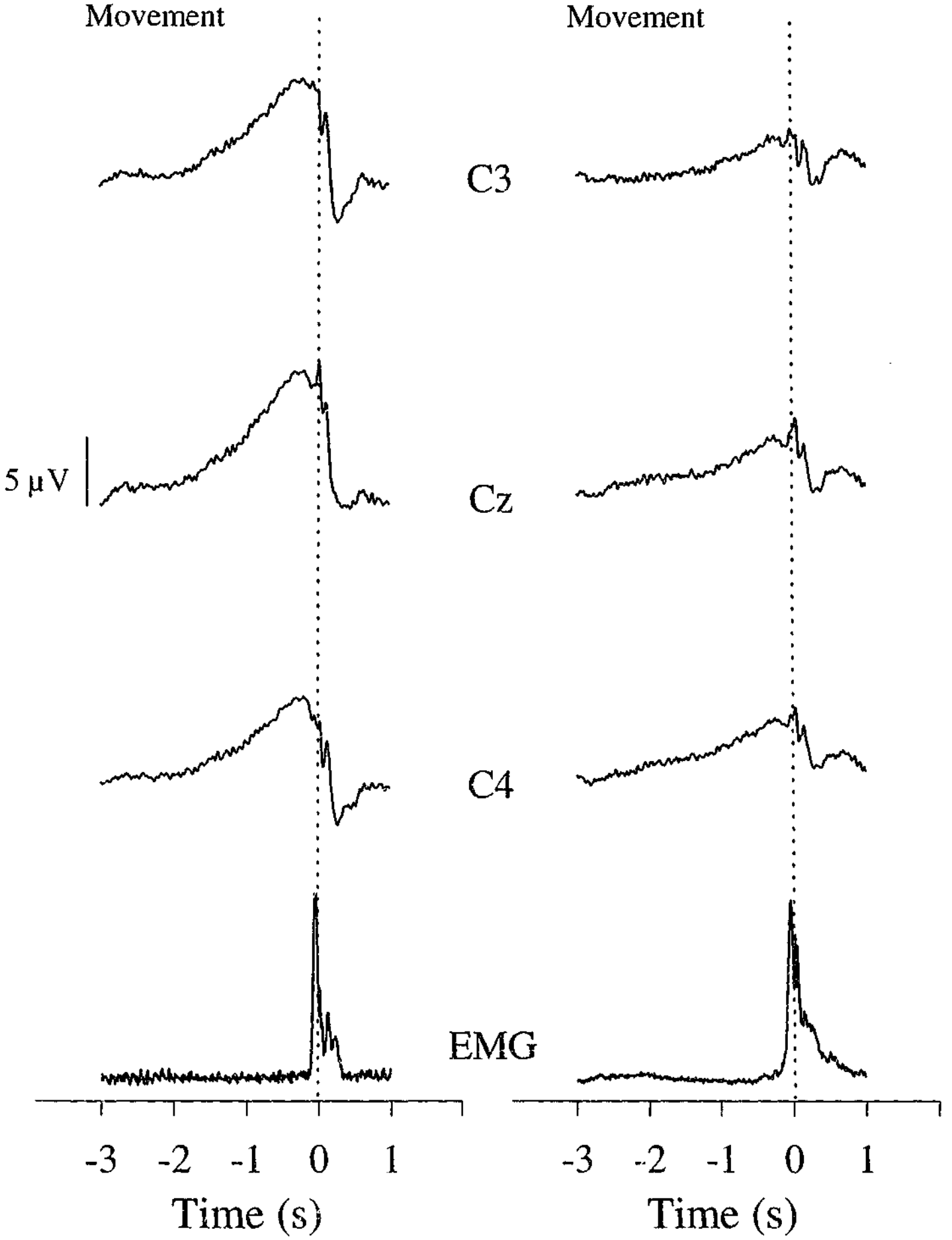


Figure 5.1: Grand average MRPs for control and Huntington's disease participants recorded from electrode positions C3, Cz, and C4, and EMGs recorded from biceps brachii, for the condition of Performed Movement. Potentials are shown from 3 s before the cue to 1 s after, with the dotted line marking the time of the cue.

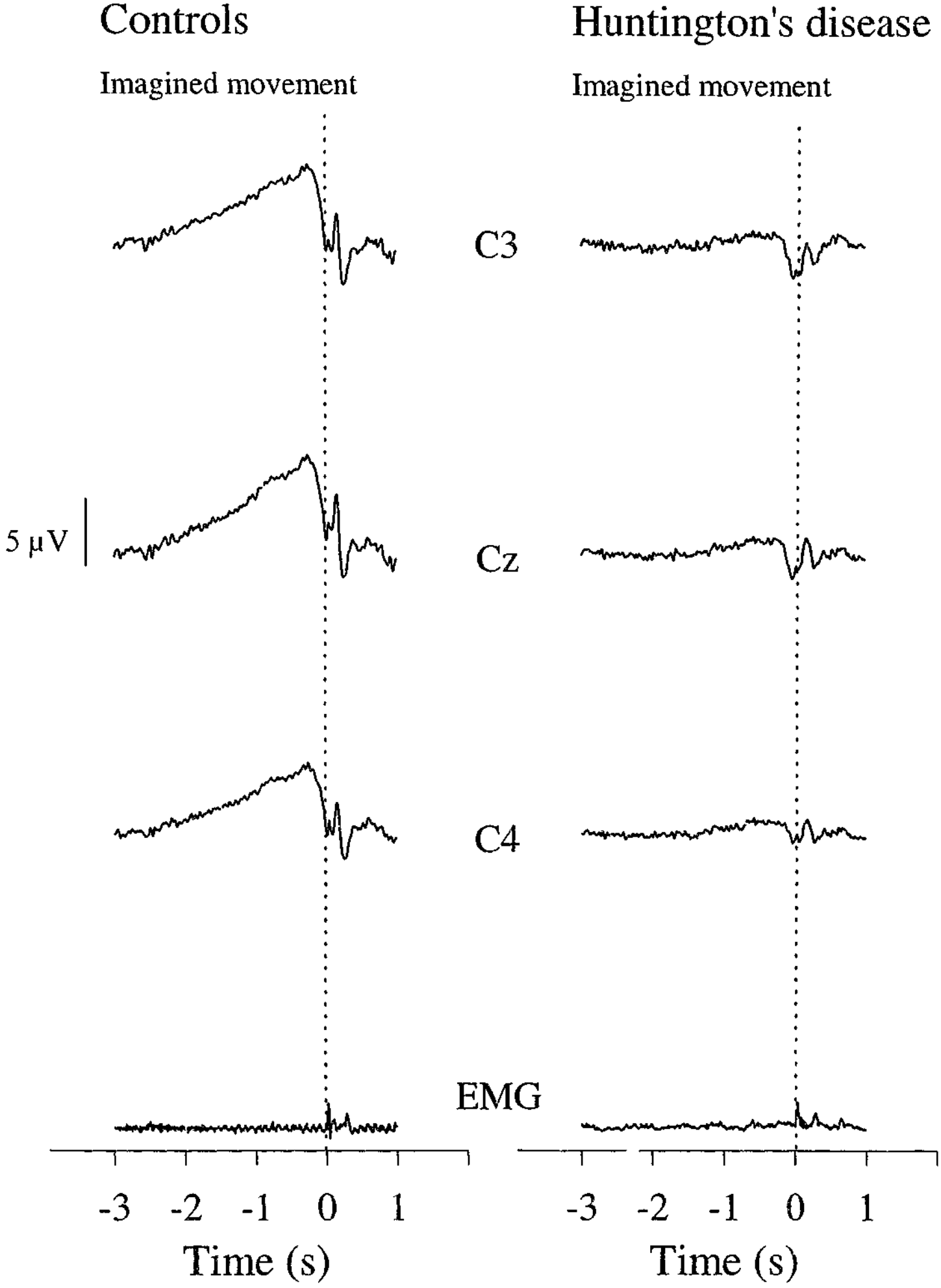


Figure 5.2: Grand average MRPs for control and Huntington's disease participants recorded from electrode positions C3, Cz, and C4, and EMGs recorded from biceps brachii, for the condition of Imagined Movement. Potentials are shown from 3 s before the cue to 1 s after, with the dotted line marking the time of the cue.

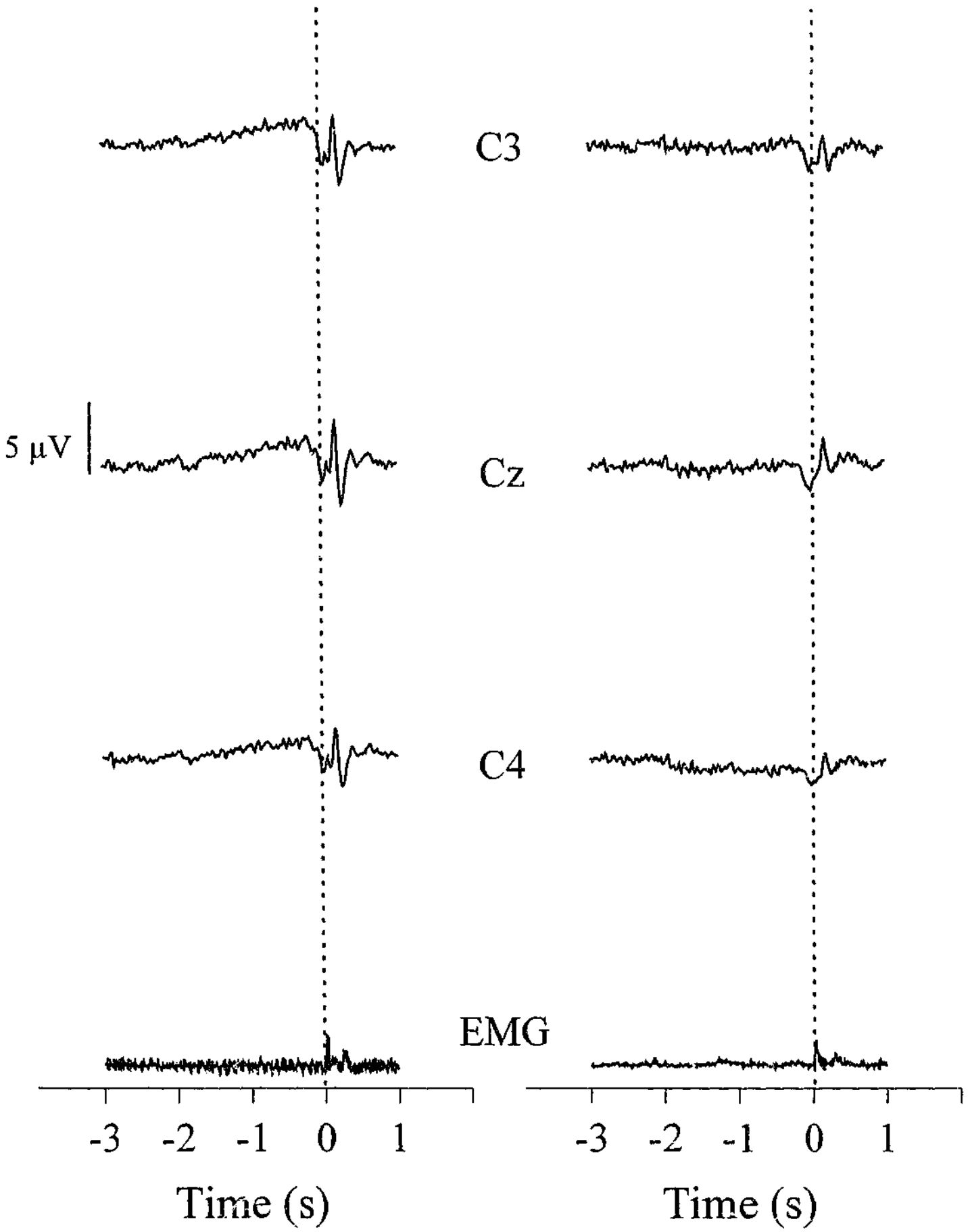


Figure 5.3: Grand average MRPs for control and Huntington's disease participants recorded from electrode positions C3, Cz, and C4, and EMGs recorded from biceps brachii, for the condition of Watching Lights. Potentials are shown from 3 s before the cue to 1 s after, with the dotted line marking the time of the cue.

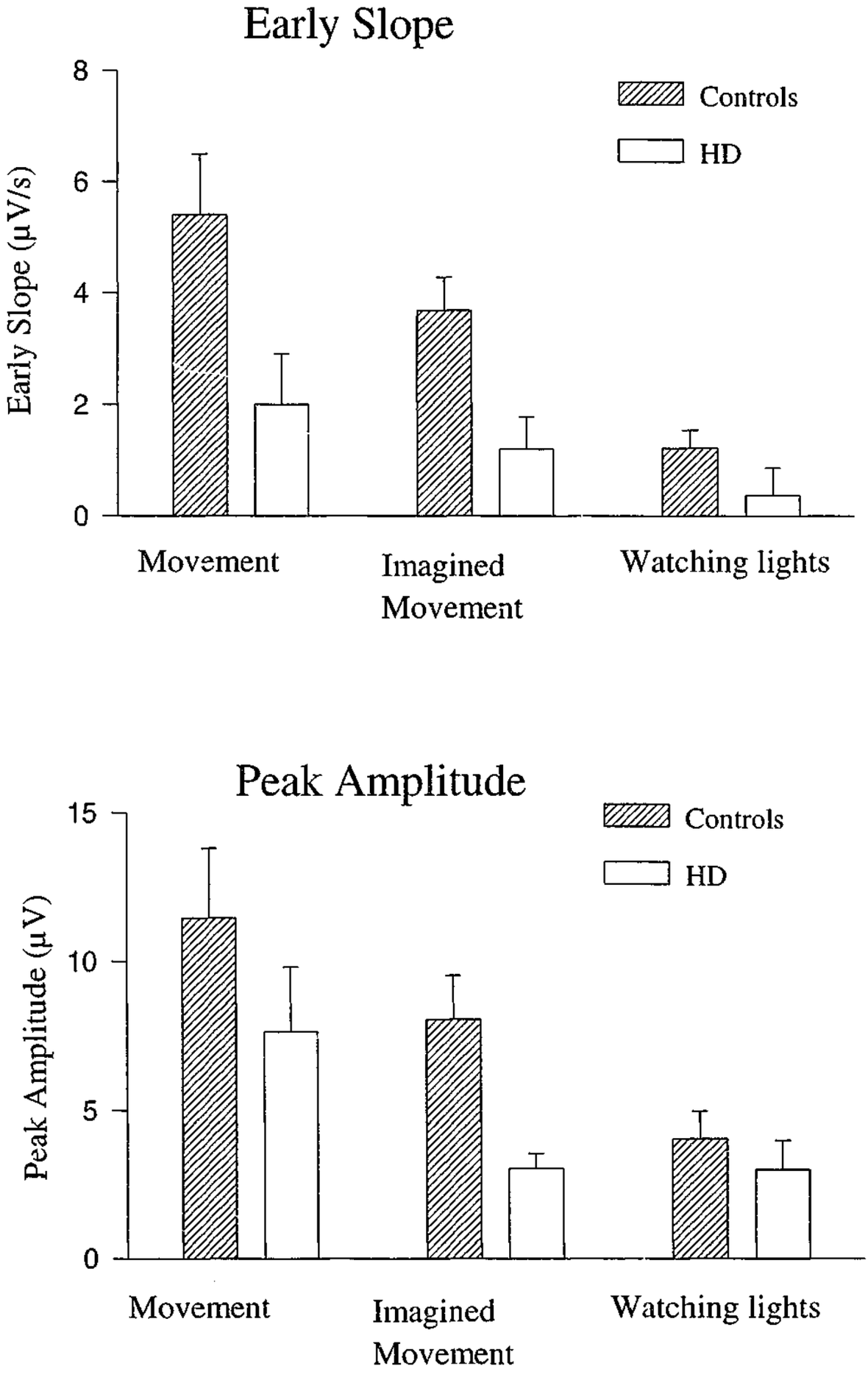


Figure 5.4: Means and standard errors of the early slope and peak amplitude for Movement, Imagined Movement and Watching Lights tasks, for the control and Huntington's disease participants.

4.63 μV) and the Huntington's disease group (mean 3.04, SD 1.60 μV), [$t(18) = 3.24$, $P < 0.05$]. There was no significant difference between the two groups for the watching lights task, [$t(18) = 0.76$, $P > 0.05$].

Preparation Component

The preparation component was found by subtracting MRPs for the watching-lights task from the MRPs for the imagined-movement task, (see Figure 5.5). The control group (mean 2.46, SD 2.18 μV/s) produced a significantly steeper early slope than the Huntington's disease group (mean 0.83, SD 1.97 μV/s), [$t(18) = 1.76$, $P < 0.05$], see Figure 5.7. The control group (mean 4.02, SD 4.48 μV) also produced a significantly higher peak amplitude than the Huntington's disease group (mean 0.03, SD 2.53 μV), [$t(18) = 2.45$, $P < 0.05$], and the control group (mean 15.58, SD 12.12 μV/s) produced a significantly steeper post-peak slope than the Huntington's disease group (mean 3.72, SD 8.18 μV/s), [$t(18) = 2.57$, $P < 0.05$].

Execution Component

The execution component was found by subtracting MRPs for imagined-movements from MRPs for the performed movement task, (see Figures 5.6 and 5.7). There was no difference between the two groups for the early slope [$t(18) = 0.83$, $P > 0.05$], peak amplitude [$t(18) = 0.56$, $P > 0.05$], or post-peak slope [$t(18) = 0.41$, $P > 0.05$].

DISCUSSION

MRPs were recorded from the Huntington's disease and control groups whilst they performed and imagined performing simple, sequential finger tapping. The components of the MRPs relating to movement preparation and movement execution were separated via subtraction, by employing a control condition of watching the visual cues used during the tapping task. When compared with the controls, the Huntington's disease group had particular deficits in the preparation of movement.

For the movement task, the Huntington's disease group produced an early slope, which was significantly reduced in comparison with the control group, indicating a reduction in cortical preparatory activity. The height of the peak amplitude was not significantly different from that of the control group. This lack of a significant difference may be due to a lack of statistical power (n = 10) or it may possibly reflect relatively normal

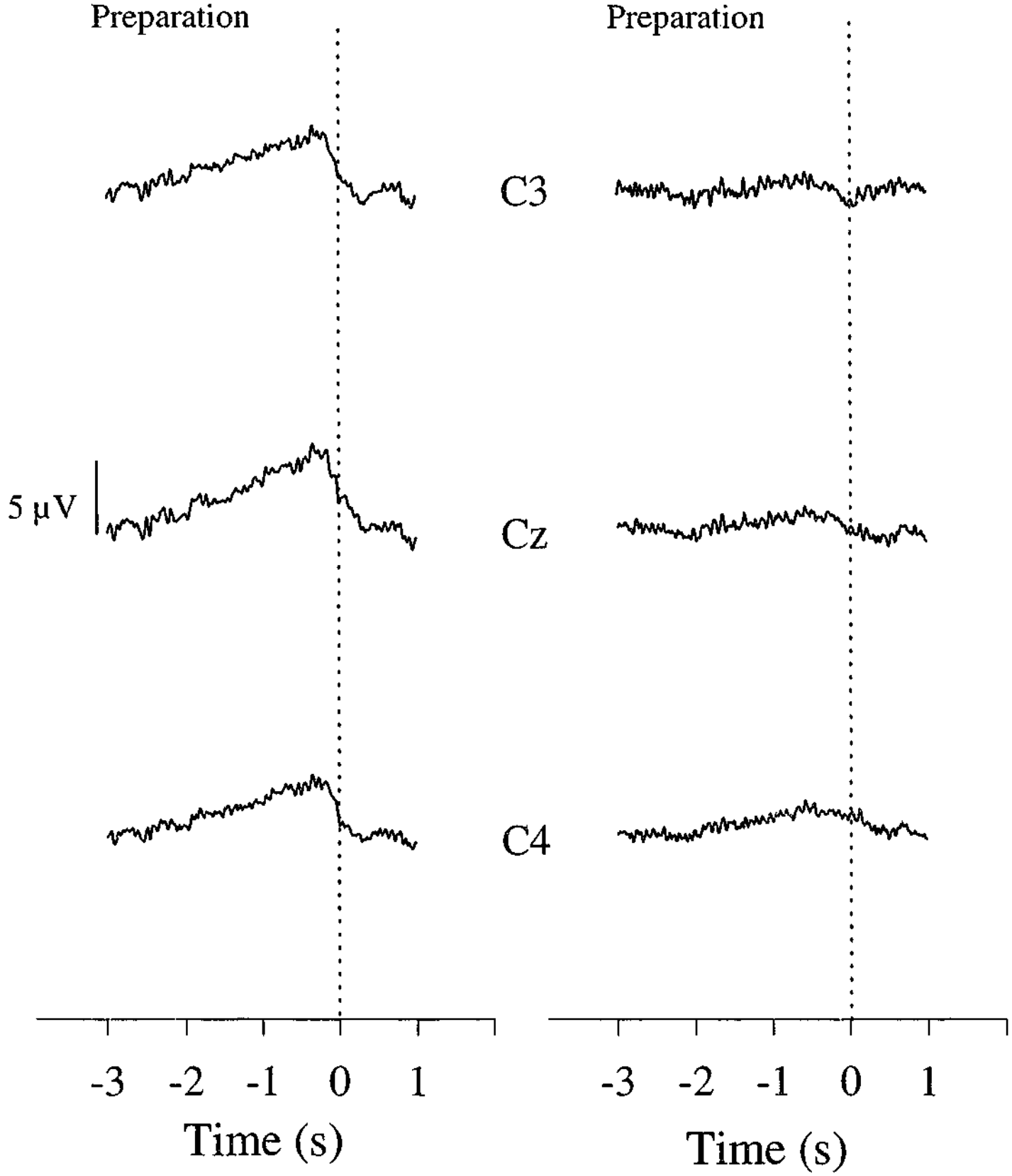


Figure 5.5: Grand average Movement Preparation components of the MRPs recorded from electrode positions C3, Cz, and C4, for control and Huntington's disease participants. Potentials are shown from 3 s before the cue to 1 s after, with the dotted line marking the time of the cue.

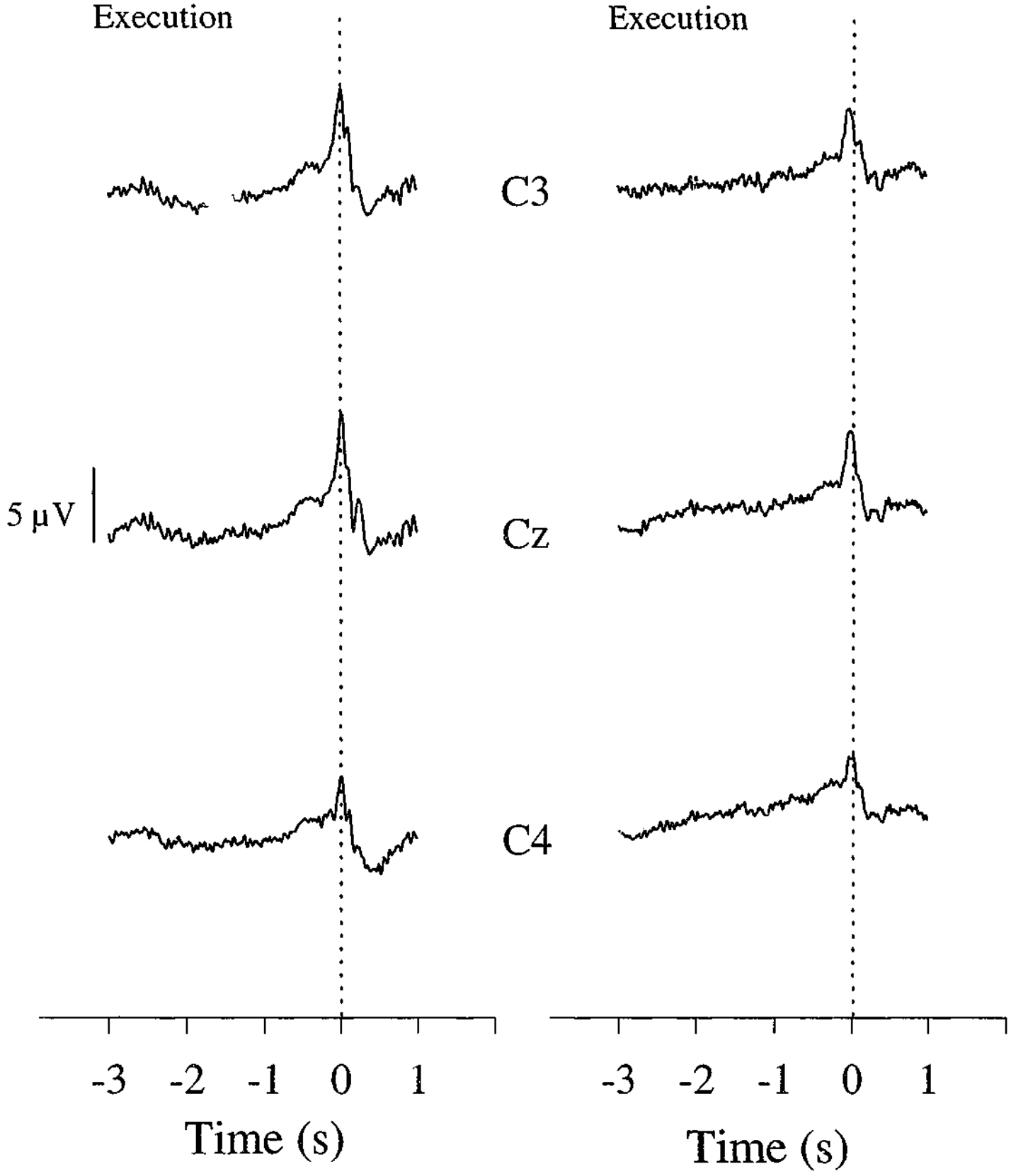


Figure 5.6: Grand average Movement Execution components of the MRPs recorded from electrode positions C3, Cz, and C4, for control and Huntington's disease participants. Potentials are shown from 3 s before the cue to 1 s after, with the dotted line marking the time of the cue.

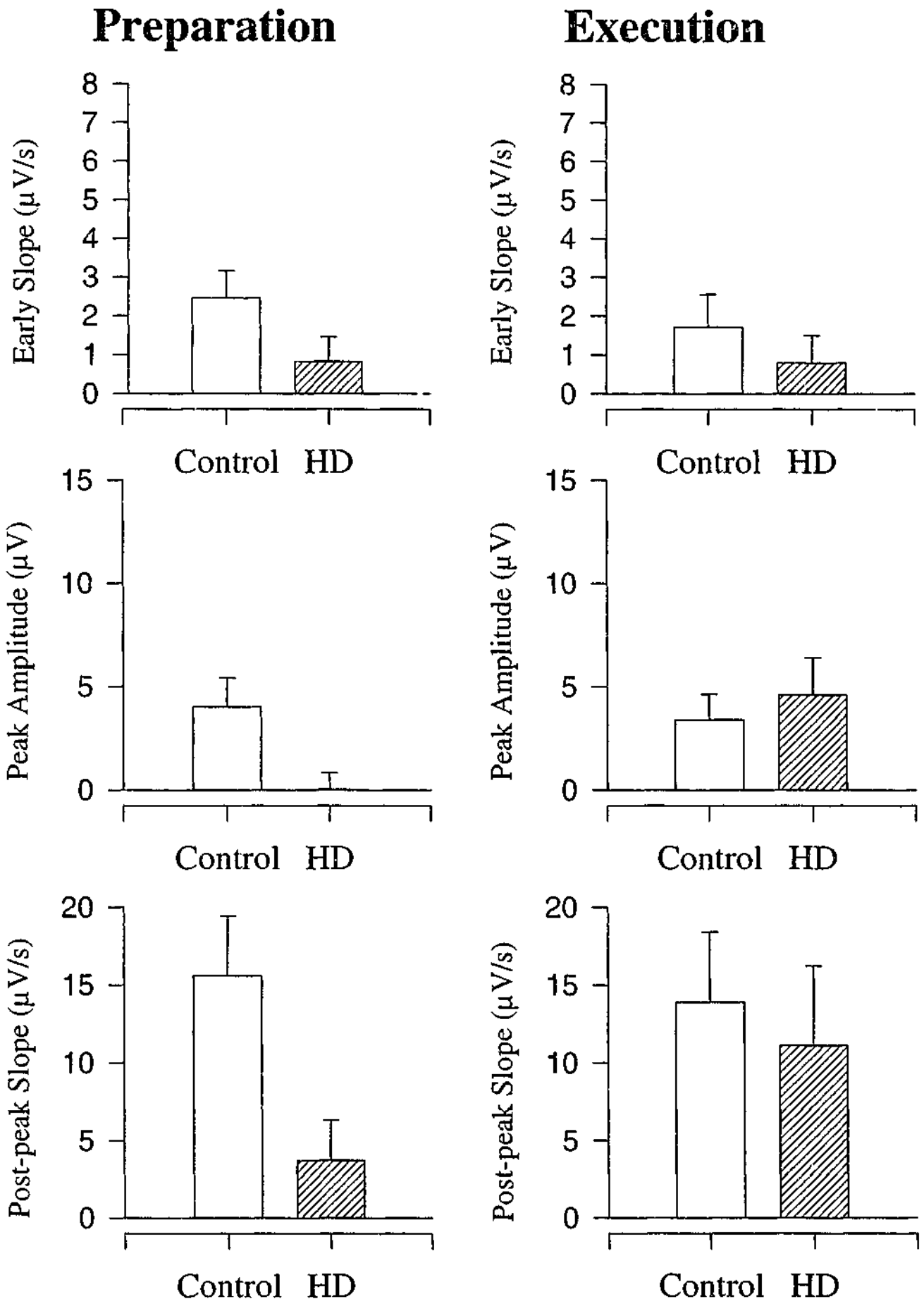


Figure 5.7: Means and standard errors of the Early Slope, Peak Amplitude and Post-peak Slope for the Movement Preparation and Execution components of the MRPs, for the control and Huntington's disease participants.

primary motor cortex activity in Huntington's disease. For imagined movement, the Huntington's disease group's early slope was again significantly less steep than that of the control group and the peak amplitude was significantly lower than that of the control group, indicating a reduction in cortical preparatory activity.

The component which was thought to relate to movement preparation, found by subtracting the MRPs related to the watching-lights task from the imagined-movement task, was significantly reduced in Huntington's disease, in terms of the early slope, peak amplitude and post-peak slope. The motor imagery deficits shown by the Huntington's disease patients on the movement imagery scale may represent impairments in the internal representation of movement. With such internal representation deficits, Huntington's disease patients may have problems in preparing or pre-programming movements for which such internal representations are necessary. The impaired MRP of the Huntington's disease patients during the preparation period reflects this internal representation deficit. It is possible that with impaired activation of the parietal area (Weeks *et al.*, 1997), the ability of Huntington's disease participants to represent internally movement may be seriously compromised, as the parietal area is believed to be involved in imagined movement (Sirigu *et al.*, 1996).

The component of the MRP, which was thought to relate to movement execution, was found by subtracting the MRPs relating to imagined movement from those recorded from actual movement execution. On all three dependent variables, the Huntington's disease group was normal, compared with the control group, possibly reflecting relatively normal primary motor cortex activity.

Voluntary movement in Huntington's disease has been characterized as inconsistent and inefficient (Phillips *et al.*, 1996). This has led to the suggestion that production of movement may be intact, but construction of the motor program for a particular movement may be affected by the disease (Jahanshahi *et al.*, 1993; Phillips *et al.*, 1994; Thompson *et al.*, 1988). The MRP reflects cortical activity from the SMA, M1 and possibly the CMA. With damage to the striatothalamocortical circuit, Huntington's disease may lead to cortical dysfunction, especially that of the SMA. Indeed, $H_2{}^{15}O$ rCBF studies indicate impaired activation of the SMA during huntingtonian performance of sequential motor tasks (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997). The SMA is believed to be involved particularly in movement preparation (Cunnington

et al., 1997). The present study indicates that the MRP in Huntington's disease is abnormal, particularly the component likely to relate to movement preparation.

On exactly the same task (Cunnington *et al.*, 1997), Parkinson's disease patients, like the Huntington's disease group, showed a reduced early slope (reflecting the early component) for the movement and imagined movement tasks. The MRP component relating to movement execution was normal in both Parkinson's disease and Huntington's disease, but preparation of movement was found to be deficient in both groups, which may be indicative of the malfunctioning SMA.

In conclusion, abnormal MRPs in Huntington's disease were reported in comparison with controls, particularly in terms of the component relating to movement preparation, a finding which may further explain the clinical reports of movement deficits in the disorder.

Chapter Six - The MRP of Huntington's disease patients over time

Huntington's disease is a progressive neurodegenerative disease, which manifests in the post-reproductive age-range. The disease course is usually 10 – 20 years, resulting in death. There is a progression of well-defined symptoms involving the motor, limbic and cognitive systems. Of interest to this thesis is the motor symptomotology. In the early stages of the disease there are mild saccadic and fine motor abnormalities. There is gradual development of chorea, from more overt abnormalities to definite chorea. Dysarthria will often develop, frequently accompanied by dysphagia. Parkinsonism and dystonia develop later in the disease, and worsen, until chorea declines. In the advanced stages, rigidity and dystonia occur (Penney and Young, 1998). Bradykinesia is present from the early stages and remains a constant symptom of the disease (Thompson *et al.*, 1988). Changes over time in relation to the preparation and execution of movement in Huntington's disease, however, are unknown.

Current knowledge about the disease progression has come from a number of different methodologies, including post-mortem anatomical, neurochemical and receptor change studies and *in vivo* studies. The action of the Huntington's disease gene in relation to the start and progression of the disease is unknown. The process and anatomy of cell loss in Huntington's disease is poorly understood. Like many diseases, it is thought however, that the age of onset of the illness is closely related to the degree of neuropathologic severity, such that the younger the age of onset, the more severe the progression of neuropathology (Myers *et al.*, 1988). The age of onset is significantly influenced by the sex of the affected parent, with paternal transmission having a lower mean age of onset (Myers *et al.*, 1988). Of interest is the finding that the functional rating of physical disability is closely related to the neuropathologic involvement of the striatum and neuronal cell count. The functional capability of the Huntington's disease participants may be largely determined by the degree of neuropathology of the disease (Myers *et al.*, 1988).

The brain of a person with Huntington's disease is smaller and lighter than that of the normal brain, with apparent atrophy of the frontal lobes and general shrinkage of brain tissue (Macmillan and Quarrell, 1996). From post-mortem examinations, it is known

that the basal ganglia are most prominently affected by the disease, with neuronal loss and astrocytosis occurring in the caudate and putamen (Myers *et al.*, 1991; Vonsattel *et al.*, 1985). In detail, there is progressive and marked atrophy and gliosis of the γ-aminobutyric acid (GABA)-containing medium spiny neurons of the caudate nucleus and putamen, accompanied by fibrillary astrocytosis (Hedreen and Folstein, 1995). The output areas of the basal ganglia, the GPi and the SNr, suffer gliosis and atrophy (Penney and Young, 1998).

Vonsattel *et al.,* (1985) categorized the pathological changes occurring in the brains of people with Huntington's disease from a set of 163 brains which ranged from pre-clinical to late disease stages. From these data a classification was formed, from grade 0 (no macroscopic or microscopic changes despite neurological signs) to grade 4 (gross neostriatal atrophy, neuronal loss and astrocytosis). There is a 'wave' of neuronal loss, starting in the dorsomedial tail of the caudate and the dorsal putamen in grade 1. This cell loss becomes more prominent and spreads ventrally in grade 2 and 3. There is widespread severe neuronal loss and gliosis in caudate and putamen with moderate gliosis in the nucleus accumbens in grade 4 (Macmillan and Quarrell, 1996; Myers *et al.*, 1988). Other authors have found 'islands' of caudate and putamen striosome cell loss in grade 0, suggesting the possibility that pathological change may begin before clinical symptoms (Hedreen and Folstein, 1995). The globus pallidus and the cerebral cortex suffer cell loss from Grade 3 (Vonsattel and DiFiglia, 1998). The thalamus and subthalamic nucleus suffer cell loss regularly in Grade 4 and to a lesser extent in Grade 3. The cerebellum findings are less conclusive. The cerebellum may be smaller than normal in Grade 3 and 4 but less atrophic than the other affected areas. The substantia nigra, hypothalamus, hippocampus and brain stem also suffer some cell loss (Macmillan and Quarrell, 1996; Vonsattel *et al.*, 1985).

Neurochemical studies have reported changes in the neurotransmitters of striatal neurons in Huntington's disease. For instance, there is marked loss of GABA in the striata of Huntington's disease patients (Perry *et al.*, 1973). Enkephalin, dynorphin, and substance P are also found in decreased amounts in the striatal projection neurons, globus pallidus and substantia nigra of Huntington's disease patients. Enkephalin neurons may be the first striatopallidal neurons to be lost in the disease process (Albin *et al.*, 1990). The percentage of neurons containing neurotransmitters such as

dopamine, noradrenaline, somatostatin, nitric oxide synthetase or neuropeptide-Y, typically aspiny striatal interneurones, increases in Huntington's disease (Kowall *et al.*, 1987; Penney and Young, 1998).

Huntington's disease is also associated with receptor changes. Striatal acetylcholine, GABA and benzodiazepine, dopamine (D_1 and D_2), kainic acid and glutamic acid receptors are decreased (Ginovart *et al.*, 1997; Penney and Young, 1998; Turjanski *et al.*, 1995). There are increases in $GABA_A$ and benzodiazepine receptors in the globus pallidus and substantia nigra (Faull *et al.*, 1996). This may reflect the greater involvement of the striatolateral pallidal pathway in the disease process (Penney and Young, 1998).

