Saccades, eye-hand movement and cognition in Huntington’s disease: a 12 month study

Eng Ann Toh

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Saccades, eye-hand movement and cognition in Huntington’s disease: a 12 month study

Eng Ann Toh

A thesis submitted for the Doctor of Philosophy in Medicine degree at the University of Otago, Christchurch School of Medicine, Christchurch, New Zealand.

2016
This thesis is dedicated to

all the people who never stopped
believing in me

and also

all the HD patients who
participated in this research
project.
A. Abstract

Huntington’s disease (HD), a genetically inherited neurodegenerative disease caused by CAG trinucleotide repeat expansion, is characterised by movement disorders, cognitive impairment, and behavioural disorders. Saccadic and manual dexterity abnormalities are established deficits in manifest HD but short-term changes (i.e. 12 months) in saccades and eye-hand coordination have not been well-explored.

Given the progressive nature of cognitive, saccadic, and manual dexterity abnormalities, it is hypothesized that measurement of these abnormalities can be useful progression markers for monitoring short-term longitudinal disease changes in manifest HD. The overarching aim of the thesis work is to identify potentially objective biomarkers for measuring HD status and short-term progression that could be employed in clinical research, therapeutic trials, and clinics.

Saccades and eye-hand coordination in 22 manifest HD patients (stage 1 – 4) and 22 demographically-matched controls were measured using high-speed video-oculography and an electromagnetic motion detection system at baseline and after 12 months. Saccadic and eye-hand coordination tasks consisted of a series of visually-guided reflexive, rhythmical, and complex movement tasks. A comprehensive neuropsychological battery was used to assess cognition in both groups whereas the HD group alone was also assessed using the full Unified Huntington’s Disease Rating Scale (UHDRS) at both time points. The relationships between saccades and eye-hand coordination, and current disease status in the HD group were also examined.

Linear mixed-effect models showed that, in general, there was a strong effect of HD upon almost all cognitive measures, and saccadic and eye-hand parameters at baseline. This study also revealed that there was an impairment in the predictive behaviour of oculomotor and somatomotor movements in HD. Most of the saccadic and eye-hand parameters correlated well with cognitive status and motor scores of HD patients. Performance of reflexive saccades in a 2D (combined horizontal and vertical) task and self-paced eye-hand movement were sensitive measures of disease severity and progression over 12 months. The basal ganglia are involved in regulating rhythmical movement and the decline in performance in self-paced eye-hand task at follow-up may reflect short-term neuropathological changes in the basal ganglia in HD. There
were no significant differences, in terms of 12 month longitudinal changes, in a majority of the other saccadic and eye-hand parameters, between the HD and control group after 12 months. These findings suggest that there is a slow and heterogeneous disease progression and also a compensating mechanism to maintain behavioural performance over short-time intervals in HD.

Saccades may provide a better measurement of disease severity and short-term disease changes than somatomotor parameters in manifest HD. In summary, this study provided novel perspectives on eye-hand coordination in HD. Several potential useful markers for monitoring short-term disease changes, which could be easily adapted for use in longitudinal research studies, clinical trials, and clinics, were also identified. Due to the exploratory nature of this research, results should be confirmed in future studies.
B. Preface

This thesis is an original intellect product of the author, Eng Ann Toh. All of the work presented herein was conducted at the New Zealand Brain Research Institute (formerly known as the Van der Veer Institute for Parkinson’s Disease and Brain Research) in Christchurch, New Zealand. The project and associated methods were approved by the New Zealand Ministry of Health Upper South B Regional Ethics Committee [Ethics reference: URB/11/02/2006 and URB/12/EXP/011]. I conceptualized the study design with the assistance of my supervisors, Professor Tim Anderson, Dr Michael MacAskill, Professor John Dalrymple-Alford, and Dr Daniel Myall. I implemented the experimental design, collected the data and performed data analysis in its entirety for all aspects of this project.


Different aspects of this research study have been presented in posters and oral papers at both national and international conferences:


Footnotes
1 Posters were selected for the Guided Poster Tours at the 4th Asian and Oceania Parkinson’s Disease and Movement Disorders Congress 2014 in Pattaya, Thailand. As defined by the congress scientific committee, the Guided Poster Tours are intended to highlight the most significant research.
2 Poster was awarded the Best Poster Award at the 2014 Annual Canterbury Health Research Society Poster Evening held at the University of Canterbury, Christchurch, New Zealand. It was the author’s second time in the competition.
3 Poster was selected for the Guided Poster Tours at the 17th International Congress of Parkinson’s Disease and Movement Disorders 2013 in Sydney, Australia. As defined by the congress scientific committee, the Guided Poster Tours are intended to highlight the most significant research.
4 Poster was awarded the Best Poster Award at the 2012 Annual Canterbury Health Research Society Poster Evening held at the University of Canterbury, Christchurch, New Zealand.
C. Acknowledgments

First and foremost, I would like to express my sincere gratitude to my primary supervisors, Professor Tim Anderson and Dr Michael MacAskill for giving me, then a 5th year medical student and novice to medical research, an opportunity to read an intercalated MB ChB/PhD degree via an upgrade of my Bachelor of Medical Science (Hons) degree. I appreciate their vast knowledge and skills, patience, continuous guidance, and moral support along the way, which had added immensely to my whole graduate experience. I doubt that I will ever be able to fully convey my appreciation to them.

I would also like to thank Professor John Dalrymple-Alford, my secondary supervisor for his assistance in designing the neuropsychological aspect of the study and his insightful comments and suggestions at all levels of this research study. Appreciation also goes out to Dr Daniel Myall, my other secondary supervisor, who assisted in setting up the MoVElab for eye-hand coordination assessment and most importantly, provided me with technical assistance and statistical advice on all aspects of this project.

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Special thanks go out to Ms Maggie Jury, Dr Sandy MacLeod, and Dr Caroline Lintott, who are members of the HD clinical services team for the Canterbury District Health Board. Ms Maggie Jury, the coordinator of HD clinical services in Canterbury helped considerably in the recruitment phase of the study, for she promoted the project to all HD patients and family members under her care. I am very grateful to all participants in the study who volunteered their time for this study. I have full admiration of the resilience demonstrated by all HD patients. I cherished the time I spent with them in the different laboratories as they enlightened me with
life stories and personal experiences living with HD. Their stories and sufferings strengthened my determination and passion to contribute to the understanding of HD via medical research.

A special acknowledgement to my family, namely my parents, Pemanca Dr Francis Chiew Peng Toh and Mdm Catherine Hui Yong Lau, and my only sister, Ms Siew Siew Toh and brother-in-law, Mr Benjamin Min Joo Toh for my upbringing, and whose unconditional love and encouragement has enabled me to partake on this unique journey and to complete this thesis.

Last but not least, this research project would not have been possible without the financial support from the McGee Fellowship and the legacy of Mrs Jane Gooding. I am also deeply gratitude with the generous doctoral scholarship from the University of Otago and the funding from the Department of Medicine at the Christchurch School of Medicine and Health Sciences during my graduate years.
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<td>Alzheimer’s disease</td>
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<tr>
<td>AES</td>
<td>Apathy Evaluation Scale</td>
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<tr>
<td>BAI</td>
<td>Beck’s Anxiety Inventory</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck’s Depression Inventory</td>
</tr>
<tr>
<td>BVMT-R</td>
<td>Brief Visuospatial Memory Test – Revised</td>
</tr>
<tr>
<td>C V L T – I I</td>
<td>California Verbal Learning Test – II</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre(s)</td>
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<tr>
<td>cm/s</td>
<td>centimetre per second</td>
</tr>
<tr>
<td>CN</td>
<td>caudate nucleus</td>
</tr>
<tr>
<td>CDHB</td>
<td>Canterbury District Health Board</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>d</td>
<td>Cohen’s d effect size</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>deg</td>
<td>degree</td>
</tr>
<tr>
<td>deg/s</td>
<td>degree per second</td>
</tr>
<tr>
<td>dlPFC</td>
<td>dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>D1</td>
<td>dopamine type 1</td>
</tr>
<tr>
<td>D2</td>
<td>dopamine type 2</td>
</tr>
<tr>
<td>FEF</td>
<td>frontal eye field</td>
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<tr>
<td>FRS</td>
<td>Functional Capacity Rating Scale</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GPe</td>
<td>globus pallidus external segment</td>
</tr>
<tr>
<td>GPi</td>
<td>globus pallidus internal segment</td>
</tr>
<tr>
<td>HD</td>
<td>Huntington’s disease</td>
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<tr>
<td>HED</td>
<td>head-mounted eye tracking device</td>
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<tr>
<td>Hz</td>
<td>hertz</td>
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<tr>
<td>htt</td>
<td>huntingtin</td>
</tr>
<tr>
<td>ISI</td>
<td>inter-stimulus interval(s)</td>
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<tr>
<td>JOL</td>
<td>Judgement of Line Orientation Test</td>
</tr>
<tr>
<td>LCD</td>
<td>Liquid crystal display</td>
</tr>
<tr>
<td>MCI</td>
<td>mild cognitive impairment</td>
</tr>
<tr>
<td>mm</td>
<td>millimetre(s)</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
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<tr>
<td>ms</td>
<td>millisecond(s)</td>
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<tr>
<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
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<tr>
<td>NZBRI</td>
<td>New Zealand Brain Research Institute</td>
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<tr>
<td>PC</td>
<td>personal computer</td>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PEF</td>
<td>parietal eye field</td>
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<td>PPN</td>
<td>pedunculopontine nucleus</td>
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<tr>
<td>RMS</td>
<td>root mean squared</td>
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<td>s</td>
<td>second(s)</td>
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<tr>
<td>SAMARA</td>
<td>Saccade and Movement Analysis Research Application</td>
</tr>
<tr>
<td>SC</td>
<td>superior colliculus</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SDMT</td>
<td>Symbol Digit Modalities test</td>
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<tr>
<td>SEF</td>
<td>supplementary eye field</td>
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<tr>
<td>SNc</td>
<td>substantia nigra pars compacta</td>
</tr>
<tr>
<td>SNr</td>
<td>substantia nigra pars reticulata</td>
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<tr>
<td>STN</td>
<td>subthalamic nucleus</td>
</tr>
<tr>
<td>UHDRS</td>
<td>Unified Huntington’s Disease Rating Scale</td>
</tr>
<tr>
<td>VC</td>
<td>visual cortex</td>
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<tr>
<td>95% CI</td>
<td>95 percent confidence interval</td>
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Chapter I

General introduction

I.1. Huntington’s disease

I.1.1. Disease overview

The origin of Huntington’s disease (HD) can be traced back to the 1600s in what was then Great Britain, where it was reported that there was a widespread yet unknown malady featuring choreic-type movements. The disease characteristics of HD were purportedly first described in the medical literature by Dr. Charles Waters via his correspondence to Professor Dunglison in the early 1840s (Duff et al., 2007b; Dunglison, 1842). However, it was not another 30 years before it was given the name, Huntington’s disease, named after Dr George Huntington, an American physician who had given a detailed clinical description of the disease in his academic essay (Critchley, 1973; Huntington, 1872).

HD is an autosomal dominant progressive neurodegenerative disease. The clinical features (to be discussed in the following sections) include motor deficits, cognitive impairment, and
psychiatric disorders. Prevalence varies across the world, ranging from around 0.5 per 100,000 in Asian and African nations to 5 – 10 per 100,000 in western populations (Walker, 2007). The disease typically presents itself in mid-life, i.e. in the third or fourth decade of life. However, seven percent of all HD cases occur in the paediatric age group, known as juvenile form HD, while 25 percent are categorised as late-onset HD, with onset of symptoms at the age of 60 years and above (Guitton et al., 1985; Kirkwood et al., 2001; Lipe & Bird, 2009; Myers et al., 1985; Nance & Myers, 2001; Ribai et al., 2007). HD tends to have an insidious onset and gradually worsens over 15 – 20 years (Butler et al., 1999; Guitton et al., 1985; O'Keeffe et al., 2009). By contrast, disease progression is usually faster in juvenile HD whereas in late-onset HD, it assumes a slower and less aggressive disease course (Foroud et al., 1999). The relatively young age of most symptomatic patients contributes to a low incidence of comorbid medical conditions in HD (Nance, 1998). Nance & Saunders (1996) noted that the cause of death in 45% of all HD cases is directly linked to terminal infection, most notably aspiration pneumonia contributed by dysphagia (Heemskerk & Roos, 2012).

I.1.2. An overview of neuropathology in HD

The basal ganglia and cerebral cortex are the two key areas affected in the neuropathology of HD (Vonsattel et al., 2011). A detailed discussion of HD pathology in the basal ganglia is provided in section I.2.4 of this chapter. Most symptoms observed in manifest HD are directly attributed to degenerative changes in the basal ganglia (Vonsattel & DiFiglia, 1998). However, some of these symptoms, especially those presenting in early HD, are linked to physiological changes at the cellular level in the cerebral cortex (Raymond et al., 2011). Raymond et al. (2011) also noted that pyramidal neurons in layers III, IV, and VI of the cortex are susceptible to degeneration in HD. Topological changes in the cerebral cortex, regional degeneration of the cortex, and reduction in the cerebral cortex volume are consistently reported in structural neuroimaging studies (Montoya et al., 2006; Rosas et al., 2002; Rosas et al., 2008; Tabrizi et al., 2010). Changes in the cerebral cortex are closely associated with cognitive impairment in manifest HD (Backman et al., 1997; Bohanna et al., 2008; Poudel et al., 2014; Rosas et al., 2005), and also with the heterogeneity and complexity of clinical presentations in this disease (Rosas et al., 2008). Further, Thu et al. (2010) reported that the degree of degeneration in the primary motor cortex reflects the severity of motor impairment. HD neuropathology extends beyond these structures, whereby thalamus, hypothalamus, and cerebellum are also affected (Raymond et al., 2011).
I.1.3. Clinical presentation

I.1.3.1. Motor deficits

The presence of motor symptoms is often a key element in determining the phenoconversion of at-risk individual to manifest HD. Motor deficits in HD can be broadly divided into two main categories: (1) involuntary movements; and (2) disturbances in voluntary movements. Involuntary movements in HD, most notably ‘chorea’, are arrhythmic, irregular and often ballistic in nature (Walker, 2007). In early stages of manifest HD, affected individuals often present with subtle changes in motor function, such as restlessness or fidgetiness, resulting in some being misdiagnosed as having restless legs syndrome (Nance, 1998). Most patients with mild chorea can often hold on to a normal life (Bates et al., 2002). In most patients, however, chorea becomes increasingly prominent and disabling with disease progression. Chorea however, is absent in some HD patients, especially those with juvenile onset HD, in whom rigidity and akinesia are the predominant motor symptoms (Nance & Myers, 2001). Bradykinesia and rigidity, i.e. parkinsonism, are usually the dominating symptoms in late stage HD (Phillips et al., 2008) and these symptoms often preclude patients from engaging in vocational activities and other activities of daily living (Bates et al., 2014b). The control of volitional movements requires the integration of multiple cognitive processes (Nance, 1998). In light of this, Nance (1998) suggested that impairment in volitional movements is closely associated with cognitive impairment in this disease.

I.1.3.2. Cognitive deficits

Cognitive impairment in HD, especially in early HD, is clinically distinct from Alzheimer’s disease (AD) (Aretouli & Brandt, 2010; Brandt et al., 1988; Paulsen et al., 1995). AD primarily affects language comprehension, naming ability, and memory disturbances whereas in HD, the main cognitive deficits are decline in executive function and information processing, and language comprehension and naming ability is usually preserved until advanced stages (Nance, 1998). The dementia syndrome in HD is often termed ‘subcortical dementia’ because the pattern of cognitive impairment is related to dysfunctional frontal-subcortical circuits (Zakzanis, 1998). Cognitive impairment in HD usually begins with short-term memory loss and with progression, other cognitive processes such as executive function, processing speed, and visuospatial function are affected (Zakzanis, 1998), eventually leading to profound global dementia in end stage HD (Nance, 1998).
I.1.3.3. Psychiatric disorders

In HD, major psychiatric changes are often claimed to precede motor symptoms (Chin et al., 1996) and cognitive impairment (Julien et al., 2007). Affective disorders (typically depression), anxiety disorders (e.g. generalised anxiety and panic disorder), and personality disorder (e.g. obsessive compulsive disorder) are commonly reported in premanifest (Duff et al., 2007b; Julien et al., 2007) and manifest HD (Paulsen et al., 2001). Depression is one of the most prevalent psychiatric disorders in manifest HD, affecting about 30% of patients (Slaughter et al., 2001). It is hypothesized that the neurodegeneration of the structures in the basal ganglia circuit, particularly the dorsolateral-prefrontal, anterior cingulate, and orbitofrontal circuits, which contribute to the control of behaviour, is likely to contribute to the development of psychiatric disorders in HD (Bonelli & Cummings, 2007; Paulsen et al., 2001). In addition, depression is thought to be a contributing factor for an increased suicide risk in HD (Walker, 2007).

I.1.4. The mutant HD gene

In 1983, HD became one of the first diseases to be mapped (to the short arm of chromosome 4) via linkage analyses of polymorphic DNA (Gusella et al., 1983). However, it took the HD Collaborative Research Group, a specialised study group established by the Hereditary Disease Foundation, another ten years to isolate the defective gene, IT-15, located between D4S127 and D4S180 of chromosome 4p16.3 (The Huntington's Disease Collaborative Research Group, 1993).

<table>
<thead>
<tr>
<th>CAG repeat number</th>
<th>Clinical outcomes</th>
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<tbody>
<tr>
<td>&lt; 27</td>
<td>No disease expression</td>
</tr>
<tr>
<td>27 – 35</td>
<td>Unlikely to have disease expression</td>
</tr>
<tr>
<td></td>
<td>Offspring might get CAG expansion</td>
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<tr>
<td>36 – 39</td>
<td>Reduced disease penetrance</td>
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<tr>
<td></td>
<td>Possible disease expression</td>
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<tr>
<td>&gt; 39</td>
<td>Full disease penetrance</td>
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<td>Full disease expression</td>
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Table I.1 CAG repeat number and HD clinical outcomes (Myers, 2004)

The IT-15 gene causes the disproportionate expansion of trinucleotide (CAG) repeats which in turn, results in the excessive production of mutant huntingtin (htt) protein. Analyses of the IT-15 gene have revealed that those with the defective gene usually have a CAG trinucleotide repeat number of greater than 40, whereas the wild-type variant is usually 30 or less (The Huntington's Disease Collaborative Research Group, 1993; Watts & Koller, 1997). The CAG trinucleotide repeat has direct influence on disease onset timing and progression (Table I.1). Individuals with juvenile onset HD tend to have a higher number of CAG trinucleotide repeats and faster disease progression than late-onset HD patients, who by contrast have a smaller
repeat size (Brinkman et al., 1997; Nance & Myers, 2001; Rosenblatt et al., 2012; Rosenblatt et al., 2006). The mode of gene transmission (paternal or maternal transmission) and gender of the offspring can also influence the CAG repeats size (Duyao et al., 1993; Ranen et al., 1995; Trottier et al., 1994; Wheeler et al., 2007).

I.1.5. The role of mutant htt protein in HD pathology

The wild-type htt protein, which has a relatively long half-life of 24 hours (Persichetti et al., 1996), can be found in the cell nucleus and also cytoplasm. This protein is thought to function as a nucleocytoplasmic shuttling protein (Truant et al., 2007). The mutant htt protein, compared to its wild-type counterpart, has an even longer half-life and a propensity to accumulate within cells (Kaytor et al., 2004). In addition, there is a tendency for the mutant htt protein to misfold and form insoluble aggregates intracellularly (Davies et al., 1997), known as mutant htt inclusion bodies or aggregates. It was found that the presence and rate at which these aggregates occur is closely related to the CAG repeat size of affected individuals (Becher et al., 1998; Scherzinger et al., 1999). Further, these aggregates can also increase in size with disease progression (Gutekunst et al., 1999). These mutant htt aggregates, which are present both within (DiFiglia et al., 1997) and outside the central nervous system (Moffitt et al., 2009; Tabrizi et al., 2000), are extensively branched and are not separated from their surroundings by any membranes (Dahlgren et al., 2005; DiFiglia et al., 1997).

Despite the presence of a direct link between HD and the mutant htt aggregates, current animal models of HD have yet to reach a consensus on the exact role of these aggregates in the pathogenesis of HD. One study found that the mutant htt aggregates, when introduced into cell culture, induce cell death (Yang et al., 2002) while another showed that switching off the mutant htt gene reverses aggregate formation and also phenotype expression (Yamamoto et al., 2000), suggesting that mutant htt aggregates can have damaging effects on neuronal cells. On the contrary, other studies suggested that these aggregates may actually have protective effects on neurons in HD. This was shown in one study, in which a reduction in mutant htt inclusions resulted in an increase in neuronal cell death (Okamoto et al., 2009), while it was demonstrated in another study that there is an enhancement of mutant htt clearance in affected cells in the presence of mutant htt aggregates (Ravikumar et al., 2004).

There are different ways of which mutant htt protein can interfere with cell physiology, either by disrupting the degradation process of proteins or hampering the vesicular transport system.
There are two main pathways for the degradation of proteins at cellular level: (1) the ubiquitin-proteasome system (UPS) for smaller sized cytoplasmic and nuclear proteins (Schwartz & Ciechanover, 2009); and (2) the autophagy pathway for protein complexes that are too large to pass through the proteasome pore of the UPS. Both mouse (Davies et al., 1997) and human (DiFiglia et al., 1997) models of HD have shown that mutant htt protein can cause a disruption of the protein degradation pathway in the UPS. Although mutant htt protein is capable of inducing its own autophagic clearance to reduce its toxicity within cells (Sarkar & Rubinsztein, 2008), there is evidence to suggest that mutant htt protein interferes with the cargo loading process of other protein products into the autophagic vacuoles, hence affecting the operation of autophagy pathways, which in turn has a negative effect on cell integrity (Martinez-Vicente et al., 2010).

Wild-type htt protein has been shown to interact with other proteins to induce vesicular trafficking activity within cells (DiFiglia et al., 1995). The mutant htt protein, despite being malformed, still assumes the role of its wild-type counterpart. However, the mutant protein was found to reduce the efficiency of the vesicular transport system by abnormally interacting with other proteins (Kaltenbach et al., 2007; Modregger et al., 2002; Singaraja et al., 2002) or causing physical obstruction to other proteins (Gutekunst et al., 1995; Smith et al., 2009). An efficient intracellular transport system is essential for supporting the physiological processes for the maintenance of neuronal architecture and promotion of neuronal growth (Gauthier et al., 2004; Trushina et al., 2004). Given this, the interference of mutant htt protein on the vesicular transport system may well contribute to neuronal cell death in HD.

Overstimulation of neurons by excessive glutamate intake has been implicated to be one of the key processes in HD pathology (Coyle & Schwarcz, 1976; McGeer & McGeer, 1976). Several lines of evidence propose that the overstimulation of glutamatergic receptors, likely to be an effect of an impaired glutamate transport system, results in the disruption of Ca$^{2+}$ homeostasis in the mitochondria, leading to increased mitochondrial stress and eventually neuronal cell death (Tang et al., 2005; Wu et al., 2006). Mutant htt protein has been implicated to cause impairment in glutamate transport system by altering the function of one major glutamate transporter, the glial glutamate transporter 1 (GLT-1) (Sari, 2011).