In-vivo studies, such as [^{18}F] fluorodeoxyglucose-PET measures, have suggested reduced activity within the caudate, putamen and lentiform nucleus early in the disease (Harris *et al.*, 1996; Harris *et al.*, 1992; Kuhl *et al.*, 1982; Kuwert *et al.*, 1990; Starkstein *et al.*, 1992), and in the frontal cortex as the disease progresses (Kuwert *et al.*, 1993; Leenders *et al.*, 1986). As shown from this evidence, Huntington's disease is associated with progressive neuronal loss, neurotransmitter and receptor change at the cortical and sub-cortical levels.

There is a significant relationship between the severity of neuronal loss, as graded by the Vonsattel system, and the degree of rated physical disability before death (Myers *et al.*, 1988). The change in physical disability can be evaluated by the Unified Huntington's Disease Rating Scale (UHDRS) (Huntington Disease Group, 1996). A group of 78 Huntington's disease patients was evaluated on the UHDRS twice, one year apart. The group total motor scale score increased significantly, by 5.97 units per year, from the first to the second evaluation (Siesling *et al.*, 1998). From this data, it would appear that the change in Huntington's disease progression, especially in terms of motor disturbance, is measurable.

Motor changes in Huntington's disease, such as bradykinesia and dystonia, may be more reliable as measures of stage of disease than measures of chorea (Girotti *et al.*, 1988). Longitudinal assessment is important in understanding disease progression. The MRP paradigm offers a valuable measure of the movement preparatory activity of the cortex, and bradykinesia is readily measured by the tapping task.

The MRP of nine early to middle stage Huntington's disease and nine age-matched controls was recorded twice, once at the end of 1997 and more than two years later in early 2000. They performed an externally cued tapping task, with a strategy to anticipate and prepare the movement in advance. It was expected that there would be a decrease in pre-movement activity of the Huntington's disease group over the two-year period between the two testing sessions, due to the cortical and sub-cortical neurodegeneration associated with the disease.

METHOD

Participants

Eight male and one female Huntington's disease patient, age at first testing session 44 - 63 years (mean age 54.1, SD 6.7 years), and seven male and two female control participants, age at first testing session 46 - 59 (mean age 53.9, SD 5.3 years) were tested. All participants were right handed (Patterson and Bradshaw, 1975).

The diagnosis of Huntington's disease was confirmed by CAG repeat length for five of the participants and their CAG repeat lengths varied from 42-44. One other Huntington's disease participant had significant linkage with two family members with confirmed CAG lengths above 40. The other three Huntington's disease participants all had family histories of the disease and were assessed by a psychiatrist who confirmed diagnosis.

The Huntington's disease patients were assessed on the UHDRS at the second testing session (Huntington Disease Group, 1996), and scored between 3 and 55 (mean UHDRS score 28.00, SD 17.90). The UHDRS scores unfortunately were not available from the first testing session. On the Shoulson and Yahn rating scale (Shoulson and Fahn, 1979), all patients scored between 0 and 2.5. The duration of disease at the first testing session of the Huntington's disease group, varied between one and sixteen years (mean 6.22, SD 4.47 years).

All participants were screened for histories of stroke, serious head injury and other neurological disturbances. All participants were screened for dementia using the STMS (Kokmen *et al.*, 1987). There was no differential change over time for either group, as found by a two-way ANOVA (Group by Testing Session). Only one Huntington's

disease patient scored beneath the cut-off point of 29, in the second testing session. He was included in the experiment, as he understood the testing instructions.

Participants' depression levels were assessed using the MAS at the 1997 and 2000 testing sessions (Yesavage *et al.*, 1983). There was no significant difference between the two groups on the MAS scores and there was no differential change in scores between the two groups over the two testing sessions, as tested by a two-way ANOVA (Group by Testing Session).

Participants were not withdrawn from their medication. Clinical data are shown in Table 6.1. Informed consent was obtained from each participant in accord with the Helsinki declaration and all experimental work was carried out under the approval of the Kingston Centre Research and Ethics Committees and the Monash University Standing Committee on Ethics in Research on Humans.

Procedure

Participants performed a right-handed, sequential button-pressing task using the tapping board, consisting of two parallel rows of ten buttons, beneath which were LEDs. The LEDs illuminated a ten-button pathway for sequential button pressing, which was used for all tasks of the experiment (see Figure 2.2). All the LEDs were initially illuminated and during the experimental trials the lights progressively extinguished from right to left at a rate of one every four seconds.

Participants were required to hold down each illuminated button (moving from right to left) until the light underneath was extinguished (always a period of 4 s), then to press the next illuminated button in the sequence as quickly as possible.

Participants were explicitly instructed to try to anticipate extinction of the light cue, so that when the cue was given they were ready to respond. Thus they were given the strategy used in the previous experiments.

The methodology involved in recording the MRPs was described in Chapter Two. Characteristics of average potentials and subtracted functional components for each participant in each task were quantified by the following measures.

Table 6.1: Clinical data for Huntington's disease patients.

Participant	Age (years) 1997	Sex	Duration of disease (years) 1997	STMS 1997	STMS 2000	MAS 1997	MAS 2000	Medication	Dose (mg/day)	UHDRS motor subscale 2000	Triplet repeat score
1	60	M	8	37	37	0	1	-	-	31	42
2	54	M	8	31	31	8	2	Tetrabenazine	75	48	43
3	52	M	4	29	25	16	5	-	-	26	
4	58	M	16	35	36	7	7	-	-	55	**
5	63	F	8	33	29	15	10	-	-	44	
6	44	M	3	35	35	11	11	-	-	19	44
7	47	M	1	36	33	4	2	Sertraline	100	15	42
8	57	M	5	36	37	4	3	-	-	3	
9	47	M	3	36	37	0	3	-	-	11	43

Notes: Dashes indicate that the participant was not taking medication.
STMS – Short Test of Mental Status
MAS – Mood Assessment Scale
UHDRS – Unified Huntington's Disease Rating Scale
** HD participant had two family members with confirmed CAG lengths above 40.

Early Slope

Linear regression was used to calculate the average slope of the potential over the period from 1500 to 500 ms prior to movement onset. This is a measure of neural activity relating to the early component of the MRP.

Peak amplitude

The maximum amplitude of the potential occurs near the time of the cue, and reflects the combined activity of early and late components of the MRP, which overlap around the time of movement onset. The measure of the peak amplitude is arithmetically different from the peak amplitude of group mean MRPs. Peak amplitudes for the individual MRP traces vary slightly in time, and as a consequence are partly averaged out when combined into group mean MRPs. Therefore, this measure of peak amplitude may appear quite different from the peak amplitudes in mean MRPs, since it is measured from individual traces before averaging group data.

All measures were analyzed by two-way ANOVA (Group x Testing Session), and *t*-tests where appropriate.

RESULTS

Mean MRPs for the Huntington's disease patients and the controls, for the 1997 and 2000 testing sessions, recorded at electrode sites Cz, C3 and C4, are shown in Figures 6.1 and 6.2. Qualitatively, the control group appears to show greater pre-movement cortical activity prior to movement than the Huntington's disease group, at both time points. The greatest activity was always recorded at electrode site Cz. Therefore the quantitative statistics were confined to the recordings from site Cz. Single sample one-tailed *t*-tests were used to indicate whether the pre-movement preparatory activity, recorded from electrode Cz, significantly differed from zero. The control group's mean MRPs in 1997 (mean 5.72, SD 3.40 μV/s) [$t(8) = 5.040$, $p < 0.001$] and 2000 (mean 6.35, SD 3.08 μV/s) [$t(8) = 6.189$, $p < 0.01$] showed significantly increasing pre-movement activity prior to movement. The Huntington's disease group clearly showed increasing pre-movement activity before movement for both the 1997 (mean 2.50, SD 3.00 μV/s) [$t(8) = 2.501$, $p < 0.037$], and the 2000 testing session (mean 2.19, SD 3.52 μV/s) [$t(8) = 1.868$, $p < 0.05$].

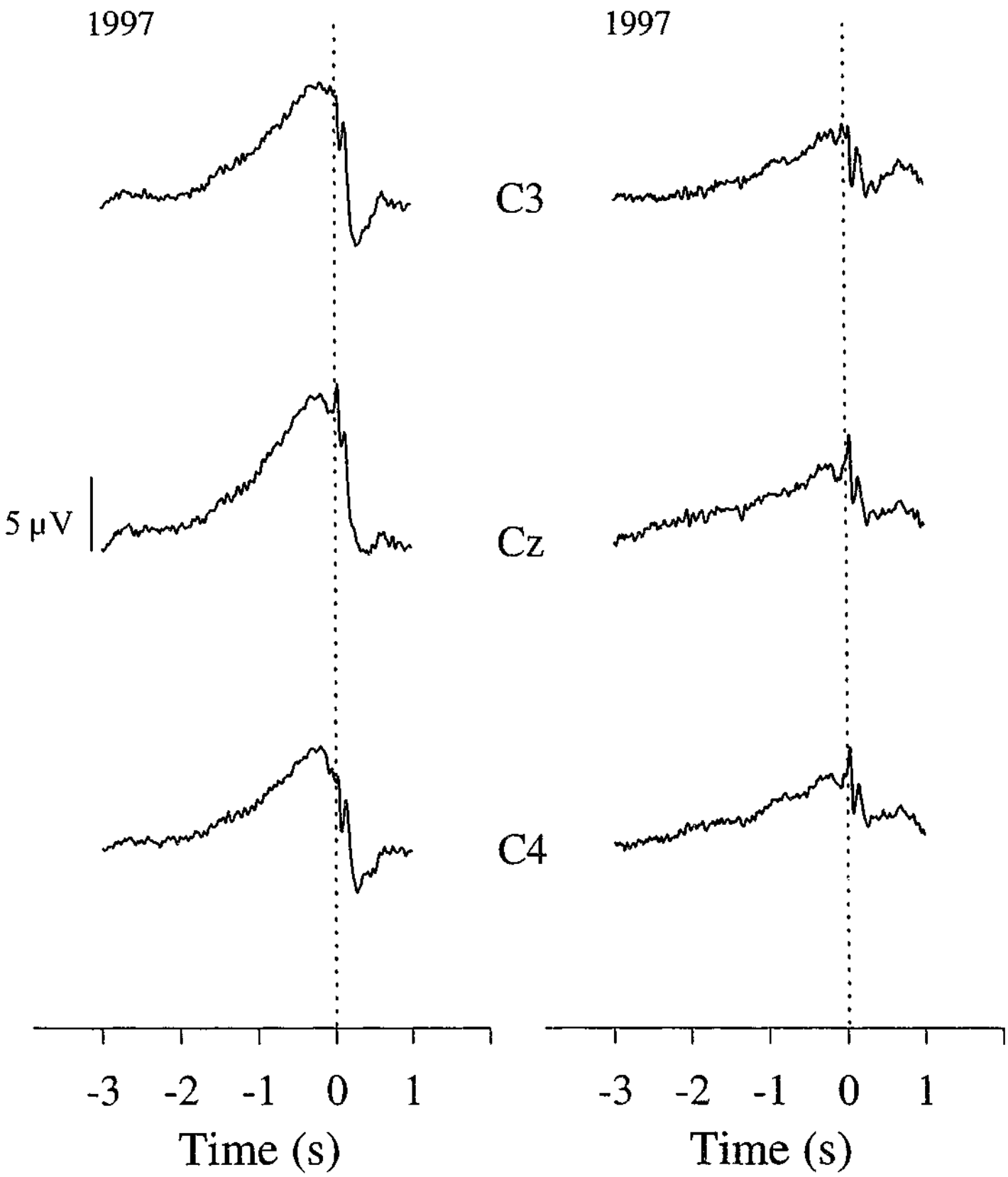


Figure 6.1: Grand average MRPs for control and Huntington's disease participants in the year 1997, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

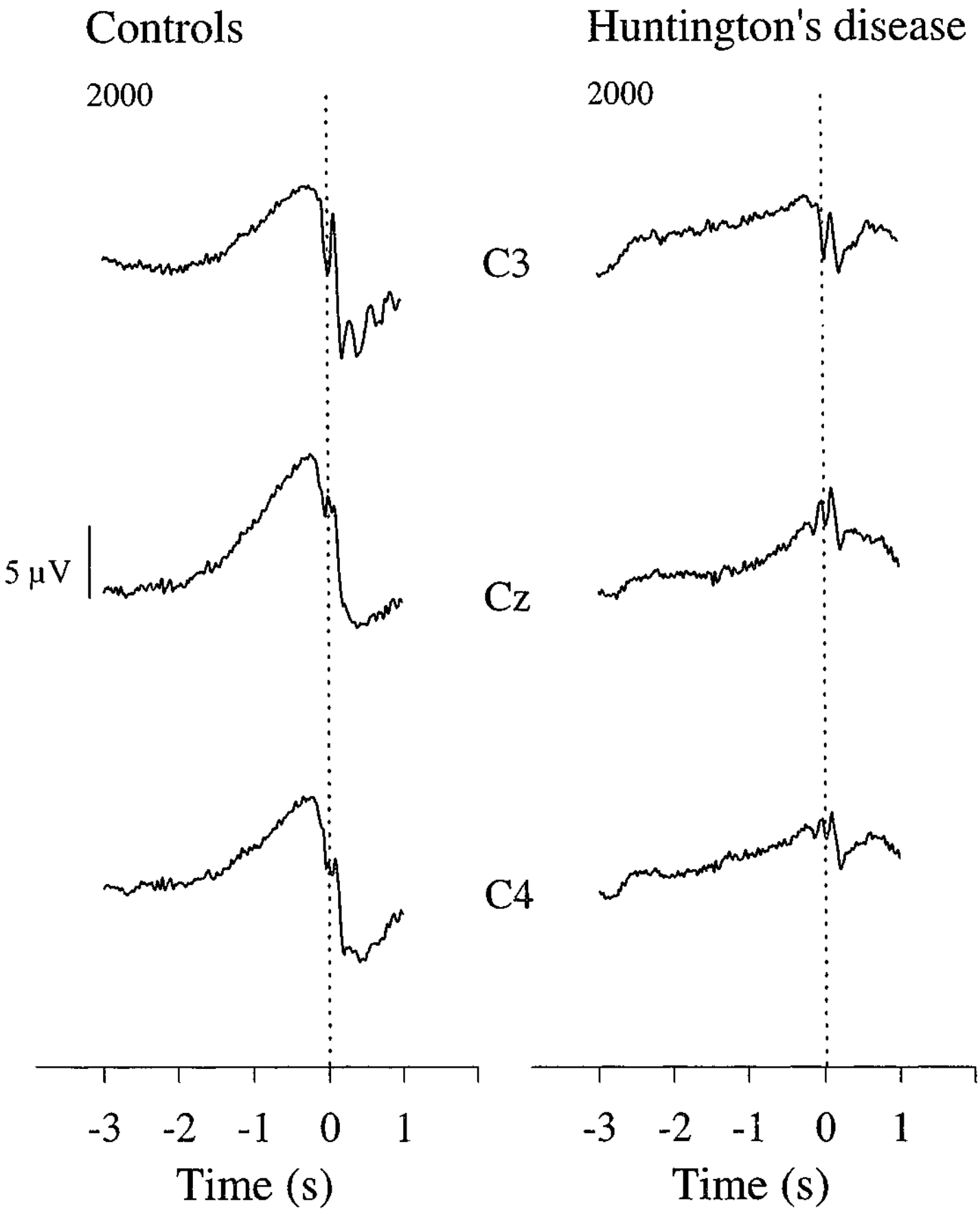


Figure 6.2: Grand average MRPs for control and Huntington's disease participants in the year 2000, recorded at electrode positions C3, Cz and C4. Potentials are shown from 3 s before to 1 s after movement, with the dotted line marking time of movement.

The control group (mean 6.03, SD 3.16 μV/s) produced a significantly greater early slope at position Cz than the Huntington's disease group (mean 2.35, SD 3.18 μV/s), [$F(1,16) = 6.603$, $p < 0.021$], over both testing sessions, (see Figure 6.3). There was no significant difference over time in the early slope for either group, and the Huntington's disease group did not significantly differentially change over time in comparison with the control group for early slope. Thus there was no Group by Testing Session interaction. Although the ANOVA produced no significant change over time in the early slope for the Huntington's disease group, the early slope of the pre-movement activity recorded in the year 2000 (mean 2.19 μV/s) was 12.4% (SD 17%) less than the 1997 early slope (mean 2.50 μV/s). In comparison, the early slope of the control group in the year 2000 (mean 6.35 μV/s) was 11% (SD 10%) more than the 1997 early slope (mean 5.72 μV/s).

The two groups did not significantly differ in the peak amplitude of the movement potential (see Figure 6.3). The peak amplitudes did not significantly change over time, and there was no significant interaction between the two groups and the testing sessions over time.

The control group (mean 234, SD 50 ms) was significantly faster in moving from one button to the next on the tapping board than the Huntington's disease group (mean 476, SD 232 ms), [$F(1,16) = 9.248$, $p < 0.009$]. There was no significant change over time in Movement Time for either group, and the Huntington's disease group did not differentially change in comparison with the control group.

DISCUSSION

The pre-movement cortical activity of nine Huntington's disease patients and age-matched controls was recorded twice, just over two years apart, to investigate any changes over time, which might reflect neurodegeneration. Unexpectedly, there was no significant change in the early slope or peak amplitude of the pre-movement potential, recorded at Cz, for either the Huntington's disease or control groups. This invariance of the pre-movement potential concurred with stability in the bradykinesia (from the Movement Time data), the STMS and the MAS scores for both groups.

As previously found in this thesis, the control group produced a steeper pre-movement potential than the Huntington's disease group, suggesting a deficient generation of pre-

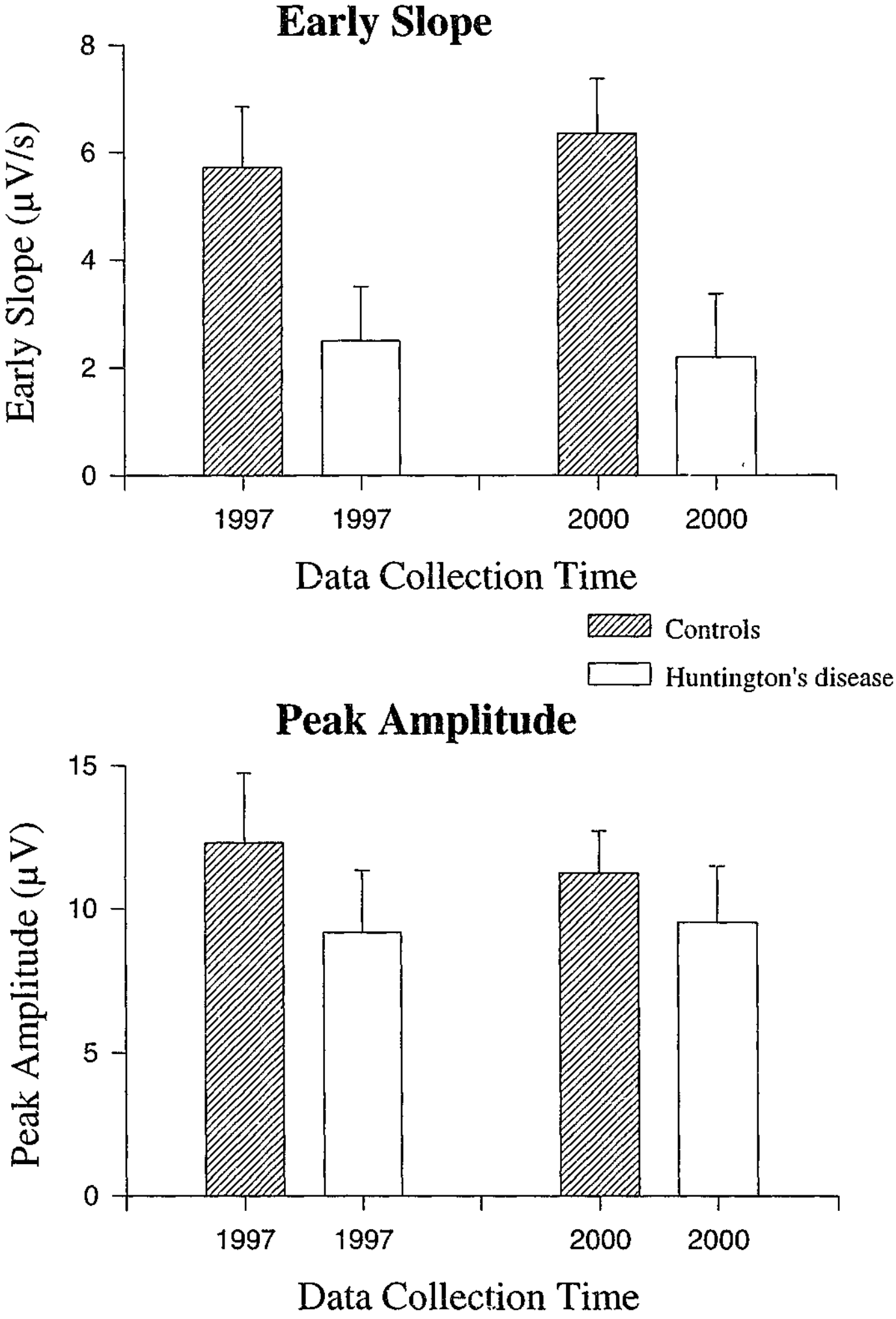


Figure 6.3: Means and standard errors of the Early Slope and Peak Amplitude of the control and Huntington's disease participants, in the years 1997 and 2000.

movement cortical activity within the diseased group. The peak amplitude of the two groups did not differ, as was previously found in Chapter 4, suggesting normal motor execution cortical activity in Huntington's disease. There was a significant difference between the two groups in how quickly they moved from one button to the next in the sequence, as has been shown in the last four chapters.

With the loss of medium spiny neurons within the caudate and putamen, output from the globus pallidus and substantia nigra to the thalamus and subsequently to the SMA, will be deficient in Huntington's disease (Albin *et al.*, 1989). This change in cortical activity due to sub-cortical cell loss would, it was expected, be reflected within the pre-movement cortical activity. If this loss of cells continued over time then it would be expected that there would also be a concurrent reduction of the pre-movement potential. This was not the case in this experiment. There are a number of possible reasons why this was not found.

Many of the Huntington's disease patients did show a slight decrease in early slope over time, but the amount of change was highly variable across all the Huntington's disease participants and only marginally different from the variability of amplitude changes over time found for the control participants. With only nine participants per group, this small apparent difference was not significant. Further research with a greater number of participants is recommended.

The Huntington's disease group was in the early to middle stages of the disease. The group had been diagnosed with the disease for a mean of 6.22 years at the first testing session. It is possible that the loss of cells within the caudate and putamen was widespread and maximal within the group by the first testing session, so that no further changes to the pre-movement potential were present to be detected. The people within the group, however, were only mildly to moderately affected, scoring between 0 and 2.5 on the Shoulson and Fahn rating scale (Shoulson and Fahn, 1979), and between 3 and 55 (mean 28) on the UHDRS, recorded only at the second testing session (Huntington Disease Group, 1996). Chorea was, however, present in all of the patients. The relationship between cell loss and clinical disability is still poorly understood and more research certainly needs to be done in this area.

Alternatively, the pre-movement potential may not be a sensitive enough measure to detect changes in the medial motor pathway, over a two-year degeneration time period.

Another explanation is that the cognitive strategy given to the participants enabled a number of different areas of the brain to participate in the preparatory activity, masking a deficiency due to the progressive loss of medial motor system neurons. Further longitudinal research would enable a better understanding of any changes in the preparatory activity due to the neurodegeneration of Huntington's disease and indeed any aging effects.

Behavioural Studies

To further document the motor deficits in Huntington's and Parkinson's diseases, a series of three experiments were conducted.

The SMA is known to be involved in the preparation of complex, sequential, internally derived, automatic movements. The output from the basal ganglia to the SMA is known to be disrupted in both Parkinson's and Huntington's diseases. Subsequently, the symptoms of both diseases involve bradykinesia and dysdiadochokinesis. The motor deficits in Parkinson's disease have been well studied: those of Huntington's disease understudied.

The aim of Chapters Seven and Eight was to document basic motor deficits in Huntington's disease. Bradykinesia is a motor feature of both Huntington's disease and Parkinson's disease. The bradykinesia of some patients with Parkinson's disease is improved upon the provision of external cues and the reason behind this phenomenon is equivocal. It is unknown if the same effect is found with Huntington's disease. Similarly, one symptom of Parkinson's disease is the bradykinetic sequencing effect. Some of the literature on Huntington's disease suggests that a sequencing effect is also found in this disease, but this claim is not beyond dispute. Chapter Seven described an experiment that investigated the effect of visual and auditory external cues on motor behaviour in Huntington's disease. Chapter Eight described an experiment that investigated if there was a deficit in the ability of HD patients to sequence movements together.

The aim of Chapter Nine was to provide further information about the effect of Parkinson's disease on sequential movement. Chapter Nine asked whether a complex, sequential, co-ordinated bimanual task improved with the provision of anti-parkinsonian medication in Parkinson's disease, in the presence and absence of external cues. By examining these motor deficits, a further examination of the role of the medial motor circuit in sequential, automatic, complex tasks was possible.

Chapter Seven - External cueing and movement performance in Huntington's disease

The provision of external cues facilitates the movement of Parkinson's disease patients (Martin, 1967). Horizontal lines set at appropriate stride lengths for the individual greatly improve gait performance in Parkinson's disease (Morris *et al.*, 1996). Micrographic handwriting of these patients can be normalised with the use of appropriately spaced horizontal lines and dots indicating the required height of the letters (Oliveira *et al.*, 1997). Abnormally low speech volume increases when Parkinson's disease patients are asked to speak more quickly (indirect method) or more loudly (direct cue) than normal (Ho *et al.*, 1999). The accuracy of finger tapping synchronised to an auditory signal will be significantly impaired when the external timing signal is withdrawn from Parkinson's disease patients (Freeman *et al.*, 1993). Bimanual co-ordination of these patients is significantly more variable and less accurate in the absence of an external timing cue (Johnson *et al.*, 1998).

A study by Georgiou *et al.* (1993) investigated different types of external cueing and their relative effects on Movement Time in Parkinson's disease (Georgiou *et al.*, 1993). Participants were asked to press buttons on a sequential, learned pathway. When the buttons of the pathway were illuminated with an LED, the Parkinson's disease patients performed the task in the fastest time. When the pathway was not illuminated the performance of the Parkinson's disease patients significantly slowed. In another condition, a metronome sounded at 4.8 Hz (the average speed of the control group) and the participants were required to press the buttons in time with this beat, in the absence of the light cue. In the presence of this auditory cue, the Movement Time of the Parkinson's disease group was as fast as in the presence of the visual light cue. The metronome gave *temporal* cues but the spatial aspects of the task were required to be internally determined. The visual cue gave *spatial* cues, but the temporal features of the task needed to be self-determined. There was no significant difference between these two types of cueing. It appears that the Parkinson's disease patients, in order to quicken movement, utilized the presence of an external type of cue, regardless of the sensory or dimensional input.

It is unclear why these external cues should benefit parkinsonian movement. There are a number of possible explanations. The external cue may act as a 'trigger' replacing a deficient internally-generated cue from the basal ganglia to the SMA, which may be impaired in the disease process (Brotchie *et al.*, 1991; Playford *et al.*, 1992; Schell and Strick, 1984). The cerebellum-lateral premotor area circuit may be playing a greater role in the preparation of movement when an external cue is available (Hanakawa *et al.*, 1999; Samuel *et al.*, 1997). This may explain the apparent reliance on external forms of cueing (Flowers, 1976). With the greater anatomical and functional loss in Huntington's disease, especially in terms of lateral premotor area functioning (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997), there may not be such a reliance upon external cues to aid movement in this disease.

An alternative explanation is that the external cue may be drawing attention to particular aspects of the task, allowing a bypass of deficient automatic processes and allowing more conscious processes to control movement (Morris *et al.*, 1996).

A comparison of motor performance between Parkinson's and Huntington's disease patients in the presence and absence of external cues may enable further understanding of the brain processes involved. In contrast with Parkinson's disease, it is unclear whether and under what conditions the provision of external cues will improve huntingtonian motor performance. For instance, it is unknown if the mere presence of a cue (be it visual or auditory) will benefit the Huntington's disease group's motor performance, as was found in Parkinson's disease. Only a limited number of studies have investigated the effect of external cues on motor performance of people with Huntington's disease (Bradshaw *et al.*, 1992; Churchyard *et al.*, 2000; Currá *et al.*, 2000; Georgiou *et al.*, 1995; Johnson *et al.*, 2000).

Earlier studies interpreted their Huntington's disease results in a similar fashion to those of Parkinson's disease, arguing that Huntington's disease patients showed a reliance on external cues (Bradshaw *et al.*, 1992; Georgiou *et al.*, 1995). "Huntington's disease patients, like parkinsonian patients, who also suffer from a basal ganglia disorder, require external visual cues to sequence motor programs effectively" (Georgiou *et al.*, 1995, p.472). These studies, however, failed to include a non-cued control condition, and unintended additional cognitive loads may have confounded their results.

In the Bradshaw *et al.* (1992) study, participants were required to tap buttons along a board under varying amounts of visual advance information. In a condition where the next movement to make was cued two movements ahead of the participant's current position (Cue C), an extra cognitive load of remembering the pathway was introduced. This was used to advantage by the control group to speed up movement, but proved particularly deleterious to Huntington's disease movement performance. The additional cognitive load may have confounded the results, making interpretation of reliance upon external cues difficult. Additionally, the Huntington's disease patients may have had difficulty with the preparation and initiation of the two sub-movements required in condition Cue A. In Cue A, the next button in the sequential, novel pathway was illuminated when the current button was released. Huntington's disease patients might have had particular difficulties in sequencing the two sub-movements together, rather than showing reliance upon external cues.

In the Georgiou *et al.* (1995) study, participants were required to tap buttons along a board under varying amounts of reduction in visual advance information. The Huntington's disease group was particularly poor at performing in the "high reduction in advance information" condition. In this condition participants were required to remember the correct button to press, three Movement Times and two Down Times (the time spent holding the button down) (in total approximately 1591 ms for Huntington's disease participants and 620 ms for control participants) in advance of the actual button press. The high reduction in advance information, with its inherent discrimination against bradykinetic movement, disadvantaged the Huntington's disease participants. The longer Movement Time and the progressive slowing found during this condition in the Huntington's disease group therefore may have been confounded by the cognitive loading of the high reduction in advance information.

A more recent study by Currà *et al.* (2000) investigated externally and internally cued well-learnt, sequential movement by Huntington's disease patients (Currá *et al.*, 2000). Targets changing from white to black on the pathway externally cued the movement. Participants waited a randomly variable time before the next sub-movement was cued. The contrast condition was internally cued. For both condition types, the Huntington's disease group was significantly slower than the control group. Both groups executed the externally cued movement more slowly than the internally cued movement, a result

that to some extent may be explained by the variable timing nature of the externally cued condition. Due to the variable nature of the external cue, the participants would not have been able to model the movement as effectively as in a predictably or self-timed sequence.

The variability and accuracy of Huntington's disease patients' bimanual co-ordination (Johnson *et al.*, 2000) did not improve with the presence of an external auditory cue, in contrast with the performance of Parkinson's disease patients (Johnson *et al.*, 1998). A similar result was found with the gait performance of Huntington's disease patients (Churchyard *et al.*, 2000), which did not improve in the presence of an external auditory cue, in comparison with that of Parkinson's disease patients (Morris *et al.*, 1994). As argued in Chapters Two and Four, with the greater anatomical and functional loss, Huntington's disease patients may not rely upon external cues.

This experiment was designed to assess if the provision of external cues would facilitate unimanual sequential upper-limb movement by patients with Huntington's disease. Care was taken to avoid any confounding of results due to unintended cognitive loads. A non-cued condition was included in the design. Potential sub-movement issues were avoided by not including a condition where a movement was required before the cue was presented. The cue was always available and so movement time was not partially reliant upon the presentation time of the cue, and the movement was well-learnt. Participants were asked to perform a right-handed, sequential, button-pressing task on a well-learnt pathway on the tapping board, under a number of conditions. In the Visual Cue 1 condition, visual spatial light cues were available outlining the pathway to be performed on the board. In the No Visual Cue 1 condition, the lights were extinguished, and participants needed to cue internally the movement themselves. In the Auditory condition, an external auditory metronome cue was used to provide timing cues to the participants. The Visual Cue and No Visual Cue conditions were then repeated to control for fatigue and practice effects.

It was hypothesised that the Huntington's disease group would generally be slower in movement than the control group. It was also hypothesised that there would be no effect of Cue for either group, i.e. that there would be no difference between performance under the visual cues (Visual Cue 1), auditory cues (Auditory), or the absence of any type of cue (No Visual Cue 1), for either group.

METHOD

Participants

Nine male and three female participants with Huntington's disease, aged 39-65 (mean age 52.9, SD 8.1 years), and nine male and three female control participants, aged 38-65 (mean age 53.7, SD 8.9 years) took part in the study. All were right-handed (Patterson and Bradshaw, 1975).

The diagnosis of Huntington's disease was confirmed by CAG repeat length (Huntington's Disease Collaborative Research Group, 1993) for 5 of the participants (Gusella *et al.*, 1997). One other Huntington's disease participant had two family members with confirmed CAG lengths above 40. The remaining Huntington's disease participants had family histories of the disease, were assessed and a psychiatrist confirmed diagnosis.

On the Shoulson and Fahn rating scale ((Shoulson and Fahn, 1979), all participants scored between 0 and 2.5. All of the Huntington's disease participants were rated on the UHDRS (Huntington Disease Group, 1996) and scored between 11 and 55 (mean UHDRS score 37.25, SD 14.75). The duration of disease varied between 2 and 12 years (mean 6.42, SD 3.26 years).

All participants were screened for histories of stroke, serious head injury, other neurological disturbances, and for dementia using the STMS (Kokmen *et al.*, 1987), when English was the first language of the participant. Participants' depression levels were assessed using the Beck Depression Inventory (BDI) (Beck *et al.*, 1961). The Huntington's disease group (mean BDI score 6.67, SD 4.31) was significantly more depressed than the control group (mean BDI score 3.17, SD 2.86), [$F(1,22) = 5.494$, $p < 0.029$].

Participants were not withdrawn from their medication. Clinical data are shown in Table 7.1. Informed consent was obtained from each participant in accord with the Helsinki declaration and all experimental work was carried out under the approval of the Kingston Centre Research and Ethics Committees and the Monash University Standing Committee on Ethics in Research on Humans.

Table 7.1: Clinical data for Huntington's disease patients.

Chapter 7

Participant	Age (years)	Sex	Duration of disease (years)	STMS	BDI	Medication	Dose (mg/day)	UHDRS motor subscale	Triplet repeat score
1	62	M	10	37	0	-	-	31	42
2	56	M	10	31	6	Tetrabenazine	75	48	43
3	54	M	4	29	9	-	-	40	
4	39	M	5	30	16	Carbamazepine Thioridazine	300 35	50	
5	60	M	12	35	7	-	-	55	**
6	53	F	4	35	2	-	-	45	
7	45	M	4	34	7	-	-	19	44
8	48	M	2	33	3	Sertraline hydrochloride	100	15	42
9	47	M	4	34	4	-	-	11	43
10	65	F	7	31	11	-	-	44	
11	57	M	10	30	9	-	-	41	
12	42	F	5	*	6	-	-	48	

Notes: Dashes indicate that the participant was not taking medication.
STMS – Short Test of Mental Status
BDI – Beck Depression Inventory
UHDRS – Unified Huntington's Disease Rating Scale
* English was this participant's second language
** HD participant had two family members with confirmed CAG lengths above 40.

Procedure

Participants performed a right-handed, sequential button-pressing task using the tapping board, as described in Chapter Two. The same ten-button pathway was used for all conditions of the experiment; movement was from right to left along the board (see Figure 2.2). Participants were asked to move as quickly as possible along the pathway. Each participant was practiced on the pathway with the lights on, until they were confident they would be able to perform the movement without a light cue. Participants were required to perform the pathway error free, with no cue, four times before they could continue with the experiment.

There were five conditions in the experiment performed in the following order – Visual Cue 1, No Visual Cue 1, Auditory, No Visual Cue 2, Visual Cue 2. For statistical purposes, Block One refers to Visual Cue 1, No Visual Cue 1 and Auditory Cue and Block Two refers to Auditory Cue, No Visual Cue 2 and Visual Cue 2. Each condition consisted of 8 trials of 10 button presses, from which the group averages were derived. For all participants, at least two trials were practiced prior to the start of each recorded condition.

In the Visual Cue conditions, the LEDs illuminated the pathway and as the participant pressed each button, that particular LED extinguished, leaving the rest of the pathway still illuminated.

In the No Visual Cue conditions, the pathway was not illuminated and the participants needed to remember the pathway.

In the Auditory condition, the pathway was not illuminated and participants were required to press the buttons in the pathway in time with a metronome beat, which was preset at the particular rate of button pressing of each participant from the Visual Cue 1 condition previously performed.

There were three dependent variables recorded:

Movement Time

This is a measure of the mean time taken to move from the release of one button to the depression of the next button in the sequence, per group. This measure may reflect the

time taken to execute a movement (Georgiou *et al.*, 1993), but will also involve movement preparation components as well.

Down Time

This is a measure of the mean time that each button was held down for each condition, per group. This may reflect some aspects of the time needed to switch off the previous movement and the time needed to prepare for or initiate the next (Georgiou *et al.*, 1993).

Metronome pace

This is the mean of the participants' movement times of the Visual Cue 1 condition, which was used to set the individually tailored beat for the Auditory condition.

Data Analysis

All measures were analyzed by ANOVA (mixed factorial with unweighted means) and *t*-tests where appropriate.

RESULTS

The group averages, with standard error bars, for the dependent variables of Movement Time (MT) and Down Time (DT) are shown in Figures 7.1 and 7.2, for each of the task conditions.

Cues – Block One

Movement Time

To investigate the effects of the provision of Visual Cues, Auditory Cues and the control condition of No Visual Cue on Movement Time, a two-way ANOVA (mixed factorials with unweighted means) [Group (Huntington's disease and control) x Cue Type (Visual Cue 1, No Visual Cue 1 and Auditory)] was performed. There was a significant main effect for Group, [$F(1,22) = 28.603$, $p < 0.001$]. There was also a significant main effect for Cue Type, [$F(2,44) = 13.715$, $p < 0.001$]. A significant Group by Cue Type interaction was found, [$F(2,44) = 6.177$, $p < 0.004$]. There was a significant difference between the three cue types for the control group [$F(2,22) = 7.147$, $p < 0.004$] and for the Huntington's disease group [$F(2,22) = 10.101$, $p < 0.001$].

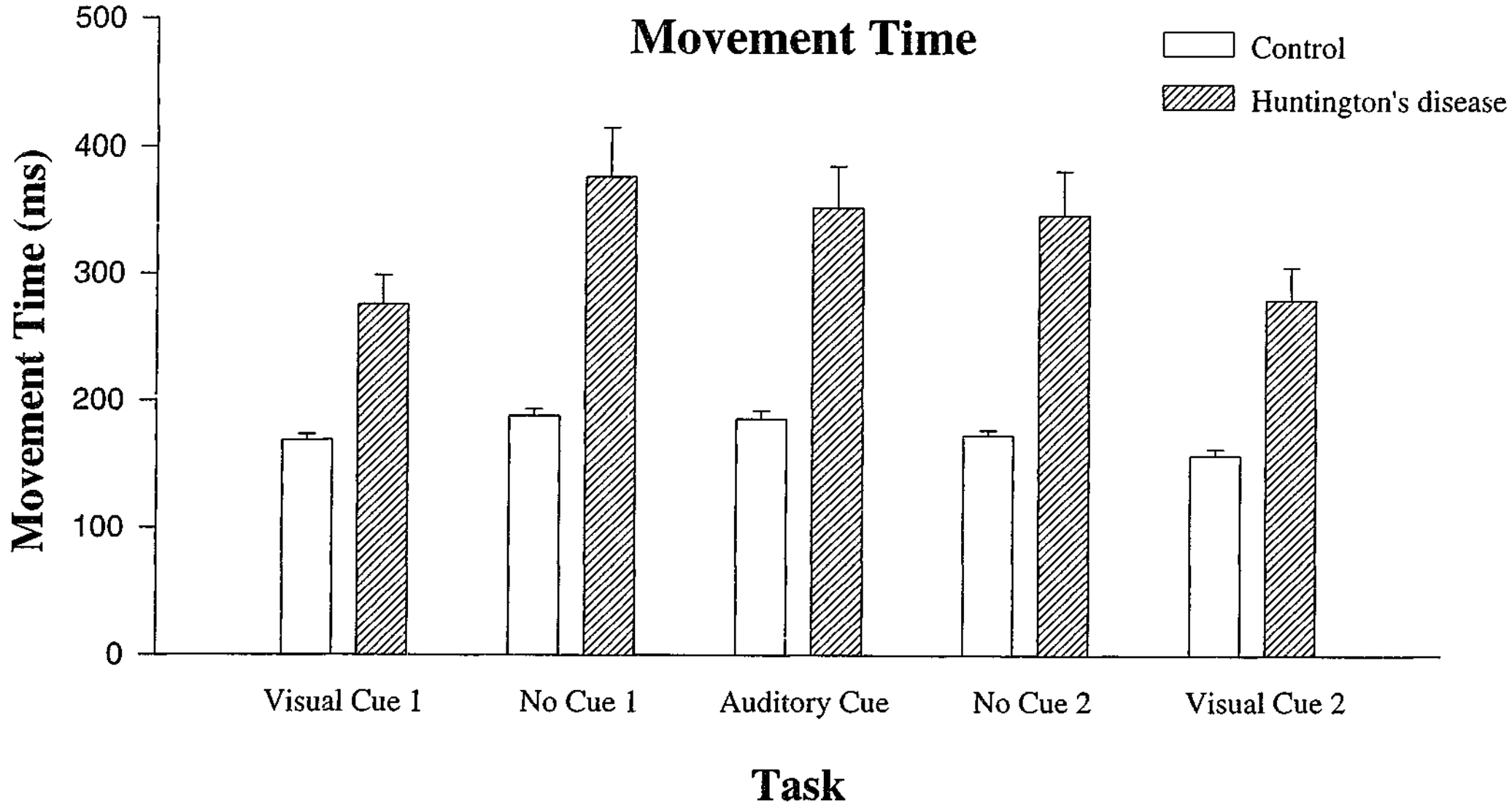


Figure 7.1: Means and standard errors of the Movement Time for the control and Huntington's disease participants, under the different task conditions.

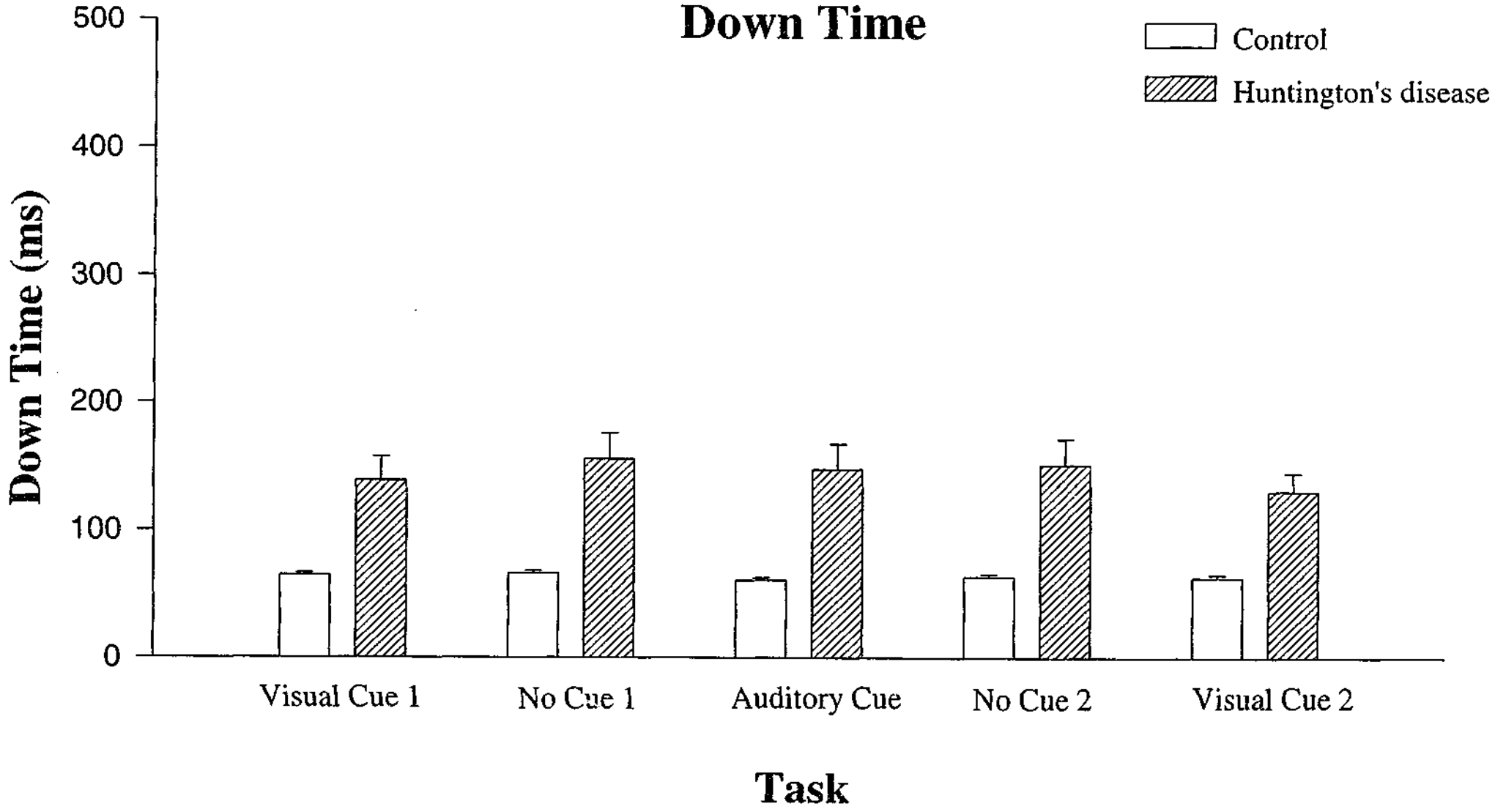


Figure 7.2: Means and standard errors of the Down Time for the control and Huntington's disease participants, under the different task conditions.

To identify which comparisons were providing the significant difference, three one-way ANOVAs were performed, per group, with the multiple comparisons corrected for Type One error using the Bonferroni correction (new alpha level of 0.016) (Keppel, 1991). For the control group, there was a significant difference between the Movement Time measured during the Visual Cue 1 (mean 169, SD 16 ms) and the No Cue 1 (mean 188, SD 17 ms) conditions, [$F(1,11) = 13.918$, $p < 0.003$], and between the Visual Cue 1 and the Auditory Cue (mean 186, SD 22 ms), [$F(1,11) = 12.868$, $p < 0.004$] conditions but there was no significant difference between the Auditory Cue and the No Cue 1 conditions, [$F(1,11) = 0.132$, $p > 0.05$]. For the Huntington's disease group, there was a significant difference between the Movement Time measured during the Visual Cue 1 (mean 276, SD 79 ms) and the No Cue 1 (mean 377, SD 38 ms) conditions, [$F(1,11) = 14.187$, $p < 0.003$], and between the Visual Cue 1 and the Auditory Cue (mean 353, SD 112 ms) conditions, [$F(1,11) = 30.880$, $p < 0.001$], but there was no significant difference between the Auditory Cue and the No Cue 1 conditions, [$F(1,11) = 0.777$, $p > 0.05$]. While the pattern of effects was similar for the two groups, the locus of the Group by Cue Type interaction probably lay in the observation that although the Huntington's disease group was overall slower than controls, the disease group was additionally slowed, compared with the controls, in the absence of the visual cue.

Down Time

To investigate the effects of the provision of Visual Cue 1, Auditory Cue and the control condition of No Visual Cue 1 on Down Time, a two-way ANOVA (mixed factorials with unweighted means) (Group x Cue Type) was performed. The Huntington's disease group (mean 147, SD 67 ms) spent a significantly longer time in the Down Time period than the control group (mean 64, SD 7 ms), [$F(1,22) = 18.633$, $p < 0.001$]. The type of Cue did not have any significant effects on Down Time and there was no interaction between Group and Cue Type.

Metronome pace

The metronome setting was significantly slower for the Huntington's disease group (mean 2.6, SD 0.70 Hz) than the control group (mean 4.34, SD 0.31 Hz), [$t(22) = 7.823$, $p < 0.001$], during the Auditory Cue condition.

Practice and fatigue effects

Movement Time

To investigate whether there were any effects of fatigue or practice over the course of the experiment, a three-way ANOVA (mixed factorials with unweighted means) [Group x Cue Type (Visual Cue or No Cue) x Order (Block One or Block Two)] was performed. There was a significant main effect for Order, with the movement time of both groups, across the two Cue Types, being just significantly faster in the second block (mean 240, SD 108 ms) than in the first block (mean 253, SD 112 ms), [$F(1,22) = 4.376$, $p < 0.048$]. There were no interactions involving Order as a factor, suggesting that neither practice nor fatigue effects affected the different Cue Types.

Down Time

To investigate whether there were any effects of fatigue or practice over the course of the experiment, a three-way ANOVA (mixed factorials with unweighted means) (Group x Cue Type x Order) was performed. There was no significant effect involving Order for Down Time.

As there was a main effect just reaching significance for the factor of Order for Movement Time, it was decided to test the Auditory condition against the Visual Cue 2 and No Cue 2 conditions. This was done to investigate whether the Cue Type effects found in the Block One Cues analysis were influenced by the practice effect.

Cues – Block Two

Movement Time

A two-way ANOVA (mixed factorials with unweighted means) [Group x Cue Type (Auditory, No Visual Cue 2, Visual Cue 2)] was performed. There was a significant main effect for Group, [$F(1,22) = 27.580$, $p < 0.001$]. There was also a significant main effect for Cue Type, [$F(2,44) = 15.351$, $p < 0.001$]. A significant Group by Cue Type interaction was found, [$F(2,44) = 4.242$, $p < 0.021$]. There was a significant difference between the three cue types for the control group, [$F(2,22) = 16.236$, $p < 0.001$], and for the Huntington's disease group, [$F(2,22) = 9.352$, $p < 0.001$]. To further determine the locus of the above interaction, three one-way ANOVAs were performed, per group, with the multiple comparisons corrected for Type One error using the Bonferroni

correction (new alpha level of 0.016) (Keppel, 1991). For the control group, there was a significant difference between the Movement Time measured during the Visual Cue 2 (mean 158, SD 17 ms) and the No Cue 2 (mean 173, SD 15 ms) conditions, [$F(1,11) = 23.786$, $p < 0.001$], and between the Visual Cue 2 and the Auditory Cue (mean 186, SD 22 ms), [$F(1,11) = 26.742$, $p < 0.001$] conditions, but there was no significant difference between the Auditory Cue and the No Cue 2 conditions, [$F(1,11) = 4.953$, $p > 0.048$]. For the Huntington's disease group, there was a significant difference between the Movement Time measured during the Visual Cue 2 (mean 280, SD 89 ms) and the No Cue 2 (mean 348, SD 120 ms) conditions, [$F(1,11) = 8.776$, $p < 0.013$], and between the Visual Cue 2 and the Auditory Cue (mean 353, SD 112 ms) conditions, [$F(1,11) = 35.175$, $p < 0.001$], but there was no significant difference between the Auditory Cue and the No Cue 2 conditions, [$F(1,11) = 0.079$, $p > 0.05$]. The locus of the Group by Cue Type interaction probably lay in the observation that the Huntington's disease group was additionally slowed, compared with the controls, in the absence of the visual cue.

The pattern of results was similar for the two groups, as it was for the Block One Cues analysis of Visual Cue 1 and No Cue 1. Overall, this shows that, although there was some general change in Movement Times between the first and the second blocks of the experiment, which differed slightly between groups, these were small in comparison with the differences between conditions. The practice effects do not therefore influence the differences between the Cue Types.

DISCUSSION

The Huntington's disease group was always significantly slower in moving from one button to the next, and spent a significantly longer time holding down each button on the tapping board than the control group, supporting the first hypothesis. This was found irrespective of the type of cue available. This suggests a generalised deficit in preparing and executing a simple button-pressing task in Huntington's disease. Bradykinetic and akinetic movements have previously been reported in Huntington's disease groups (Girotti *et al.*, 1988; Thompson *et al.*, 1988).

Both groups were significantly faster moving from one button to the next in the presence of the external Visual cue, in comparison with the Auditory cue and No Cue

conditions. The Huntington's disease group, however, was disproportionately affected by the lack of a visual cue, as indicated by the significant Group by Cue Type interaction, for Movement Time. The provision of an auditory timing cue did not significantly improve the Movement Time in comparison with the No Cue condition, for either group. This latter result is in direct contrast with those results typically found in Parkinson's disease (Georgiou *et al.*, 1993), and is similar to results found in Huntington's disease studies on bimanual co-ordination (Johnson *et al.*, 2000) and gait (Churchyard *et al.*, 2000). Although the Huntington's disease group was significantly slower overall in Movement Time than the control group, the provision of the external visual cue significantly improved movement time of both groups. Thus the second hypothesis was not supported.

Of all cue types, the Visual Cue was most beneficial to both the Huntington's disease and control groups. This cue provided congruous spatial information about where the finger was to be placed next, thus there was no additional task of remembering the pathway. The Huntington's disease group, like the control group, was able to utilise these cues, which proved to be the most salient for movement performance. The Auditory Cue did not provide any special benefit to movement performance, as both groups performed the tapping task to the same degree of movement performance as for the No Cue 1 condition. In the Auditory Cue condition, there was the additional task of remembering the pathway, as the lights had been extinguished. The Auditory Cue provided incongruous timing information and acted as a stimulus to move at the individual rate of each participant during the Visual Cue 1 condition. There was, however, a significant slowing of movement in the absence of the visual cue, suggesting that the participants were not utilising the auditory cue.

The improved performance of Parkinson's disease patients with the provision of congruent and incongruent external cues indicates that the cues are simply stimulating the overall attention of the patients. This results in improved movement production through the use of conscious control mechanisms (Morris *et al.*, 1996). It is possible that, with the cognitive decline associated with Huntington's disease, the external cues provided for the task are required to be congruous. In this tapping task, the visual light cues provided spatial information, and the movement performance was significantly faster than with the provision of the auditory and the absence of any cue.

The findings of this study may be compared with the findings from the Georgiou *et al.* (1993) study. In that study the movement of the Parkinson's disease group was as fast in the presence of the metronome (with no visual cue), as in the presence of the visual cue (Georgiou *et al.*, 1993). The Parkinson's disease group appeared to benefit from the presence of either a timing or a spatial cue to improve performance, whereas in this study the Huntington's disease group, like the control group, did not use the timing (auditory) cue. One important difference between the two studies was the pace of the metronome. In the Georgiou *et al.* (1993) study the metronome was set at 4.8 Hz, which was the average speed of the controls ascertained during a pilot study. The Parkinson's disease patients were required to perform movement at a speed much faster than even their performance with the light cue available. What they actually performed was a button press on approximately every second beat of the metronome: a speed, which incidentally was not significantly different from their speed with the light cue available. In this study, the metronome speed was tailored to the individual's mean speed during the Visual Cue 1 condition. Neither group was able to match movement performance to the auditory sound, suggesting a natural preference for visual guidance.

One other difference between the Georgiou *et al.* (1993) study and this present study was in the control group data. In the Georgiou *et al.* (1993) study the control group showed no difference between the Lights Present and the Lights Absent 1 conditions, in terms of movement time. In the present study, the control group was significantly slower without the aid of the visual cue. There may have been a differential speed/accuracy trade-off between the two studies, with the Georgiou *et al.* (1993) controls favouring speed and the controls in the present study favouring accuracy.

Huntington's disease patients did not behave in a fully parkinsonian manner with regards to the reliance on external cues. They were slower than controls across all the cue types, but like parkinsonian patients, were especially slowed in the absence of external <u>visual</u> cues. They did not show, however, the parkinsonian reliance on *any* type of external cue. It is a novel finding that there was no benefit from an external <u>auditory</u> timing cue in unimanual upper limb movements in Huntington's disease, a conclusion that is important in terms of possible rehabilitation strategies. This may have occurred because attentional resources were focused on the primary task of tapping, to which the visual cues were most congruent, (to the detriment of the auditory

cue). Alternatively, huntingtonian anatomical dysfunction incorporating the lateral premotor area may have negated the external cue benefits previously seen in Parkinson's disease (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997).

Chapter Eight - Sequential motor control in Huntington's disease

One clinical symptom of Parkinson's disease is the progressive slowing of sequential movement. If a person with the disease is asked, for instance, to perform a finger to thumb opposition task quickly, the movement will progressively slow and the movement amplitude will reduce in size. This sequencing effect is considered characteristic of the disease and is incorporated into several subscales on the Unified Parkinson's Disease Rating Scale (UPDRS) (Richards *et al.*, 1994; Weiner and Lang, 1989).

The progressive slowing of sequential movement in Parkinson's disease has been tested experimentally. Parkinson's disease patients are slower than controls to initiate and execute sequential movements (Agostino *et al.*, 1998; Jones *et al.*, 1994; Pastor *et al.*, 1992b; Stelmach *et al.*, 1987). Movement times progressively slow as the sequence progresses (Agostino *et al.*, 1992; Currá *et al.*, 1997; Georgiou *et al.*, 1994; Rogers *et al.*, 1997). Switching between two different tasks as part of a movement sequence is slower in Parkinson's disease than in controls (Benecke *et al.*, 1987; Harrington and Haaland, 1991). As movement cues are reduced, performance along the sequence becomes spatially and temporally unstable (Martin *et al.*, 1994). The extent of the sequencing effect in Parkinson's disease is probably dependent upon the number of sub-routines within the sequence, in that the longer the sequence the more severe the effect (Marsden, 1989).

Sequential movement is simply a chain of individual movements. The neural control of this type of movement may involve a higher cortical mechanism of planning, which is involved in selecting a motor program (Robertson and Flowers, 1990), or a set of neurons (Iansek *et al.*, 1995), or a neural pathway, which puts into process the execution of that movement series. If there is a problem in the mechanism of planning, this might result in an additive slowness of movement along the sequence, or it might simply result in overall bradykinesia.

Both the basal ganglia and the SMA are believed to play roles in the generation of sequences of movement. For instance, PET studies in normal humans (Böecker *et al.*, 1996) and neurophysiological recordings in monkeys (Kermadi and Joseph, 1995) have

implicated striatal involvement during sequential movements. The SMA is active during the performance of complex sequential movements (Catalan *et al.*, 1998; Jenkins *et al.*, 1994; Orgogozo and Larsen, 1979; Roland *et al.*, 1980; Shibasaki *et al.*, 1993). In comparison, single repetitive movement involves increased blood flow in the primary sensory hand area (Deiber *et al.*, 1991; Roland *et al.*, 1980). FMRI and Xenon-SPECT functional imaging studies show that the SMA-proper is more extensively activated for sequential than for fixed movements (Deiber *et al.*, 1999; Roland *et al.*, 1980). Single cell studies indicate that the SMA responds in advance of a remembered sequence of movements, or in the midst of a sequence (Tanji and Shima, 1994). Indeed, sequence specific neurones in the SMA respond to one particular movement sequence and not another (Mushiake *et al.*, 1991; Mushiake and Strick, 1995; Tanji and Shima, 1994; Tanji and Shima, 1996). MRP studies show greater pre-movement negative cortical activity prior to complex sequential rather than single movements (Lang *et al.*, 1988; Lang *et al.*, 1989; Simonetta *et al.*, 1991). The basal ganglia and the SMA may be seen as units in a greater motor preparation circuit.

Sequential movement involves the repetition of movement, and if the planning of the movement is deficient, then one result may be the additive slowing of movement down the sequence, as found in Parkinson's disease. Previous chapters in this thesis have suggested that Huntington's disease may lead to deficiencies in the preparation of movement, resulting in the bradykinesia evidenced in the disease. Deficits have been reported in sequential movement in Parkinson's disease. Huntington's disease is associated with basal ganglia cell loss and reduced activation of the SMA (Weeks *et al.*, 1997). Subsequently, Huntington's disease patients might also show a progressive sequencing effect. The UHDRS has this symptom as one of the components of the motor examination score (finger taps and pronate/supinate hands tasks), suggesting that it may be one clinical manifestation of the disease (Huntington Disease Group, 1996). It is unclear however, from experimental evidence, if this deficit in planning in Huntington's disease results in a sequencing effect as found in Parkinson's disease.

Three studies have found a sequencing effect in Huntington's disease (Georgiou *et al.*, 1995; Phillips *et al.*, 1995; Thompson *et al.*, 1988), whilst two studies have found no evidence of sequential slowing (Agostino *et al.*, 1992; Currá *et al.*, 2000). These studies varied in the type of movement, the number of different movements used in the

sequence, and the variation in movement length within the sequence. The common finding between all of these studies was that the Huntington's disease group was overall slower than the control group in performing the movements and had longer pauses between the movement elements. This study was designed to clarify this issue, with the performance of a group of Huntington's disease patients and their age- and sex-matched controls measured on a number of pathways along the tapping board.

Of related interest is the deficiency shown by Parkinson's disease patients to rescale their movements. When Parkinson's disease patients are asked to alternate between long and short movements on a pathway, their ability to speed up the long movement, so that the Movement Time between the two movement lengths is similar, appears to be affected. The long movements are disproportionately longer than those of the control group on both irregularly (Georgiou *et al.*, 1993) and regularly (Kritikos *et al.*, 1995) alternating pathways, in the presence (Georgiou *et al.*, 1993) and absence (Kritikos *et al.*, 1995) of external visual cues. This may suggest a deficiency in the preparation of movements. It might be expected that Huntington's disease patients would also show a deficit in the rescaling of movements which alternate between long and short lengths.

If Huntington's disease patients have difficulties in planning movements in advance (Georgiou *et al.*, 1995), then the regularity of the direction of movement might impact on movement performance. If the required movement involves a regular change in direction, planning of that movement may be simpler and easier to remember and subsequently movement time should be faster. In contrast, if the required movement involves irregular direction changes, then the movement will need to be constantly re-planned. If Huntington's disease patients have difficulties in preparing movements, this may be reflected in longer movement times.

This study endeavoured to map if a progressive slowness exists and if so, under what circumstances this manifests in Huntington's disease, to determine if this patient group shows a deficiency in rescaling movements of different lengths and whether the regularity of direction change has an effect on movement production. The required movement was always a finger tap, to eliminate any potential confounding effects of attentional resource allocation if two or more movement types were involved in a sequence. Four pathways were used which varied in terms of the regularity of movement direction change and the required movement length. It was expected that the

Huntington's disease group would show a sequencing effect, a deficit in rescaling movements of different lengths, and slower movement times when the movement direction changed irregularly.

METHOD

Participants

Nine male and three female participants with Huntington's disease, aged 39-65 (mean age 52.9, SD 8.1 years) and nine male and three female control participants, aged 38-65 (mean age 53.7, SD 8.11 years) took part in the study. All were right-handed (Patterson and Bradshaw, 1975).

The diagnosis of Huntington's disease was confirmed by CAG repeat length (Huntington's Disease Collaborative Research Group, 1993) for 5 of the participants (Gusella *et al.*, 1997). One other Huntington's disease participant had two family members with confirmed CAG lengths above 40. The remaining Huntington's disease participants had family histories of Huntington's disease and were assessed and diagnosed by a psychiatrist.

On the Shoulson and Fahn rating scale (Shoulson and Fahn, 1979), all participants scored between 0 and 2.5. All of the Huntington's disease participants were rated on the UHDRS (Huntington Disease Group, 1996) and scored between 11 and 55 (mean 37.25, SD 14.75). The duration of disease varied between 2 and 12 years (mean 6.42, SD 3.26).

All participants were screened for histories of stroke, serious head injury, other neurological disturbances, and for dementia using the STMS (Kokmen *et al.*, 1987), when English was the first language of the participant. Participants' depression levels were assessed using the BDI (Beck *et al.*, 1961). The Huntington's disease group (mean 6.67, SD 4.31) was significantly more depressed than the control group (mean 3.17, SD 2.86), [$F(1,22) = 5.494$, $p < 0.029$].

Participants were not withdrawn from their medication. Clinical data are shown in Table 8.1. Informed consent was obtained from each participant in accord with the Helsinki declaration and all experimental work was carried out under the approval of

Table 8.1: Clinical data for Huntington's disease patients.

Participant	Age (years)	Sex	Duration of disease (years)	STMS	BDI	Medication	Dose (mg/day)	UHDRS motor subscale	Triplet repeat score
1	62	M	10	37	0	-	-	31	42
2	56	M	10	31	6	Tetrabenazine	75	48	43
3	54	M	4	29	9	-	-	40	
4	39	M	5	30	16	Carbamazepine Thioridazine	300 35	50	
5	60	M	12	35	7	-	-	55	**
6	53	F	4	35	2	-	-	45	
7	45	M	4	34	7	-	-	19	44
8	48	M	2	33	3	Sertraline hydrochloride	100	15	42
9	47	M	4	34	4	-	-	11	43
10	65	F	7	31	11	-	-	44	
11	57	M	10	30	9	-	-	41	
12	42	F	5	*	6	-	-	48	

Notes: Dashes indicate that the participant was not taking medication.
STMS – Short Test of Mental Status
BDI – Beck Depression Inventory
UHDRS – Unified Huntington's Disease Rating Scale
* English was this participant's second language
** HD participant had two family members with confirmed CAG lengths above 40.

the Kingston Centre Research and Ethics Committees and the Monash University Standing Committee on Ethics in Research on Humans.

Procedure

Participants performed a right-handed, sequential button-pressing task using the tapping board, see Chapter Two for details. All participants were tested on four pathways on the tapping board, always moving from right to left (see Figure 8.1). These pathways varied according to the required movement length. The first pathway, called the Straight pathway, consisted entirely of short horizontal movements made along the top row of the tapping board. The second pathway, called the Zig-zag pathway, consisted entirely of long diagonal movements. The third and fourth pathways, called Mixed One and Two, were counterbalanced versions of mixed short and long movements, so when one movement was long on Mixed One, the same movement on Mixed Two was short. Overall, both were therefore of the same total length.

Participants rehearsed and then performed a pathway before any knowledge of the next pathway in the study. The order of presentation of each pathway was counterbalanced between the participants. They practised the pathways so that they were able to perform the movements without the provision of external cues, so that there would be some element of automaticity in the movements. The pathways were always illuminated with LEDs during data recording, to eliminate differential memory loads of the pathways. Data from the first, second and last button presses on the board were omitted from analysis, as these movements were of an intermediate length or no choice was involved in which button to press. Eight trials of nine button presses each were recorded of the participant's performance on each pathway, from which group averages were derived.

Two dependent variables were used to measure movement performance.

Movement Time

This is a measure of the mean time taken to move from the release of one button to the depression of the next button in the sequence. This measure may reflect aspects of the time taken to execute a movement (Georgiou *et al.*, 1993), but will also involve movement preparation components as well.

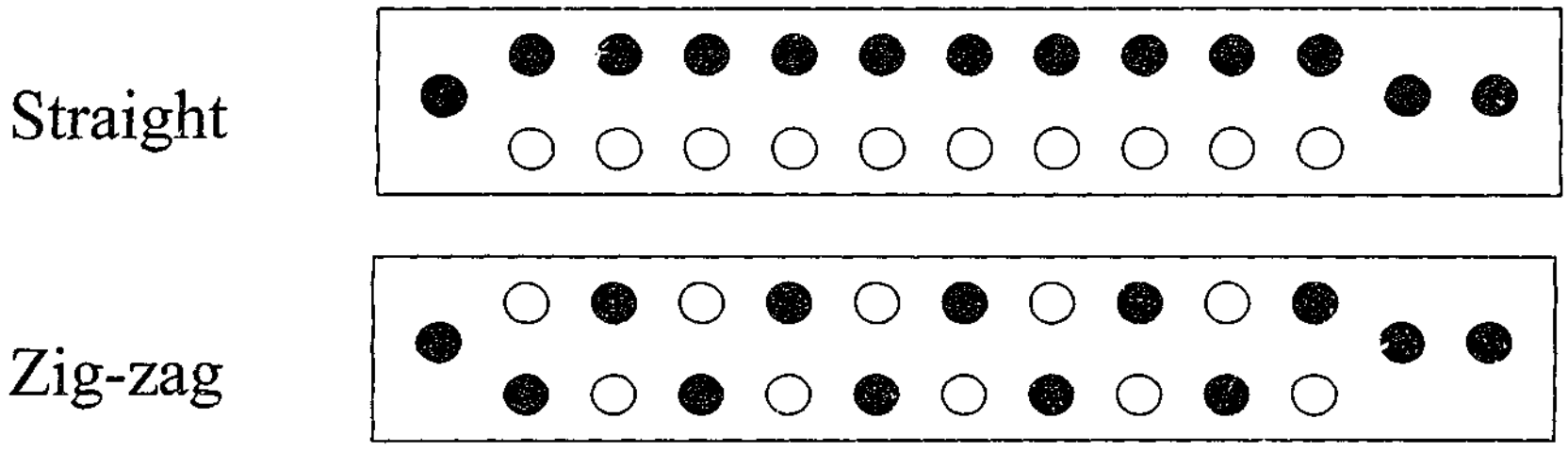


Figure 8.1: The four pathways on the tapping board, used in Chapter Eight. All participants used their right index fingers, and tapped from right to left along the board.

Down Time

This is a measure of the mean time that each button was held down for each condition. This may reflect some aspects of the time needed to switch off the previous movement and the time needed to prepare for or initiate the next (Georgiou *et al.*, 1993).

Data Analysis

There were four levels of analysis planned, to accommodate the hypotheses.

1. Overall analysis - Two-way ANOVAs [Group (Huntington's disease/Control) by Button position (1-9)] were used to analyse each pathway, to examine whether there were differences in Movement and Down Time across the different buttons in the sequence, and whether such differences varied between the controls and Huntington's disease groups.

2. Sequence effect – For the pathways where there were significant effects of Button position (above), the first three movements (early) and the last three movements (late) in the sequence were averaged and compared in a two-way ANOVA [Group by Sequence (early/late)]. This was done to determine whether significant differences in Movement and Down times across the buttons, found in the overall analysis, could be accounted for by a general slowing of movement throughout the sequence, as previously found in Parkinson's disease.

3. Movement Length – For the pathways where there were significant effects of button position, the long and the short movements were grouped and compared in a two-way ANOVA [Group by Length (long/short)]. This was to determine whether significant differences in Movement and Down time across buttons, from the overall analysis, were related to changes between long and short movement lengths, indicating difficulties in rescaling movements, as previously found in Parkinson's disease.

4. Regularity of direction - The Mixed pathway involved movements with an irregular direction change. The horizontal straight movements on the Straight pathway never involved a direction change while the diagonal zig-zag movements on the Zig-zag pathway required a regularly-alternating sequence of long movements. The three pathways cannot be directly compared as the Straight pathway consisted entirely of short movements, and the Zig-zag pathway consisted entirely of long movements,

with a mixture of long and short in the Mixed pathways. Thus the long movements on the Mixed pathways (irregular movement direction) were averaged and compared with the zig-zag movement times (long movements with a regular movement direction). The short movements on the Mixed pathways (irregular movement direction) were averaged and compared with the straight movement times (short movements with a regular movement direction). The regularity of movement direction change was analysed by two-way ANOVA [Group by Task (regular/irregular direction change)], for Movement and Down times, separately for the long, and the short, movements above.

RESULTS

The group averages, with standard error bars, for the dependent variables of Movement Time (MT) and Down Time (DT) are shown in Figures 8.2 to 8.5, for each of the pathways.

Overall analysis

Straight Pathway

Movement Time – The Huntington's disease group (mean 293, SD 84 ms) was significantly slower in moving from one button to the next on the Straight pathway than the control group (mean 193, SD 28 ms), [$F(1,22) = 16.972$, $p < 0.001$]. There was no significant difference between the Movement Times of any of the buttons, and there was no significant Group by Button position interaction.

Down Time – The Huntington's disease group (mean 135, SD 55 ms) was significantly slower in pausing between movements on the buttons than the control group (mean 64, SD 9 ms), [$F(1,22) = 18.538$, $p < 0.001$]. There was no significant difference between the Movement Times of any of the buttons, and there was no significant Group by Button position interaction.

Zig-zag pathway

Movement Time – The Huntington's disease group (mean 297, SD 73 ms) was significantly slower in moving from one button to the next on the Zig-zag pathway than the control group (mean 186, SD 28 ms), [$F(1,22) = 33.785$, $p < 0.001$]. There was no

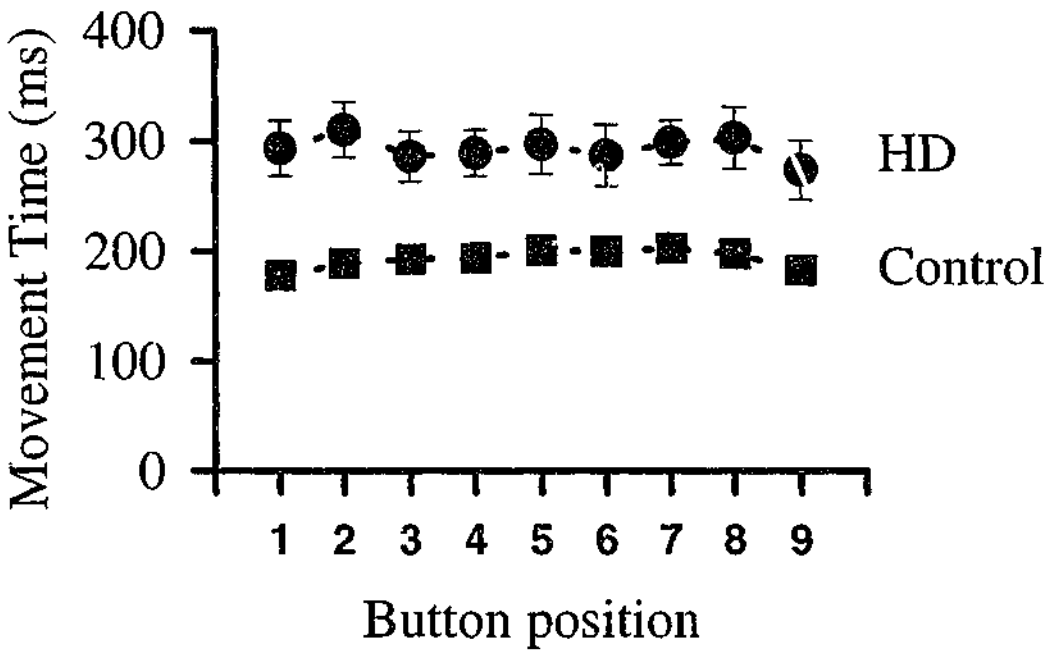


Figure 8.2: Means and standard errors of the Movement Time of the control and Huntington's disease participants, along each button position on the Straight and Zig-zag pathways.