There is no consensus on which of the proposed disease mechanisms predominates in HD, or if they occur concurrently in the disease process. The proposed disease mechanisms may be different but all of them share two common end-points, i.e. the loss of cell integrity and cell
death, which initially occur in the striatal medium spiny neurons and later, in other neurons of the central nervous system.

I.1.6. Current clinical management in HD

The management for manifest HD can be classified into three broad categories: (1) pharmacological; (2) non-pharmacological; and (3) palliative care for end stage HD. Pharmacological therapy in HD can be further sub-categorized into four main groups, with each group targeting a specific disease symptom, i.e. motor symptoms, cognitive impairment, psychiatric symptoms, and miscellaneous symptoms.

Several antipsychotics and neuroleptics are widely used with varied effects for managing chorea in HD. Antipsychotics may also be useful in controlling choreic movements in HD but they are usually only effective when given in high doses, which inevitably increase the risk for adverse effects – especially extrapyramidal symptoms (van Vugt et al., 1997). Tetrabenazine, a dopamine depleter, has good efficacy in managing hyperkinesia but the judicial use of the drug must be considered against the increased risk of developing parkinsonism and worsening of psychiatric symptoms (Kenney et al., 2006; Kenney & Jankovic, 2006).

Acetylcholinesterase inhibitors, such as rivastigmine and donezepil, have been shown to be effective in managing cognitive symptoms in AD and Lewy body disease (Burns et al., 2006) but their efficacy in improving cognition is rather ambiguous in HD (Cubo et al., 2006; de Tommaso et al., 2007). Psychiatric disturbance in HD can be very distressing for patients and family members alike. There are evidences to suggest that commonly-prescribed mood modifying medications, e.g. fluoxetine, venlafaxine, carbamazepine, and sodium valproate are effective for managing these psychiatric symptoms in HD (Holl et al., 2010; Patel et al., 1996; Phillips et al., 2008; Ross & Tabrizi, 2011; Stewart et al., 1987).

Sleep-wake cycle disruption and weight loss are the two most common physiological manifestations in HD (Silvestri et al., 1995; Trejo et al., 2004), both being considered as miscellaneous symptoms in HD. Hypnotics such as zopiclone and eszopiclone are helpful in managing sleep disturbance in HD (Phillips et al., 2008). Weight loss is best controlled with customized nutritional care plans and dietary supple-
improving HD symptoms (Bilney et al., 2003). Palliative care provided at nursing home or at patients’ own homes, allied with multidisciplinary team input into patient and family member care, is considered appropriate for managing end-stage HD (Phillips et al., 2008).

Reviews on pharmacological management stress that there is limited evidence to support the use of the majority of commonly-prescribed medications for HD (Bonelli & Wenning, 2006), with the exception of tetrabenazine and some mood stabilizing drugs (Mestre et al., 2009). Nevertheless, therapies aiming at disease modification and neuro-protection have shown some promising results in animal models of HD and these therapies may potentially be useful for HD patients (Abdulrahman, 2011).

I.2. The basal ganglia

I.2.1. Anatomy of the basal ganglia

The basal ganglia are functional grey matter entities that consist of collections of closely interconnected brain structures (Figure I.1) distributed in the telencephalon, the diencephalon, and the mesencephalon.

The caudate nucleus (CN), putamen, nucleus accumbens, and globus pallidus, which derive from the telencephalon, are collectively known as the corpus striatum. The CN, putamen, and nucleus accumbens, which share similar histological and neurochemical characteristics, and also patterns of connectivity in the basal ganglia, are usually known as the striatum (Mendoza & Foundas, 2008). The caudate nucleus, a C-shaped structure found on the lateral wall of the lateral ventricle, plays a key role in various cortico-striatal loops that serve to control cognition, voluntary movements, and physiological activities (Grahn et al., 2008, 2009). The putamen is...
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separated from the caudate nucleus by the anterior limb of the internal capsule and is involved in learning and the control of motor movements. The nucleus accumbens, which plays a role in reward circuitry (Ikemoto, 2007), is located where the head of caudate meets the anterior part of putamen, just lateral to the septum pellucidum. The striatum, which consists mainly of medium spiny neurons, is the main receiving centre for all inputs from the motor areas of the cerebral cortex and the thalamus (Hikosaka et al., 2000).

The putamen and the globus pallidus are wedged together in the corpus striatum, and due to this appearance, are recognised as the lentiform nucleus of the corpus striatum. There are two main segments to the globus pallidus, the globus pallidus interna (GPi) and the globus pallidus externa (GPe), both named according to their position within the structure (Figure I.1). Both segments receive input from the caudate nucleus and putamen and communicate with subthalamic nucleus (STN). The STN, a small lens-shaped structure found ventral to the thalamus (as implied by its name), is part of the diencephalon and the only structure in the basal ganglia that produces glutamate, an excitatory neurotransmitter. It was once considered a relay station of the basal ganglia-thalamocortical circuitry but new evidence suggest that it has a role in the regulation of associative and limbic functions in the basal ganglia (Temel et al., 2005). The substantia nigra, which is divided into substantia nigra pars reticulata (SNr) and substantia nigra pars compacta (SNC), is part of the mesencephalon and the only structure in the basal ganglia control system and significant projections are sent from them to the thalamus and superior colliculus.

I.2.2. The basal ganglia circuitry

The basal ganglia are integral to the smooth execution and control of voluntary movements (DeLong & Georgopoulos, 1981; Phillips et al., 1993). Thus the cardinal clinical signs observed in diseases with defective basal ganglia, such as HD and PD, are related to difficulties in movement initiation and disinhibition of involuntary movements (Aylward et al., 1997; Moisello et al., 2011).

Nuclei within the basal ganglia have their own distinctive roles in the control of voluntary and involuntary movements. They can be physiologically divided into three main functional groups – input stations, modulators, and output stations. The two main input stations of the basal
ganglia are the CN and putamen. They receive direct input from different areas of the cortex and also the thalamus. The STN, GPe, and SNc are interconnected to other nuclei of the basal ganglia and they mainly act as the modulators of this intricate system. The GPi and the SNr, which are the major output stations of the basal ganglia, provide electro-chemical signals to the thalamus and brainstem depending on the type of movement required (Hikosaka et al., 2000).

Neural structures both within and outside the basal ganglia rely on neurotransmitters, which either have inhibitory or excitatory effect, to exert influence on another neural structures. There are three main types of neurotransmitter in the basal ganglia-thalamocortical system: (1) gamma-amino butyric acid (GABA), an inhibitory neurotransmitter; (2) glutamate (glu), an excitatory neurotransmitter; and (3) dopamine (DA), an excitatory neurotransmitter for dopamine type 1 (D1) receptors and an inhibitory neurotransmitter for dopamine type 2 (D2) receptors (Hikosaka, 1994; Hikosaka et al., 2000; Watts & Koller, 2004).

The striatum is activated by convergent inputs from the cerebral cortex and thalamus (Groenewegen, 2003). Different populations of the striatal output neurons can be stimulated based on the type of signals received by the striatum, giving rise to the activation of the ‘direct’ or ‘indirect’ pathways of the basal ganglia circuitry (Figure I.2). The two pathways have opposing net effects on the final output of the basal ganglia circuitry. At resting state, when neither pathway is activated more than the other, the output structures exert a tonically active inhibitory effect on the thalamic and SNr target structures (Knierim, 2010). Since dopamine has differential effects on the two type of dopamine receptors, nigro-striatal neurons can simultaneously activate the ‘direct’ pathway and suppress the ‘indirect’ pathway or vice versa to produce a net effect of cortical excitation or inhibition.

Nigro-striatal output neurons activate the ‘direct’ pathway via D1 receptors and in this pathway, the striatum directly innervates the output stations of the basal ganglia via the striatal-pallidal and striatal-nigral projections. Activation of the ‘direct’ pathway produces a ‘double negative’ effect, resulting in a reduction of tonic inhibitory effects on thalamus and SNr, thereby facilitating movement initiation (Gerfen & Wilson, 1996). When the ‘direct’ pathway is activated, cortical projections to the striatum use glutamate, an excitatory neurotransmitter, to excite the striatal neurons resulting in the excitation of the striatal neurons. Striatal neurons, upon excitation, release inhibitory neurotransmitters, GABA and substance P, to reduce the activity of neurons in the GPi and SNr complex, which in turn reduces the inhibitory effect of the GPi and SNr complex on thalamus. The final outcome of this pathway is a reduction in the
Inhibition on thalamus and to enhance the excitatory drive from the thalamus to the cortex to increase motor activity (Figure I.2).

Figure I.2 A schematic illustration of the basal ganglia-thalamocortical circuits and its neurotransmitters. Both the ‘direct’ (yellow) and ‘indirect’ (blue) pathways are shown. Red arrow indicates excitatory output and black, inhibitory output. Structures illustrated are: GPe, globus pallidus externa; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; GPi/SNr, globus pallidus interna and substantia nigra pars reticulata complex; and PPN, pedunculopontine nucleus. Neurotransmitters involved are: GABA, gamma-aminobutyric acid; glu, glutamate; enk, enkephalin; subs P, substance P; and DA, dopamine. The two sub-type of DA receptors are represented as D1 and D2 respectively. Illustration adapted with permission from Watts & Koller (1997, p. 240) and Hikosaka et al., (2000).

In the ‘indirect’ pathway, the input and output stations are interposed by the GPe and STN. The predominant dopamine receptor expressed by the striatal output neurons in the ‘indirect’ pathway is the D2 receptor whilst the two main neurotransmitters in this pathway are GABA and enkephalin (Alexander, 1994; Groenewegen, 2003; Watts & Koller, 2004). The activation of the ‘indirect’ pathway excites the striatal neurons that project to GPe. This results in an increase in GABAergic activity (inhibitory effect) of the striatal neurons on the GPe, hence reducing the activity in the GPe. At resting state, the GABAergic neurons in GPe exert an inhibitory influence on the neurons in STN. Therefore, a decrease in the inhibitory activity in GPe consequentially leads to less inhibition on the STN, which in turn enhances the inhibitory effects of GPi on thalamus. The end result of the ‘indirect’ pathway is a reduction in motor activity via reducing excitatory thalamic input to the cortex (Figure I.2).
It is clear that the integrity of the basal ganglia and its associated pathways are crucial in the initiation and control of all movement generated in the thalamo-cortical and the brainstem networks (Hikosaka et al., 2000). Therefore, it is not unexpected that different pathologies of the basal ganglia (e.g. HD and PD) can lead to distinct motor signs and symptoms.

I.2.3. The basal ganglia and cognition

The functionality of the basal ganglia goes beyond the scope of being a modulator of the motor system, as it is also capable of receiving inputs with affective meaning and abstract in nature such as sensation, motivation, and etc. (Aylward et al., 1997; Huntington Disease Collaborative Research Group, 1993). For that reason, this structure participates in working memory, associative learning, modifying learned behaviour, and the control of affective functions.

Although there is no consensus on the exact pathways by which the basal ganglia influence cognitive function, it has been proposed that they utilise similar mechanisms to the motor pathways, i.e. disinhibition and inhibition mechanisms, to determine what information is to be selected and relayed to the frontal cortex for further processing (Stocco et al., 2010). In support of this notion, an animal study found that the prefrontal cortex projections to the striatum are essential in the inhibition and modification of learned behaviour (Graves et al., 2004). Further, DA, a key neurotransmitter in the basal ganglia, participates in processes involving associative and reinforcement learning (Jahanshahi et al., 1993) and the infusion of dopamine into striatum improves learned behaviour performance (Stocco et al., 2010).