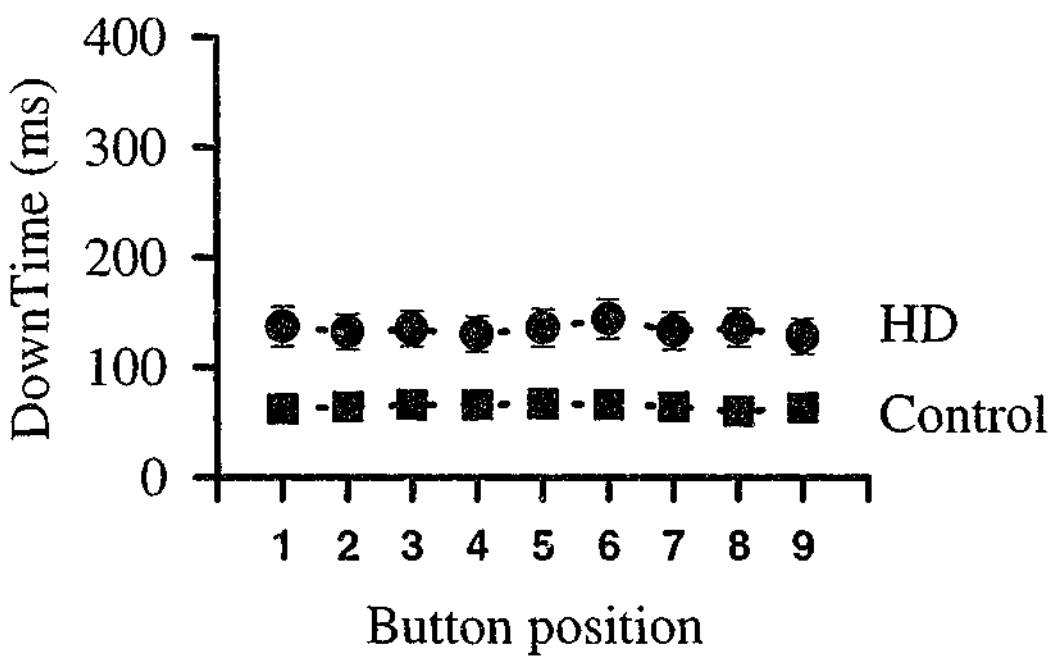
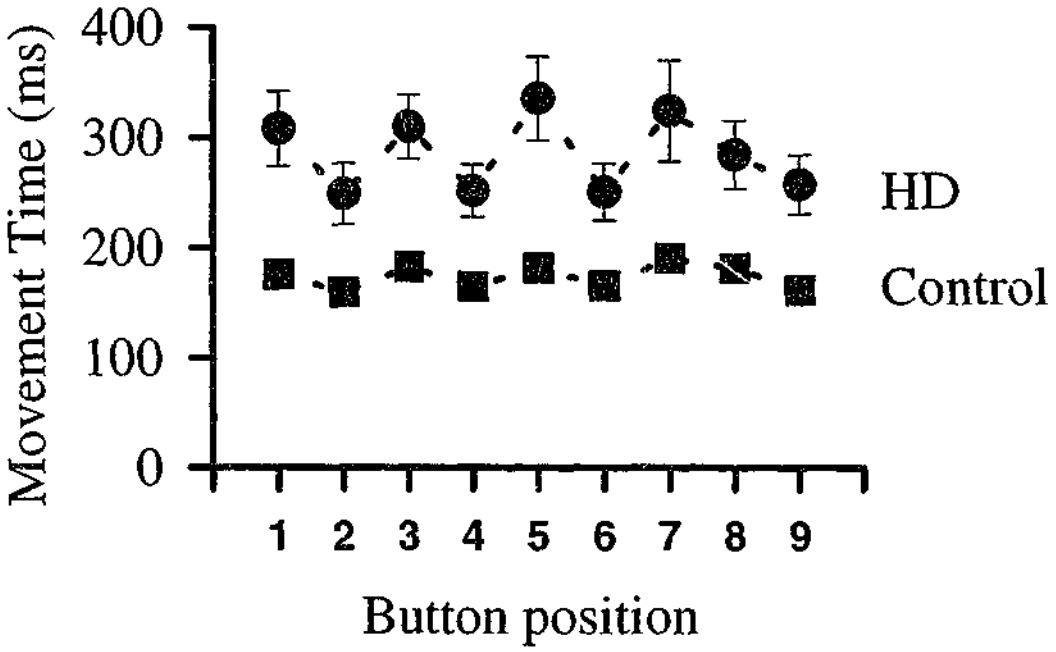


Figure 8.3: Means and standard errors of the Down Time of the control and Huntington's disease participants, along each button position on the Straight and Zig-zag pathways.

Movement Time - Mixed One Pathway



Movement Time - Mixed Two Pathway

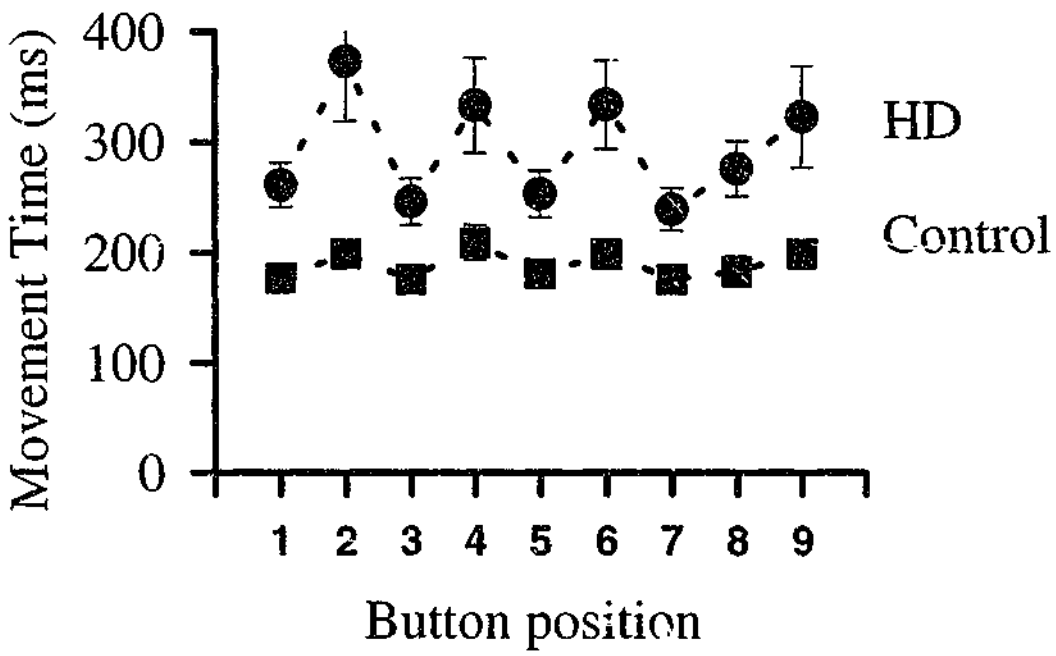
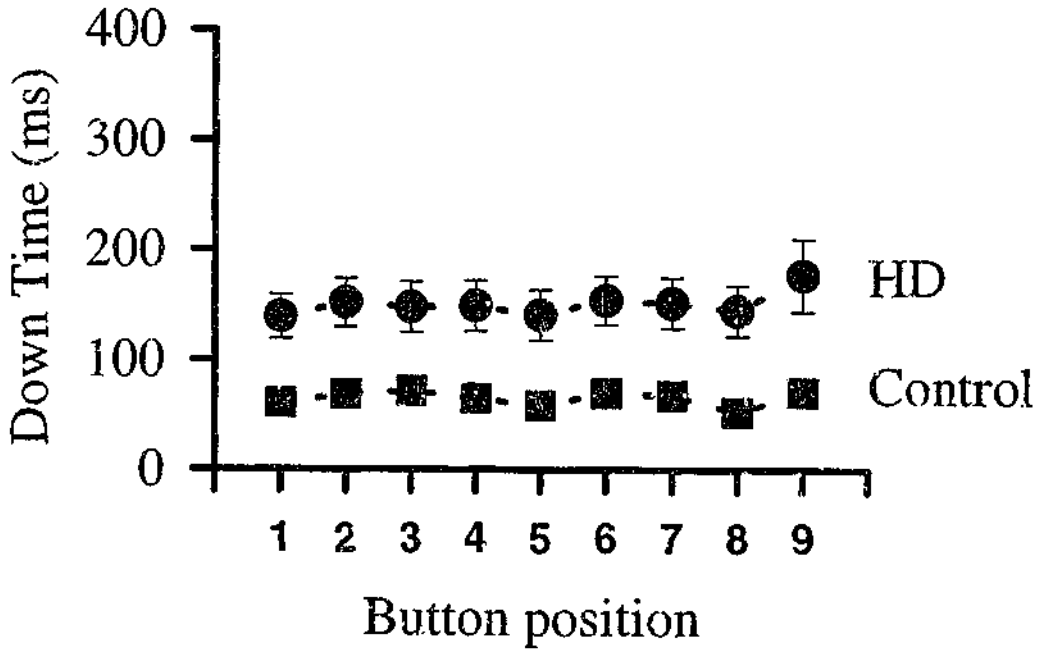


Figure 8.4: Means and standard errors of the Movement Time of the control and Huntington's disease participants, along each button position on the Mixed One and Mixed Two pathways.

Down Time - Mixed One Pathway



Down Time - Mixed Two Pathway

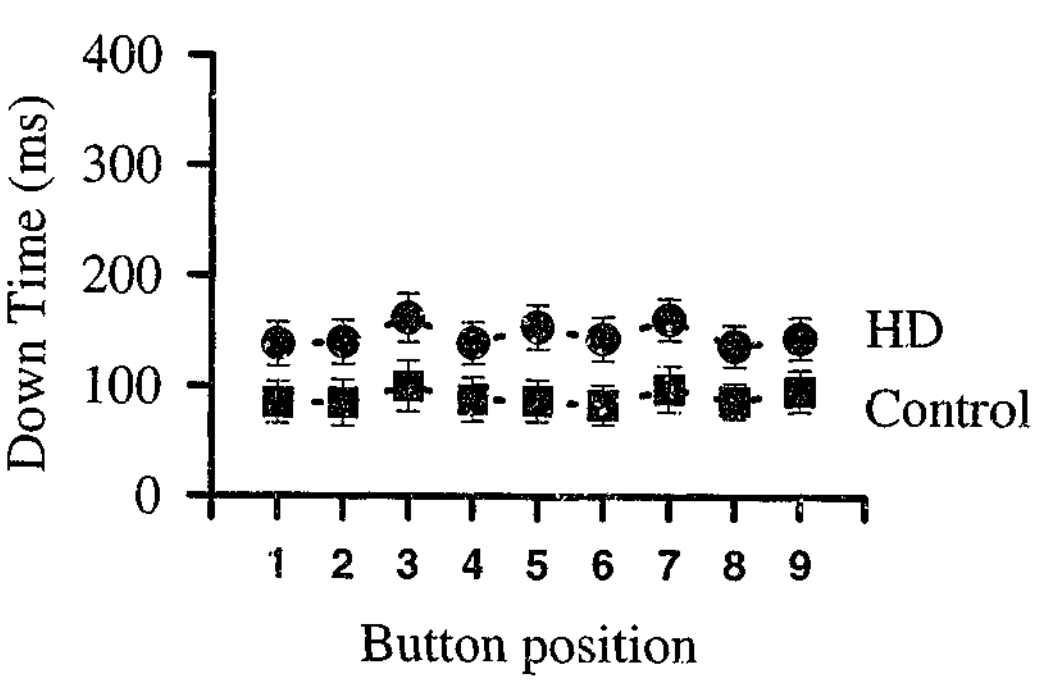


Figure 8.5: Means and standard errors of the Down Time of the control and Huntington's disease participants, along each button position on the Mixed One and Mixed Two pathways.

significant difference between the Movement Times of any of the buttons, and there was no significant Group by Button position interaction.

Down Time – The Huntington's disease group (mean 136, SD 62 ms) was significantly slower in pausing between movements on the buttons than the control group (mean 63, SD 11 ms), [$F(1,22) = 16.137$, $p < 0.001$]. There was a significant main effect for Button Position, [$F(8,176) = 5.803$, $p < 0.001$], but there was no significant Group by Button position interaction.

Mixed One pathway

Movement Time - The Huntington's disease group (mean 286, SD 112 ms) was significantly slower in moving from one button to the next on the Mixed One pathway than the control group (mean 174, SD 23 ms), [$F(1,22) = 13.734$, $p < 0.001$]. There was a significant difference between the Movement Times of the buttons, [$F(8,176) = 11.717$, $p < 0.001$], which was moderated by a significant Group by Button Position interaction, [$F(8,176) = 3.748$, $p < 0.001$]. This interaction was broken down by the factor of Group. The control group [$F(8,88) = 12.815$, $p < 0.001$] and the Huntington's disease group [$F(8,88) = 7.438$, $p < 0.001$] both showed a significant difference between the Movement Times recorded from the different Button Positions along the Mixed One pathway. With reference to Figure 8.4, this difference between the Button Positions for both groups was probably due to the difference between the long and the short movements, or may have been due to a sequencing effect. Subsequently the Movement and Down Times were analysed, in the sequencing and rescaling analyses (see below).

Down Time – The Huntington's disease group (mean 151, SD 80 ms) was significantly slower in pausing between movements on the buttons than the control group (mean 65, SD 11 ms), [$F(1,22) = 14.836$, $p < 0.001$]. There was a significant main effect for Button Position, [$F(8,176) = 2.994$, $p < 0.004$], but there was no significant Group by Button position interaction.

Mixed Two pathway

Movement Time - The Huntington's disease group (mean 293, SD 124 ms) was significantly slower in moving from one button to the next on the Mixed Two pathway than the control group (mean 189, SD 39 ms), [$F(1,22) = 11.207$, $p < 0.003$]. There was

a significant difference between the Movement Times of the buttons, [$F(8,176) = 9.088$, $p < 0.001$], which was moderated by a significant Group by Button Position interaction, [$F(8,176) = 3.476$, $p < 0.001$]. This interaction was broken down by the factor of Group. The control group [$F(8,88) = 6.780$, $p < 0.001$] and the Huntington's disease group [$F(8,88) = 6.250$, $p < 0.001$] both showed a significant difference between the Movement Times recorded from the different Button Positions along the Mixed Two pathway. The pattern of results of the Mixed Two pathway matched those of the Mixed One pathway. This is not surprising as the two pathways only differed in that when one movement was long on one pathway, the corresponding movement was short on the other pathway. Thus in a similar manner to the Mixed One pathway, the difference between the Button Positions for both groups was probably due to the difference between the long and the short movements, or may have been due to a sequencing effect. Subsequently the Movement and Down Times were again analysed, in the sequencing and rescaling analyses (see below).

Down Time – The Huntington's disease group (mean 147, SD 66 ms) was almost significantly slower in pausing between movements on the buttons than the control group (mean 90, SD 66 ms), [$F(1,22) = 4.241$, $p = 0.051$]. There was a significant main effect for Button Position, [$F(8,176) = 7.880$, $p < 0.001$], but once again there was no significant Group by Button position interaction.

Sequence Effect

Significant main effects for Button position were found in the Overall analysis in the Mixed One and Two pathways for Movement Time, and the Zig-zag, Mixed One and Two pathways for Down Time. Subsequently, two-way ANOVAs were used to compare Group with Sequence (early/late) for each dependent variable separately.

Mixed One pathway

Movement Time – The Huntington's disease group (mean 289, SD 107 ms) was significantly slower in moving from one button to the next than the control group (mean 175, SD 20 ms), [$F(1,22) = 12.980$, $p < 0.002$]. There was no significant effect of Sequence, and no significant interaction of Group by Sequence, for the Mixed One pathway.

Down Time - The Huntington's disease group (mean 152, SD 78 ms) was significantly slower in pausing between movements than the control group (mean 66, SD 9 ms), [$F(1,22) = 14.996$, $p < 0.001$]. There was no significant effect of Sequence, and no significant interaction of Group by Sequence, for the Mixed One pathway.

Mixed Two pathway

Movement Time – The Huntington's disease group (mean 286, SD 96 ms) was significantly slower in moving from one button to the next than the control group (mean 185, SD 33 ms), [$F(1,22) = 11.878$, $p < 0.002$]. There was no significant effect of Sequence, and no significant interaction of Group by Sequence, for the Mixed Two pathway.

Down Time - The Huntington's disease group (mean 147, SD 66 ms) was significantly slower in pausing between movements than the control group (mean 70, SD 10 ms), [$F(1,22) = 16.804$, $p < 0.001$]. There was no significant effect of Sequence, and no significant interaction of Group by Sequence, for the Mixed Two pathway.

Zig-zag pathway

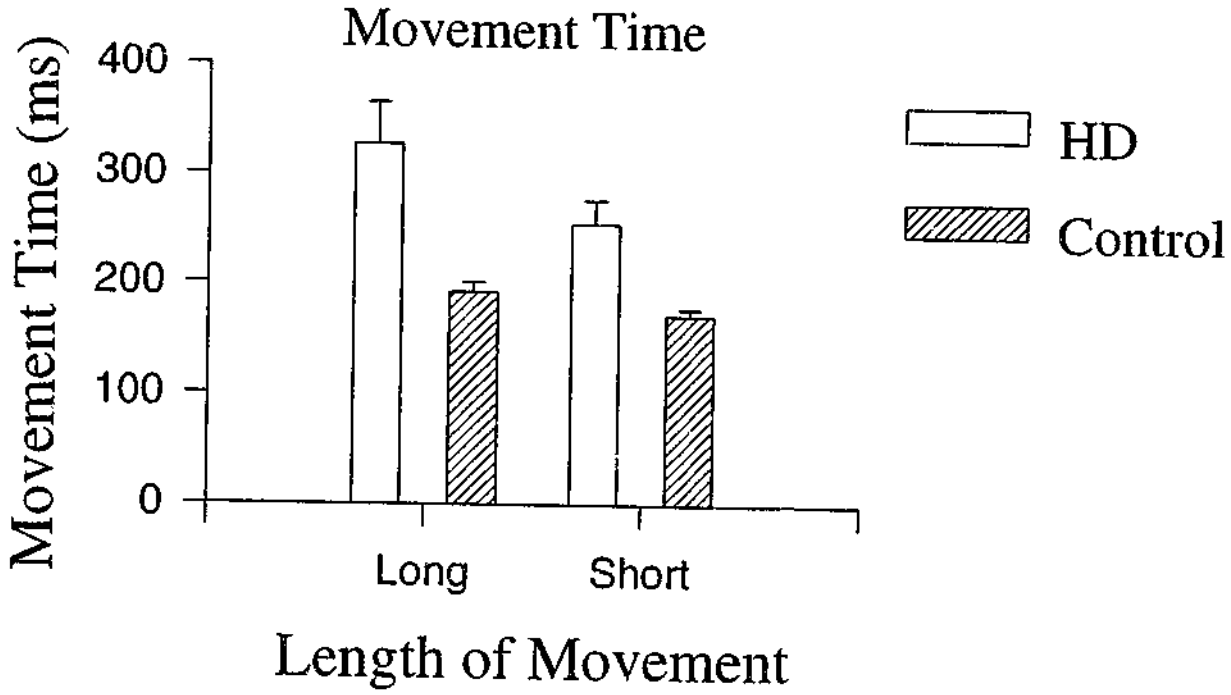
Down Time - The Huntington's disease group (mean 134, SD 61 ms) was significantly slower in pausing between movements than the control group (mean 62, SD 8 ms), [$F(1,22) = 16.214$, $p < 0.001$]. There was no significant effect of Sequence, and no significant interaction of Group by Sequence, for the Mixed Two pathway.

Movement Length and the ability to Rescale Movement

The data from the Mixed One and Mixed Two pathways were collapsed across Button Position, since they were counterbalanced versions of each other, and they showed similar main and interaction effects for the overall and the sequencing analyses.

Movement Time - There was a significant Group main effect [$F(1,22) = 12.636$, $p < 0.002$] and a significant Length main effect [$F(1,22) = 20.759$, $p < 0.001$], both of which were moderated by a significant Group by Length interaction, [$F(1,22) = 6.324$, $p < 0.020$], (see Figure 8.6). This interaction was broken down by the factor of Group. The control group moved significantly more quickly between buttons on the short movements (mean 171, SD 21 ms) than the long movements (mean 192, SD 30 ms),

Mixed Pathway



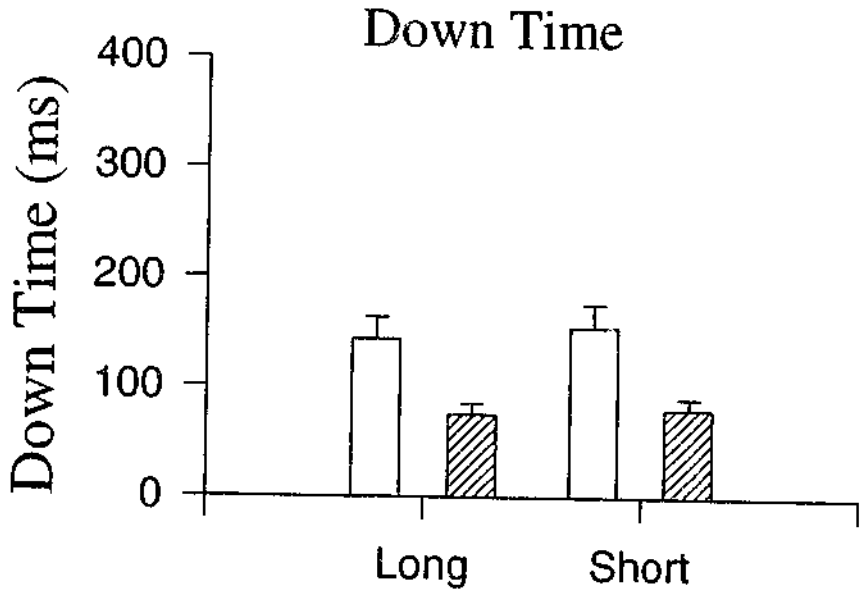


Figure 8.6: Means and standard errors of the Movement and Down Times of the control and Huntington's disease participants, for the long and short movements, averaged across the Mixed One and Mixed Two pathways.

[F(1,11) = 34.569, p < 0.001]. The Huntington's disease group also moved significantly more quickly between buttons on the short movements (mean 254, SD 78 ms) than the long movements (mean 327, SD 133 ms), [F(1,11) = 12.888, p < 0.004]. There was a difference of 29% between the short and the long lengths for the Huntington's disease group compared with a difference of only 12% for the control group on the Mixed pathways.

Down Time - There was a significant Group main effect [F(1,22) = 9.686, p < 0.005] and a significant Length main effect [F(1,22) = 22.612, p < 0.001], both of which were moderated by a significant Group by Length interaction, [F(1,22) = 4.363, p < 0.049], (see Figure 8.6). This interaction was broken down by the factor of Group. The control group spent significantly more time pausing on the buttons before the short movements (mean 80, SD 35 ms) than before the long movements (mean 75, SD 36 ms), [F(1,11) = 58.319, p < 0.001]. The Huntington's disease group also spent significantly more time pausing on the buttons before the short movements (mean 154, SD 71 ms) than before the long movements (mean 143, SD 70 ms), [F(1,11) = 12.079, p < 0.005]. There was a difference of 8% between the time taken to pause on buttons before the short and the long movement lengths for the Huntington's disease group compared with a difference of 7% for the control group on the Mixed pathways.

Regularity of Direction

Long Movements

The long movements on the irregular Mixed pathway were compared with the long movements on the regular Zig-zag pathway, with a two-way ANOVA (Group by Task).

Movement Time - The Huntington's disease group (mean 311, SD 103 ms) performed the long movements of the two pathways significantly more slowly than the control group (mean 189, SD 25 ms), [F(1,22) = 27.590, p < 0.001], see Figure 8.7. There was no effect of regularity of direction change and no interaction, thus for both groups the long movement was performed at the same speed irrespective of the regularity of the required movement.

Down Time – The Huntington's disease group (mean 140, SD 65 ms) spent a significantly longer time pausing on the buttons than the control group (mean 69, SD 26 ms), [F(1,22) = 12.776, p < 0.002], see Figure 8.7. There was no effect of regularity of

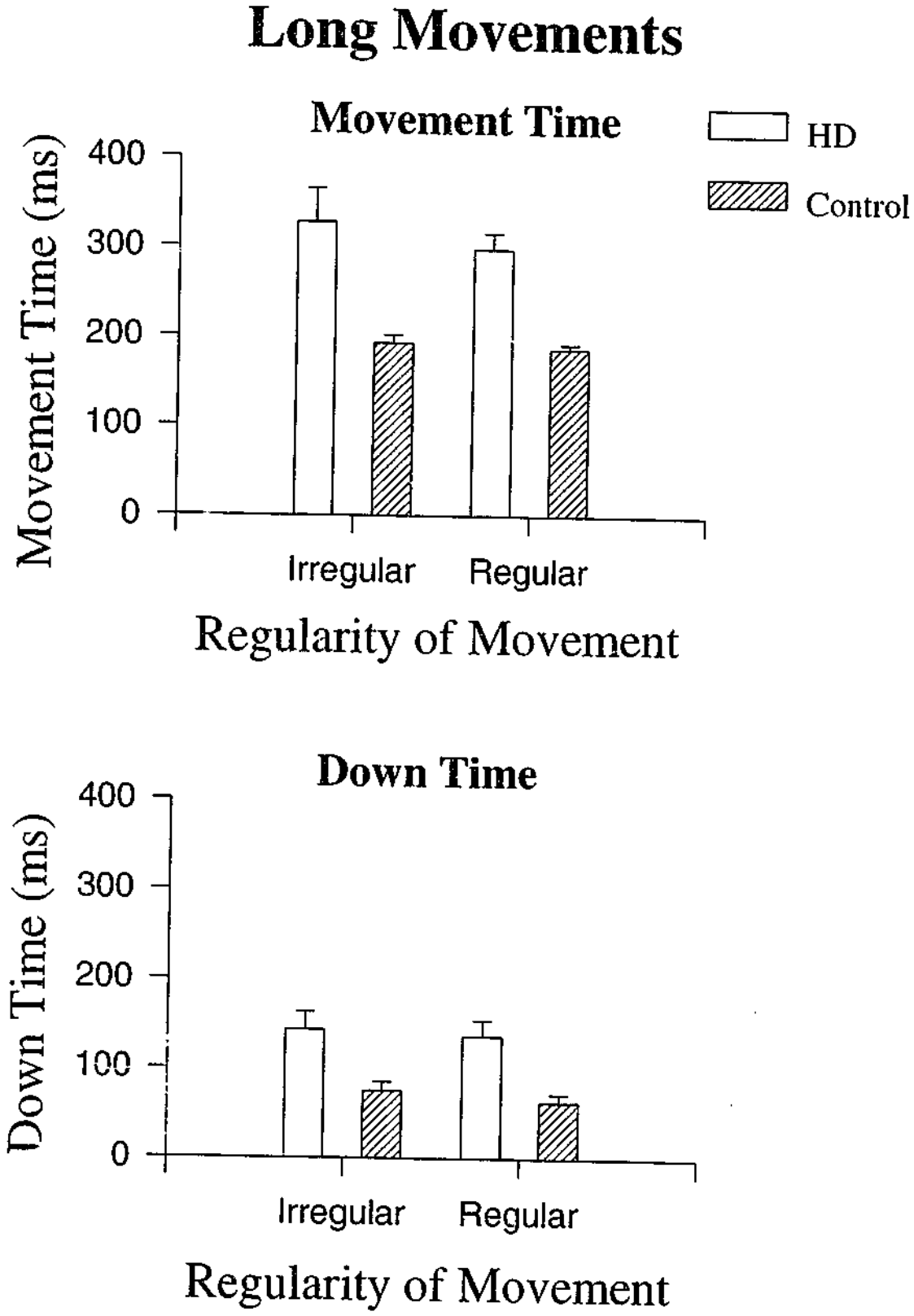


Figure 8.7: Means and standard errors of the Movement and Down Times of the control and Huntington's disease participants, for the long movements, of the irregular (Mixed) and the regular (Zig-zag) pathways.

direction change of the task and no interaction for Down Time, thus for both groups the time taken to pause on the buttons before the long movements was the same irrespective of the regularity of the required movement.

Short Movements

The short movements on the irregular Mixed pathway were compared with the short movements on the regular Straight pathway, with a two-way ANOVA (Group by Task).

Movement Time - The Huntington's disease group (mean 273, SD 80 ms) performed the short movements of the two pathways significantly more slowly than those of the control group (mean 182, SD 5 ms), [$F(1,22) = 16.043$, $p < 0.001$], (see Figure 8.8). Both groups performed the short movements on the irregular Mixed pathway (mean 212, SD 70 ms) significantly more quickly than on the regular Straight pathway (mean 243, SD 77 ms), [$F(1,22) = 22.149$, $p < 0.001$]. There was no significant interaction between Group and Task.

Down Time – The Huntington's disease group (mean 144, SD 13 ms) spent a significantly longer time pausing on the buttons than the control group (mean 72, SD 26 ms), [$F(1,22) = 14.653$, $p < 0.001$], (see Figure 8.8). Both groups spent a significantly longer time pausing between the buttons before the short movements on the irregular Mixed pathway (mean 117, SD 67 ms) than on the regular Straight pathway (mean 99, SD 53 ms), [$F(1,22) = 7.798$, $p < 0.011$].

DISCUSSION

There were four main findings of this study. Neither group showed a sequencing effect along the pathways. The Huntington's disease patients however, exhibited difficulties in the generation of a regular series of movements in that they were slower than controls in performing the movements on all four pathways, and they showed a reduced capacity to rescale their movements efficiently between the long and short movements. They behaved normally however, in that the variation in regularity of the direction of the short movements led to an improved movement time. This did not occur with the long movements.

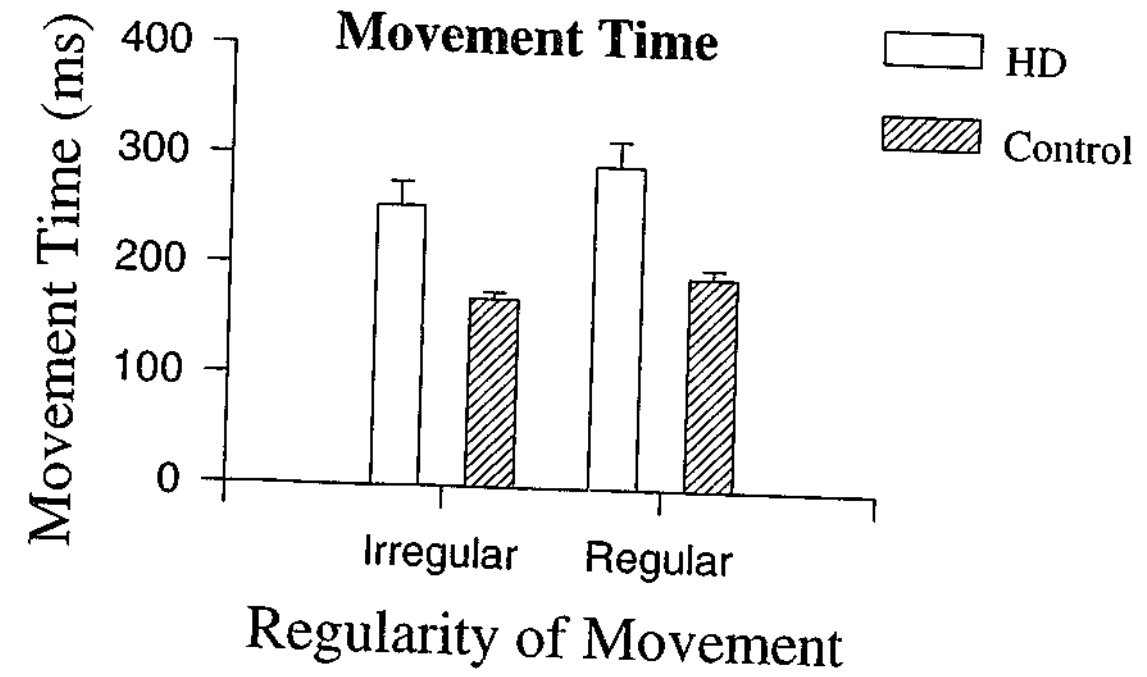


Figure 8.8: Means and standard errors of the Movement and Down Times of the control and Huntington's disease participants, for the short movements, of the irregular (Mixed) and the regular (Straight) pathways.

Bradykinesia

The Huntington's disease group was significantly slower than the control group, across all pathways. This result reflects previous studies e.g. (Agostino *et al.*, 1992; Thompson *et al.*, 1988), suggesting that Huntington's disease patients, like Parkinson's disease patients, are bradykinetic during the performance of sequential movements. This may suggest deficits in the preparation of movement. This experiment allowed a further examination of the exact deficits in the bradykinetic movement performance of this group, as described below.

Sequencing Effect

In contrast with Parkinson's disease movement, the Huntington's disease group did not show a reduction in movement speed along the sequence of movements. There was no sequencing effect found from either the control or the Huntington's disease groups, across any of the pathways. This supports two previous studies (Agostino *et al.*, 1992; Currá *et al.*, 2000) which also found no sequencing effect in Huntington's disease movement performance.

One difference between this study and these previous studies is that this study also investigated the potential influence on sequencing of changes in movement length along the pathway. Alterations of these potential factors did not influence the sequencing of movement along the pathway in Huntington's disease.

Movement Length

Both the Huntington's disease and the control groups moved more quickly between the buttons on the short than the long movements on the Mixed pathway, which was a product of the distance required to complete the movement. The Huntington's disease group however, was differentially affected by the change in movement length. The capacity of the Huntington's disease patients to rescale their movements to accommodate the different movement lengths was only about one third as efficient as the control group on the Mixed pathway. This deficit in the ability to rescale movements has been previously described in Parkinson's disease (Georgiou *et al.*, 1993; Kritikos *et al.*, 1995), and is a novel finding in Huntington's disease.

Regularity of Direction

The Huntington's disease group was significantly slower than the control group in moving from one button to the next for the long and the short movements. The patient group also spent a significantly longer time pausing between movements on the buttons, for both the short and long movements. This once again indicates difficulties in the preparation of movements.

The Movement Time taken to produce the long movements, when they irregularly alternated between the short movements on the Mixed pathway, was not significantly different from the Movement Time taken to produce the long movements on the regularly direction-changing Zig-zag pathway, for either group. The time taken to pause on the buttons between the irregular long movements on the Mixed pathway was the same as the time taken to pause between the regular long movements on the Zig-zag pathway, for both groups. The patient group was slower in Down Time than the control group, but acted in a similar manner to the control group, in that the regularity of direction change did not interfere with the planning and performance of the long movements.

In contrast, the time taken to make the short movements on the irregular-movement-direction Mixed-pathway was significantly less than the time taken on the regular-movement-direction Straight-pathway, for both groups. In addition, the time taken to pause on the buttons between the irregularly occurring short movements on the Mixed pathway was significantly shorter than the time taken to pause between the regular short movements on the Straight pathway. This result initially may appear anomalous. The Mixed pathway involved an irregular direction change and, importantly, the short movement was interspersed with the long movements. The Straight pathway involved one type of movement length and no direction changes. It might be easier to alternate two different motor plans (as in the Mixed and possibly the Zig-zag pathways) than one plan (as in the straight movement), especially over a long sequence. This has been found in articulatory control (Bradshaw, 1970). If the sequence is lengthy, there also may be difficulties in maintaining the one motor plan, as attention mechanisms may inhibit a recurring motor plan (Posner and Cohen, 1984).

The neurobiological origin of the progressive sequencing effect observed in Parkinson's disease is unknown, but is thought possibly to be linked to the loss of cells in the

striatum (Böecker *et al.*, 1996). It is known that the sequencing effect is reduced in Parkinson's disease in the presence of external cues (Georgiou *et al.*, 1994). It is noteworthy that in Huntington's disease there was no cue effect and no sequencing effect. The lack of a sequencing effect in Huntington's disease found in this study suggests a fundamental difference in the bradykinesia manifested in the two diseases, which may reflect the differential cell loss in the striatum, and it may possibly be connected to the cue effect. It is noteworthy, in the previous studies that investigated the sequencing effect in Huntington's disease, that there was no clear relationship between the provision of external cues and a significant sequencing effect. A further experiment, to investigate the possible interrelationship between the cue and the sequence effect in both disease groups, would further elucidate this issue.

In conclusion, Parkinson's and Huntington's diseases were dissociated, in that there was no sequencing effect found in the Huntington's disease group, a result typically found in Parkinson's disease. There was an association between these two groups, however, in that the rescaling of movement between the long and short movements disproportionately affected the bradykinesia of Huntington's disease, as had previously been found in Parkinson's disease. This indicates specific deficits in the preparation of movement in both disease groups.