I.2.4. The basal ganglia and motor symptoms of HD

Huntington’s disease is characterised by atrophy of the striatum, i.e. caudate nucleus and putamen. Longitudinal imaging has shown that in addition to a reduction in striatal volume, total basal ganglia volume also decreases over time in HD (Aylward et al., 1997). The main pathological manifestation of HD in the basal ganglia is the degeneration of striatal medium spiny neurons accompanied by fibrillary astrocytosis and relative preservation of aspiny neurons (Li & Li, 2006; Watts & Koller, 1997). There are two distinct populations of striatal medium spiny neurons, the D2 receptor-expressing striato-GPe neurons that are enriched with enkephalin, and the D1 receptor-expressing striato-GPi neurons that are enriched with substance P.
Figure I.3  
Functional circuitry of the basal ganglia in HD. Predicted changes in the basal ganglia consequent to: (A) a selective loss of D2 receptor striatal neurons resulting in chorea; and (B) additional loss of D1 receptor striatal neurons leading to akinesia and rigidity. Increased activity is shown by thick lines, normal by normal sized lines, and reduced activity by dashed lines. GPe, globus pallidus externa; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; GPi/SNr, globus pallidus interna and substantia nigra pars reticulata complex; and PPN, pedunculopontine nucleus. Neurotransmitters involved are: GABA, gamma-amino butyric acid; glu, glutamate; enk, enkephalin; subs P, substance P; and DA, dopamine. Illustrations adapted with permission from Watts & Koller (1997, p. 240) and Hikosaka et al., (2000).
Current evidence suggest that there is a differential pattern of striatal neuron degeneration in early HD, with striato-GPe neurons being preferentially degenerated compared to striato-GPi neurons (Albin et al., 1992; Glass et al., 2000; Reiner et al., 1988; Richfield et al., 1995). These findings provide a convenient explanation for the occurrence of chorea, which is usually the first reported motor symptom in manifest HD (Kirkwood et al., 2001). Based on the current model of basal ganglia function, a selective loss of striatal neurons that project to the GPe translates to a deficit in the ‘indirect’ pathway (Figure I.3A). This results in the enhancement of the inhibitory effects of the GPe on STN and GPi and SNr complex, which in turn reduces GPi and SNr complex inhibition on the thalamus, leading to an increased tendency of thalamocortical structures to discharge spontaneously, and hence the occurrence of involuntary movement (DeLong, 1990; Reiner et al., 1988).

As the disease progresses, striatal neurons that project to the GPi and SNr complex, which are relatively preserved in early HD, are also affected, resulting in widespread loss of striatal projection neurons (Glass et al., 2000; Hedreen et al., 1991; Sotrel et al., 1991). Chorea tends to diminish and be replaced with akinesia and rigidity in later stages of typical adult-onset HD (Roos, 2010; Storey & Beal, 1993). This change in the motor symptoms correlates well with the degenerative changes in the striatum. The extensive loss of striatal projection neurons would be expected to also cause an impairment in the ‘direct’ pathway of the basal ganglia circuit (Figure I.3B). A reduction in the participation of the cortico-striato-pallido-thalamic pathway would ensue, i.e. a reduction of inhibition on the GPi and SNr complex by striatum, thus leading to a decrease in motor activity and increasing rigidity.

In juvenile, akinetic-rigid and Westphal variant HD, akinesia and rigidity are the predominating motor symptoms and most often these motor signs occur in the absence of chorea. It has been shown that in these cases of HD, there is a non-selective degeneration of striatal neurons (Albin et al., 1990). This suggests that in these HD variants, both the ‘direct’ and ‘indirect’ pathways might be equally affected (Figure I.3B). The net effect from an impairment of ‘direct’ and ‘indirect’ pathways likely leads to an uninterrupted inhibition of thalamus by the GPi and SNr complex. This is similar to advanced stage of adult-onset HD, and hence the akinesia and rigidity in these HD variants.

Regardless of the HD phenotype, motor symptoms in HD correlate well with the current understanding of the basal-ganglia thalamocortical circuitry and basal ganglia degeneration in HD. It can therefore be summarised that chorea in HD results from a preferential loss of the D2
receptor-expressing striato-GPe neurons and that akinetic-rigid HD is likely consequent upon additional loss of D1 receptor-expressing striato-GPi neurons in the basal ganglia.

I.3. Human eye movement

All types of eye movements are affected in various neurodegenerative disorders, e.g. HD, PD, AD, and motor neuron disease (Anderson & MacAskill, 2013). The relevance of eye movement in HD pathology will be discussed in the sections to follow.

I.3.1. The purpose of human eye movement

Eye movements are highly versatile movements that may occur under wide variety of circumstances (e.g. when the head or an object of interest is stationary or in motion) (Swenson, 2006). It enables us to better perceive the surrounding environment by allowing the eyes to always keep the image of the object of interest on the fovea, the part of the retina with the highest visual acuity.

I.3.2. Types of human eye movement

There are five main types of human eye movement: (1) saccades; (2) smooth pursuit; (3) vergence; (4) the vestibular-ocular reflex (VOR); and (5) the optokinetic reflex (OKR). All five types of eye movement have their own unique function (Swenson, 2006; Vilis, 2013).

A saccade serves to bring the image of an object of interest to the fovea in a rapid manner. However, due to the rapid nature of movement, visual acuity is compromised during saccades. Smooth pursuit allows the smooth tracking of a moving object by keeping the image of that moving object stationary on the fovea while the object moves. Vergence eye movements – convergence and divergence – involve the eyes rotating in the opposite direction to one another. They serve to simultaneously direct the foveae of both eyes on an object whether it is near or far away (Purves et al., 2001). The VOR and OKR, being the first two eye movements to have developed in the course of evolution (Walls, 1962), are considered the most rudimentary type of eye movements. The VOR is a short-loop unconscious reflex that serves to maintain the image stationary on the retina during fast or slow head movements. It allows compensation for head movements by generating conjugating eye movement of equal magnitude in the opposite direction to the head motion. The VOR is effective for compensating sudden and brief head movements whilst the OKR, which is associated with the sense of self-motion, is recruited when
there is a prolonged head rotation and a slip of large full-field visual stimulus on the retina (Vilis, 2013). Under normal circumstances, it is often difficult to distinguish OKR from VOR because both types of eye movement work in a concerted effort to achieve visual stability.

I.3.3. Classification of the saccadic system

Saccades are rapid eye movements that can be generated in response to external or internal cues. Saccades can be hierarchically arranged depending on the behavioural context. The quick phases of vestibular nystagmus or optokinetic nystagmus (OKN) are innate saccades elicited in the absence of intervention by higher centres and so are regarded as relatively rudimentary (Leigh & Zee, 2006). Simple visually-guided (reflexive) and complex volitional saccades require greater involvement of the higher cortical centres (Pierrot-Deseilligny et al., 1991a, 1991b). Simple visually-guided saccades are generated through simple sensorimotor translation processes upon the appearance of external cues. By contrast, the generation of complex volitional saccades – delayed pro-saccades, memory-guided saccades, and anti-saccades – involves the interaction of multiple cognitive processes that includes saccade inhibition and interpretation of contextual cues (Hahn-Barma et al., 1998; Pierrot-Deseilligny et al., 2004). Despite a difference in the initiation process, all type of saccades share a common final neural pathway in the brainstem and ocular muscles.

I.3.4. The basic mechanics of saccades

The control of saccades involves the close interaction of both cortical and subcortical structures via multiple complex neuronal networks (Gaymard et al., 1998). Figure I.4 illustrates the interactions between cortical and subcortical structures in the control of saccades. The frontal eye field (FEF), parietal eye field (PEF), and supplementary eye field (SEF) are the key areas in the cerebral cortex involved in triggering saccade generation. The dorsal lateral prefrontal cortex (dIPFC) and the anterior cingulate gyrus are involved in governing the decisional processes of ocular motor behaviour (Gaymard et al., 1998; Pierrot-Deseilligny et al., 2005).

An external visual cue, when processed by the visual cortex of the cerebrum, is the key event for the activation of saccadic system. The visual cortex subsequently activates the PEF, a visuospatial integration centre and also a principal region for initiating reflexive saccades. The dIPFC receives afferent tracts from the posterior parietal cortex and anterior cingulate gyrus, and sends efferent tracts to the FEF, SEF, and superior colliculus (SC). This area of the prefrontal cortex has been demonstrated to play an important role in: (1) the inhibition of reflexive saccades generated by the PEF through its direct projection to SC; and (2) integrating
spatial and temporal working memory for intended saccades via its direct tract to the FEF and SEF (Pierrot-Deseilligny et al., 2005). Depending on the types of saccade that are required, specific cortical output signals are then relayed to the basal ganglia via corticostriatal projections, and thence to SC in the brainstem, to generate motor impulses for saccade initiation (Sparks, 2002).

**Figure I.4** The human saccadic pathways. A simplified schematic illustration of the brain structures involved in the initiation of saccades. VC, visual cortex; PEF, parietal eye field; FEF, frontal eye field; SEF, supplementary eye field; dIPFC, dorsolateral prefrontal cortex; CN, caudate nucleus; SNr, substantia nigra pars reticulata; and SC, superior colliculus are shown. Red arrow indicates excitatory output and black blunted arrow, inhibitory output. Illustration adapted with permission from Gaymard (1998) and Hikosaka et al., (2000).

### I.3.5. The relationship between basal ganglia and saccades

The basal-ganglia thalamocortical pathways exert influence on the saccadic system via the inhibitory and excitatory effects of the basal ganglia (Agostino et al., 1988). There is an area in the CN, termed the visuo-oculomotor region, that contains a population of neurons sensitive to visually- and saccadic-related activities in the cerebral cortex (Hikosaka et al., 2000). In addition to receiving inputs from the FEF, SEF, PEF, and dIPFC, the CN is also connected to the SNr and SC (Agostino et al., 1988).

The SNr, at resting state, exerts a tonic inhibitory effect on the SC. The CN can, however, phasically increase its inhibitory effect on the SNr via the ‘direct’ pathway to negate the tonic inhibitory effects of the SNr on SC and thus facilitate the initiation of saccades (Figure I.2). It has been postulated that the disinhibition effects of the CN on the SC provides a more efficient
control of the saccadic system compared with a system that relies on just neural excitation, since
the latter mechanism would more likely result in saccades being generated inappropriately
(Agostino et al., 1988).

By contrast, activation of the ‘indirect’ pathway increases the inhibition on GPe which results
in an enhancement of SC inhibition by the SNr (Agostino et al., 1988). This inhibitory effect of
the SNr on SC is further enhanced by the excitatory effect by STN, which is accentuated by the
inhibition of GPe. The STN can also be directly activated by the higher centres and such
continuous stimulation of STN results in the SNr being tonically activated which in turn exerts
an inhibitory effect on SC (Figure I.2), facilitating maintenance of fixation and saccade
inhibition (Hikosaka et al., 2000).

The two pathways outlined above are not mutually exclusive as they may occur concurrently
or in sequence, depending on the type of saccades required. In summary, the basal ganglia via
the two pathways contribute to the behavioural aspects of saccadic production by (1)
suppressing saccades as appropriately; and (2) supporting the preparation of an impending
(internally-cued) saccade by the suppression of unwanted reflexive saccades (Folstein et al.,
1975). Given the importance of basal ganglia in the effective control of saccades, it is no
surprise that any lesions within the basal ganglia, whether it is vascular, neoplastic or
degenerative (e.g. HD and PD), can have adverse effects on the neurophysiology of this intricate
system.

I.3.6. Eye movement in HD

Eye movement abnormalities have long been recognised to be a feature of manifest HD (Andre-
Thomas et al., 1945; Derceux, 1945) but such deficits only came to be objectively quantified
using electrooculography in the late 1960s (Starr, 1967).

Saccade apraxia and slowness in saccade initiation are the two most commonly reported
saccadic deficits in HD (Ali et al., 2006; Avanzini et al., 1979; Becker et al., 2009; Couette et
al., 2008; Fielding et al., 2006; Lasker et al., 1987; Starr, 1967). The co-occurrence of saccade
apraxia and head thrusting movements in HD have led to the suggestion that the latter are
compensatory manoeuvres used by HD patients to facilitate saccade initiation and gaze shifting
(Becker et al., 2009). Saccadic slowing is another characteristic feature, particularly in younger-
onset patients, but it is often absent in late onset cases (Avanzini et al., 1979; Becker et al.,
2009; Hotson et al., 1984; Peltsch et al., 2008; Starr, 1967). There is conflicting evidence on
whether horizontal or vertical saccades are more affected in HD. Some studies reported that saccadic performance is worse in the vertical direction than in the horizontal direction (Bollen et al., 1986; Hotson et al., 1984; Lasker et al., 1987, 1988; Leigh et al., 1985; Rupp et al., 2012). However, this suggestion is disputed by others, claiming that the opposite is true (i.e. horizontal saccades are more affected than vertical saccades) based on clinical observation (Anderson & MacAskill, 2013) and electrooculography (Beenen et al., 1986).

It has also been demonstrated that HD patients have a higher tendency than controls to make timing and directional related errors in saccadic tasks involving selective inhibition and initiation of saccades, i.e. memory-guided (Blekher et al., 2006; Blekher et al., 2004; Lasker et al., 1987; Pelsch et al., 2008) and anti-saccade (Becker et al., 2009; Blekher et al., 2006; Patel et al., 2012; Pelsch et al., 2008; Rupp et al., 2011; Turner et al., 2011) tasks. Some saccadic parameters such as saccadic velocity (Golding et al., 2006), latency (Pelsch et al., 2008; Winograd-Gurvich et al., 2003), and error rates (Patel et al., 2012; Tabrizi et al., 2010) were found to reflect disease severity in HD.

Leigh et al. (1983) and Oepen et al. (1981) demonstrated that there was an increased disruption of smooth pursuit by saccades in HD, with performance being further impaired when irrelevant visual distractors were introduced during the task. These findings suggest that in HD, in addition to saccade apraxia, there is an increased difficulty in suppressing competing motor responses (Henderson et al., 2011). OKN, vestibular nystagmus, and vergence were also found to be affected in HD (Leigh et al., 1983; Oepen et al., 1981). Although earlier evidence suggest that VOR, a reflex eye movement that stabilises gaze during head movement, is relatively preserved even in advanced HD (Leigh et al., 1983), a later study revealed that in manifest HD, there is a deficit in VOR recalibration with changing visual conditions (Fielding et al., 2004).

Eye movement abnormalities are not exclusive to manifest HD, as there are evidences to suggest that saccadic deficits precede the onset of overt motor symptoms, the ultimate criterion for clinical diagnosis of HD. Prolonged latency, increased variability in saccadic performance (Blekher et al., 2006; Blekher et al., 2004; Tabrizi et al., 2009) and higher rates of error in voluntary-guided saccadic tasks have been reported in premanifest HD (Kloppel et al., 2008; Rupp et al., 2011; Rupp et al., 2012; Turner et al., 2011). Saccadic performance declines progressively with disease progression in manifest HD but longitudinal studies in pre-clinical at-risk individuals have not been revealing (Beenen et al., 1986; Rubin et al., 1993; Tabrizi et al., 2010).
I.4. Human arm movement

I.4.1 The basic organisation of the human motor system

The human motor system is organised in a manner such that motor signals are sent from higher cortical centres via neuronal tracts to the spinal cord before diverging into individual neural pathways (via nerve roots and nerves) and ultimately, motor neurons that innervate the muscle fibres to generate the desired movement (Figure I.5).

Most of the motor commands originate from the primary motor area (Broadman’s area 4) located anterior to the central sulcus. The dorsal and ventral premotor cortices, which are anterior to the primary motor area and occupy part of Broadman’s area 6, modulate voluntary movement relative to the surrounding environment and participate in the generation of movements that are triggered by arbitrary cues (Dum & Strick, 2002). An area rostral to the primary motor area, termed the supplementary motor area (SMA) (Dum & Strick, 2002), contributes to the programming of internally-generated movement and movement sequences (Rothwell, 2012). The axons of motor projection neurons from these areas give rise to the corticospinal and reticulospinal tracts. The corticospinal tract provides a direct route from the cortical centres to the spinal cord and carries motor signals intended predominantly for the distal muscles of the limbs (Rothwell, 2012). The reticulospinal tract which mainly supplies the proximal and axial muscles, is interposed by the pons and reticular formation of the brain (Rothwell, 2012).
Three subcortical structures – the vestibular system, cerebellum, and basal ganglia – have distinct roles in the control of motor movement (Rothwell, 2012). The vestibular system, which constitutes of semicircular canals and otolith organs of the inner ear, is the only subcortical structure to have direct projections to the spinal cord and it is responsible for balance during posture. Both the cerebellum and basal ganglia interact with motor areas in the cortex. The cerebellum is considered a feedback centre as it compares the motor outputs from cortical areas to sensory inputs that relay the outcome of the motor signals. The basal ganglia functions as an information processing centre for the motor system (Rothwell, 2012).

Neurons in the spinal cord are arranged according to the proximity of the muscle fibres to the spinal cord. Motor neurons innervating the distal muscles travel in the dorsolateral pathway of the spinal cord whereas the proximal and axial muscles are innervated by motor neurons in the ventro-medial pathway (Figure I.5). The final common pathway of the motor system (Figure I.5) involves the termination of a descending tract at the anterior horn of spinal cord and motor impulses are then projected to an interneuron before getting sent to the destined motor neurons which ultimately activates the muscle fibres to generate movements (Lemon, 2008).

I.4.2. The basis of human arm movement control

The control of human movement can be described as an interaction of processes involving ideation, planning, selecting, executing, and learning (Campos & Calado, 2009). An idea, defined as the goal of the movement, must first be conceptualised by an individual to initiate the processes involved in movement control. Action plans required to achieve the goal are then developed and subsequently, motor signals related to these action plans are generated to ultimately stimulate the different muscle groups to execute the desired movement.

Decades of human arm movement control research have highlighted the dynamic nature of processes like planning, executing, and learning in the control of arm movement (Flash & Sejnowski, 2001). As commented by Campos et al. (2009), the complexity of motor control is mainly due to the great redundancy in the human motor system. For instance, in a simple reaching movement, there are multiple paths and velocity profiles that an individual may choose to perform that movement, and these variables will all contribute to redundancy in the system (Campos & Calado, 2009). Humans, however have surprisingly been consistent in movement control and several motor control theories have attributed this to the ability of the motor system to modify these processes (e.g. planning, executing, and learning) and movement specifications
(e.g. movement paths and velocity profiles) involved in movement control (Campos & Calado, 2009). Despite the different views on how specifications in movement control may be modified to solve redundancy, there is a general consensus on the hierarchical structure involved (Figure I.6).

![Figure I.6](image)

**Figure I.6** The hierarchical structure for movement specification in arm movement control. Illustration adapted with permission from Campos et al., (2009).

One aspect of limb control system that has garnered significant interest in recent years is response inhibition, which refers to the ability to suppress unwanted somatic actions that are deemed inappropriate in a given behavioural context. Several areas in the ventral and medial prefrontal cortex, specifically the inferior frontal gyrus, SMA, and pre-SMA, are implicated in motor suppression, as it was found that damage in these area results in a significant delay in response cancelling (Chambers et al., 2009). In addition, the basal ganglia and their associated neural circuits are essential to response inhibition. Evidence of this is that the extent of deficit in movement inhibition found in a circumscribed lesion of the basal ganglia is comparable to damage in the prefrontal cortex (Rieger et al., 2003). Response inhibition is, however, not limited to just inhibition of motor response. Several behavioural related processes such as response selection, working memory and attention were found to contribute to the underlying control mechanism. Consistent with this, performance in motor response inhibition declines with an increased working memory load of the task. Further, a review by Chambers et al. (2009) provided evidence of activation in various cortical areas associated with maintenance of working memory and attention, such as dIPFC, anterior cingulate cortex, and right parietal cortex, during response inhibition. In summary, inhibitory control of somatic actions is likely composed of multiple components, with a motor component that inhibits a pre-potent motor response, and a series of cognitive processes that exert cognitive influences on the inhibitory control system.
I.4.3. The role of vision in the control of somatic actions

In the course of evolution, many foveate animals of different evolutionary backgrounds have developed a similar pattern of eye movement, often described as the ‘saccade and fixate’ strategy (Land et al., 1999). This strategy enables the rapid redirection of gaze to a new object in the environment, and keeping the eyes still during fixation to allow visual information to be taken in. The concerted interactions between these two types of eye movement form the basis for visual perception for foveate animals, which is essential for comprehension of self-orientation in relation to the external world.

One of the earliest studies to identify the relationship between this eye movement strategy and somatic actions was that of Buswell et al., (1920) who demonstrated that the duration of fixations during reading varied according to setting, with fixations being longer when a person was reading aloud than when reading silently. It was however, not until the development of head-mounted eye movement recording devices that the significance of eye movement during naturalistic and unnaturalistic tasks could be appreciated.

In a study of eye movement when performing normal daily tasks, approximately 250 fixations were made over a short period of two minutes and most of these fixations were in relation to the tasks being performed (Hayhoe, 2000). The relationship between eye movement and somatic actions was further explored by Land et al. (1999), who showed that one third of all fixations were related to subsequent somatic actions whereas the other two thirds were linked to the somatic action that was being performed currently. One might assume that fixation would be obsolete in automated actions (i.e. those that can be performed with minimal consciousness) but the same study demonstrated that to the contrary, fixations were still performed in this setting, albeit to a lesser extent than in non-automated actions (Land et al., 1999). Thus, vision has a vital role in the human motor control system, especially locating, directing, guiding, and checking during somatic movement (Hayhoe, 2000; Land et al., 1999).

I.4.3.1 The coordination of eye, head, and body movements in the gaze system

The relocation of gaze (location where one is looking), depending on the size of rotation (gaze rotation), can be done by eye movement alone or in combination of head and trunk movements. When necessary, eye movement can achieve up to ± 50° of gaze rotation in the horizontal plane. However, eye movement is often accompanied by head movement when gaze rotation is greater than 10°. Given that neck rotation allows a maximum of ± 90° of head movement, desired gaze
rotation greater than 140° would require additional involvement of trunk rotation (Land, 2006). In any given gaze rotation, eye movement generally precedes head movement, with trunk movement recruited when combined eye and head movements cannot achieve the gaze rotation required (Figure I.7).

![Diagram](image)

**Figure I.7** Relationship between eye and head movements. In facilitating gaze rotation of less than 50°, gaze movement (green line) is initially facilitated by the eye (purple line) and via VOR, the head (blue line) would subsequently catch up to return the eyes to neutral position. Illustration modified with permission from Land (2006).

### 4.3.2. The gaze-action system

Land (2009) postulated that there are four distinct but linked systems in performing visually-mediated actions and these systems are collectively known as the gaze-action system. Firstly, the gaze system initiates eye movement to direct the eyes to the visual stimulus. The visual system will then process this visual information for the motor system to enable the motor system to generate appropriate motor actions. These systems are controlled by a ‘master controller' termed the schema system, which is capable of reprogramming activities and interactions of the different systems based on the internal representation of a desired task, to produce a sequence of coherent and meaningful actions (Figure I.8).