Chapter Nine - The effect of anti-parkinsonian medication on the bimanual co-ordination of patients with Parkinson's disease

Clinical observations suggest that Parkinson's disease patients have difficulties in producing co-ordinated bimanual movements. Deficits in bimanual co-ordination have been tested experimentally, but the results are equivocal. Most studies have shown a deficit in the ability of these patients to perform two manual movements either sequentially or simultaneously (Benecke *et al.*, 1986; Benecke *et al.*, 1987; Horne, 1973; Horstink *et al.*, 1990; Johnson *et al.*, 1998; Lazarus and Stelmach, 1992; Schwab *et al.*, 1954; Shimizu *et al.*, 1987; Suri *et al.*, 1998; Talland and Schwab, 1964; van den Berg *et al.*, 2000). A few studies have found no deficits in bimanual co-ordination by Parkinson's disease patients, compared with control participants (Brown *et al.*, 1993; Cohen, 1970; Stelmach and Worringham, 1988). The most common difficulties shown by the Parkinson's disease patients included slower movement times, longer pauses between movements and an inability to perform the movements simultaneously.

Many of the studies contained methodologies that used a different task for either hand, such as tapping a pattern with one hand and moving buttons with the other (Brown *et al.*, 1993). This type of methodology may have confounded the data, in terms of the inherent attentional dual task loading, which may have disadvantaged the Parkinson's disease patients. The methodology used in a previous study by the author (Johnson *et al.*, 1998) allows a kinematic analysis of the co-ordination of the two hands, where both hands are performing the same task. A common programming element may be involved in the movement production, especially if the movement involves homologous muscle systems (Stelmach and Worringham, 1988). A mirror-symmetrical task is relatively easy to produce, as the timing of the two hands is identical. An example of this type of task is the in-phase movement, which involves both hands performing simultaneous, synchronous, mirror-symmetrical cyclical movements, the right hand moving in a clockwise direction and the left hand moving in an anti-clockwise direction. A more complex version of this movement is the anti-phase movement, where both hands perform the same movement, with the same timing, but at different points in the movement cycle. An example is the anti-phase task, where one hand is 180° out of phase with the other. The action is no longer mirror-symmetrical and the homologous

muscles are activated in sequence, rather than simultaneously, resulting in a more complex movement.

Successfully co-ordinated bimanual movement requires control over the integration of the performance of the two hands. Often this will involve arranging movements together in a specific sequence, using exact rhythms and timing of movements. It is known that Parkinson's disease patients have particular difficulties in initiating and executing sequential movements (Agostino *et al.*, 1998; Currá *et al.*, 1997). Timing and rhythm reproduction is more variable in Parkinson's disease than in controls (Freeman *et al.*, 1993; Nakamura *et al.*, 1978; Pastor *et al.*, 1992a). The provision of external cues will generally improve the bradykinesia of Parkinson's disease during sequential movement (Georgiou *et al.*, 1993; Jackson *et al.*, 1995). In the absence of external cues, Parkinson's disease patients show a marked impairment in rhythm generation (Freeman *et al.*, 1993). Indeed, bimanual co-ordination is known to improve in Parkinson's disease with the provision of an external timing cue (Johnson *et al.*, 1998; Verschueren *et al.*, 1997).

Parkinson's disease is associated with a loss of dopamine producing cells in the substantia nigra of the basal ganglia. As previously discussed, one of the major output regions of the basal ganglia is the SMA (Alexander and Crutcher, 1990a). The SMA appears to be anatomically and functionally bilaterally organised (DeVito and Smith, 1959) and may be involved in facilitating bimanual co-ordination (Stephan *et al.*, 1999). The effect of dopamine replacement on the bimanual co-ordination of patients with Parkinson's disease is unknown. It is known, however, that anti-parkinsonian medication improves the accuracy of timing of a repetitive flexion-extension movement of the right hand of patients with Parkinson's disease (Pastor *et al.*, 1992b). Anti-parkinsonian medication has also been implicated in the improved activity levels of the SMA in Parkinson's disease (Haslinger *et al.*, 2001; Rascol *et al.*, 1994). Cortical preparatory activity has also been shown to improve significantly with the administration of L-DOPA in Parkinson's disease (Dick *et al.*, 1987; Feve *et al.*, 1992; Oishi *et al.*, 1995). Bimanual co-ordination may therefore be improved significantly in Parkinson's disease with the administration of anti-parkinsonian medications.

The aim of this experiment was to investigate the effect of anti-parkinsonian medication therapies on the bimanual co-ordination of patients with Parkinson's disease, using a

methodology which clearly differentiates the variability and accuracy of co-ordination patterns between Parkinson's disease patients and their controls. The Parkinson's disease patients were expected to show significantly more variability and less accuracy when they were off medication, and to show significant improvement in their bimanual co-ordination when on medication. In a comparison with a control group, the Parkinson's disease group was expected to be significantly more variable and less accurate for both the in-phase and anti-phase movements.

METHOD

Participants

Seven male and three female patients with Parkinson's disease were tested. They ranged in age from 48 to 75 years (mean age 67.20, SD 7.98 years). The Parkinson's disease patients were tested during both the on and off stages of the medication cycle. The consulting neurologist and physiotherapists classified these stages. The United Parkinson's Disease Rating Scale was used to assess disease severity. The mean UPDRS score for the Parkinson's disease group when on medication (mean UPDRS score 7.30, SD 4.11) was significantly lower than the UPDRS score when the group was off medication (mean UPDRS score 20.40, SD 10.36), [$F(1,18) = 13.809$, $p < 0.002$]. The duration of disease for this group of Parkinson's disease patients varied between 6 and 17 years (mean duration of disease 10.00, SD 3.62 years). Parkinsonian performance on the Purdue pegboard task was assessed (Tiffin, 1968). The average number of pegs placed by the patient group using the right hand when on medication (mean 9.40, SD 2.50) was significantly greater than when off medication (mean 7.90, SD 3.60), [$F(1,9) = 7.642$, $p < 0.022$]. When using the left hand, the average number of pegs placed by the patient group when on medication (mean 7.90, SD 1.60) was also significantly greater than when off medication (mean 6.20, SD 2.78), [$F(1,9) = 9.256$, $p < 0.014$]. The Parkinson's disease patients were also assessed on the Get-Up-And-Go task (Podsiadlo and Richardson, 1991). There was no significant difference between the time taken to complete the Get-Up-And-Go task on (mean 9.80, SD 2.61 s) or off (mean 12.78, SD 7.01 s) medication, [$F(1,9) = 2.910$, $p > 0.05$]. The Parkinson's disease medication included L-DOPA preparations (Sinemet, Madopar) and dopamine agonists, see Table 9.1. Control participants were matched for age and sex; their ages ranged from 49 to 75 years (mean age 67.7, SD 8.1 years).

Table 9.1: Clinical data for Parkinson's disease patients.

Participant	Age (years)	Sex	UPDRS on	UPDRS off	STMS	Duration of disease (years)	Get-up -and-go (seconds) On	Get-up -and-go (seconds) Off	Purdue On LH	Purdue Off LH	Purdue On RH	Purdue Off RH	Side of disease onset	Medication
1	74	M	15	43	35	17	9:71	13:03	7	6	8	7	R	Sinemet 100/25 x 2.5
2	74	M	4	19	32	7	8:81	9:91	7	5	9	7	L	Madopar 100/25 x 2.5
3	61	M	3	22	29	15	12:27	30:73	7	0	7	2	L	Sinemet 200/50
4	68	M	3	22	33	9	6:98	7:98	10	9	12	10	L	Tasmar 100 Madopar 300 x 1.5
5	67	F	6	17	31	10	7:81	9:75	8	8	11	8	L	Sinemet 2.5 x 100/25
6	48	M	6	16	36	6	7:75	7:40	10	9	12	13	L	Comptan 1 x 200mg
7	69	M	12	27	29	10	15:77	18:19	5	2	4	2	L	Sinemet 100/25 x 1.5
8	75	F	5	6	33	9	9:96	10:89	7	7	11	11	R	Sinemet 100/25 x 1.5
9	70	F	8	8	31	6	8:38	9:03	9	7	10	10	L	Madopar 100/25 x 0.75
10	66	M	11	24	36	11	10:52	10:92	9	8	10	9	R	Madopar 200 x 1.25

Notes: UPDRS – Unified Parkinson's Disease Rating Scale
STMS - Short Test of Mental Status
RH – right hand
LH – left hand

Sinemet – levodopa and carbidopa – dopamine precursor
Madopar – levodopa and benserazide – dopamine precursor
Permax – pergolide mesylate – dopamine agonist
Comptan – catechol-O-methyltransferase inhibitor
Tasmar - catechol-O-methyltransferase inhibitor

All participants were right-handed (Patterson and Bradshaw, 1975). Potential participants were excluded if they had a history of stroke, head injury or other neurological disturbance, suffered dementia [below 29 out of 37 on the STMS (Kokmen *et al.*, 1987)] or suffered from severe, disabling arthritis. For all experiments, consent was obtained from each participant in accordance with the Helsinki declaration, and all experimental work was carried out under the approval of the ethical committees of Monash University and Kingston Centre.

Apparatus

The apparatus has been described previously in Johnson *et al.* (1998). Movements were performed on a pair of manual cranks, consisting of two wheels (26 cm in diameter), side by side, in the same vertical plane, with handles located 8 cm from the axis of rotation of each wheel. Participants sat at a table with the cranks directly in front of them and the apparatus centered on the body midline. They turned the cranks by the handles in the vertical plane. The wheels were individually mounted, enabling monitoring of movements of each hand independently via separate data channels. A code-wheel and optical decoder unit determined the angular position of each wheel, which was re-calibrated before each use. The angular position of each wheel relative to a fixed reference point was sampled at 200 Hz. Upon each rotation this reference point was re-calibrated for each wheel by a light pulse. A metronome was used to pace the movements of the participants.

Procedure

The procedure was as per Johnson *et al.* (1998). Eight different movement conditions were examined, involving two movement types (bimanual in-phase and anti-phase, both using the homologous muscle groups), performed at fast (2 Hz) and slow (1 Hz) speeds, with and without an external timing cue. The bimanual in-phase movement consisted of both hands starting at the top of the cranks, with the left hand moving towards the left and the right hand towards the right, concurrently. The bimanual anti-phase task consisted of the left hand beginning at the bottom of the left crank and the right hand at the top of the right crank, with the hands moving in the same directions as the in-phase task. The participants were asked to produce a continuous, smooth movement for a period of 20 s for each trial.

The participants were highly practiced for all movement conditions. A practice session at the first speed, on the two movement configurations (in-phase and anti-phase), was followed by the first set of trials. After a rest, the participants practiced the second speed on the movement configurations, then their movements were recorded. All participants were requested to direct their eye gaze to a schematic diagram on a wall ~ 1 m in front of them, [illegible] above the axis connecting axle of the two cranks. The schematic diagram was used to explain the required movement for each trial. Participants were instructed to grasp the crank handles firmly in the palms of the hands at all times, in a 'chuck' grip.

For half of the trials a metronome acted as an external cue, and the participants were required to make one rotation per beat. For the remaining trials, the participants were required to remember the beat of the metronome and to produce the movement at the same speed without the aid of the external timing cue. Participants performed 16 trials in all, two trials for each movement type. Each trial ran for 20 s at 200 Hz, generating hand positions every 5 ms. The order of trials was counterbalanced across participants. The total duration of the experiment was ~ 30 min.

The Parkinson's disease patients were tested during the 'off' stage of the medication cycle, approximately 12 hours after taking their last medications. After the 'off' testing session, normal medication was taken. The consulting neurologist, physiotherapist and the patients themselves then determined when the patients had entered the 'on' period of the medication cycle. Once this was classified, the patients were re-tested.

Data Analysis

Phase histograms

To describe the movement performance of each group the difference between the two hands was calculated every 50 ms. These data were placed into one of 24 data bins that separately represented 15° segments of the rotational circle. A phase histogram represented the data, which indicated how well the groups could perform the required bimanual task. A perfect performance for the in-phase task would score 0°, reflecting a zero phase difference between the hands. A perfect performance for the anti-phase task would score 180°. Data on the right side of zero indicated that the right hand was

slightly leading the left. Data on the left side indicated that the left hand was slightly leading the right.

The derivative of the displacement data was calculated to determine the velocity of each crank at each 50 ms interval. From these time-series data, four dependent variables were calculated.

Variation in co-ordination pattern

This measures the ability to maintain a constant, stable relationship between the two hands. It is the standard deviation of the difference (in degrees) between the right and left hands over time, and measures interhand coupling, i.e. the variability of the difference between the left and right hands. The lower the score, the better the performance.

Accuracy in co-ordination pattern

This is a measure of the relationship maintained by the two hands over time. It is calculated as the mean absolute difference (in degrees) between the two hands. A perfect performance would score zero. A measure is thus obtained of the accuracy of the co-ordination pattern of the two-hands over time, in absolute terms.

Variation in velocity

This measure represents the stability of the movement in terms of velocity. It is the standard deviation of velocity. A low score indicates a stable well-controlled movement whilst a high score denotes an unstable, poorly controlled movement in terms of velocity.

Accuracy of velocity

This measures the mean signed difference between the target velocity (fast = 2 Hz, slow = 1 Hz) and the actual velocity. A negative score indicates movement that is too slow for the target speed, and a positive score indicates movement that is too fast.

Two separate analyses of the data were completed. Firstly, the effect of medication on the Parkinson's disease group was analysed. Second, a comparison between the Parkinson's disease and control groups was analysed. Three conditions were employed:

Group (Parkinson's disease off medication, Parkinson's disease on medication) and (Parkinson's disease, control), Cue (on, off), and Speed (slow 1 Hz, fast 2 Hz) according to a three-way mixed factorial ANOVA design (Group x Cue x Speed), for each of the four dependent variables separately.

RESULTS

The effect of anti-parkinsonian medication on the bimanual performance of Parkinson's disease patients

In-Phase task

Phase Histograms

Qualitatively, the histograms (Figures 9.1 and 9.2) indicate that both with and without medication the Parkinson's disease group performed the required movement for the majority of time, at both the fast and slow speeds (most scores centered around zero). From these histograms, there appears to be no difference in performance of the Parkinson's disease group on or off the anti-parkinsonian replacement medication. Nor does there appear to be any difference in co-ordination pattern whether the cue was present or absent, for this patient group.

Variation in co-ordination pattern

The Parkinson's disease group performed the in-phase movement with the same variability in co-ordination pattern irrespective of whether the group was on (23°) or off (31°) medication, [$F(1,18) = 0.887$, $p > 0.05$]. The presence (27°) or absence (27°) of the external cue did not significantly alter the variability of co-ordination pattern for this patient group, either on or off medication, [$F(1,18) = 0.046$, $p > 0.05$]. Irrespective of medication status, the co-ordination pattern was significantly more variable during the fast (32°) than the slow speed (22°), [$F(1,18) = 9.203$, $p < 0.007$], for the Parkinson's disease group. There were no significant interactions between Group, Cue or Speed.

Accuracy in co-ordination pattern

The Parkinson's disease group performed the in-phase movement with the same accuracy in co-ordination pattern irrespective of whether the group was on (35°) or off medication (34°), [$F(1,18) = 2.284$, $p > 0.05$]. The presence (35°) or absence (34°) of

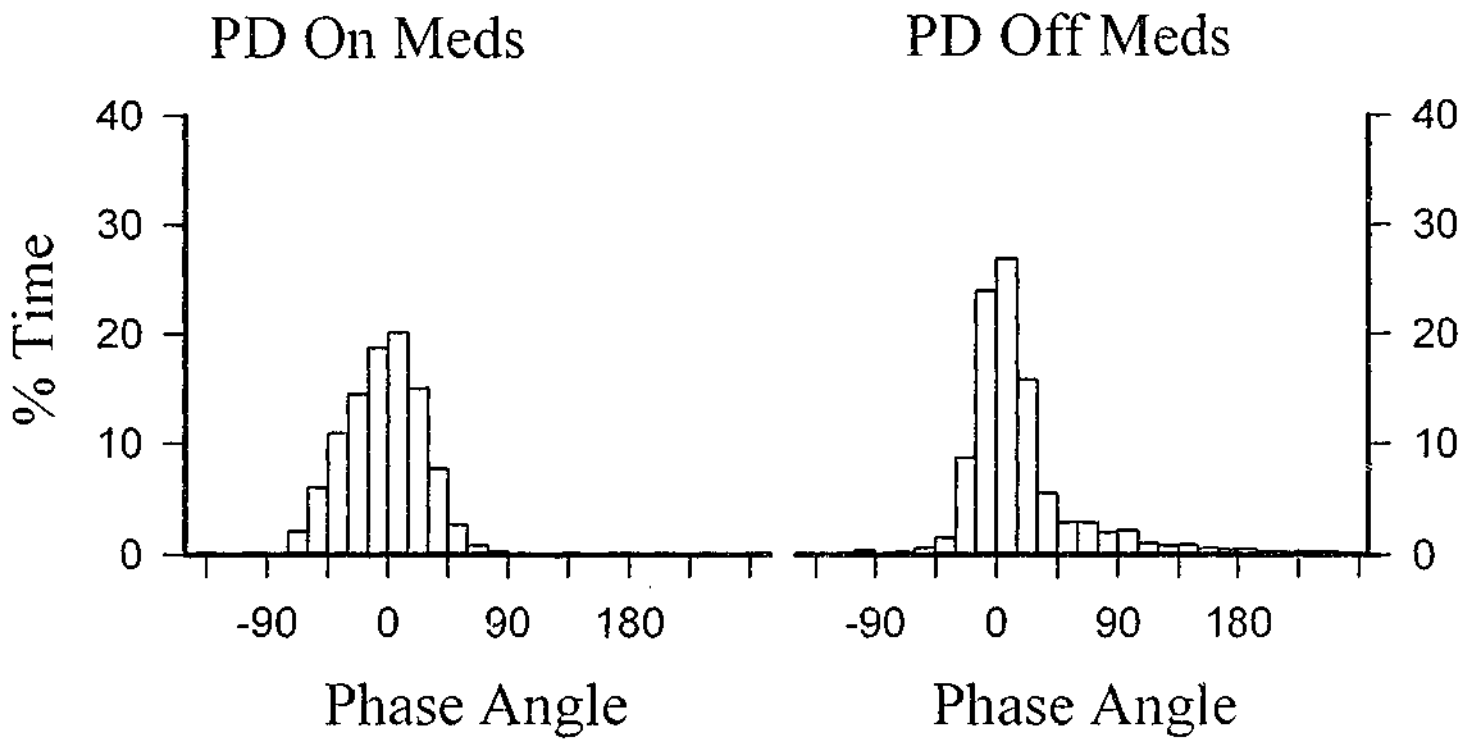


Figure 9.1: Slow movements: in-phase histograms for Parkinson's disease (PD) participants, on and off anti-parkinsonian medication, for cued and non-cued movements, at the slow speed.

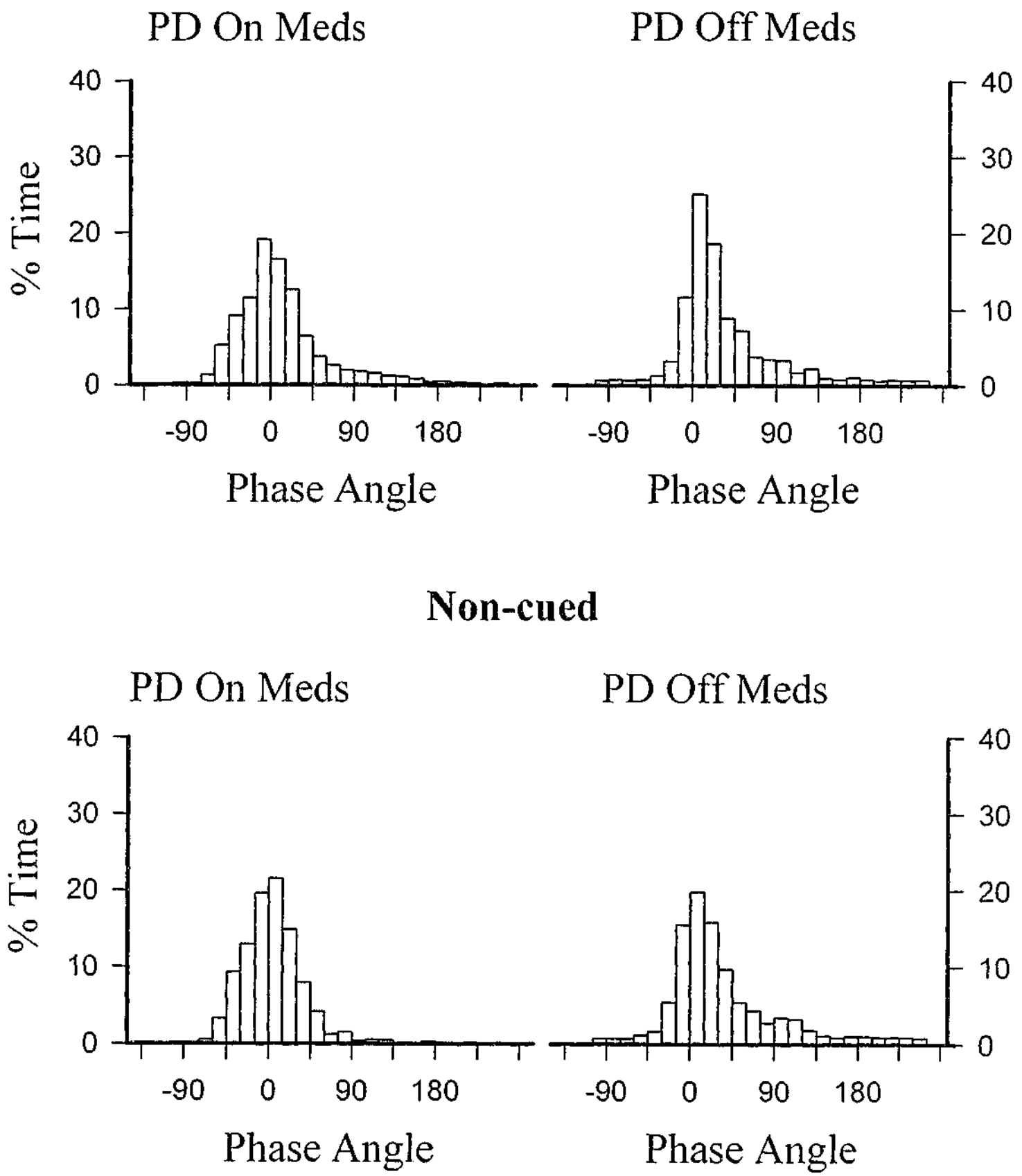


Figure 9.2: Fast movements: in-phase histograms for Parkinson's disease (PD) participants, on and off anti-parkinsonian medication, for cued and non-cued movements, at the fast speed.

the external cue did not significantly alter the accuracy of co-ordination pattern for this patient group, either on or off medication, [$F(1,18) = 0.042$, $p > 0.05$]. The co-ordination pattern was significantly more accurate during the slow (31°) than the fast speed (39°), [$F(1,18) = 5.862$, $p < 0.026$], for the Parkinson's disease group, irrespective of medication status. There were no significant interactions between Group, Cue or Speed.

Variation in Velocity

The Parkinson's disease group performed the in-phase movement with the same variation in velocity irrespective of whether the group was on (0.187 Hz) or off medication (0.172), [$F(1,18) = 0.463$, $p > 0.05$]. The presence (0.176 Hz) or absence (0.183 Hz) of the external cue did not significantly alter the variability in velocity for this patient group [$F(1,18) = 1.438$, $p > 0.05$]. There was no Group by Cue interaction. The velocity of movement was significantly less variable during the slow (0.160 Hz) than the fast speed (0.198 Hz), [$F(1,18) = 8.455$, $p < 0.009$], for the Parkinson's disease group, irrespective of medication status. There were no interactions involving Group, Cue or Speed.

Accuracy of velocity

The Parkinson's disease group when on medication (mean error, 0.024 Hz) was significantly more accurate in maintaining the correct speed than when off medication (mean error, 0.257 Hz), [$F(1,18) = 6.842$, $p < 0.018$], for the in-phase movement. The accuracy of velocity did not significantly vary according to the presence (mean error, 0.142 Hz) or absence (mean error, 0.139 Hz) of the external cue, [$F(1,18) = 0.028$, $p > 0.05$]. There was no interaction of Group and Cue. The velocity of performance of the in-phase task was more accurate at the slow (mean error, –0.074 Hz) than at the fast (mean error, –0.355 Hz) speed, [$F(1,18) = 32.504$, $p < 0.001$]. There was no interaction of Group, Cue or Speed.

Anti-Phase task

Phase Histogram

Qualitatively, the phase histograms (Figures 9.3 and 9.4) indicate that, at neither speed, were the Parkinson's disease patients able to perform the anti-phase task, either on or off anti-parkinsonian medication, in the presence or absence of the external cue. If the group was able to perform the anti-phase task, the scores would center around the 180 phase angle.

Variability in co-ordination pattern

The Parkinson's disease group performed the anti-phase movement with the same variability in co-ordination pattern irrespective of whether the group was on (47°) or off medication (53°), [$F(1,18) = 0.277$, $p > 0.05$]. The presence (50°) or absence (50°) of the external cue did not significantly alter the variability of co-ordination pattern for this patient group, either on or off medication, [$F(1,18) = 0.017$, $p > 0.05$]. There was no significant main effect of Speed, but there was a significant Group by Speed interaction, [$F(1,18) = 5.562$, $p < 0.030$], which was modified by a significant three-way interaction of Group by Cue by Speed, [$F(1,18) = 5.662$, $p < 0.029$]. This interaction was broken down by Group. When the Parkinson's disease group was on medication, there was no significant interaction between Cue and Speed, [$F(1,9) = 0.334$, $p > 0.05$], nor were there any simple main effects. When the Parkinson's disease group was off medication, there was a significant interaction between Cue and Speed, [$F(1,9) = 13.005$, $p < 0.006$]. The co-ordination pattern was significantly more variable at the slow speed with the cue on (50°) than with the cue off (38°), [$F(1,9) = 10.083$, $p < 0.011$]. It was this interaction which was driving the three-way interaction. There was no difference between the variability in co-ordination pattern at the fast speed with the cue on (57°) or off (65°), [$F(1,9) = 2.021$, $p > 0.05$], for the Parkinson's disease group off medication.

Accuracy in co-ordination pattern

The Parkinson's disease group performed the anti-phase movement with the same accuracy in co-ordination pattern irrespective of whether the group was on (112°) or off medication (106°), [$F(1,18) = 0.140$, $p > 0.05$]. The presence (110°) or absence (108°) of the external cue did not significantly alter the accuracy of co-ordination pattern for

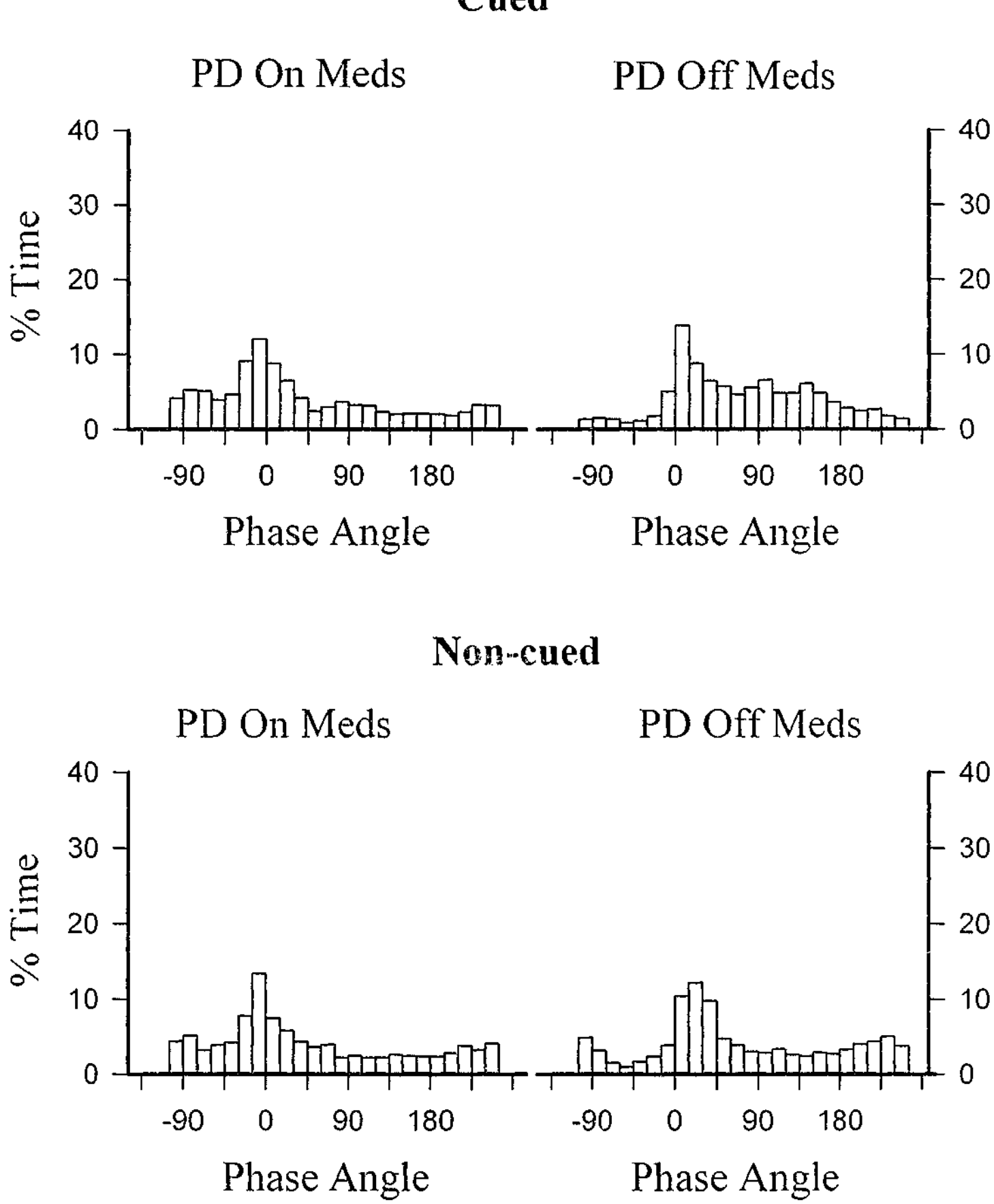


Figure 9.3: Slow movements: anti-phase histograms for Parkinson's disease (PD) participants, on and off anti-parkinsonian medication, for cued and non-cued movements, at the slow speed.

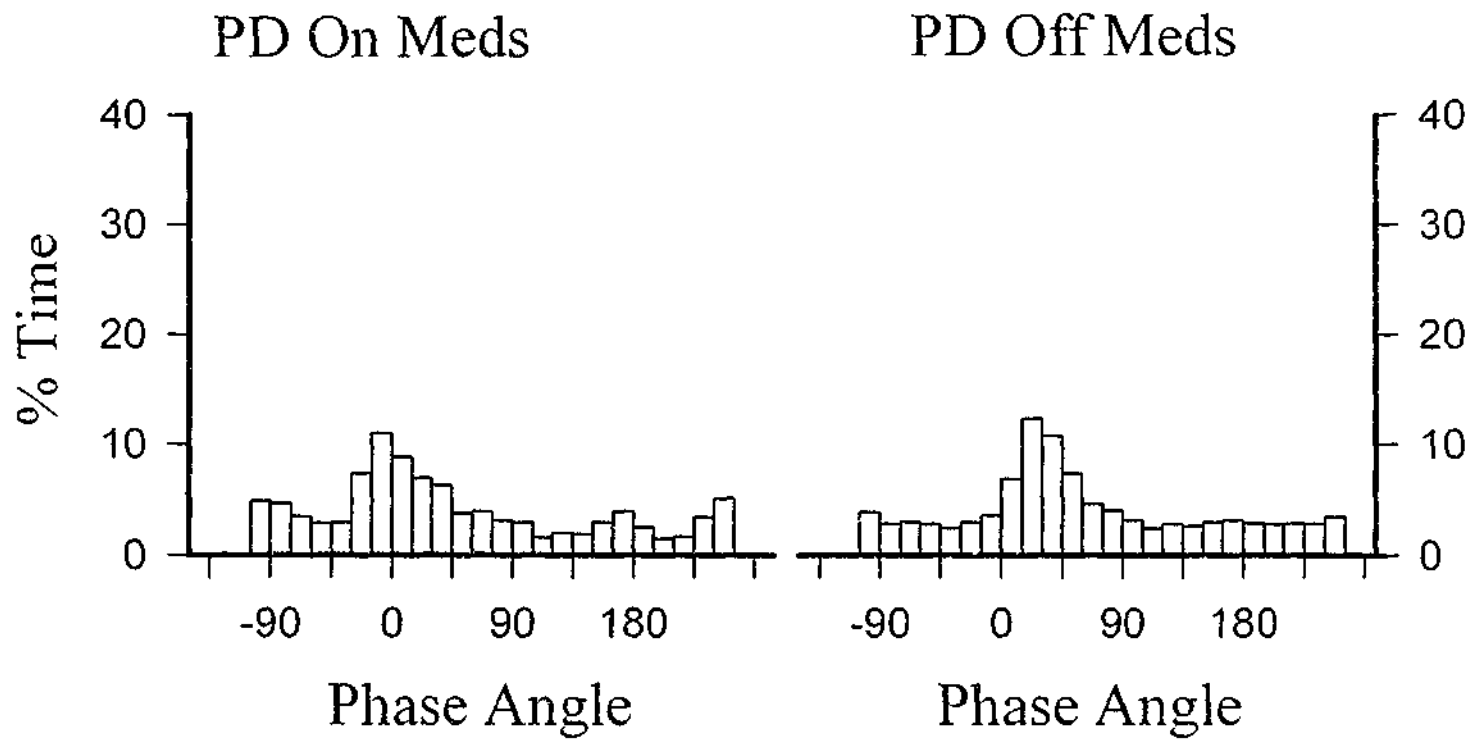


Figure 9.4: Fast movements: anti-phase histograms for Parkinson's disease (PD) participants, on and off anti-parkinsonian medication, for cued and non-cued movements, at the fast speed.

this patient group, either on or off medication, [$F(1,18) = 0.210$, $p > 0.05$]. The speed of movement did not significantly alter the accuracy of co-ordination pattern of the patient group, whether the group was on or off medication, at the slow (105°) or fast (112°) speeds [$F(1,18) = 0.867$, $p > 0.05$]. There were no significant interactions between Group, Cue or Speed.

Variation in velocity

The Parkinson's disease group performed the anti-phase movement with the same variation in velocity irrespective of whether the group was on (0.194 Hz) or off medication (0.187), [$F(1,18) = 0.106$, $p > 0.05$]. The presence (0.191 Hz) or absence (0.189 Hz) of the external cue did not significantly alter the variability in velocity for this patient group, either on or off medication, [$F(1,18) = 0.012$, $p > 0.05$]. The velocity of movement was significantly less variable during the slow (0.172 Hz) than the fast speed (0.209 Hz), [$F(1,18) = 12.038$, $p < 0.003$], for the Parkinson's disease group, irrespective of medication status. There was a significant three-way interaction between Group, Cue and Speed, [$F(1,18) = 5.068$, $p < 0.037$]. The Parkinson's disease group on medication did not differ in the variation in velocity during the anti-phase movement at either the fast (0.209 Hz) or slow (0.178 Hz) speed [$F(1,9) = 2.933$, $p > 0.05$], or in the presence (0.187 Hz) or absence (0.201 Hz) of the external cue, [$F(1,9) = 1.745$, $p > 0.05$]. When off medication, the Parkinson's disease group did not differ in variation in velocity during the anti-phase movement in the presence (0.195 Hz) or absence (0.179 Hz) of the external cue, [$F(1,9) = 1.829$, $p > 0.05$]. The velocity at the fast (0.209 Hz) speed was significantly more variable than at the slow speed (0.166 Hz), [$F(1,9) = 14.476$, $P < 0.004$], when the Parkinson's disease group was off medication. It was this difference which drove the three-way interaction.

Accuracy of velocity

The Parkinson's disease group when on medication (mean error, 0.104 Hz) was significantly more accurate in maintaining the correct speed for the anti-phase movement than when off medication (mean error, 0.401 Hz), [$F(1,18) = 9.478$, $p < 0.006$]. The accuracy of velocity did not significantly vary according to the presence (mean error, 0.250 Hz) or absence (mean error, 0.255 Hz) of the external cue, [$F(1,18) = 0.063$, $p > 0.05$]. There was no interaction of Group and Cue. The velocity of

performance of the anti-phase task was more accurate at the slow (mean error, -0.023 Hz) than at the fast (mean error, 0.535 Hz) speed, [$F(1,18) = 117.475$, $p < 0.001$]. There was no interaction of Group, Cue or Speed.

From these results, it is determined that the only difference between the Parkinson's disease group on and off medication was in the ability to maintain accurately the correct velocity of movement. Keeping this in mind, the data on and off medication of the Parkinson's disease group were combined and then compared with age- and sex-matched controls.

A comparison between the Parkinson's disease group and an age- and sex-matched control group

In-Phase task

Phase Histograms

Qualitatively, the histograms (Figures 9.5 and 9.6) indicate that both the Parkinson's disease and the control group performed the required movement for the majority of time, at both speeds (most scores were around zero). The Parkinson's disease group, however, was far more variable, spending a lower proportion of time in the correct phase relationship (as shown by the spread of data on the histogram). They were also less accurate than the control group, at both speeds (as shown by the reduced height of the histogram at the correct 0° phase relationship). There does not appear to be any difference in co-ordination pattern in the presence or absence of the external cue, for either group.