![Diagram](image)

**Figure I.8** Components of the gaze-action system. The interactions of the four sub-systems (schema, gaze, visual, and motor systems) during a visually-mediated motor action are depicted. Illustration adapted with permission from Land (2009).
Upon the activation of a movement by the motor system, the visual system, with the necessary adjustments made by the gaze system, monitors the execution of that motor action. The schema system is informed when the action is completed and depending on the task involved, this information would either act as a feedback mechanism for the existing schema to modify the action involved or lead to the creation of a new schema for a new motor action. The significance of the schema system acting as the master control of the three systems was highlighted in an eye-hand movement study in which it was found that prior to the start of an eye-hand task, the ‘intrinsic salience’ of objects was found to have an effect on eye movement (i.e. where to look) but such an effect dissipated on the commencement of an eye-hand task, suggesting that there is a ‘top-down’ control (i.e. schema system) on the behaviour of the eye when performing a visually-mediated motor action (Land & Hayhoe, 2001).

An action is closely supervised by the visual system but gaze often abandons the current motor action prior to the completion of the task, in order to provide new visual formation necessary for generating an impending (i.e. successive) action. However, the pattern of gaze movement in relation to somatic movement changes according to the familiarity of the task (Land, 2006). Fixation has repeatedly been shown to precede learned somatic action by up to one second (Butsch, 1932; Patla & Vickers, 2003; Weaver, 1943) whereas during the process of acquiring new motor skills, fixations tend to be more closely coupled, in terms of timing, to the somatic actions involved (Sailer et al., 2005).

In humans, the ability to express and adapt learned motor movement is dependent upon varying combinations of feedback control and feed-forward control. Generalisation of motor learning enables humans to apply a motor skill learned in one context to another context. However, generalisation can either be beneficial or detrimental depending on the contexts of an intended movement. A beneficial example of generalisation might be that playing tennis may confer advantage when learning other types of racquet sport. In these circumstances, knowledge is compatible with intended action. An example of a conflict between knowledge and action is the ‘broken escalator’ phenomenon. This effect, which is usually accompanied by a brief sensation of imbalance, causes a person to step inappropriately fast on a moving platform that is no longer moving even when this is obvious to the person. The main mechanism for this is that via feed-forward adaption, there is a build-up and internalisation of a specific visuospatial context leading to the adaptation of gait which persisted even when the action, termed aftereffect, is no longer appropriate (Bronstein et al., 2009). Aftereffects can, however, be enhanced or inhibited.
via high-level interactions between procedural and declarative memory, which are subserved by various cortical and subcortical structures (Bronstein et al., 2009).

### 1.4.4. Upper limb movement in HD

Motor impairment, in addition to being a characteristic sign of HD, is the key criterion for determining the onset of phenoconversion in at-risk individuals. A study by Hefter et al. (1987) was one of the earliest studies to objectively measure the kinematics of somatic movement in manifest HD. The authors reported that in manifest HD, there was marked prolongation in contraction time to reach peak force in various muscle groups of the hand during ballistic forefinger movement. Further, relative to controls, there was increased variability in muscle contraction time in over 90% of manifest HD patients and 38% of premanifest HD individuals. Bradykinesia in HD is not limited to ballistic forefinger movement, as slowing is also observed in both simple and complex movement tasks in other muscle groups (Carella et al., 2003; Curra et al., 2000; Lemay et al., 2008).

Subsequent studies on the kinematics of upper limb movement in HD have consistently demonstrated the presence of akinesia, i.e. prolonged reaction time in manifest HD (Berardelli et al., 1999; Boulet et al., 2005; Gordon et al., 2000; Lemay et al., 2008; Quinn et al., 1997; Say et al., 2011; Schwarz et al., 2001). Manifest HD is also associated with less efficient control of upper limb movement. Unlike controls, who were found to generally move in a straight path, manifest HD patients had a greater tendency to produce a more curvilinear path during reaching (Carella et al., 2003; Quinn et al., 1997; Quinn et al., 2001). Movement accuracy is also impaired in manifest HD, with higher rates of movement error (Phillips et al., 1996; Say et al., 2011) and greater difficulty in correcting erroneous movements (Boulet et al., 2005; Smith et al., 2000) than controls.

Somatic movements of HD patients are associated with a greater number of sub-movements and greater cycles of acceleration and deceleration (Phillips et al., 1996; Quinn et al., 1997) than controls. Motor performance in manifest HD is also influenced by the motor-task involved (Carella et al., 2003; Georgiou et al., 1997). In a quantitative study of chorea, Mann et al. (2012) noted that there was a greater fluctuation in arm velocity in manifest HD in a task involving subjects maintaining their hands in a constant position. Despite an increase in velocity variance at resting state, velocity of purposeful upper limb movement in HD, at least at movement initiation, is comparable to controls (Carella et al., 2003; Quinn et al., 1997). There is however, considerable delay in movement transition in sequential movement tasks in manifest HD.
indicating an impairment in movement planning and selection in HD (Agostino et al., 1992; Gordon et al., 2000; Serrien et al., 2002; Thompson et al., 1988). There is also a greater reliance on visual guidance when performing a motor task as evidenced by observations that the availability of advance visual information (Georgiou et al., 1995) and visual feedback information (Boulet et al., 2005; Carella et al., 2003) have stronger influence on motor performance in HD patients than in controls.

Quantitative changes in motor function have also been reported in premanifest HD with movements being slower (Heftet et al., 1987), more variable (Rao et al., 2011; Smith et al., 2000), less efficient (Smith et al., 2000), and less accurate than controls. Further, Rao et al. (2011) demonstrated that the coordination of movement sequences is impaired in premanifest individuals. Based on these observations, it is natural to suggest that the objective measurement of motor function in HD may potentially be a useful marker of disease progression for HD (Rao et al., 2011; Smith et al., 2000). There are however, conflicting findings when attempting to correlate these measurable motor changes with disease severity (Gordon et al., 2000; Ruiz et al., 2000), suggesting that kinematic changes of motor movement in HD do not perfectly reflect disease status.

I.5 Biomarkers and HD

The term biomarker was previously applied only to a biological samples that could determine patient’s disease state or response to a drug (Baker, 2005). It has evolved over time, however, to include any biological measurements, such as physiological or proteomic analysis, that may reflect the underlying pathological changes in a disease. In 2001, the National Institutes of Health defined the term biomarker as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention or other health care intervention’ (Biomarkers Definitions Working Group, 2001).

Biomarkers are useful across the entire disease spectrum of a disease (Figure I.9), i.e. before, during, and after diagnosis (Kumar & Sarin, 2009). Before diagnosis, the role of biomarkers is to identify at-risk individuals who may benefit from early intervention, or to predict disease onset. During diagnosis, biomarkers are used as tools for objective and reliable identification of patients with a disease. After diagnosis, biomarkers may assess severity of a disease, provide an indication of disease prognosis, or can be used as a disease monitoring tool.
The role of biomarkers across the course of HD. The pathological process will begin at some point in a gene positive individual, initially resulting in non-specific symptoms and later, overt clinical signs that enable the clinical diagnosis of HD. *A global marker can be used for monitoring the underlying neuropathological changes that may or may not be accompanied with disease phenotype progression. An ideal progression marker tracks clinical changes in premanifest HD and continues to monitors clinical progression and disease state over the course of manifest HD. A process marker, which may not relate to disease state, may provide insights into the biological compounds involved in the disease process. The diagnosis of manifest HD can be expedited if there is a diagnostic marker that can positively identify those premanifest HD individuals with non-specific symptoms. Early diagnosis of manifest HD may potentially allow the use of disease-modifying therapies at the earliest possible. *A pharmacodynamics marker is likely to be helpful in determining pharmacological efficacy of these therapies. Illustration adapted with permission from Michell et al., (2004).

According to Hersch and Rosas (2011), an ideal biomarker in HD should: (1) clearly reflect disease conversion from premanifest to manifest HD and disease progression from early to advanced HD; (2) be objective and reproducible; (3) be specific to changes in disease status; (4) be safe and non-invasive; (5) be inexpensive and user-friendly; (6) be easily repeated on the same patient so as to provide a profile of disease progression. Based on the roles of biomarkers in HD, they can be divided into four main categories: (1) global biomarkers; (2) process biomarkers; (3) pharmacodynamics biomarkers; and (4) progression biomarkers (Figure I.9).

Global biomarkers are measurements (e.g. brain size and basal ganglia volume) that might possibly capture the global direction of HD. Process biomarkers (e.g. proteomics and metabolomics approaches) are laboratory measures of biological compounds that contribute to the disease process. Pharmacodynamics markers are measures of drug-body interactions that provide indications to whether a treatment modulates a desired target and sequentially assess the pharmacological efficacy of such treatment. Any measures that closely correspond to the clinical progression of HD (e.g. disease phenotypes, disease state, and etc.) are termed progression markers. An ideal progression marker should be able to track clinical changes in both premanifest and manifest HD. Such markers may potentially serve as surrogate endpoints.
for monitoring treatment efficacy and may also reflect the underlying biological progression of a disease. Although a definitive biomarker is yet to be identified in HD, several promising ones are emerging.

A well-established genetic diagnostic marker for HD is the direct genetic identification of the defective HD gene and the quantification of CAG repeat size, which essentially determine if individuals will develop HD in their lifetime. It is widely acknowledged that despite there is a strong inverse relationship between CAG repeat size and the onset age for manifest HD, repeat size is a poor predictor of disease onset (Andrew et al., 1993; Myers, 2004; Stine et al., 1993). Nevertheless, CAG repeat size has an effect on the rate of progression in HD (Rosenblatt et al., 2006), making it a useful tool for predicting disease prognosis. The expanded repeat in HD, can exhibit tissue-specific variability. That is, there are slight differences in CAG repeat size between different tissue types (Telenius et al., 1994), but these remain relatively consistent in the same tissue type across time (Cannella et al., 2009; Wheeler et al., 2007). The stable nature of CAG repeat size limits its value for longitudinal tracking of disease changes in HD.

The motor component, functional capacity scale, and cognitive component of the UHDRS are thus far the dominant tools for monitoring longitudinal progression in HD. These scales respectively assess the motor features and functional capabilities of HD patients. The motor component is useful for tracking longitudinal motor changes in premanifest (Tabrizi et al., 2012) and manifest HD (Huntington Study Group, 1996; Siesling et al., 1998; Tumas et al., 2004). By contrast, there is a gradual decline in score in the functional capacity scale over time in manifest but not premanifest HD (Tabrizi et al., 2012). Despite the sensitive nature of these measures, there are limitations to their use in monitoring longitudinal progression of HD. Both components may provide adequate assessment of decline in patients with early and moderate stages of HD but floor effects can hamper evaluation in advanced HD (Marder et al., 2000; Youssov et al., 2013). In addition, functional capability in HD is found to be heavily influenced by disease duration and neuropsychological performance of HD patients (Marder et al., 2000), limiting its utility in monitoring disease progression in HD. Finally, these measures, due to issues related to test designs, are often argued to be lacking objectivity. These issues would be discussed in section I.6. Cognitive impairment in HD is evident even in premanifest HD and continues to decline in manifest HD (Duff et al., 2010; Paulsen, 2011), suggesting that cognitive measures, such as SDMT and Stroop tests (both are neuropsychological tests in the UHDRS cognitive component), might be useful for monitoring disease progression in HD.
Structural and functional imaging techniques, which include structural magnetic resonance imaging (MRI), functional MRI (fMRI), and positron emission tomography (PET), are being actively investigated as possible global markers of HD. Structural MRI techniques can detect neuropathological changes in premanifest HD years before clinical onset of HD and are sensitive to longitudinal deterioration in both premanifest and manifest HD. In premanifest HD, there is increased in cerebrospinal fluid (CSF) volume, atrophy of both grey and white matter in the years leading up to phenoconversion of HD (Squitieri et al., 2009). Further, relative to controls, there is a faster rate of atrophy in the basal ganglia and white matter, and also a greater reduction in global brain volume over time in premanifest HD (Aylward et al., 2011; Dominguez et al., 2013; Tabrizi et al., 2012). Longitudinal reduction in basal ganglia volume is one of key neuroimaging finding in manifest HD (Aylward et al., 1997; Tabrizi et al., 2012). Lobe-specific atrophic changes in the cortex have been observed in just a two year period (Tabrizi et al., 2012), particularly in the frontal lobe (Aylward et al., 2011). Measurable white matter degeneration continues in manifest HD (Weaver et al., 2009). Of all these cerebral components, the caudate nucleus and white matter demonstrate the largest effect sizes for atrophy rates in patients with early HD in comparison to healthy controls (Tabrizi et al., 2012). Most of these neuropathological changes correlate with individual patient disease status (Georgiou-Karistianis et al., 2013), suggesting that structural MRI is a potentially valuable tool for monitoring disease progression and assessing the efficacy of neuroprotective agents in HD.

Functional MRI studies (fMRI) have consistently demonstrated a reduction in brain activation in premanifest and manifest HD when compared to controls during both motor and cognitive tasks (Kim et al., 2004; Reading et al., 2004; Wolf et al., 2007) whilst PET scanning in manifest HD has demonstrated a progressive loss of striatal D2 receptor binding (Pavese et al., 2003). Striatal metabolism remains abnormally low throughout the premanifest phase, but there is a switch from an increased to sub-normal thalamic glucose metabolism at onset of manifest HD (Feigin et al., 2007). The clear association of findings with underlying pathology and its mostly non-invasive nature makes neuroimaging technology an appealing candidate for use as a biomarker in HD. However, neuroimaging technology is mostly expensive and its application may be restricted to research centres or tertiary hospitals.

‘Omics’ approaches, namely proteomics and metabolomics, have been utilised in the search for potential biochemical markers in blood or cerebrospinal fluid samples in both premanifest and manifest HD. Proteomic (the study of protein structures and functions) investigations have reported increased release of pro-inflammatory cytokines in premanifest HD (Bjorkqvist et al.,
The metabolomics (a study of small molecule metabolite profiles in a living system) strategy has led to indications of a pro-catabolic profile of metabolism (Underwood et al., 2006) in premanifest HD in the years leading up to phenoconversion of HD. The close association between a change in cellular activity and phenoconversion suggests that these ‘omics’ approaches might be useful for early diagnosis of premanifest HD individuals. However, it could be argued that these changes are constitutional abnormalities of HD and may not actually reflect disease status of individual patients and thereby limiting their use as diagnostic or progression markers. Nevertheless, these approaches have definitely provided insights to HD effect on biological processes and though their utility as diagnostic or progression markers is still a matter of debate, they may have the potential to be considered as process biomarkers of HD.

As reviewed by O’Keeffe et al. (2009), rapid alternating movement and saccadic movement assessments are two promising motor measures for use as progression biomarkers in HD. For rapid alternating movement, changes in arm and hand performance could be detected as early as two decades before clinical diagnosis in premanifest HD (Paulsen et al., 2008) whereas manifest HD showed deterioration in performance level over a 2-year period (Antoniades et al., 2010). Using saccadometry, gene negative individuals, premanifest and manifest HD patients were readily differentiated from one another on the basis of their saccadic latency distributions (Antoniades et al., 2007). A key feature of these objective motor measures is that, unlike UHDRS for example, these measures allow objective quantification of disease status in HD as well as change over time. Additionally, in contrast to some other potential progression markers, the ability of these measures to detect impaired performance even in premanifest HD, renders them applicable across the entire course of HD. Relative to other biomarkers (e.g. neuroimaging techniques and ‘omics’ approaches), these measures are cheap and easily repeatable without compromising patients’ safety. Table I.2 summarises the potential HD biomarkers and their associated longitudinal changes.

In conclusion, there are certain limitations (e.g. cost, not accurate as progression marker, not sensitive to all phases of the disease) in the application of a number of potential biomarkers in HD research and in clinic. Genetic testing in HD is clearly indispensable to clinicians in diagnosis and to some extent prognosis, but lacks any utility in detecting phenoconversion or tracking disease changes in patients. Components (motor and cognitive) of the UHDRS, though sensitive to disease changes, are hampered by ceiling or floor effects, and confounding factors. The high cost and accessibility of neuroimaging techniques limit their routine use as HD
biomarkers in clinical setting. The objective measurement of cognitive and motor functions, however, appears to be very promising; they are practical, relatively cheap, easy to perform and capable of providing quantifiable measurement of clinical performance that can be monitored across disease course. Therefore, this study aimed to capitalise on the strengths of cognitive and motor measures to possibly identify cognitive- or motor-related progression markers that can effectively monitor longitudinal disease changes in HD and also be easily translated for use in a clinical setting. Subsequent sections detail the unresolved issues in the current literature related to the use of saccadic and somatic measures for detecting and tracking disease changes in HD and discuss how the present study seeks to answer these unresolved issues.

Table I.2  Potential HD biomarkers and their associated longitudinal changes

<table>
<thead>
<tr>
<th>Measures</th>
<th>Longitudinal changes in HD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UHDRS</strong></td>
<td></td>
</tr>
<tr>
<td>Motor component</td>
<td>Progressive increase in score</td>
</tr>
<tr>
<td>Functional capacity scale</td>
<td>Gradual decline in score</td>
</tr>
<tr>
<td>Cognitive component</td>
<td>Deterioration in score</td>
</tr>
<tr>
<td>SDMT</td>
<td></td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
</tr>
<tr>
<td><strong>Motor measures</strong></td>
<td></td>
</tr>
<tr>
<td>Rapid alternating arm and hand movements</td>
<td>Decline in performance</td>
</tr>
<tr>
<td>Horizontal reflexive saccade</td>
<td>Increase in latency and reduction in velocity</td>
</tr>
<tr>
<td><strong>Neuroimaging</strong></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>Gradual reduction in cortical and subcortical volume</td>
</tr>
<tr>
<td>fMRI</td>
<td>Changes in brain activation when performing motor or cognitive tasks</td>
</tr>
<tr>
<td>PET</td>
<td>Progressive loss of striatal D2 receptor binding</td>
</tr>
<tr>
<td><strong>“Omics” approaches</strong></td>
<td></td>
</tr>
<tr>
<td>Proteomics</td>
<td>Increased release of pro-inflammatory cytokines</td>
</tr>
<tr>
<td>Metabolomics</td>
<td>A switch to pro-catabolic profile of metabolism prior to phenoconversion</td>
</tr>
</tbody>
</table>

I.6. Unresolved issues in the literature and research questions

Medical research has contributed much to understanding the pathogenesis of HD but thus far, no effective treatments for this disease have been discovered, let alone treatments for modifying or curing it. The UHDRS is the favoured tool for monitoring disease progression in HD. It has high inter-rater agreement and the motor component is sensitive to short- and medium-term longitudinal changes (Huntington Study Group, 1996; Siesling et al., 1998; Tumas et al., 2004). However, inter-rater reliability is low in non-clinicians and high only in clinicians with considerable clinical experience in HD (Hogarth et al., 2005).

Klemprir et al. (2006) however, highlighted that longitudinal changes in total motor score did not mirror the proportional change in individual items in the motor component of UHDRS. In addition, the same authors noted that cognitive status may influence items in the motor
component such as the ‘Luria’ test in which the successful execution of the task is dependent on executive functioning. There are also doubts about the utility of this disease rating scale for patients at the extremes of HD disease spectrum (i.e. premanifest HD, very early stage HD, and advanced stage HD). This argument is supported by the finding of poor inter-rater agreement among clinicians assessing patients with very early signs of manifest HD (Boo et al., 1998). Further, a floor effect may alter the validity of the UHDRS score in those patients in advance stage HD (Youssov et al., 2013). Thus, the UHDRS is not without its limitations in clinical application and a more objective and sensitive measure of disease status and progression is definitely warranted.

Deficits in oculomotor function are common features in movement disorders in which there may be distinct oculomotor signs (Clark & Eggenberger, 2012). For instance, whilst there is selective degeneration of neurons in the basal ganglia in both PD and HD, the ocular features of each are distinct from one another on clinical examination and laboratory recordings (Anderson & MacAskill, 2013). Upon clinical examination, the authors noted that there is mild hypometria of up-going voluntary saccades and mild impairment in smooth pursuit in PD whereas in manifest HD patients, apraxia of saccades and slowing of saccadic velocity are key features (Anderson & MacAskill, 2013). Further, they noted that in laboratory assessment of eye movement in PD, there is an increase in latency of reflexive and voluntary saccades only in those with cognitive impairment whereas prolongation of latency and error rates in voluntary saccades are closely associated with disease severity in manifest HD (Anderson & MacAskill, 2013). As discussed above, oculomotor signs have long been hallmarks of HD, with for example, prolongation in saccade initiation and reduced velocity being consistently reported. A study by Beenen et al. (1986) was one of the earliest to demonstrate longitudinal changes in saccadic function in manifest HD but this was based on the observation of only four patients over a variable time frame of 1 to 4 years. Those shortcomings have been redressed in subsequent studies utilising better experimental designs. Rubin et al. (1993) observed a prolongation of latency and slowing of velocity in saccades over a two year period in manifest HD patients.

In a large longitudinal study employing multiple modalities to investigate progression in premanifest and early manifest HD patients, anti-saccade error rate seemed to be sensitive to disease changes at one year follow-up (Tabrizi et al., 2010). However, the authors reported in a subsequent publication (Tabrizi et al., 2012) that anti-saccade changes were relatively small and present only in the early manifest HD group at two years follow-up. Thus, there is
conflicting evidence on the utility of oculomotor recordings in reflecting disease progression in longitudinal studies. It is perhaps pertinent that most cross-sectional studies (Blekher et al., 2006; Lasker et al., 1987; Peltsch et al., 2008; Winograd-Gurvich et al., 2003) employed a variety of saccadic paradigms to show various saccadic abnormalities in HD whilst longitudinal studies (Rubin et al., 1993; Tabrizi et al., 2012) focussed only on a specific aspect of oculomotor function in premanifest or early manifest HD and not in more established manifest HD.

The adoption of bipedalism in human evolution has enabled humans to acquire great flexibility in terms of movement and acquiring skills in the upper limbs (Darwin, 1871; Sigmon, 1971; Washburn, 1960). Precise control of movement of our upper limbs is crucial for even simple daily activities such as eating, drinking, and reaching movements. With the basal ganglia being a key ‘modulator’ for movement control and also the seat of HD pathology, it is unsurprising that there is a generalised motor impairment affecting speech, swallowing, gait, and upper limbs in HD. Upper limb movements in both manifest and premanifest HD, as discussed in section I.4.4, are different from and frequently less efficient than those in controls. There is however, conflicting evidence on the closeness of the relationship between motor impairment and disease state in HD. Some studies have found that the degree of motor dysfunction was closely associated with clinical severity of HD patients (Ruiz et al., 2000; van Vugt et al., 1996) whereas others have shown the opposite due to the large variance in motor performance across patients (Gordon et al., 2000). Sample sizes in some of these studies have been small thus limiting the impact of their conclusions.

Ruiz et al. (2002), were the first to describe quantitative longitudinal changes in upper limb function in HD. Their findings were supported by a large longitudinal study, which showed that there were measurable changes in various force related motor tasks in early HD at 12 month and 24 month follow-ups (Tabrizi et al., 2012; Tabrizi et al., 2010). In the Ruiz et al. (2002) study, HD patients at different disease stages were analysed collectively, meaning that there could be either exaggeration or underestimation of longitudinal changes in motor function of HD patients depending on disease stage. The reason for this is that in HD, there are differences in longitudinal changes across disease stages and one stage might demonstrate greater change than the other over time (Dominguez et al., 2013; Poudel et al., 2015; Solomon et al., 2008), thus the collective analysis of patients across the disease spectrum may provide misleading impression on the actual longitudinal disease changes in HD. The longitudinal study of Tabrizi and colleagues (2012; 2010) utilised only force-related motor tasks and were limited to premanifest and early stage HD. Thus, these initial longitudinal studies, while promising in
providing motor-related biomarkers of HD disease progression, have some limitations. Kinematic analysis of motor function is a relatively new area of research in HD and further studies on its applicability to the documentation of disease progression is warranted.