Variation in co-ordination pattern

The Parkinson's disease group (27°) was significantly more variable in co-ordination pattern than the control group (11°), [$F(1,18) = 7.066$, $p < 0.016$]. There was no significant effect of the presence (19°) or absence (19°) of the external cue, [$F(1,18) = 0.137$, $p > 0.05$]. There was no interaction between Group and Cue. The in-phase co-ordination pattern was significantly less variable at the slow (16°) than the fast (22°) speed, [$F(1,18) = 8.813$, $p < 0.008$]. There was no interaction involving Speed.

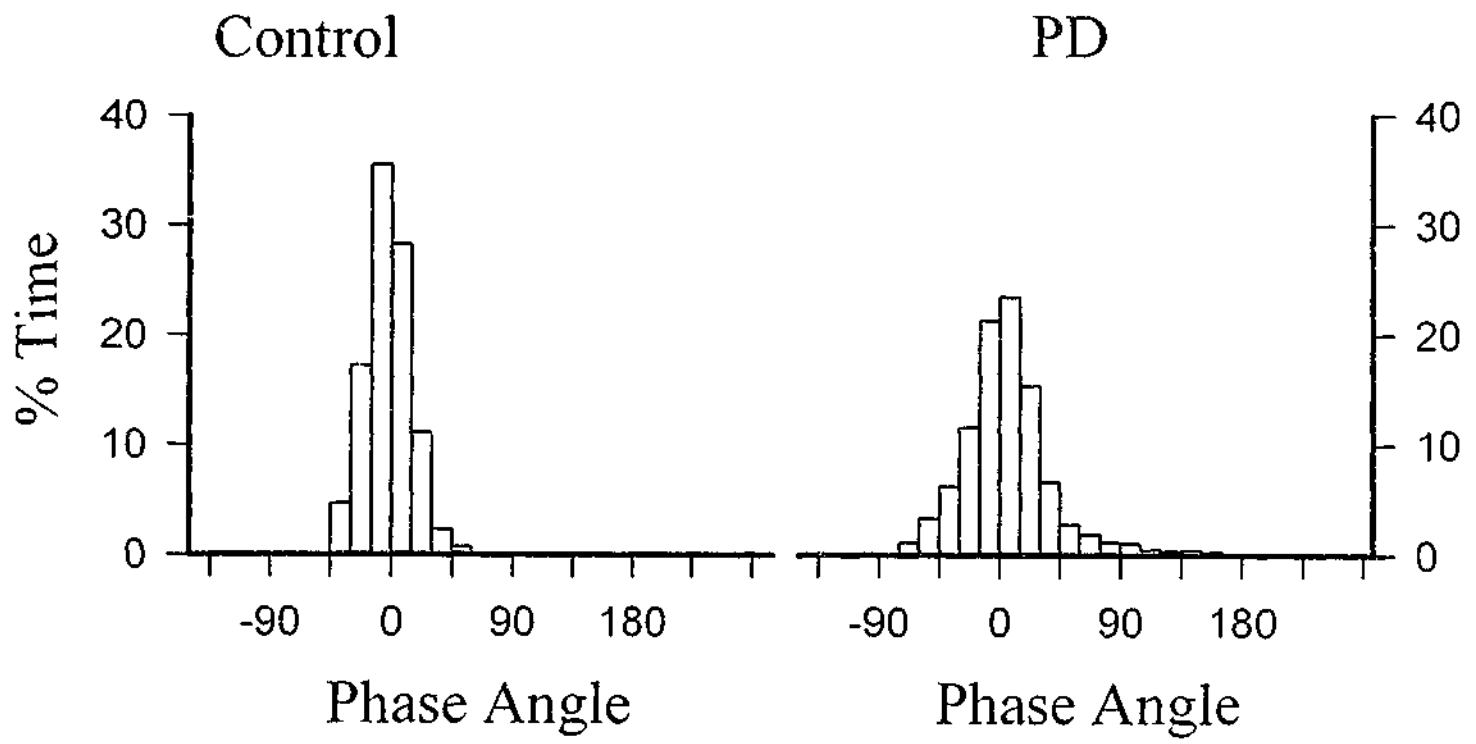


Figure 9.5: Slow movements: in-phase histograms for control and Parkinson's disease (PD) participants, for cued and non-cued movements, at the slow speed.

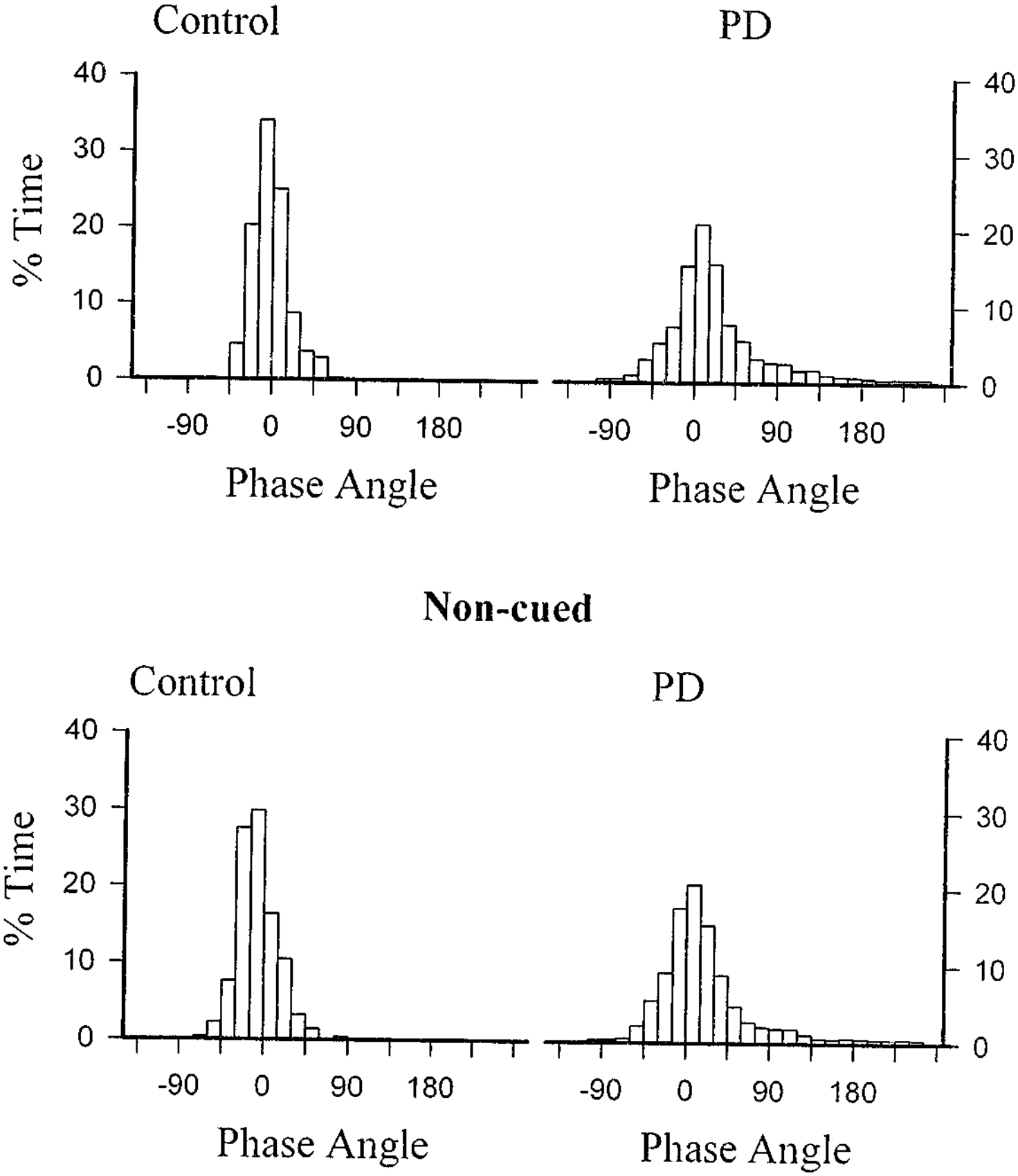


Figure 9.6: Fast movements: in-phase histograms for control and Parkinson's disease (PD) participants, for cued and non-cued movements, at the fast speed.

Accuracy of co-ordination pattern

The Parkinson's disease group (35°) was significantly less accurate in co-ordination pattern than the control group (15°), [$F(1,18) = 6.165$, $p < 0.023$]. There was no significant effect of the presence (25°) or absence (24°) of the external cue, [$F(1,18) = 0.104$, $p > 0.05$]. There was no interaction between Group and Cue. The in-phase co-ordination pattern was significantly less variable at the slow (23°) than the fast (26°) speed, [$F(1,18) = 4.786$, $p < 0.042$]. There was a significant interaction between Group and Speed, [$F(1,18) = 8.509$, $p < 0.009$]. There was no significant difference between the accuracy of co-ordination pattern of the fast (14°) and the slow (15°) speeds for the control group, [$F(1,9) = 0.347$, $p > 0.05$]. The interaction was driven by the significant difference between the accuracy of co-ordination pattern of the Parkinson's disease group, for the fast (39°) and the slow (31°) speeds, [$F(1,9) = 10.555$, $p < 0.010$].

Variability of velocity

There was no difference between the Parkinson's disease (0.179 Hz) and the control (0.161 Hz) groups, in terms of variation in velocity, [$F(1,18) = 1.209$, $p > 0.05$], for the in-phase co-ordination pattern. Neither the presence (0.168 Hz) or the absence (0.172 Hz) of the external cue affected the variability of velocity, [$F(1,18) = 0.943$, $p > 0.05$]. The velocity of movement was significantly more variable at the fast (0.193 Hz) than at the slow speed (0.148 Hz), [$F(1,18) = 19.397$, $p < 0.001$]. There were no interactions between Group, Cue or Speed.

Accuracy of velocity

There was no difference between the Parkinson's disease (mean error, 0.141 Hz) and the control (mean error, 0.035 Hz) groups, [$F(1,18) = 2.865$, $p > 0.05$], in terms of accuracy of velocity for the in-phase co-ordination pattern. There was no difference in the accuracy of velocity in the presence (mean error, 0.083 Hz) or the absence (mean error, 0.094 Hz) of the external cue, [$F(1,18) = 0.427$, $p > 0.05$]. The velocity of movement was more accurate at the slow (mean error, -0.045 Hz) than the fast speed (mean error, 0.223 Hz), [$F(1,18) = 22.803$, $p < 0.001$]. This main effect was modified by a Group by Speed interaction, [$F(1,18) = 8.455$, $p < 0.009$]. There was no significant difference between the slow (mean error, -0.018 Hz) and the fast (mean error, 0.088 Hz)

speeds for the control group, [$F(1,9) = 3.310$, $p > 0.05$]. There was, however, a significant difference between the slow (mean error, -0.074 Hz) and the fast (mean error, 0.356 Hz) speeds for the Parkinson's disease group, [$F(1,9) = 20.034$, $p < 0.002$].

Anti-phase task

Phase Histograms

Qualitatively, the phase histograms (Figures 9.7 and 9.8) indicate that, at both the slow and fast speeds, the control group was able to perform the anti-phase task more successfully than the Parkinson's disease group. In particular, the control group's data peaked around 180°, the target angle, whereas the Parkinson's disease group's data peaked at around 0°, which is the target angle for the in-phase pattern. This pattern of results does not vary according to the presence or absence of the cue.

Variation in co-ordination pattern

The Parkinson's disease group (50°) was as variable in co-ordination pattern as the control group (40°), [$F(1,18) = 1.466$, $p > 0.05$]. There was no significant effect of the presence (44°) or absence (46°) of the external cue, [$F(1,18) = 0.229$, $p > 0.05$]. There was no interaction between Group and Cue. The anti-phase co-ordination pattern was significantly less variable at the slow (40°) than the fast (50°) speed, [$F(1,18) = 7.437$, $p < 0.014$]. There was no interaction involving Speed.

Accuracy of co-ordination pattern

The Parkinson's disease group (109°) was significantly less accurate in co-ordination pattern than the control group (43°), [$F(1,18) = 35.911$, $p < 0.001$]. There was no significant effect of the presence (77°) or absence (75°) of the external cue, [$F(1,18) = 0.108$, $p > 0.05$]. There was no interaction between Group and Cue. There was no main effect of speed, and no interactions involving speed.

Variability of velocity

There was no difference between the Parkinson's disease (0.190 Hz) and the control (0.203 Hz) groups, in terms of variability in velocity, [$F(1,18) = 0.352$, $p > 0.05$], for the anti-phase co-ordination pattern. Neither the presence (0.196 Hz) nor the absence

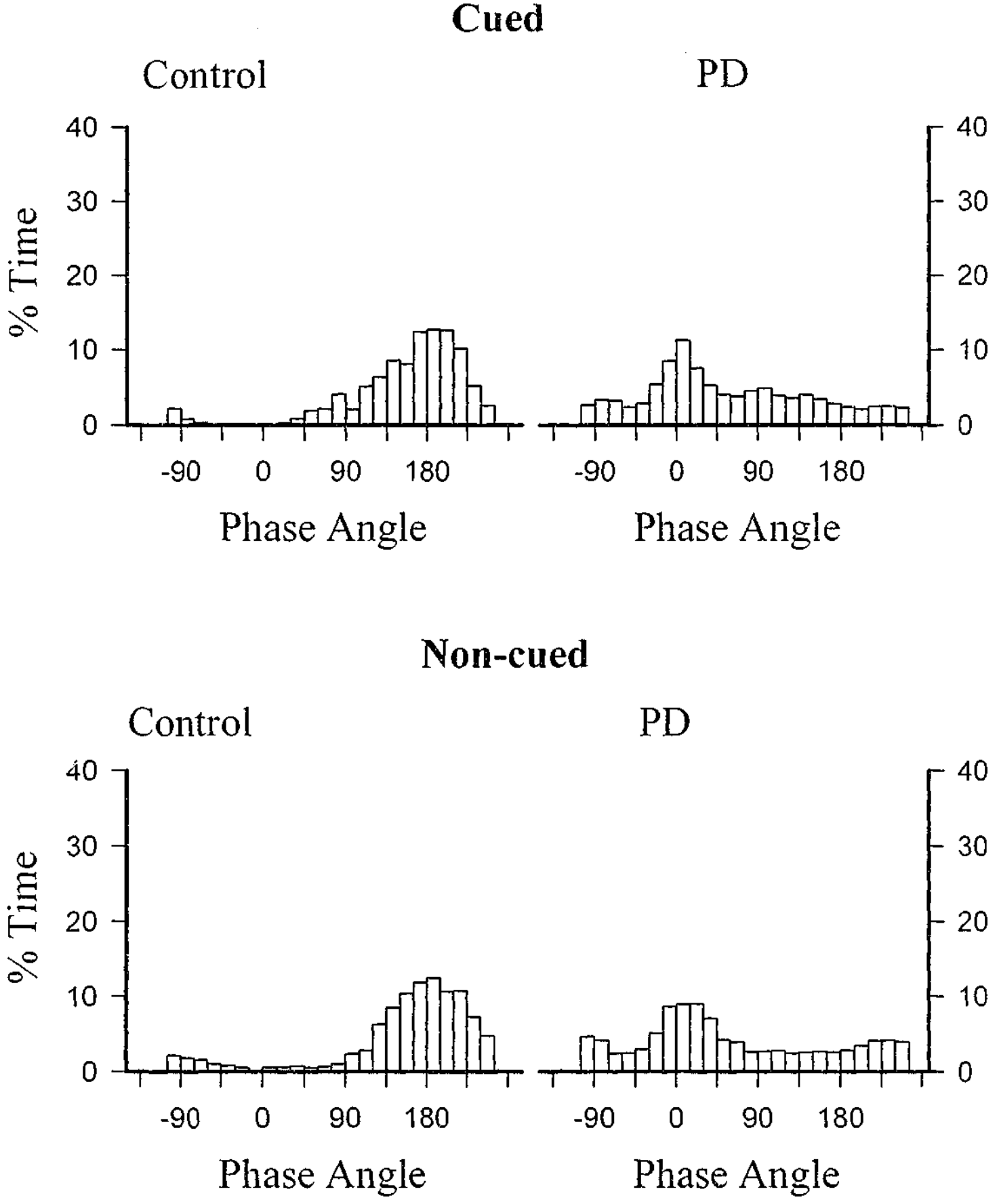


Figure 9.7: Slow movements: anti-phase histograms for control and Parkinson's disease (PD) participants, for cued and non-cued movements, at the slow speed.

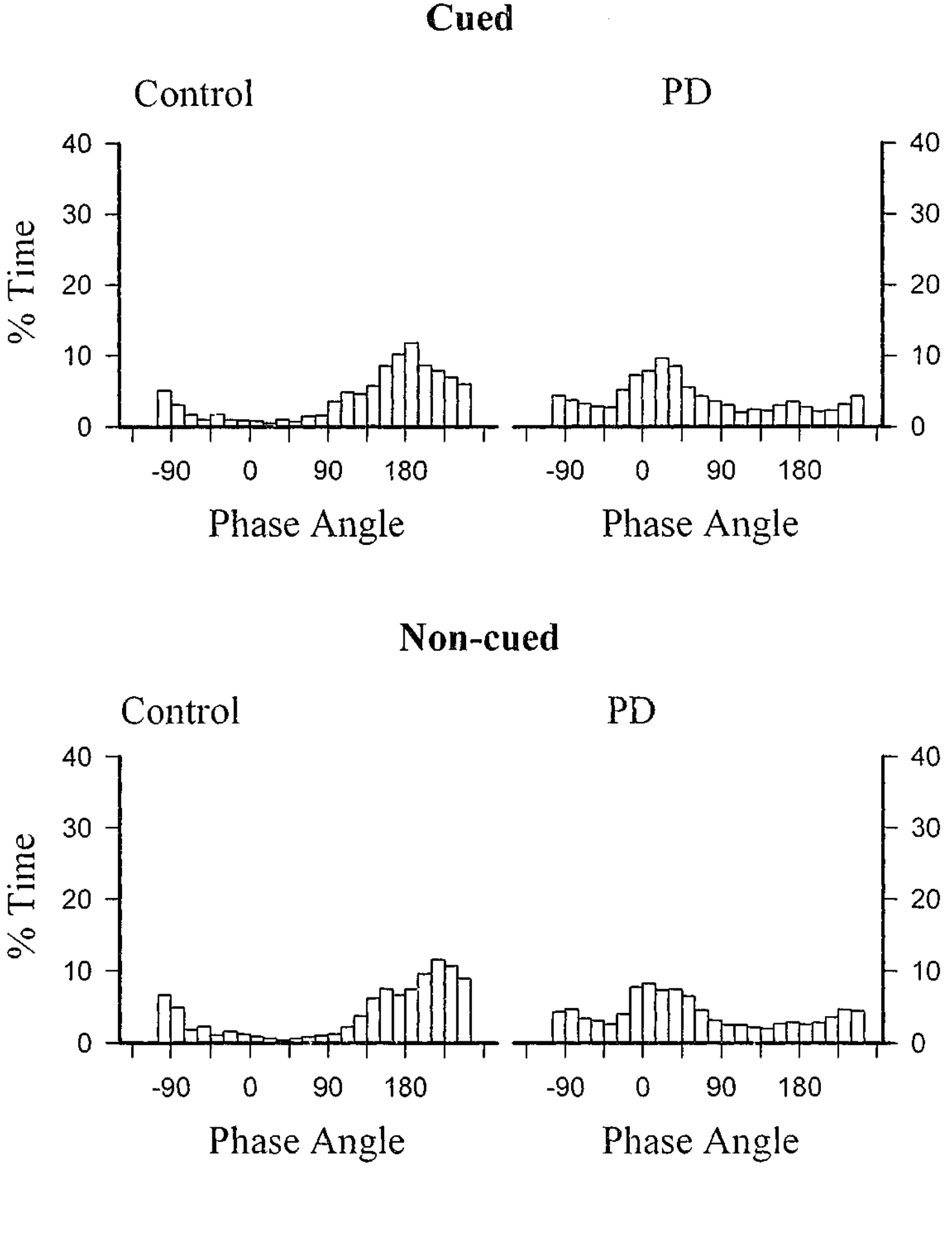


Figure 9.8: Fast movements: anti-phase histograms for control and Parkinson's disease (PD) participants, for cued and non-cued movements, at the fast speed.

(0.197 Hz) of the external cue affected the variability of velocity, [$F(1,18) = 0.070$, $p > 0.05$]. The velocity of movement was significantly more variable at the fast (0.223 Hz) than at the slow speed (0.171 Hz), [$F(1,18) = 25.310$, $p < 0.001$]. There were no interactions between Group, Cue or Speed.

Accuracy of velocity

There was a significant difference between the Parkinson's disease (mean error, 0.253 Hz) and the control (mean error, 0.074 Hz) groups, [$F(1,18) = 4.529$, $p < 0.047$], in terms of accuracy of velocity for the anti-phase co-ordination pattern. There was no difference in the accuracy of velocity in the presence (mean error, 0.170 Hz) or the absence (mean error, 0.157 Hz) of the external cue, [$F(1,18) = 1.066$, $p > 0.05$]. The velocity of movement was more accurate at the slow (mean error, -0.061 Hz) than the fast speed (mean error, 0.388 Hz), [$F(1,18) = 75.054$, $p < 0.001$]. This main effect was modified by a Group by Speed interaction, [$F(1,18) = 4.977$, $p < 0.039$]. There was a significant difference between the slow (mean error, -0.093 Hz) and the fast (mean error, 0.241 Hz) speeds for the control group, [$F(1,9) = 15.951$, $p < 0.003$]. There was also a significant difference between the slow (mean error, -0.030 Hz) and the fast (mean error, 0.535 Hz) speeds for the Parkinson's disease group, [$F(1,9) = 84.406$, $p < 0.001$]. The locus of the interaction lay with the Parkinson's disease group, who were much less accurate in velocity at the fast speed than the control group.

DISCUSSION

In summary, the anti-parkinsonian medication did not have a significant effect on the bimanual co-ordination performance of the group of Parkinson's disease patients. These patients were able to perform the simpler in-phase movement, but were unable to perform the complex anti-phase movement. In contrast, the control group was able to perform both co-ordination tasks, albeit the in-phase pattern was better performed than the anti-phase pattern. Surprisingly, the Parkinson's disease group showed no improvement in performance in the presence of the external cue, as had previously been reported (Johnson *et al.*, 1998).

The medication status of the Parkinson's disease group did not alter the variation in and accuracy of the in-phase and anti-phase co-ordination patterns. The patient group performed the in-phase and anti-phase co-ordination patterns with the same variation in

velocity on and off the medication. The only dependent variable that was affected by the medication status was the accuracy of velocity. When the Parkinson's disease patients were on medication, they were more accurate in maintaining the required speed than when they were off medication. The general result of no medication effect is quite surprising. There are a number of explanations for this finding. The significant Purdue Pegboard task results certainly suggest that there was a significant difference in manual dexterity between the on and off medication states in this set of patients. This pegboard task requires very fine manual dexterity, which is an entirely different movement performance task compared with the bimanual co-ordination task of this experiment, which is a whole arm gross movement. In contrast, there was no significant medication effect for the Parkinson's disease group for the Get-Up-And-Go task, which is a whole body movement task. It is possible that in this group of patients, the medication was very effective (and statistically significant) for the fine, manual task of the Purdue Pegboard, but did not have a significant effect on the larger amplitude gross movements, such as the bimanual co-ordination and walking tasks. This difference in the effect of medication on the size of movement is a very interesting phenomenon, and is certainly amenable to further investigation.

Another possible explanation for the lack of a medication effect is that of attention. The testing of each patient on and off medication was performed in the same session, thus circumventing any potential differential, and thus confounding, effect of state factors. The time of experimentation was reasonably early in the morning, and while not ideal, was an imposed hospital requirement. The lack of a difference between the two medication states, and as argued below, the lack of a cue effect, may be due to a generalized lowering of attention and motivation. All of the patients were in hospital, undergoing long-term changes in medication, and their motivation and thus concentration and attention to the task may have been sub-optimal. My clinical impression is that this group of Parkinson's disease patients was performing with suboptimal attentional capacities, in comparison with the previous group of Parkinson's disease patients, who were tested in their own homes (Johnson *et al.*, 1998). The relationship between medication status and mental well-being (incorporating state factors such as motivation, mood, concentration and attention) is not well understood, and requires further investigation. Nevertheless, any beneficial effect of the anti-

parkinsonian medication on bimanual coordination may have been masked by the severe attentional impairments in this particular group.

The Parkinson's disease group was able to perform the in-phase task, but was significantly less accurate and more variable in co-ordination pattern than the control group, as has been found previously (Johnson *et al.*, 1998). The patient group performed the in-phase task at the same speed and with the same variation in velocity as the control group. The in-phase pattern is relatively easy to perform as there is only one timing pattern. Both hands produce the same mirror-symmetrical movement, facilitating inter-limb coupling.

The Parkinson's disease group was not able to perform the anti-phase task, unlike the control group. This finding concurs with previous work (Johnson *et al.*, 1998). The patient group was significantly less accurate in co-ordination pattern and velocity than the control group, but was similar to the control group in terms of variability in co-ordination pattern and velocity for the anti-phase task. This lack of a difference in variability in co-ordination pattern and velocity suggests that both groups maintained their co-ordination patterns and speed of movement, over time, reasonably well, despite the incorrect in-phase pattern by the Parkinson's disease group. The actual movement is, of course, exactly the same as the in-phase condition, but the anti-phase task is a more complex movement to perform as it involves mirror-asymmetrical movement, which is in opposition to the naturally occurring tendency towards inter-limb coupling. The timing of the two hands is very difficult as the hands rotate to the top in turn, which may constitute two sequential sub-movements. The Parkinson's disease patients were unable to perform this movement at either speed. The anti-phase task may require particular activation from the SMA. Lesions to the SMA in monkeys and humans lead to a tendency to revert to mirror-symmetric movements, when the requisite movement is mirror-asymmetrical (Brinkman, 1981; Chan and Ross, 1988; Luria, 1966). It is also known that unilateral SMA lesions disrupt bimanual co-ordination in monkeys (Brinkman, 1981) and humans (Laplane *et al.*, 1977), leading to deficits in the ability to perform alternating bimanual movements (Dick *et al.*, 1986). The SMA is known to be particularly activated for movements which are asymmetrical rather than symmetrical (Uhl *et al.*, 1993), or sequential rather than simultaneous (Lang *et al.*, 1989; Lang *et al.*, 1990). The inability to perform the anti-phase movement is thus not surprising in

Parkinson's disease, with the proposed deficient function of the SMA (Samuel *et al.*, 1997).

The absence of an effect of the external cue was another surprising result. In a previous study the presence of the external metronome-timing cue significantly improved the performance of the Parkinson's disease group. In particular, the in-phase movement was significantly more accurate and less variable in the presence of the cue (Johnson *et al.*, 1998). During the anti-phase movement in that study, the Parkinson's disease group performed the incorrect in-phase movement, and in the presence of the external timing cue, the performance of the (incorrect) in-phase movement became less variable and more accurate. In the present experiment, the external cue had no effect on movement performance, except during the anti-phase movement when the Parkinson's disease group, off medication, at the slow speed was significantly more variable *with* the external cue than without the cue. This suggests that problems in attention may have been an issue for this particular group of patients. As noted above, this particular group of patients was disadvantaged by the fact that they were inpatients, tested very early in the morning, and their motivation to complete the study may have been questionable. The Johnson *et al.* (1998) group of Parkinson's disease patients was tested at home, they were only tested during the on phase of their medication cycle, and their medication cycle was not perturbed in any way. The bimanual co-ordination task is quite a demanding experimental procedure, and the perturbation of the medication cycle, hospital admission, and an early time of the day for testing, might have disrupted the attentional capacity of the patients to utilise the external cue.

In conclusion, this study has found that the Parkinson's disease group showed no difference in bimanual co-ordination ability between the 'on' and the 'off' stages of the anti-parkinsonian medication cycle. As previously found, the Parkinson's disease group was not able to perform the anti-phase movement, but instead reverted to the more stable in-phase movement. Unlike a previous study, there was no cue effect on the bimanual co-ordination of the Parkinson's disease group. The lack of any improvement in performance as a function of both medication cycle and cueing, may reflect compromised attentional capacities in this group of patients. A further investigation of these issues would provide additional information about the role of anti-parkinsonian

medication on large and small amplitude movements and motivational states, and how these factors influence bimanual co-ordination in Parkinson's disease.

Chapter Ten - General Discussion

A comparison of results from Parkinson's and Huntington's diseases, two disease models of frontostriatal function, affords further information about the neurological underpinnings of bradykinesia, and speculation about the preparation and execution of sequential voluntary movement. Parkinson's disease is associated with loss of dopaminergic cells in the substantia nigra of the basal ganglia. The physiological consequence is believed to be increased inhibition of the thalamus, and reduced output to the SMA (Young and Penney, 1998). The SMA is known to be significantly under-active in Parkinson's disease (Owen *et al.*, 1998). Behaviourally, Parkinson's disease is associated with difficulties in initiating and executing voluntary movements (Agostino *et al.*, 1998). Movement times progressively slow as a sequence of movements continues (Agostino *et al.*, 1992). Huntington's disease is primarily associated with neuronal loss and astrocytosis of the caudate, putamen and globus pallidus (Myers *et al.*, 1991). As a manifestation of the disease process, the damage to the brain is more widespread in Huntington's, in comparison with Parkinson's disease (Macmillan and Quarrell, 1996). The ramifications of Huntington's disease, in terms of physiology, are poorly understood (Mansuy and Bujard, 2000). The involuntary choreic movements characteristic of the disease may be a result of damage to the striatal inhibitory GABA- and enkephalin-containing neurons which project to the GPe, possibly leading to disinhibition of the thalamus and disturbed output to the SMA (Berardelli *et al.*, 1999). The bradykinesia of Huntington's disease may be a result of loss of striatal GABA-substance P neurons which project directly to the GPi, resulting in increased inhibition of the thalamus and reduced output to the SMA; the end result mirrors Parkinson's disease (Young and Penney, 1998). The SMA is significantly under-active in Huntington's disease during the performance of sequential movements (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997). Behaviourally, Huntington's disease is associated with difficulties in initiating and executing voluntary sequential movements (Hefter *et al.*, 1987).

Patients suffering from either Parkinson's or Huntington's disease typically show bradykinetic deficits in the production of sequential movements. The MRP studies performed on patients with Parkinson's disease, e.g. (Praamstra *et al.*, 1996) have provided valuable information about the timing of cortical activity preceding voluntary

movement (Deecke *et al.*, 1969). Prior to this thesis, no MRP studies had been reported in Huntington's disease. The reported effects of the provision of external cues on the movement performance on Huntington's disease patients were ambiguous. The possible progressive slowing of movement down a sequence by Huntington's disease patients, which is characteristic of Parkinson's disease, was also equivocal. The possibly beneficial effect of anti-parkinsonian medication on the (compromised) bimanual co-ordination of patients with Parkinson's disease was unknown.

The set of experiments described in this thesis was designed to provide further information about the preparation and execution of sequential movement primarily in Huntington's disease, and also in Parkinson's disease. Two methodological approaches were taken. The electrophysiological approach provided the first description of movement-related potentials in Huntington's disease. With the experimental design reflecting previous work on Parkinson's disease, e.g. (Cunnington *et al.*, 1995), comparisons were made between the two disease groups. This subset of experiments provided information about the effect of the provision of external cues and attentional strategies on the cortical pre-movement activity in Huntington's disease. The deficits in the components of the activity relating to preparation and execution were clarified in this disease. The change over time of the pre-movement cortical activity in Huntington's disease was measured. The behavioural approach was the other methodology used in this thesis. Huntington's disease was further differentiated from Parkinson's disease by the absence of a beneficial effect of an auditory cue on unimanual upper limb movement, characteristic of Parkinson's disease. Absence of a sequencing effect in Huntington's disease was described and discussed. Finally, the effect of anti-parkinsonian medication on the ability to co-ordinate the two arms in Parkinson's disease was reported.

In the following sections, the significance of the findings reported in this thesis will be reviewed, with respect to the effects of internal and external cues, the adoption of strategies, movement preparation and execution of sequential unimanual and bimanual movement, and the effects of neurodegeneration.

External cues, attention and strategy

One main difference between the performance of the Huntington's disease group, in comparison with previous findings on Parkinson's disease, was the lack of an effect of the provision of an external auditory timing cue on unimanual sequential movement. Patients with Parkinson's disease will often show a significant improvement in the performance of movements in the presence of a generic external cue. This external cue may take the form of an auditory (Freeman *et al.*, 1993) or visual (Oliveira *et al.*, 1997) cue. Georgiou *et al.* (1993) had previously found that an auditory timing cue and a visual spatial cue were equipotent in terms of improving the quality of movement in Parkinson's disease (Georgiou *et al.*, 1993). In Huntington's disease, this is not the case. The provision of an auditory external cue in Chapter Seven did not significantly improve the movement time of the Huntington's disease patients to match the time recorded in the presence of the visual cue. Indeed, there was no significant difference in movement time between the condition with no external cue and the condition with only the auditory cue. The Huntington's disease patients were slower than controls across all the cue types, and like parkinsonian patients, were especially slowed in the absence of external visual cues. The most pertinent point from Chapter Seven was that the provision of an auditory cue, with only timing aspects associated with it, was not enough to improve significantly movement time to the speeds recorded in the presence of the visual cue, in Huntington's disease or in controls. The lack of an auditory cue effect on movement control in Huntington's disease has previously been shown in bimanual co-ordination (Johnson *et al.*, 2000), and in gait (Churchyard *et al.*, 2000). In both of these studies, the auditory cue was incongruent with the required task. With the additional cognitive decline associated with Huntington's disease, any external cue provided might need to be congruent with the nature of the task. This is a clear dissociation with the results found in Parkinson's disease.

In the MRP paradigm in Chapter Two, the Huntington's disease group presented pre-movement cortical activity that was significantly reduced in comparison with the control group, for both the cued and non-cued conditions. In the absence of the cue, rising pre-movement activity was recorded, although it was significantly reduced in comparison with the control group. This mirrors results from studies on Parkinson's disease, where the pre-movement activity is reduced in comparison with control participants, in the absence of an external cue (Cunnington *et al.*, 1995; Praamstra *et al.*,

1995). In the absence of an external cue, the SMA is believed to be preferentially involved in the preparation of movement (Tanji and Shima, 1994). The significant reduction in pre-movement activity in Huntington's disease during the non-cued condition suggests that the SMA contribution to motor preparatory activity is impaired. This finding concurs with recent PET studies (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997).

In the presence of the external cue, there was no significant level of pre-movement preparatory activity recorded from the Huntington's disease group (Chapter Two). This result was also found in Parkinson's disease (Cunnington *et al.*, 1995). With an external cue present, the movement may have been prepared in areas other than those believed to be recorded in the MRP (Ohara *et al.*, 2000). In a comparison of the two disease groups, in the presence and absence of external cues, Huntington's and Parkinson's disease patients produced similar patterns of pre-movement cortical activity.

The results of Chapters Two and Seven invite speculation about the similarities and differences of the two disease groups, in terms of responsivity to an external cue. The results from Chapter Two suggest that areas other than the SMA may have prepared the movements made by the patients with Huntington's disease. This may also be the case in Parkinson's disease. Parkinson's disease patients show improvements in movement performance in the presence of external cues. It is unclear why spatial and timing cues benefit parkinsonian movement.

One possibility is that the reliance upon external cues reflects a compensatory mechanism of utilisation of the lateral premotor area (Deiber *et al.*, 1991; Mushiake *et al.*, 1991). The lateral premotor area is believed to be involved to a greater degree in the preparation of externally rather than internally cued movements (Halsband *et al.*, 1993). This area receives striatal input from anatomically and functionally different areas than the SMA (Hoover and Strick, 1993). During the performance of externally cued finger sequences, Parkinson's disease patients show a greater degree of activation of the lateral premotor area than control participants (Samuel *et al.*, 1997). This area may be used in a compensatory manner by patients with Parkinson's disease (Praamstra *et al.*, 1996). In Chapter Seven it was demonstrated that Huntington's disease patients do not show improved movement performance in the presence of external auditory cues in the same way as Parkinson's disease patients. The lateral premotor area shows evidence of

considerable damage in Huntington's disease (Bartenstein *et al.*, 1997). In Huntington's disease, the parietal motor area is hyperactive during the performance of sequential movements (Bartenstein *et al.*, 1997), suggesting possible recruitment of this area in the preparation of movement. Further whole brain scanning, using externally and internally cued movement in Huntington's disease, would further elucidate this issue.

Another possibility is that the external cues act to draw attention to the task: in Parkinson's disease, the cues may not need to engage directly all elements of the task, but in Huntington's disease, the cues may need to be more closely matched to the task requirements. Attentional mechanisms may then aid the preparation of the movement. These two explanations of the obtained results are not necessarily mutually exclusive.

Movement performance of patients with Parkinson's disease has been shown to improve if the patient attends consciously to the parameters of the task (Ho *et al.*, 1999; Morris *et al.*, 1996; Oliveira *et al.*, 1997). A similar pattern of results has been found in Huntington's disease patients (Georgiou *et al.*, 1997; Sprengelmeyer *et al.*, 1995). When a strategy was introduced to attend consciously to and anticipate the cue, and internally generate a response, there was a significant improvement in the pre-movement cortical activity of both Parkinson's (Cunnington *et al.*, 1999) and Huntington's (Chapter Three) patients. The ability to use a cognitive strategy to improve the pre-movement cortical activity appears to be intact in Huntington's disease, which has important implications for rehabilitation in this disease group.

In the absence of an external cue, an individual will self-time and self-guide a movement, possibly modelling the movement via top-down processing and preparing the movement in advance via the medial motor circuit. In a predictably timed movement paradigm, control participants show pre-movement activity during externally cued movements (Cunnington *et al.*, 1995) suggesting they are still internally modelling the movement. Indeed, in Chapter Two, no difference was found between the pre-movement activity recorded in the cued and non-cued conditions, for the control group. This internal modelling may be likened to the increase in pre-movement activity in the imagined movement condition in Chapter Five. The significantly reduced pre-movement activity in both Parkinson's (Cunnington *et al.*, 1999; Cunnington *et al.*, 1995) and Huntington's diseases (Chapter Two) suggested that these patient groups were not intuitively modelling the movement. As mentioned above, when a cognitive

strategy was given to these two groups, there was a significant increase in the pre-movement cortical activity, in the presence of the external cue.

Chapter Four questioned the importance of the external cue to the success of the cognitive strategy, in the Huntington's and the control groups. The control group may internally model movement, regardless of the presence or absence of the external cue. There was no difference in the pre-movement activity of the control group in the cued and non-cued conditions in Chapters Two, Four and in Jahanshahi *et al.* (1995). The medial motor system may be involved in both the cued and non-cued conditions, due to the internal modelling. With the addition of the strategy, more conscious attentional processes may be called upon and be reflected in the pre-movement potential. This conscious processing appears to be dependent upon the provision of an external cue. The external cue may have promoted the concentration of the control participants, enabling better usage of the strategy. This effect is apparently lost in Huntington's disease, in that there was no difference in the pre-movement potential in the cued and non-cued conditions, irrespective of the presence or absence of the strategy.

In the presence of the external cue there was no pre-movement rising potential in Huntington's disease, indicating that the movement was prepared in an unconventional manner. In the absence of the external cue, when the movement must be self-timed and self-guided, there was a significantly reduced pre-movement potential which was not significantly different from the potential recorded during the cued movement. The Huntington's disease group showed a strong trend towards a significant difference between the strategy and non-strategy conditions, with the lower number of participants possibly affecting the power of the experiment. The results of Chapter Two suggest that the Huntington's disease group is able to make use of the strategy in increasing the pre-movement cortical activity. The presence or absence of the external cue, however, had no effect on the pre-movement cortical activity in Huntington's disease, in the presence or absence of the strategy. This has been a consistent result throughout the thesis. As discussed above, it is possible that another circuit within the brain, incorporating the parietal motor area, may be involved in preparing the movement in Huntington's disease. This issue could also be resolved with further research using high resolution spatial and temporal scanning.

Movement Preparation and Execution

It is difficult to separate the components of preparation and execution of movement. If the preparation of movement is defective in some way, then the consequences will likely be felt in the execution of that movement. In Huntington's disease, the movement difficulties described in the literature are suggestive of problems in the initiation and execution of movement. Apart from the bradykinesia (Berardelli *et al.*, 1999; Currá *et al.*, 2000; Thompson *et al.*, 1988), huntingtonian movement is characterised by variability in execution of unimanual (Phillips *et al.*, 1996) and bimanual (Johnson *et al.*, 2000) movements. One approach in separating the components of preparation and execution is to use imagined movement (Chapter Five). The Huntington's disease patients showed particular deficits in the pre-movement cortical activity relating to the preparation of movement. Parkinson's disease patients also showed a particular deficit in the preparation component of the pre-movement potential (Cunnington *et al.*, 1997). This result is suggestive of impaired activation of the SMA in Huntington's and Parkinson's diseases.

Sequencing of movement

One characteristic of Parkinson's disease is the sequential slowing of movement (Agostino *et al.*, 1992; Currá *et al.*, 1997). If planning of movement is deficient, then one consequence may be additive slowing, down a repetitive sequence of movements. It is noteworthy that the provision of external cues significantly improves the sequencing effect in Parkinson's disease (Georgiou *et al.*, 1994). It may be that the external cues draw the attention of the Parkinson's disease patients to the task, aiding the production of the sequential movement. The results of Chapter Eight suggest that Huntington's disease patients do not slow their movements in an additive fashion down a sequence, which is in accord with some previous findings (Agostino *et al.*, 1992; Currá *et al.*, 2000). They were significantly slower than control participants, but this was found over all the button positions. The pathways used in the experiment varied in a number of ways, allowing an investigation of the modulation of movement length and regularity of direction change. The Huntington's disease group was differentially affected by the change in movement length. The capacity to rescale their movements to conform to the different movement lengths was very much less efficient than the control group. This deficit in rescaling movement is a novel finding in Huntington's disease,

and suggests difficulties in preparing movements; it should be subjected to further investigation.

Bimanual co-ordination

The ability to co-ordinate the two hands is a prime model of a sequential task. Chapter Nine investigated the ability of Parkinson's disease patients to perform bimanually co-ordinated movements when on and off anti-parkinsonian medications. It was expected that the anti-parkinsonian medication would significantly improve the variability and accuracy of the in-phase and anti-phase co-ordinated movements. The Parkinson's disease group was significantly more variable and less accurate than the control group in their performance of both the in-phase and anti-phase tasks, in a similar manner to a previous study using the same methodology (Johnson *et al.*, 1998). Unlike the previous study however, no cue effect was found in Chapter Nine. The lack of the cue effect and the lack of an improvement with medication may have been due to a generalised lowering of attention and motivation in the patient group, situated in unfavourable testing conditions (on ward in hospital, tested early in the morning off and then on medication). It is possible that a lowering of attention will interfere with the internal modelling of movement, resulting in poorer movement execution. A further investigation is recommended on the role of medication and motivational and attentional factors on bimanual co-ordination in Parkinson's disease.

Neurodegeneration in Huntington's disease

The MRP provides an established index of pre-movement cortical preparatory activity. The MRP of nine Huntington's disease patients and matched controls, in the early to middle stages of the disease was recorded in late 1997 and early 2000, as part of an ongoing study of neurodegeneration and its effects on the pre-movement cortical activity. There was no significant difference in the cortical activity between the two testing sessions, although there was a trend towards a reduction in activity. This experiment will continue, as a measure of functional change in people suffering from an ongoing neurodegenerative disease.

Speculation about movement preparation and execution in Huntington's and Parkinson's diseases

It is probable that there may be a number of different circuits involved in the preparation of movement, some of which may enable more efficient and smoother movement execution than other circuits. Figure 10.1 represents a schematic concept of movement preparation in the two disease groups. The SMA and the lateral premotor area are both involved in movement preparation and project to the movement execution areas of the brain. The provision and absence of external cues may influence the operation of both areas, although the lateral premotor area is thought to be preferentially influenced by external cues and the SMA by internally-derived cues. Normal movement production may involve internal modelling of the movement, which may be aided by the provision of external cues, as found in Chapter Four. Attentional processes may promote this internal modelling and influence movement execution, possibly via the CMA. Other areas of the brain, such as the parietal motor area, may also be involved in the internal modelling and preparation of movement.

From MRP and PET studies, it is apparent that the functioning of the SMA is deficient in both Huntington's (Chapter Two; Weeks *et al.*, 1997), and Parkinson's diseases (Cunnington *et al.*, 1995; Owen *et al.*, 1998). The lateral premotor area may be acting in a compensatory manner in Parkinson's disease, as directly evidenced in PET studies (Samuel *et al.*, 1997), and indirectly in behavioural studies (Georgiou *et al.*, 1993). This area may not be as useful in Huntington's disease, as directly evidenced in PET studies (Bartenstein *et al.*, 1997; Weeks *et al.*, 1997), and indirectly in behavioural studies (Chapter Seven). Instead, the parietal motor area may have to be recruited in the preparation of movement in Huntington's disease (Bartenstein *et al.*, 1997). Attentional processes improve the preparation of movement in both Parkinson's (Cunnington *et al.*, 1999) and Huntington's (Chapters Three and Four) diseases. It may be the case that if attentional mechanisms are compromised, as perhaps in the Parkinson's disease patients studied in Chapter Nine, then the utilisation of the external cues is also limited.

Further research directions

A number of further research directions have already been suggested above. The huntingtonian pre-movement cortical deficiencies described in this thesis should be explored more fully with additional electrode coverage in an endeavour to examine

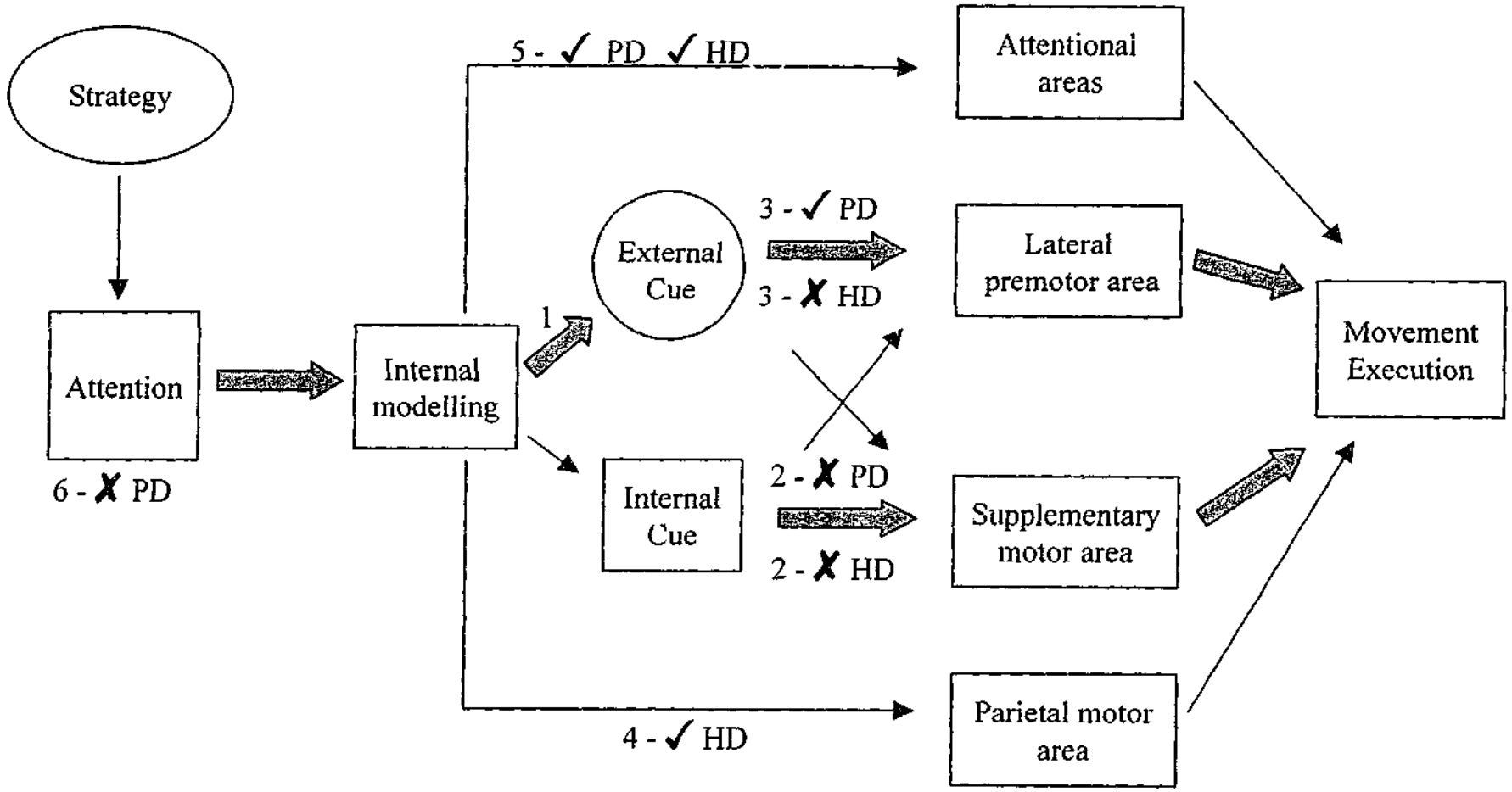


Figure 10.1 - This is a schematic feed-forward diagram of movement preparation. The block arrows represent greater involvement than the thin arrows. The ticks represent utilisation of the pathways by the patient groups, and the crosses represent deficiencies. The circles represent external manipulations used in experiments, and the rectangles represent internal processes or areas. 1 - External cues aid the use of attentional strategies in normals (Chapter 4). 2 - SMA functioning is deficient in PD and HD (Chapter 2). 3 - Lateral premotor area may compensate in PD, but not in HD. 4 - Parietal motor area may compensate in HD. 5 - Attentional processes benefit PD and HD patients (Chapters 3 and 4). 6 - If attentional mechanisms are compromised in PD, as perhaps occurred in Chapter Nine, then utilisation of external cues is limited.

whether the lateral premotor or parietal areas contribute to the movement-related activity in Huntington's disease. This would allow greater spatial resolution of the neuropathology of the disease. The combination of cued and non-cued movement with and without the provision of a strategy in Parkinson's disease is another very important area that should be investigated. Does the provision of external cues have an impact on the successful implementation of strategy in Parkinson's disease? One very interesting observation made during the testing of the MRP in Chapter Five, but not reported, was that the female control participants all showed a greater amount of pre-movement cortical activity during the imagined rather than the actual movement condition. These women were all post-menopausal, and this observation poses the question of the role of estrogen as a neuromodulator in the basal ganglia and associated output regions.

Summary and Conclusion

This thesis aimed to provide further information about the preparation and execution of sequential movement primarily in Huntington's disease, and also in Parkinson's disease. The pre-movement cortical activity of the Huntington's disease group was described for the first time. It was found that the pre-movement cortical activity was significantly reduced in this disease group, in comparison with the control group, regardless of whether the movement was internally or externally cued. This was similar to results found previously in Parkinson's disease. The provision of a strategy significantly improved this pre-movement activity in Huntington's disease, as has also been found previously in Parkinson's disease. The interaction of external and internal cues and strategies on the pre-movement activity in Huntington's disease was investigated. The provision of the external cue had no significant effect on the pre-movement cortical activity. There was a strong trend towards the presence of a strategy having an effect on increasing the pre-movement cortical activity for the Huntington's disease patients. For the control group, it appeared that in order for the strategy to influence significantly the pre-movement cortical activity, the external cue must also be present. The components of the pre-movement cortical activity relating to the preparation and execution of movement in Huntington's disease were delineated, and the possibility of deficits in the preparation of movement was discussed, with reference to Parkinson's disease. The pre-movement cortical activity of Huntington's disease was recorded over a period of time, and there was no significant change, although there was a trend towards decreased

pre-movement cortical activity over the two-year time span in Huntington's disease. The Huntington's disease group was further differentiated from the Parkinson's disease group by the lack of an effect of the provision of an external auditory timing cue on unimanual sequential movement. The lack of a sequencing effect in Huntington's disease was contrasted with the well-documented effects in Parkinson's disease. Finally, the effect of anti-parkinsonian medication on bimanual co-ordination was measured.

As a result of these experiments, it was speculated that Huntington's disease is associated with particular deficits in the preparation of movement. This may be due to deficient functioning of the medial motor pathway, due to damage to the striatum and globus pallidus of the basal ganglia. Parkinson's disease patients may be able to utilise the lateral premotor area as an alternative, parallel circuit. This area may be less available to patients with Huntington's disease, due to greater cell death. The possible use of these alternative areas may lead to characteristic patterns of less efficient movement preparation, which nevertheless result in the typical bradykinesia associated with both diseases.

Appendices

Chapter Two

MAS scores

One way-ANOVA: Group (control, Huntington's disease)

SOURCE	SS	df	MS	F	p
mean	1072.6538	1	1072.6538	48.307	0.000 ***
S/g	532.9167	24	22.2049		
group	201.4295	1	201.4295	9.071	0.006 **
S/g	532.9167	24	22.2049		

Early Slope

Two-way ANOVA: Group (control, Huntington's disease) v Cue (cued, non-cued)

SOURCE	SS	df	MS	F	p
mean	288.5718	1	288.5718	64.847	0.000 ***
S/g	115.7010	26	4.4500		
group	171.4240	1	171.4240	38.522	0.000 ***
S/g	115.7010	26	4.4500		
cue	14.6622	1	14.6622	2.132	0.156
cS/g	178.8143	26	6.8775		
gc	16.7820	1	16.7820	2.440	0.130
cS/g	178.8143	26	6.8775		

Movement Time

Two-way ANOVA: Group (control, Huntington's disease) v Cue (cued, non-cued)

SOURCE	SS	df	MS	F	p
mean	9722431.9130	1	9722431.9130	160.867	0.000 ***
S/g	1571379.5035	26	60437.6732		
group	387762.7556	1	387762.7556	6.416	0.018 *
S/g	1571379.5035	26	60437.6732		
cue	122285.4053	1	122285.4053	9.671	0.005 **
cS/g	328767.7949	26	12644.9152		
gc	553.2372	1	553.2372	0.044	0.836
cS/g	328767.7949	26	12644.9152		

Chapter Three

MAS scores

One way-ANOVA: Group (control, Huntington's disease)

SOURCE	SS	df	MS	F	p	
mean	770.6667	1	770.6667	33.419	0.000	***
S/g	507.3333	22	23.0606			
group	96.0000	1	96.0000	4.163	0.053	
S/g	507.3333	22	23.0606			

Early Slope

Two-way ANOVA: Group (control, Huntington's disease) v Strategy (strategy, no strategy)

SOURCE	SS	df	MS	F	p	
mean	401.0948	1	401.0948	67.334	0.000	***
S/g	131.0496	22	5.9568			
group	148.7267	1	148.7267	24.968	0.000	***
S/g	131.0496	22	5.9568			
strategy	74.3130	1	74.3130	14.188	0.001	**
sS/g	115.2340	22	5.2379			
gs	0.0007	1	0.0007	0.000	0.991	
sS/g	115.2340	22	5.2379			

Movement Time

Two-way ANOVA: Group (control, Huntington's disease) v Strategy (strategy, no strategy)

SOURCE	SS	df	MS	F	p	
mean	4820524.3543	1	4820524.3543	354.327	0.000	***
S/g	299303.7125	22	13604.7142			
group	360906.0952	1	360906.0952	26.528	0.000	***
S/g	299303.7125	22	13604.7142			
strategy	5584.6895	1	5584.6895	1.815	0.192	
sS/g	67677.6355	22	3076.2562			
gs	8841.3975	1	8841.3975	2.874	0.104	
sS/g	67677.6355	22	3076.2562			

Chapter Four

MAS scores

One way-ANOVA: Group (Huntington's disease, control)

SOURCE	SS	df	MS	F	p	
mean	460.0556	1	460.0556	20.063	0.000	***
S/g	366.8889	16	22.9306			
group	68.0556	1	68.0556	2.968	0.104	
S/g	366.8889	16	22.9306			

Early Slope

Three-way ANOVA: Group (control, Huntington's disease) v Cue (cue, no cue) v Strategy (strategy, no strategy)

SOURCE	SS	df	MS	F	p	
mean	790.9007	1	790.9007	101.641	0.000	***
S/g	124.5008	16	7.7813			
group	174.8458	1	174.8458	22.470	0.000	***
S/g	124.5008	16	7.7813			
cue	3.9436	1	3.9436	0.594	0.452	
cS/g	106.1471	16	6.6342			
gc	33.1095	1	33.1095	4.991	0.040	*
cS/g	106.1471	16	6.6342			
strat	83.5631	1	83.5631	8.834	0.009	**
sS/g	151.3504	16	9.4594			
gs	0.5127	1	0.5127	0.054	0.819	
sS/g	151.3504	16	9.4594			
cs	9.0778	1	9.0778	5.319	0.035	*
csS/g	27.3074	16	1.7067			
gcs	10.1046	1	10.1046	5.920	0.027	*
csS/g	27.3074	16	1.7067			

Two-Way ANOVA: Cue (cue, no cue) v Strategy (strategy, no strategy) for the Huntington's disease group.

SOURCE	SS	df	MS	F	p	
mean	111.0054	1	111.0054	15.091	0.005	**
S/	58.8465	8	7.3558			
cue	7.0998	1	7.0998	1.230	0.300	
cS/	46.1957	8	5.7745			
strat	35.4925	1	35.4925	4.342	0.071	
sS/	65.3865	8	8.1733			
cs	0.0138	1	0.0138	0.009	0.928	
csS/	12.6650	8	1.5831			

Two-Way ANOVA: Cue (cue, no cue) v Strategy (strategy, no strategy) for the control group.

SOURCE	SS	df	MS	F	p	
mean	854.7411	1	854.7411	104.151	0.000	***
S/	65.6543	8	8.2068			
cue	29.9533	1	29.9533	3.997	0.081	
cS/	59.9514	8	7.4939			
strat	48.5834	1	48.5834	4.521	0.066	
sS/	85.9639	8	10.7455			
cs	19.1686	1	19.1686	10.473	0.012	*
csS/	14.6424	8	1.8303			

One-Way ANOVA: Strategy (strategy, no strategy) for the control group, with cue.

SOURCE	SS	df	MS	F	p	
mean	602.3544	1	602.3544	65.138	0.000	***
S/	73.9790	8	9.2474			
strat	64.3928	1	64.3928	8.070	0.022	*
sS/	63.8362	8	7.9795			

One-Way ANOVA: Strategy (strategy, no strategy) for the control group, with no cue.

SOURCE	SS	df	MS	F	p	
mean	282.3399	1	282.3399	43.751	0.000	***
S/	51.6266	8	6.4533			
strat	3.3592	1	3.3592	0.731	0.417	
sS/	36.7701	8	4.5963			

Movement Time

Three-way ANOVA: Group (control, Huntington's disease) v Cue (cue, no cue) v Strategy (strategy, no strategy).

SOURCE	SS	df	MS	F	p	
mean	10599443.9651	1	10599443.9651	95.238	0.000	***
S/g	1780712.5090	16	111294.5318			
group	756353.6497	1	756353.6497	6.796	0.019	*
S/g	1780712.5090	16	111294.5318			
cue	49228.4195	1	49228.4195	8.965	0.009	**
cS/g	87863.2504	16	5491.4531			
gc	4819.8190	1	4819.8190	0.878	0.363	
cS/g	87863.2504	16	5491.4531			
strat	554.5006	1	554.5006	0.043	0.839	
sS/g	208416.4740	16	13026.0296			
gs	42475.9228	1	42475.9228	3.261	0.090	
sS/g	208416.4740	16	13026.0296			
cs	273.0393	1	273.0393	0.087	0.772	
csS/g	50358.5495	16	3147.4093			
gcs	1292.2677	1	1292.2677	0.411	0.531	
csS/g	50358.5495	16	3147.4093			

Chapter Five

MAS scores

One way-ANOVA: Group (control, Huntington's disease)

SOURCE	SS	df	MS	F	p
mean	530.4500	1	530.4500	29.978	0.000 ***
S/g	318.5000	18	17.6944		
group	76.0500	1	76.0500	4.298	0.053
S/g	318.5000	18	17.6944		

Items from the Florida Praxis Imagery Scale

Which joint is causing the action? (Not which moves a greater distance in space).

Kinaesthetic

1. Imagine you are using a handsaw. Which joint moves more, your shoulder or your wrist?
2. Imagine you are using a pair of scissors. Which joint moves more, your wrist or your finger joints?
3. Imagine you are writing with a pencil. Which joint moves more, your wrist or your finger joints?
4. Imagine you are hammering a nail. Which joint moves more, your shoulder or your elbow?
5. Imagine you are carving with a knife. Which joint moves more, your elbow or your wrist?
6. Imagine you are rolling up a car window. Which joint moves more, your elbow or your finger joints?
7. Imagine you are firing a handgun. Which joint moves more, your wrist or your finger joints?
8. Imagine you are using a fingernail clipper. Which joint moves more, your finger joints or your wrist?
9. Imagine you are shaving with a disposable razor. Which joint moves more, your wrist or your finger joint?

Position

1. Imagine you are shaving with a disposable razor. Which finger is higher, your index finger or your little finger?
2. Imagine you are hammering a nail on a wall out in front of you. Which is closer to your body, the head of the hammer or the claw of the hammer?
3. Imagine you are using a carving knife. Does your palm face the ceiling or the floor?
4. Imagine you are writing with a pencil. Which is closer to the paper, your index finger or your little finger.
5. Imagine you are using a handsaw. Which is lower, your index finger or your little finger?
6. Imagine you are firing a handgun. Which finger rests on the trigger, your index finger or your ring finger?
7. Imagine you are using a pair of scissors. Which is higher, your thumb or index finger?
8. Imagine you are rolling up a car window. Is your arm straight or bent?
9. Imagine you are using an axe. Is your hand open or closed?

Action

1. Imagine you are using a pair of scissors. Does your hand move toward or away from your body?
2. Imagine you are hammering a nail on the wall out in front of you. Which part of the hammer moves more, the handle or the head?
3. Imagine you are firing a handgun. Does the trigger finger move toward or away from your body?
4. Imagine you are writing a sentence with a pencil. Does your hand move toward or away from your body?
5. Imagine you are shaving with a disposable razor. Does your hand move in a circle or up and down?
6. Imagine you are using a nail file to file your nails. Does your hand move in a circle or back and forth?

Object

1. Is the head of a hammer shaped like the letter "S" or the letter "T"?
2. Which is wider, the head of an axe or the handle of the axe?
3. Is the head of a disposable razor shaped like a square or rectangle?
4. Is the blade of a carving knife wider where it meets the handle or at the tip?
5. When a pair of scissors is opened which letter do the blades and handle make, an X or W?
6. Which is wider, the eraser at the end of a pencil or the point?
7. Is the trigger of a handgun above or below the barrel?
8. Is a handsaw wider at the tip or at the handle?

Chapter Six

STMS scores over time

Two-way ANOVA: Group (control, Huntington's disease) v Testing Session (1997, 2000)

SOURCE	SS	df	MS	F	p	
mean	45227.1111	1	45227.1111	3751.558	0.000	***
S/g	192.8889	16	12.0556			
group	100.0000	1	100.0000	8.295	0.011	*
S/g	192.8889	16	12.0556			
time	2.7778	1	2.7778	2.198	0.158	
tS/g	20.2222	16	1.2639			
gt	1.0000	1	1.0000	0.791	0.387	
tS/g	20.2222	16	1.2639			

MAS scores over time

Two-way ANOVA: Group (control, Huntington's disease) v Testing Session (1997, 2000)

SOURCE	SS	df	MS	F	p	
mean	676.0000	1	676.0000	25.862	0.000	***
S/g	418.2222	16	26.1389			
group	106.7778	1	106.7778	4.085	0.060	
S/g	418.2222	16	26.1389			
time	13.4444	1	13.4444	2.890	0.109	
tS/g	74.4444	16	4.6528			
gt	11.1111	1	11.1111	2.388	0.142	
tS/g	74.4444	16	4.6528			

Early Slope

Two-way ANOVA: Group (control, Huntington's disease) v Testing Session (1997, 2000)

SOURCE	SS	df	MS	F	p	
mean	631.8039	1	631.8039	34.180	0.000	***
S/g	295.7512	16	18.4844			
group	122.0436	1	122.0436	6.603	0.021	*
S/g	295.7512	16	18.4844			
time	0.2283	1	0.2283	0.083	0.777	
tS/g	43.8350	16	2.7397			
gt	1.9894	1	1.9894	0.726	0.407	
tS/g	43.8350	16	2.7397			

Two-way ANOVA: Group (control, Huntington's disease) v Testing Session (1997, 2000)

SOURCE	SS	df	MS	F	p	
mean	4025.5006	1	4025.5006	59.083	0.000	***
S/g	1090.1271	16	68.1329			
group	52.8261	1	52.8261	0.775	0.392	
S/g	1090.1271	16	68.1329			
time	1.0533	1	1.0533	0.159	0.695	
tS/g	105.8746	16	6.6172			
gt	4.4314	1	4.4314	0.670	0.425	
tS/g	105.8746	16	6.6172			

Movement Time

Two-way ANOVA: Group (control, Huntington's disease) v Testing Session (1997, 2000)

SOURCE	SS	df	MS	F	p	
mean	4538412.4837	1	4538412.4837	79.955	0.000	***
S/g	908193.3584	16	56762.0849			
group	524950.9826	1	524950.9826	9.248	0.008	**
S/g	908193.3584	16	56762.0849			
time	1959.3904	1	1959.3904	0.684	0.420	
tS/g	45823.5044	16	2863.9690			
gt	3866.9742	1	3866.9742	1.350	0.262	
tS/g	45823.5044	16	2863.9690			

Chapter Seven

BDI scores

One-way ANOVA: Group (control, Huntington's disease)

SOURCE	SS	df	MS	F	p	
mean	580.1667	1	580.1667	43.365	0.000	***
S/g	294.3333	22	13.3788			
group	73.5000	1	73.5000	5.494	0.029	*
S/g	294.3333	22	13.3788			

Movement Time - First Block

Two-way ANOVA: Group (Huntington's disease, control) v Cue Type (Visual Cue 1, No Visual Cue 1 and Auditory)

SOURCE	SS	df	MS	F	p	
mean	4804044.2268	1	4804044.2268	321.133	0.000	***
S/g	329112.7945	22	14959.6725			
group	427897.2940	1	427897.2940	28.603	0.000	***
S/g	329112.7945	22	14959.6725			
cue1	47932.5300	2	23966.2650	13.715	0.000	***
cS/g	76888.5380	44	1747.4668			
gc	21588.6663	2	10794.3332	6.177	0.004	**
cS/g	76888.5380	44	1747.4668			

One-way ANOVA: Cue Type (Visual Cue 1, No Visual Cue 1 and Auditory) for control group.

SOURCE	SS	df	MS	F	p	
mean	1182221.2966	1	1182221.2966	1868.182	0.000	***
S/	6961.0097	11	632.8191			
cue1	2628.2406	2	1314.1203	7.147	0.004	**
cS/	4044.9455	22	183.8612			

One-way ANOVA: Cue Type (Visual Cue 1, No Visual Cue 1 and Auditory) for Huntington's disease group.

SOURCE	SS	df	MS	F	p	
mean	4049720.2242	1	4049720.2242	138.279	0.000	***
S/	322151.7849	11	29286.5259			
cue1	66892.9557	2	33446.4779	10.101	0.001	***
cS/	72843.5925	22	3311.0724			

One-way ANOVA: Cue Type (Visual Cue 1, No Visual Cue 1) for control group.

SOURCE	SS	df	MS	F	p	
mean	767391.7317	1	767391.7317	2026.083	0.000	***
S/	4166.3191	11	378.7563			
cue1	2212.8003	1	2212.8003	13.918	0.003	**
cS/	1748.8180	11	158.9835			

One-way ANOVA: Cue Type (Visual Cue 1, Auditory) for control group.

SOURCE	SS	df	MS	F	p	
mean	757144.3278	1	757144.3278	1292.724	0.000	***
S/	6442.6639	11	585.6967			
cue1	1695.1204	1	1695.1204	12.868	0.004	**
cS/	1449.0544	11	131.7322			

One-way ANOVA: Cue Type (No Visual Cue 1, Auditory) for control group.

SOURCE	SS	df	MS	F	p	
mean	841220.6542	1	841220.6542	1734.310	0.000	***
S/	5335.5092	11	485.0463			
cue1	34.4401	1	34.4401	0.132	0.723	
cS/	2869.5458	11	260.8678			

One-way ANOVA: Cue Type (Visual Cue 1, No Visual Cue 1) for Huntington's disease group.

SOURCE	SS	df	MS	F	p
mean	2559498.9206	1	2559498.9206	133.732	0.000 ***
S/	210529.9590	11	19139.0872		
cue1	61276.7232	1	61276.7232	14.187	0.003 **
cS/	47511.3053	11	4319.2096		

One-way ANOVA: Cue Type (Visual Cue 1, Auditory) for Huntington's disease group.

SOURCE	SS	df	MS	F	p
mean	2374600.8485	1	2374600.8485	135.130	0.000 ***
S/	193299.7914	11	17572.7083		
cue1	35597.1028	1	35597.1028	30.880	0.000 ***
cS/	12680.1536	11	1152.7412		

One-way ANOVA: Cue Type (No Visual Cue 1, Auditory) for Huntington's disease group.

SOURCE	SS	df	MS	F	p
mean	3198787.1571	1	3198787.1571	127.076	0.000 ***
S/	276895.6156	11	25172.3287		
cue1	3465.6076	1	3465.6076	0.777	0.397
cS/	49073.9299	11	4461.2664		

Down Time – First Block

Two-way ANOVA: Group (Huntington's disease, control) v Cue Type (Visual Cue 1, No Visual Cue 1 and Auditory)

SOURCE	SS	df	MS	F	p
mean	805286.2575	1	805286.2575	120.798	0.000 ***
S/g	146661.0807	22	6666.4128		
group	124217.8928	1	124217.8928	18.633	0.000 ***
S/g	146661.0807	22	6666.4128		
cue1	1092.0763	2	546.0381	2.532	0.091
cS/g	9487.9530	44	215.6353		
gc	806.9316	2	403.4658	1.871	0.166
cS/g	9487.9530	44	215.6353		

Practice and Fatigue Effects – Movement Time

Three-way ANOVA: Group (Huntington's disease, control) v Cue Type (Visual Cue, No Visual Cue) v Order (1, 2)

SOURCE	SS	df	MS	F	p	
mean	5815613.8143	1	5815613.8143	312.203	0.000	***
S/g	409808.6662	22	18627.6666			
group	525807.0036	1	525807.0036	28.227	0.000	***
S/g	409808.6662	22	18627.6666			
cue	61841.4189	1	61841.4189	20.727	0.000	***
cS/g	65638.1425	22	2983.5519			
gc	27046.3426	1	27046.3426	9.065	0.006	**
cS/g	65638.1425	22	2983.5519			
order	4133.7191	1	4133.7191	4.376	0.048	*
oS/g	20783.1199	22	944.6873			
go	1.6669	1	1.6669	0.002	0.967	
oS/g	20783.1199	22	944.6873			
co	2107.0320	1	2107.0320	2.488	0.129	
coS/g	18633.6399	22	846.9836			
gco	1299.1138	1	1299.1138	1.534	0.229	
coS/g	18633.6399	22	846.9836			

Practice and Fatigue Effects – Down Time

Three-way ANOVA: Group (Huntington's disease, control) v Cue Type (Visual Cue, No Visual Cue) v Order (1, 2)

SOURCE	SS	df	MS	F	p	
mean	1044981.8012	1	1044981.8012	134.547	0.000	***
S/g	170866.9820	22	7766.6810			
group	151185.5635	1	151185.5635	19.466	0.000	***
S/g	170866.9820	22	7766.6810			
cue	2357.1925	1	2357.1925	7.294	0.013	*
cS/g	7109.3451	22	323.1520			
gc	1903.7111	1	1903.7111	5.891	0.024	*
cS/g	7109.3451	22	323.1520			
order	438.6150	1	438.6150	1.800	0.193	
oS/g	5362.2501	22	243.7386			
go	105.0016	1	105.0016	0.431	0.518	
oS/g	5362.2501	22	243.7386			
co	11.6204	1	11.6204	0.162	0.691	
coS/g	1580.9156	22	71.8598			
gco	34.3204	1	34.3204	0.478	0.497	
coS/g	1580.9156	22	71.8598			

Movement Time - Second Block

Two-way ANOVA: Group (Huntington's disease, control) v Cue Type (Visual Cue 2, No Visual Cue 2 and Auditory)

SOURCE	SS	df	MS	F	p	
mean	4484114.0435	1	4484114.0435	287.706	0.000	***
S/g	342886.1547	22	15585.7343			
group	429849.9148	1	429849.9148	27.580	0.000	***
S/g	342886.1547	22	15585.7343			
cue	34935.2510	2	17467.6255	15.351	0.000	***
cS/g	50065.9435	44	1137.8624			
gc	9653.2676	2	4826.6338	4.242	0.021	*
cS/g	50065.9435	44	1137.8624			

One-way ANOVA: Cue Type (Visual Cue 2, No Visual Cue 2 and Auditory) for control group.

SOURCE	SS	df	MS	F	p	
mean	1068639.0678	1	1068639.0678	1555.191	0.000	***
S/	7558.5746	11	687.1431			
cue	4775.2628	2	2387.6314	16.236	0.000	***
cS/	3235.3656	22	147.0621			

One-way ANOVA: Cue Type (Visual Cue 2, No Visual Cue 2 and Auditory) for Huntington's disease group.

SOURCE	SS	df	MS	F	p	
mean	3845324.8905	1	3845324.8905	126.141	0.000	***
S/	335327.5801	11	30484.3255			
cue	39813.2557	2	19906.6279	9.352	0.001	**
cS/	46830.5779	22	2128.6626			

One-way ANOVA: Cue Type (Visual Cue 2, No Visual Cue 2) for control group.

SOURCE	SS	df	MS	F	p	
mean	656786.8827	1	656786.8827	1426.724	0.000	***
S/	5063.8061	11	460.3460			
cue	1382.4427	1	1382.4427	23.786	0.000	***
cS/	639.3160	11	58.1196			

One-way ANOVA: Cue Type (Visual Cue 2, Auditory) for control group.

SOURCE	SS	df	MS	F	p	
mean	709431.3215	1	709431.3215	1214.235	0.000	***
S/	6426.8828	11	584.2621			
cue	4765.8016	1	4765.8016	26.742	0.000	***
cS/	1960.3413	11	178.2128			

One-way ANOVA: Cue Type (No Visual Cue 2, Auditory) for control group.

SOURCE	SS	df	MS	F	p	
mean	773447.5628	1	773447.5628	1622.367	0.000	***
S/	5244.1431	11	476.7403			
cue	1014.6499	1	1014.6499	4.953	0.048	*
cS/	2253.3911	11	204.8537			

One-way ANOVA: Cue Type (Visual Cue 2, No Visual Cue 2) for Huntington's disease group.

SOURCE	SS	df	MS	F	p	
mean	2361878.6690	1	2361878.6690	123.229	0.000	***
S/	210831.7018	11	19166.5183			
cue	27421.9411	1	27421.9411	8.776	0.013	*
cS/	34372.3431	11	3124.7585			

One-way ANOVA: Cue Type (Visual Cue 2, Auditory) for Huntington's disease group.

SOURCE	SS	df	MS	F	p	
mean	2403880.7912	1	2403880.7912	123.164	0.000	***
S/	214694.2391	11	19517.6581			
cue	32112.8500	1	32112.8500	35.175	0.000	***
cS/	10042.3115	11	912.9374			

One-way ANOVA: Cue Type (No Visual Cue 2, Auditory) for Huntington's disease group.

SOURCE	SS	df	MS	F	p	
mean	2944796.9487	1	2944796.9487	120.623	0.000	***
S/	268544.5081	11	24413.1371			
cue	185.0925	1	185.0925	0.079	0.784	
cS/	25831.2123	11	2348.2920			

Chapter Eight

BDI scores

One-way ANOVA: Group (control, Huntington's disease)

SOURCE	SS	df	MS	F	p
mean	580.1667	1	580.1667	43.365	0.000 ***
S/g	294.3333	22	13.3788		
group	73.5000	1	73.5000	5.494	0.029 *
S/g	294.3333	22	13.3788		

Movement Time - Overall Analysis

Movement Time – Straight Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (1,2,3,4,5,6,7,8,9)

SOURCE	SS	df	MS	F	p
mean	12766007.5567	1	12766007.5567	402.536	0.000 ***
S/g	697707.2199	22	31713.9645		
group	538251.4178	1	538251.4178	16.972	0.000 ***
S/g	697707.2199	22	31713.9645		
button	11537.5370	8	1442.1921	1.986	0.051
bS/g	127779.4676	176	726.0197		
gb	6181.5509	8	772.6939	1.064	0.390
bS/g	127779.4676	176	726.0197		

Movement Time -Zig-Zag Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (1,2,3,4,5,6,7,8,9)

SOURCE	SS	df	MS	F	p	
mean	12590120.6123	1	12590120.6123	635.859	0.000	***
S/g	435604.0810	22	19800.1855			
group	668946.3900	1	668946.3900	33.785	0.000	***
S/g	435604.0810	22	19800.1855			
button	14548.6481	8	1818.5810	1.670	0.109	
bS/g	191708.5231	176	1089.2530			
gb	16891.9954	8	2111.4994	1.938	0.057	
bS/g	191708.5231	176	1089.2530			

Movement Time – Mixed One Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (1,2,3,4,5,6,7,8,9)

SOURCE	SS	df	MS	F	p	
mean	11425250.0289	1	11425250.0289	230.897	0.000	***
S/g	1088603.9051	22	49481.9957			
group	679561.7604	1	679561.7604	13.734	0.001	**
S/g	1088603.9051	22	49481.9957			
button	96293.5231	8	12036.6904	11.717	0.000	***
bS/g	180803.1574	176	1027.2907			
gb	30804.8750	8	3850.6094	3.748	0.000	***
bS/g	180803.1574	176	1027.2907			

Movement Time – Mixed One Pathway

One-way ANOVA: Button Position (1,2,3,4,5,6,7,8,9) for control group

SOURCE	SS	df	MS	F	p	
mean	3265981.1204	1	3265981.1204	1025.351	0.000	***
S/	35037.5463	11	3185.2315			
button	11523.6296	8	1440.4537	12.815	0.000	***
bS/	9891.2037	88	112.4000			

Movement Time -- Mixed One Pathway

One-way ANOVA: Button Position (1,2,3,4,5,6,7,8,9) for Huntington's disease group

SOURCE	SS	df	MS	F	p	
mean	8838830.6690	1	8838830.6690	92.284	0.000	***
S/	1053566.3588	11	95778.7599			
button	115574.7685	8	14446.8461	7.438	0.000	***
bS/	170911.9537	88	1942.1813			

Movement Time -- Mixed Two Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (1,2,3,4,5,6,7,8,9)

SOURCE	SS	df	MS	F	p	
mean	12529595.0417	1	12529595.0417	238.964	0.000	***
S/g	1153527.1620	22	52433.0528			
group	587605.3519	1	587605.3519	11.207	0.003	**
S/g	1153527.1620	22	52433.0528			
button	172724.1667	8	21590.5208	9.088	0.000	***
bS/g	418142.5880	176	2375.8102			
gb	66074.6898	8	8259.3362	3.476	0.001	***
bS/g	418142.5880	176	2375.8102			

Movement Time – Mixed Two Pathway

One-way ANOVA: Button Position (1,2,3,4,5,6,7,8,9) for control group

SOURCE	SS	df	MS	F	p	
mean	3845215.3912	1	3845215.3912	341.927	0.000	***
S/	123702.9699	11	11245.7245			
button	15518.4630	8	1939.8079	6.780	0.000	***
bS/	25176.4259	88	286.0957			

Movement Time – Mixed Two Pathway

One-way ANOVA: Button Position (1,2,3,4,5,6,7,8,9) for Huntington's disease group

SOURCE	SS	df	MS	F	p	
mean	9271985.0023	1	9271985.0023	99.038	0.000	***
S/	1029824.1921	11	93620.3811			
button	223280.3935	8	27910.0492	6.250	0.000	***
bS/	392966.1620	88	4465.5246			

Down Time – Overall Analysis

Down Time – Straight Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (1,2,3,4,5,6,7,8,9)

SOURCE	SS	df	MS	F	p	
mean	2133581.2789	1	2133581.2789	147.351	0.000	***
S/g	318550.9421	22	14479.5883			
group	268428.7512	1	268428.7512	18.538	0.000	***
S/g	318550.9421	22	14479.5883			
button	1377.5648	8	172.1956	1.838	0.073	
bS/g	16492.2037	176	93.7057			
gb	1127.0093	8	140.8762	1.503	0.159	
bS/g	16492.2037	176	93.7057			

Down Time – Zig-Zag Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (1,2,3,4,5,6,7,8,9)

SOURCE	SS	df	MS	F	p	
mean	2150410.6667	1	2150410.6667	119.222	0.000	***
S/g	396816.2361	22	18037.1016			
group	291060.3750	1	291060.3750	16.137	0.001	***
S/g	396816.2361	22	18037.1016			
button	5916.4375	8	739.5547	5.803	0.000	***
bS/g	22430.4306	176	127.4456			
gb	963.3542	8	120.4193	0.945	0.481	
bS/g	22430.4306	176	127.4456			

Down Time – Mixed One Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (1,2,3,4,5,6,7,8,9)

SOURCE	SS	df	MS	F	p	
mean	2521044.2604	1	2521044.2604	94.348	0.000	***
S/g	587856.7014	22	26720.7592			
group	396422.5104	1	396422.5104	14.836	0.001	***
S/g	587856.7014	22	26720.7592			
button	11980.5417	8	1497.5677	2.994	0.004	**
bS/g	88025.4861	176	500.1448			
gb	4073.2500	8	509.1563	1.018	0.424	
bS/g	88025.4861	176	500.1448			

Down Time – Mixed Two Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (1,2,3,4,5,6,7,8,9)

SOURCE	SS	df	MS	F	p	
mean	3019986.7604	1	3019986.7604	74.189	0.000	***
S/g	895552.3125	22	40706.9233			
group	172635.8438	1	172635.8438	4.241	0.051	
S/g	895552.3125	22	40706.9233			
button	11616.7708	8	1452.0964	7.880	0.000	***
bS/g	32433.5000	176	184.2812			
gb	2152.5625	8	269.0703	1.460	0.175	
bS/g	32433.5000	176	184.2812			

Movement Time – Sequence Effect

Movement Time – Mixed One Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (early, late)

SOURCE	SS	df	MS	F	p	
mean	2589045.5461	1	2589045.5461	216.258	0.000	***
S/g	263383.9067	22	11971.9958			
group	155401.4821	1	155401.4821	12.980	0.002	**
S/g	263383.9067	22	11971.9958			
button	100.6302	1	100.6302	0.265	0.612	
bS/g	8358.5763	22	379.9353			
gb	84.8894	1	84.8894	0.223	0.641	
bS/g	8358.5763	22	379.9353			

Movement Time – Mixed Two Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (early, late)

SOURCE	SS	df	MS	F	p	
mean	2664604.5471	1	2664604.5471	257.357	0.000	***
S/g	227782.1473	22	10353.7340			
group	122984.9997	1	122984.9997	11.878	0.002	**
S/g	227782.1473	22	10353.7340			
button	414.1878	1	414.1878	1.483	0.236	
bS/g	6143.1666	22	279.2348			
gb	794.8981	1	794.8981	2.847	0.106	
bS/g	6143.1666	22	279.2348			

Down Time – Mixed One Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (early, late)

SOURCE	SS	df	MS	F	p	
mean	570251.6828	1	570251.6828	95.199	0.000	***
S/g	131782.0086	22	5990.0913			
group	89830.2578	1	89830.2578	14.996	0.001	***
S/g	131782.0086	22	5990.0913			
button	228.9588	1	228.9588	0.563	0.461	
bS/g	8949.1634	22	406.7802			
gb	732.4219	1	732.4219	1.801	0.193	
bS/g	8949.1634	22	406.7802			

Down Time – Mixed Two Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (early, late)

SOURCE	SS	df	MS	F	p	
mean	550622.5208	1	550622.5208	119.771	0.000	***
S/g	101140.3076	22	4597.2867			
group	77253.9990	1	77253.9990	16.804	0.000	***
S/g	101140.3076	22	4597.2867			
button	128.9260	1	128.9260	1.706	0.205	
bS/g	1662.7686	22	75.5804			
gb	80.0832	1	80.0832	1.060	0.314	
bS/g	1662.7686	22	75.5804			

Down Time – Zig-Zag Pathway

Two-way ANOVA: Group (Huntington's disease, control) v Button Position (early, late)

SOURCE	SS	df	MS	F	p	
mean	464133.3483	1	464133.3483	121.773	0.000	***
S/g	83851.8626	22	3811.4483			
group	61800.6708	1	61800.6708	16.214	0.001	***
S/g	83851.8626	22	3811.4483			
button	261.3333	1	261.3333	3.449	0.077	
bS/g	1666.9512	22	75.7705			
gb	93.5209	1	93.5209	1.234	0.279	
bS/g	1666.9512	22	75.7705			

Movement Length and the ability to Rescale Movement

Movement Time

Two-way ANOVA: Group (Huntington's disease, controls) v Length (long, short)

SOURCE	SS	df	MS	F	p	
mean	2669397.4980	1	2669397.4980	237.218	0.000	***
S/g	247564.5362	22	11252.9335			
group	142188.0329	1	142188.0329	12.636	0.002	**
S/g	247564.5362	22	11252.9335			
length	26573.8398	1	26573.8396	20.759	0.000	***
lS/g	28162.9782	22	1280.1354			
gl	8095.7577	1	8095.7577	6.324	0.020	*
lS/g	28162.9782	22	1280.1354			

Movement Time

One-way ANOVA: Length (long, short) for Huntington's disease group

SOURCE	SS	df	MS	F	p	
mean	2021874.2367	1	2021874.2367	95.225	0.000	***
S/	233558.2904	11	21232.5719			
length	32002.2924	1	32002.2924	12.888	0.004	**
lS/	27314.2343	11	2483.1122			

Movement Time

One-way ANOVA: Length (long, short) for control group

SOURCE	SS	df	MS	F	p
mean	789711.2942	1	789711.2942	620.211	0.000 ***
S/	14006.2458	11	1273.2951		
length	2667.3052	1	2667.3052	34.569	0.000 ***
lS/	848.7439	11	77.1585		

Down Time

Two-way ANOVA: Group (Huntington's disease, controls) v Length (long, short)

SOURCE	SS	df	MS	F	p
mean	615349.5665	1	615349.5665	98.068	0.000 ***
S/g	138044.3776	22	6274.7444		
group	60774.5527	1	60774.5527	9.686	0.005 **
S/g	138044.3776	22	6274.7444		
length	705.7165	1	705.7165	22.612	0.000 ***
lS/g	686.6059	22	31.2094		
gl	136.1816	1	136.1816	4.363	0.049 *
lS/g	686.6059	22	31.2094		

Down Time

One-way ANOVA: Length (long, short) for Huntington's disease group

SOURCE	SS	df	MS	F	p
mean	531446.6367	1	531446.6367	53.038	0.000 ***
S/	110220.4517	11	10020.0411		
length	730.9581	1	730.9581	12.079	0.005 **
lS/	665.6808	11	60.5164		

Down Time

One-way ANOVA: Length (long, short) for control group

SOURCE	SS	df	MS	F	p
Mean	144677.4825	1	144677.4825	57.197	0.000 ***
S/	27823.9260	11	2529.4478		
length	110.9400	1	110.9400	58.319	0.000 ***
lS/	20.9251	11	1.9023		

Regularity of Direction - Long Movements

Movement Time

Two-way ANOVA: Group (Huntington's disease, control) v Task (Long, Zig-Zag)

SOURCE	SS	df	MS	F	p
mean	3009371.1679	1	3009371.1679	456.862	0.000 ***
S/g	144915.0814	22	6587.0492		
group	181736.9935	1	181736.9935	27.590	0.000 ***
S/g	144915.0814	22	6587.0492		
task	3855.1699	1	3855.1699	0.785	0.385
tS/g	108067.9024	22	4912.1774		
gt	1660.4397	1	1660.4397	0.338	0.567
tS/g	108067.9024	22	4912.1774		

Down Time

Two-way ANOVA: Group (Huntington's disease, control) v Task (Long, Zig-Zag)

SOURCE	SS	df	MS	F	p
mean	525014.4429	1	525014.4429	112.121	0.000 ***
S/g	103016.5853	22	4682.5721		
group	59823.7949	1	59823.7949	12.776	0.002 **
S/g	103016.5853	22	4682.5721		
task	1108.7616	1	1108.7616	2.471	0.130
tS/g	9871.9883	22	448.7267		
gt	94.7462	1	94.7462	0.211	0.650
tS/g	9871.9883	22	448.7267		

Regularity of Direction - Short Movements

Movement Time

Two-way ANOVA: Group (Huntington's disease, control) v Task (Short, Straight)

SOURCE	SS	df	MS	F	p	
mean	2488697.7322	1	2488697.7322	398.627	0.000	***
S/g	137349.6812	22	6243.1673			
group	100156.6488	1	100156.6488	16.043	0.001	***
S/g	137349.6812	22	6243.1673			
task	11394.8035	1	11394.8035	22.149	0.000	***
tS/g	11318.3231	22	514.4692			
gt	862.8023	1	862.8023	1.677	0.209	
tS/g	11318.3231	22	514.4692			

Down Time

Two-way ANOVA: Group (Huntington's disease, control) v Task (Short, Straight)

SOURCE	SS	df	MS	F	p	
mean	562183.4783	1	562183.4783	130.528	0.000	***
S/g	94754.0110	22	4307.0005			
group	63108.9356	1	63108.9356	14.653	0.001	***
S/g	94754.0110	22	4307.0005			
task	3747.7133	1	3747.7133	7.798	0.011	*
tS/g	10573.6415	22	480.6201			
gt	48.7165	1	48.7165	0.101	0.753	
tS/g	10573.6415	22	480.6201			

Chapter Nine

UPDRS scores

One-way ANOVA: Medication (on, off)

SOURCE	SS	df	MS	F	p
mean	3836.4500	1	3836.4500	61.740	0.000 ***
S/g	1118.5000	18	62.1389		
group	858.0500	1	858.0500	13.809	0.002 **
S/g	1118.5000	18	62.1389		

Purdue Pegboard Task

One-way ANOVA: Medication (On v Off) - for Right Hand of PD group

SOURCE	SS	df	MS	F	p
mean	1496.4500	1	1496.4500	84.149	0.000 ***
S/	160.0500	9	17.7833		
med	11.2500	1	11.2500	7.642	0.022 *
mS/	13.2500	9	1.4722		

One-way ANOVA: Medication (On v Off) - for Left Hand of PD group

SOURCE	SS	df	MS	F	p
mean	994.0500	1	994.0500	114.040	0.000 ***
S/	78.4500	9	8.7167		
med	14.4500	1	14.4500	9.256	0.014 *
mS/	14.0500	9	1.5611		

Get Up and Go Test

One-way ANOVA: Medication Status (On v Off) for PD group

SOURCE	SS	df	MS	F	p
mean	2549.0562	1	2549.0562	62.776	0.000 ***
S/	365.4486	9	40.6054		
med	44.6108	1	44.6108	2.910	0.122
mS/	137.9861	9	15.3318		

THE EFFECT OF ANTI-PARKINSONIAN MEDICATION

In-Phase task

Variation in co-ordination pattern – PD on v PD off – In-Phase task

Three-way ANOVA: Group (PD On, PD Off), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p
mean	58378.3609	1	58378.3609	34.108	0.000 ***
S/g	30808.0548	18	1711.5586		
group	1518.4219	1	1518.4219	0.887	0.359
/g	30808.0548	18	1711.5586		
cue	4.9859	1	4.9859	0.046	0.832
cS/g	1945.0758	18	108.0598		
gc	57.3392	1	57.3392	0.531	0.476
cS/g	1945.0758	18	108.0598		
speed	2229.8113	1	2229.8113	9.203	0.007 **
sS/g	4361.0748	18	242.2819		
gs	85.7715	1	85.7715	0.354	0.559
sS/g	4361.0748	18	242.2819		
cs	73.2955	1	73.2955	0.800	0.383
csS/g	1648.7808	18	91.5989		
gcs	79.4172	1	79.4172	0.867	0.364
csS/g	1648.7808	18	91.5989		

Accuracy in co-ordination pattern – PD on v PD off – In-Phase task

Three-way ANOVA: Group (PD On, PD Off), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p	
mean	96214.5572	1	96214.5572	35.418	0.000	***
S/g	48898.1950	18	2716.5664			
group	6205.7751	1	6205.7751	2.284	0.148	
S/g	48898.1950	18	2716.5664			
cue	6.0843	1	6.0843	0.042	0.841	
cS/g	2631.3499	18	146.1861			
gc	403.7332	1	403.7332	2.762	0.114	
cS/g	2631.3499	18	146.1861			
speed	1228.3287	1	1228.3287	5.862	0.026	*
sS/g	3771.7132	18	209.5396			
gs	192.6545	1	192.6545	0.919	0.350	
sS/g	3771.7132	18	209.5396			
cs	209.9598	1	209.9598	1.682	0.211	
csS/g	2247.5225	18	124.8624			
gcs	12.1183	1	12.1183	0.097	0.759	
csS/g	2247.5225	18	124.8624			

Variation in Velocity – PD on v PD off – In-Phase task

Three-way ANOVA: Group (PD On, PD Off), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p
mean	2.5742	1	2.5742	251.258	0.000 ***
S/g	0.1844	18	0.0102		
group	0.0047	1	0.0047	0.463	0.505
S/g	0.1844	18	0.0102		
cue	0.0009	1	0.0009	1.438	0.246
cS/g	0.0110	18	0.0006		
gc	0.0001	1	0.0001	0.083	0.776
cS/g	0.0110	18	0.0006		
speed	0.0287	1	0.0287	8.455	0.009 **
sS/g	0.0610	18	0.0034		
gs	0.0010	1	0.0010	0.295	0.594
sS/g	0.0610	18	0.0034		
cs	0.0010	1	0.0010	1.034	0.323
csS/g	0.0176	18	0.0010		
gcs	0.0001	1	0.0001	0.121	0.732
csS/g	0.0176	18	0.0010		

Accuracy of Velocity – PD on v PD off – In-Phase task

Three-way ANOVA: Group (PD On, PD Off), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p
mean	1.5869	1	1.5869	9.983	0.005 ***
S/g	2.8611	18	0.1590		
group	1.0876	1	1.0876	6.842	0.018
S/g	2.8611	18	0.1590		
cue	0.0002	1	0.0002	0.028	0.870
cS/g	0.1159	18	0.0064		
gc	0.0046	1	0.0046	0.719	0.408
cS/g	0.1159	18	0.0064		
speed	3.6857	1	3.6857	32.504	0.000 **
sS/g	2.0410	18	0.1134		
gs	0.4782	1	0.4782	4.217	0.055
sS/g	2.0410	18	0.1134		
cs	0.0131	1	0.0131	2.790	0.112
csS/g	0.0847	18	0.0047		
gcs	0.0020	1	0.0020	0.435	0.518
csS/g	0.0847	18	0.0047		

Anti-Phase task

Variation in co-ordination pattern – PD on v PD off – Anti-Phase task

Three-way ANOVA: Group (PD On, PD Off), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p	
mean	199556.4044	1	199556.4044	97.963	0.000	***
S/g	36667.0154	18	2037.0564			
group	564.2725	1	564.2725	0.277	0.605	
S/g	36667.0154	18	2037.0564			
cue	2.9412	1	2.9412	0.017	0.898	
cS/g	3149.7217	18	174.9845			
gc	84.2759	1	84.2759	0.482	0.497	
cS/g	3149.7217	18	174.9845			
speed	914.2680	1	914.2680	2.470	0.133	
sS/g	6661.4553	18	370.0808			
gs	2058.4463	1	2058.4463	5.562	0.030	*
sS/g	6661.4553	18	370.0808			
cs	251.2734	1	251.2734	1.943	0.180	
csS/g	2327.7873	18	129.3215			
gcs	732.2748	1	732.2748	5.662	0.029	*
csS/g	2327.7873	18	129.3215			

Variation in co-ordination pattern – PD on v PD off – Anti-Phase task

Two-way ANOVA: Cue (on, off), Speed (fast, slow) for PD On Medication group

SOURCE	SS	df	MS	F	p	
mean	89448.8258	1	89448.8258	48.827	0.000	***
S/	16487.6795	9	1831.9644			
Cue	27.8646	1	27.8646	0.125	0.731	
CS/	1999.6576	9	222.1842			
Speed	114.5074	1	114.5074	0.218	0.652	
SS/	4732.5888	9	525.8432			
CS	62.8205	1	62.8205	0.334	0.577	
CSS/	1690.5989	9	187.8443			

Variation in co-ordination pattern – PD on v PD off – Anti-Phase task

Two-way ANOVA: Cue (on, off), Speed (fast, slow) for PD Off Medication group

SOURCE	SS	df	MS	F	p	
mean	110671.8511	1	110671.8511	49.360	0.000	***
S/	20179.3359	9	2242.1484			
Cue	59.3526	1	59.3526	0.464	0.513	
CS/	1150.0641	9	127.7849			
Speed	2858.2068	1	2858.2068	13.336	0.005	**
SS/	1928.8665	9	214.3185			
CS	920.7277	1	920.7277	13.005	0.006	**
CSS/	637.1883	9	70.7987			

Variation in co-ordination pattern – PD on v PD off – Anti-Phase task

One-way ANOVA: Cue (on, off) for PD Off Medication group at the slow speed.

SOURCE	SS	df	MS	F	p	
mean	38979.5562	1	38979.5562	38.385	0.000	***
S/	9139.2973	9	1015.4775			
Cue	723.8084	1	723.8084	10.083	0.011	*
CS/	646.0937	9	71.7882			

Variation in co-ordination pattern – PD on v PD off – Anti-Phase task

One-way ANOVA: Cue (on, off) for PD Off Medication group at the fast speed.

SOURCE	SS	df	MS	F	p
mean	74550.5017	1	74550.5017	51.736	0.000 ***
S/	12968.9051	9	1440.9895		
Cue	256.2720	1	256.2720	2.021	0.189
CS/	1141.1588	9	126.7954		

Accuracy in co-ordination pattern – PD on v PD off – Anti-Phase task

Three-way ANOVA: Group (PD On, PD Off), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p
mean	948848.9972	1	948848.9972	202.884	0.000 ***
S/g	84182.5478	18	4676.8082		
group	654.1014	1	654.1014	0.140	0.713
S/g	84182.5478	18	4676.8082		
cue	136.2845	1	136.2845	0.210	0.652
cS/g	11679.3946	18	648.8553		
gc	1560.0136	1	1560.0136	2.404	0.138
cS/g	11679.3946	18	648.8553		
speed	999.0752	1	999.0752	0.867	0.364
sS/g	20750.9764	18	1152.8320		
gs	1743.9525	1	1743.9525	1.513	0.235
sS/g	20750.9764	18	1152.8320		
cs	50.5580	1	50.5580	0.077	0.784
csS/g	11803.1885	18	655.7327		
gcs	7.6988	1	7.6988	0.012	0.915
csS/g	11803.1885	18	655.7327		

Variation in Velocity – PD on v PD off – Anti-phase task

Three-way ANOVA: Group (PD On, PD Off), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p	
mean	2.8981	1	2.8981	325.037	0.000	***
S/g	0.1605	18	0.0089			
group	0.0009	1	0.0009	0.106	0.749	
S/g	0.1605	18	0.0089			
cue	0.0000	1	0.0000	0.012	0.915	
cS/g	0.0226	18	0.0013			
gc	0.0045	1	0.0045	3.570	0.075	
cS/g	0.0226	18	0.0013			
speed	0.0277	1	0.0277	12.038	0.003	**
sS/g	0.0415	18	0.0023			
gs	0.0007	1	0.0007	0.320	0.579	
sS/g	0.0415	18	0.0023			
cs	0.0008	1	0.0008	0.738	0.402	
csS/g	0.0194	18	0.0011			
gcs	0.0055	1	0.0055	5.068	0.037	
csS/g	0.0194	18	0.0011			

Variation in Velocity – PD on v PD off – Anti-phase task

Two-way ANOVA: Cue (on, off), Speed (fast, slow) for PD On Medication group

SOURCE	SS	df	MS	F	p	
mean	1.5018	1	1.5018	156.129	0.000	***
S/	0.0866	9	0.0096			
cue	0.0020	1	0.0020	1.745	0.219	
cS/	0.0103	9	0.0011			
speed	0.0097	1	0.0097	2.933	0.121	
sS/	0.0298	9	0.0033			
cs	0.0052	1	0.0052	3.401	0.098	
csS/	0.0138	9	0.0015			

Variation in Velocity – PD on v PD off – Anti-phase task

Two-way ANOVA: Cue (on, off), Speed (fast, slow) for PD Off Medication group

SOURCE	SS	df	MS	F	p
mean	1.3972	1	1.3972	170.116	0.000 ***
S/	0.0739	9	0.0082		
cue	0.0025	1	0.0020	1.829	0.209
cS/	0.0123	9	0.0014		
speed	0.0188	1	0.0188	14.476	0.004 ***
sS/	0.0117	9	0.0013		
cs	0.0010	1	0.0010	1.677	0.228
csS/	0.0056	9	0.0006		

Accuracy of Velocity – PD on v PD off – Anti-Phase task

Three-way ANOVA: Group (PD On, PD Off), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p
mean	5.1032	1	5.1032	27.529	0.000 ***
S/g	3.3368	18	0.1854		
group	1.7569	1	1.7569	9.478	0.006 **
S/g	3.3368	18	0.1854		
cue	0.0004	1	0.0004	0.063	0.805
cS/g	0.1232	18	0.0068		
gc	0.0043	1	0.0043	0.623	0.440
cS/g	0.1232	18	0.0068		
speed	6.3809	1	6.3809	117.475	0.000 ***
sS/g	0.9777	18	0.0543		
gs	0.2003	1	0.2003	3.688	0.071
sS/g	0.9777	18	0.0543		
cs	0.0147	1	0.0147	1.833	0.193
csS/g	0.1445	18	0.0080		
gcs	0.0239	1	0.0239	2.973	0.102
csS/g	0.1445	18	0.0080		

A COMPARISON BETWEEN THE PARKINSON'S DISEASE AND CONTROL GROUPS

In-Phase task

Variation in co-ordination pattern – PD v control – In-Phase task

Three-way ANOVA: Group (PD, control), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p	
mean	28948.9550	1	28948.9550	40.045	0.000	***
S/g	13012.5219	18	722.9179			
group	5108.2779	1	5108.2779	7.066	0.016	*
S/g	13012.5219	18	722.9179			
cue	3.0760	1	3.0760	0.137	0.716	
cS/g	405.4761	18	22.5265			
gc	0.2295	1	0.2295	0.010	0.921	
cS/g	405.4761	18	22.5265			
speed	799.7829	1	799.7829	8.813	0.008	**
sS/g	1633.4943	18	90.7497			
gs	358.7402	1	358.7402	3.953	0.062	
sS/g	1633.4943	18	90.7497			
cs	15.6219	1	15.6219	0.377	0.547	
csS/g	746.7446	18	41.4858			
gcs	21.2413	1	21.2413	0.512	0.483	
csS/g	746.7446	18	41.4858			

Accuracy in co-ordination pattern – PD v control – In-Phase task

Three-way ANOVA: Group (PD, control), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p	
mean	48457.8413	1	48457.8413	36.840	0.000	***
S/g	23676.6818	18	1315.3712			
group	8109.5955	1	8109.5955	6.165	0.023	*
S/g	23676.6818	18	1315.3712			
cue	4.6811	1	4.6811	0.104	0.751	
cS/g	812.6620	18	45.1479			
gc	0.0918	1	0.0918	0.002	0.965	
cS/g	812.6620	18	45.1479			
speed	225.6103	1	225.6103	4.786	0.042	*
sS/g	848.5134	18	47.1396			
gs	401.0881	1	401.0881	8.509	0.009	**
sS/g	848.5134	18	47.1396			
cs	109.2243	1	109.2243	2.548	0.128	
csS/g	771.6139	18	42.8674			
gcs	16.3131	1	16.3131	0.381	0.545	
csS/g	771.6139	18	42.8674			

Accuracy in co-ordination pattern – PD v control – In-Phase task

One-way ANOVA: Speed (fast, slow), for control group, collapsed across Cue.

SOURCE	SS	df	MS	F	p	
mean	4230.0796	1	4230.0796	21.961	0.001	***
S/	1733.5843	9	192.6205			
Speed	6.2672	1	6.2672	0.347	0.570	
SS/	162.4092	9	18.0455			

Accuracy in co-ordination pattern – PD v control – In-Phase task

One-way ANOVA: Speed (fast, slow), for Parkinson's disease group, collapsed across Cue.

SOURCE	SS	df	MS	F	p	
mean	24053.6392	1	24053.6392	21.424	0.001	***
S/	10104.7562	9	1122.7507			
Speed	307.0819	1	307.0819	10.555	0.010	*
SS/	261.8474	9	29.0942			

Variation in Velocity – PD v control – In-Phase task

Three-way ANOVA: Group (PD, control), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p	
mean	2.3205	1	2.3205	426.540	0.000	***
S/g	0.0979	18	0.0054			
group	0.0066	1	0.0066	1.209	0.286	
S/g	0.0979	18	0.0054			
cue	0.0003	1	0.0003	0.943	0.344	
cS/g	0.0060	18	0.0003			
gc	0.0001	1	0.0001	0.423	0.524	
cS/g	0.0060	18	0.0003			
speed	0.0395	1	0.0395	19.397	0.000	***
sS/g	0.0367	18	0.0020			
gs	0.0009	1	0.0009	0.425	0.522	
sS/g	0.0367	18	0.0020			
cs	0.0008	1	0.0008	1.887	0.186	
csS/g	0.0072	18	0.0004			
gcs	0.0000	1	0.0000	0.045	0.834	
csS/g	0.0072	18	0.0004			

Accuracy of Velocity – PD v control – In-Phase task

Three-way ANOVA: Group (PD, control), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p	
mean	0.6215	1	0.6215	8.016	0.011	*
S/g	1.3956	18	0.0775			
group	0.2222	1	0.2222	2.865	0.108	
S/g	1.3956	18	0.0775			
cue	0.0023	1	0.0023	0.427	0.522	
cS/g	0.0982	18	0.0055			
gc	0.0038	1	0.0038	0.695	0.415	
cS/g	0.0982	18	0.0055			
speed	1.4238	1	1.4238	22.802	0.000	***
sS/g	1.1239	18	0.0624			
gs	0.5279	1	0.5279	8.455	0.009	**
sS/g	1.1239	18	0.0624			
cs	0.0125	1	0.0125	4.030	0.060	
csS/g	0.0561	18	0.0031			
gcs	0.0000	1	0.0000	0.002	0.964	
csS/g	0.0561	18	0.0031			

Accuracy of Velocity – PD v control – In-Phase task

One-way ANOVA: Speed (fast, slow) for control group, collapsed across Cue

SOURCE	SS	df	MS	F	p
mean	0.0251	1	0.0251	2.099	0.181
S/	0.1078	9	0.0120		
Speed	0.0544	1	0.0544	3.310	0.102
SS/	0.1480	9	0.0164		

Accuracy of Velocity – PD v control – In-Phase task

One-way ANOVA: Speed (fast, slow) for Parkinson's disease group, collapsed across Cue

SOURCE	SS	df	MS	F	p
mean	0.3967	1	0.3967	6.051	0.036
S/	0.5901	9	0.0656		
Speed	0.9214	1	0.9214	20.034	0.002 ***
SS/	0.4139	9	0.0460		

Anti-phase task

Variation in co-ordination pattern – PD v control – Anti-Phase task

Three-way ANOVA: Group (PD, control), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p
mean	160963.7080	1	160963.7080	113.893	0.000 ***
S/g	25439.1196	18	1413.2844		
group	2071.5721	1	2071.5721	1.466	0.242
S/g	25439.1196	18	1413.2844		
cue	33.9903	1	33.9903	0.229	0.638
cS/g	2668.7093	18	148.2616		
gc	56.9288	1	56.9288	0.384	0.543
cS/g	2668.7093	18	148.2616		
speed	1823.3721	1	1823.3721	7.437	0.014 *
sS/g	4412.9376	18	245.1632		
gs	155.3536	1	155.3536	0.634	0.436
sS/g	4412.9376	18	245.1632		
cs	2.2490	1	2.2490	0.024	0.878
csS/g	1680.6695	18	93.3705		
gcs	301.0666	1	301.0666	3.224	0.089
csS/g	1680.6695	18	93.3705		

Accuracy in co-ordination pattern – PD v control – Anti-Phase task

Three-way ANOVA: Group (PD, control), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p
mean	461279.9720	1	461279.9720	190.459	0.000 ***
S/g	43594.9976	18	2421.9443		
group	86973.5944	1	86973.5944	35.911	0.000 ***
S/g	43594.9976	18	2421.9443		
cue	35.5400	1	35.5400	0.108	0.747
cS/g	5939.0935	18	329.9496		
gc	32.6333	1	32.6333	0.099	0.757
cS/g	5939.0935	18	329.9496		
speed	1443.6584	1	1443.6584	3.654	0.072
sS/g	7112.2313	18	395.1240		
gs	40.7982	1	40.7982	0.103	0.752
sS/g	7112.2313	18	395.1240		
cs	7.4312	1	7.4312	0.019	0.893
csS/g	7172.5323	18	398.4740		
gcs	19.2229	1	19.2229	0.048	0.829
csS/g	7172.5323	18	398.4740		

Variation in Velocity – PD v control – Anti-Phase task

Three-way ANOVA: Group (PD, control), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p	
mean	3.0931	1	3.0931	342.841	0.000	***
S/g	0.1624	18	0.0090			
group	0.0032	1	0.0032	0.352	0.561	
S/g	0.1624	18	0.0090			
cue	0.0000	1	0.0000	0.070	0.795	
cS/g	0.0115	18	0.0006			
gc	0.0001	1	0.0001	0.172	0.683	
cS/g	0.0115	18	0.0006			
speed	0.0539	1	0.0539	25.310	0.000	***
sS/g	0.0383	18	0.0021			
gs	0.0043	1	0.0043	2.021	0.172	
sS/g	0.0384	18	0.0021			
cs	0.0011	1	0.0011	0.930	0.348	
csS/g	0.0207	18	0.0012			
gcs	0.0000	1	0.0000	0.017	0.896	
csS/g	0.0207	18	0.0012			

Accuracy of Velocity – PD v control – Anti-Phase task

Three-way ANOVA: Group (PD, control), Cue (on, off), Speed (fast, slow)

SOURCE	SS	df	MS	F	p
mean	2.1340	1	2.1340	15.171	0.001 **
S/g	2.5320	18	0.1407		
group	0.6371	1	0.6371	4.529	0.047 *
S/g	2.5320	18	0.1407		
cue	0.0030	1	0.0030	1.066	0.316
cS/g	0.0510	18	0.0028		
gc	0.0057	1	0.0057	2.023	0.172
cS/g	0.0510	18	0.0028		
speed	4.0351	1	4.0351	75.054	0.000 ***
sS/g	0.9677	18	0.0538		
gs	0.2676	1	0.2676	4.977	0.039 *
sS/g	0.9677	18	0.0538		
cs	0.0039	1	0.0039	0.726	0.405
csS/g	0.0958	18	0.0053		
gcs	0.0035	1	0.0035	0.658	0.428
csS/g	0.0958	18	0.0053		

Accuracy of Velocity – PD v control – Anti-Phase task

One-way ANOVA: Speed (fast, slow) for the control group, collapsed across Cue

SOURCE	SS	df	MS	F	p
mean	0.1098	1	0.1098	1.891	0.202
S/	0.5225	9	0.0581		
Speed	0.5561	1	0.5561	15.951	0.003 **
SS/	0.3138	9	0.0349		

Accuracy of Velocity – PD v control – Anti-Phase task

One-way ANOVA: Speed (fast, slow) for the Parkinson's disease group, collapsed across Cue

SOURCE	SS	df	MS	F	p	
mean	1.2758	1	1.2758	15.444	0.003	
S/	0.7435	9	0.0826			
Speed	1.5952	1	1.5952	84.406	0.000	***
SS/	0.1701	9	0.0189			

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