The control of somatic movement calls upon the concerted interactions between a schema and gaze, visual, and motor systems. Manifest HD patients, as discussed above, exhibit strong reliance on visual guidance in the control of upper arm movement. It has been suggested that in HD, there are great similarities between eye and arm movement abnormalities (Berardelli et al., 1999) but eye movement deficits in HD are evident in premanifest at-risk individuals implying that such abnormalities may precede the development of overt motor signs, i.e. phenoconversion (Blekher et al., 2006; Rupp et al., 2011; Rupp et al., 2012). In light of this, the question is whether oculomotor deficits might contribute to impairment in somatic movement in HD. Thus far, no study has examined the relationship between eye movement and somatic movement in HD and filling this gap is one of the aims of the work contained in this thesis.

There are three main aspects to the symptomatology of HD, motor impairment, cognitive impairment, and behavioural disturbances. In the knowledge that disordered behaviour in HD does not exhibit progressive deterioration over time (Huntington Study Group, 1996; Youssov et al., 2013) and also correlates poorly with clinical severity (Klempir et al., 2006), monitoring disease progression in HD is likely to be more useful using measures of cognitive and motor impairment. Deficits in somatic and eye movements together are present in many neurodegenerative movement disorders and especially those involving the basal ganglia e.g. HD and PD. It follows then that a detailed longitudinal study of both these motor features might improve the understanding of HD, and in particular be useful in reflecting disease progression.

I.7. Study aims and hypotheses

I.7.1 Study aims

One of the key aims of this study is to redress some of the above unresolved issues in the literature, and primarily to examine the short-term (12 month) longitudinal changes in saccadic deficits in more established manifest HD by employing a variety of saccadic paradigms. The work contained in this thesis also seeks to determine the relationship between the eye and hand in coordinated eye-hand movements, which is an aspect that has received scant attention in the literature. Thirdly, the intent of the thesis work is also to examine the utility of a selection of
widely-used disease measures, for example brief cognitive tests, a comprehensive neuropsychological battery, total motor scores of the UHDRS motor component, and neuropsychiatric (i.e. depression, anxiety, and etc.) measures for monitoring short-term disease changes in manifest HD and to determine the relationship between these standard disease measures and saccadic and eye-hand performance. The overarching aim of the thesis work is to identify potentially objective biomarkers for measuring HD status and progression that could be employed in clinical research, therapeutic trials, and clinics. Each specific aim is discussed in the introductory section of each chapter to follow. The hypotheses, based on the above review of the prevalent literature, are outlined in the concluding section below.

I.7.2 Study hypotheses

Based on the review of the literature, I therefore hypothesized that cognitive, saccadic, and motor deficits are highly likely to correlate to the disease state, motor and cognitive impairment in particular, of manifest HD patients. Because of this close relationship, a change (decline) in performance in these functions is presumably quantifiable over a relatively short follow-up period of 12 months, hence revealing a potentially useful progression marker for HD that can be easily adapted for use in a clinical setting and also future therapeutic trials. I further hypothesised that a detailed assessment of saccadic function and eye-hand coordination with simple task and complex tasks in manifest HD may assist in gaining greater insight into effect of HD on the behavioural aspect of movement control that includes movement prediction, inhibition, and interaction between eye and hand movements.
Chapter II

Methods

II.1. Study design

The study was divided into two main phases, a baseline phase and a 12 month follow-up. The baseline phase was conducted over a period of eight months, from July, 2011 to March, 2012. All participants were invited for follow-up assessment which began in July, 2012 and was completed in March, 2013, twelve months after their baseline assessments. The baseline phase of the study was approved by the New Zealand Ministry of Health Upper South B Ethics Committee in March, 2011 [Ethics reference: URB/11/02/006] and the 12 month follow-up, in March, 2012 [Ethics reference: URB/12/EXP/011] (please refer Appendix). All participants were consented prior to study participation.

II.2. Demographics

Study participants were a convenience sample of 22 manifest HD patients (10 males and 12
females) with mild to moderate disease severity and 22 age, gender, and education-matched control volunteers recruited through the New Zealand Brain Research Institute database (Table II.1). Patients were genetically verified, with CAG repeats ranging from 39 to 55 (refer Table A of the Appendix for patient-specific CAG repeat number and mode of inheritance) and had been diagnosed clinically by Professor Tim Anderson, a movement disorders specialist. All participants self-identified as native speakers of English.

<table>
<thead>
<tr>
<th>Demographics at baseline</th>
<th>Control group</th>
<th>HD group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>49.8 (15.3)</td>
<td>49.7 (15.1)</td>
</tr>
<tr>
<td>Education</td>
<td>12.8 (2.1)</td>
<td>12.8 (2.1)</td>
</tr>
<tr>
<td>CAG repeat number</td>
<td>-</td>
<td>44.1 (3.8)</td>
</tr>
<tr>
<td>Range</td>
<td>-</td>
<td>39 - 55</td>
</tr>
<tr>
<td>Gender (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Ethnicity (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZ European</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>NZ Maori</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>South African Indian</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Disease stages (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Stage 2</td>
<td>-</td>
<td>8</td>
</tr>
<tr>
<td>Stage 3</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Stage 4</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Stage 5</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

II.3 Disease rating scale

The UHDRS is the standard assessment scale used in determining disease severity of HD. The scale assesses four main domains of HD: motor function, cognitive function, behavioural function, and functional capacity (Huntington Study Group, 1996). The motor component of the UHDRS consists of items that assess oculomotor function and other motor signs commonly observed in HD (Huntington Study Group, 1996). The UHDRS cognitive component includes three tests of executive function (letter fluency test, Symbol Digit Modalities test, and Stroop test) that have been corrected to attenuate the impact of demographic variables (O'Bryant & O'Jile, 2004; Sheridan et al., 2006). The UHDRS behavioural component contains a standardised questionnaire that focuses on mood-related, behavioural, and psychotic symptoms (Huntington Study Group, 1996). There are three main subsections in the UHDRS functional capacity assessment scale: (1) a 25-question functional assessment survey; (2) an independence scale; and (3) a five-domain functional capacity assessment (Huntington Study Group, 1996). The functional rating scale (FRS), which is adapted from the Shoulson-Fahn Disease Rating Scale (Shoulson et al., 1989) and a common tool used for disease staging in HD (Nance et al., 2012), uses the aggregated score of the UHDRS functional capacity assessment. This scale
divides manifest HD into five disease stages and the clinical description for each stage is detailed in Table II.2. Permission to use the UHDRS in this study was granted by the Huntington Study Group on the 26th January 2011 (please see Appendix).

Table II.2  Disease staging in manifest HD

<table>
<thead>
<tr>
<th>Stage</th>
<th>FRS score</th>
<th>Engagement in occupation</th>
<th>Ability to manage finance</th>
<th>Ability to manage domestic responsibilities</th>
<th>Ability to perform activities of daily living</th>
<th>Care level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11 - 13</td>
<td>Normal</td>
<td>Fully capable</td>
<td>Fully capable</td>
<td>Fully capable</td>
<td>Home</td>
</tr>
<tr>
<td>2</td>
<td>7 – 10</td>
<td>Lower level</td>
<td>Slight assistance needed</td>
<td>Capable</td>
<td>Capable</td>
<td>Home</td>
</tr>
<tr>
<td>3</td>
<td>3 – 6</td>
<td>Marginal</td>
<td>Major assistance needed</td>
<td>Impaired</td>
<td>Mildly impaired</td>
<td>Home</td>
</tr>
<tr>
<td>4</td>
<td>1 – 2</td>
<td>Unable</td>
<td>Unable</td>
<td>Unable</td>
<td>Moderately impaired</td>
<td>Home/ Extended care facility</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>Unable</td>
<td>Unable</td>
<td>Unable</td>
<td>Severely impaired</td>
<td>Total care facility only</td>
</tr>
</tbody>
</table>

Source: A Physician’s Guide to the Management of Huntington’s Disease (Nance et al., 2012) and Shoulson-Fahn Functional Capacity Rating Scale (Shoulson & Fahn, 1979)

II.4. Cognitive measures

II.4.1. Neuropsychological assessment

The Mini Mental State Examination (MMSE) (Folstein et al., 1975), Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), and a comprehensive neuropsychological test battery were administered to all participants at baseline and 12 month follow-up. The comprehensive assessment used 19 neuropsychological tests to assess six domains of cognitive function: executive function; working memory and attention; processing speed; learning and memory; language; and visuospatial function (Table II.3). The number of tests administered was evenly distributed over two separate sessions, one week apart and each session was 1 – 1.5 hours in duration. Neuropsychological tests were presented in the same order for all participants, with verbal tests alternating with non-verbal tests. The test order in session one was: MMSE; California Verbal Learning Test–II (CVLT–II) Recall and Short Delay trials; Judgment of Line Orientation Test; CVLT–II Long Delay Free Recall, Cued Recall, and Yes/No Recognition trials; Brief Boston Naming Test; Trail Making Tests (Part A and Part B); and Rey Complex Figure Copy Test. In session two, the order of tests was: MoCA; Stroop – colour naming, word reading, and interference tests; Brief Visuospatial Memory Test–Revised (BVMT–R) Immediate Recall trial; Symbol Digit Modalities Test (SDMT); Letter fluency test; Action fluency test; Digit forward, backward and sequencing tests; BVMT–R Delayed Recall, Recognition, and Copy trials; Ruff 2 and 7 Cancellation Test; Category fluency test; Category switching test; and Indiana University Token Test.
II.4.2. Cognitive screening tests

The MMSE comprises eleven questions spanning five aspects of cognitive function: executive function, language, memory function, visuospatial ability, and orientation (Folstein et al., 1975). It has good inter-rater, test and re-test reliability in differentiating cognitive status in dementia syndromes (Tombaugh & McIntyre, 1992) and other disorders featuring cognitive impairment (Godefroy et al., 2011b). Nevertheless, it is influenced by demographic factors such as age, education, and cultural background (Scanzufca et al., 2009; Tombaugh & McIntyre, 1992; Wind et al., 1997). For the MMSE, both alternatives (‘World’ spelled backwards and serial sevens) were assessed.

The MoCA places greater emphasis than MMSE on naming, attention, abstraction, and delayed recall, functions that are most likely to be compromised in the earlier stages of cognitive impairment and, unlike MMSE, it compensates for education level (Nasreddine et al., 2005). Both the MMSE and MoCA have been used as measures of cognitive performance in manifest HD (Bezdicek et al., 2013; Gluhm et al., 2013; Mickes et al., 2010; Videnovic et al., 2010). However, the MoCA was found to have higher sensitivity than MMSE without losing specificity in identifying HD patients with cognitive impairment (Mickes et al., 2010). Furthermore, Bezdicek et al. (2013) demonstrated statistical significant correlations ($p < 0.05$) between almost all MoCA subtests and the cognitive tests in a neuropsychological battery in manifest HD.

II.4.3. Executive function

Executive function is defined as the ability to control and coordinate different higher-order cognitive processes involving working memory tasks, task switching, planning, and goal-directed activities (Elliott, 2003; Miller & Wallis, 2009). The ability to monitor verbal output was assessed with Letter fluency and Action fluency tests (Delis et al., 2001; Piatt et al., 2004). The Category switching test (Delis et al., 2001) incorporates semantic switching during verbal fluency (Corbett et al., 2009). As HD is expected to cause an impairment in executive function (Lange et al., 1995; Lemiere et al., 2004; Paulsen, 2011), this study also included the standardised Trails Making Test (Part B) (Arbuthnott & Frank, 2000) and Stroop – interference test (Delis et al., 2001; Gyurak et al., 2009; Kramer et al., 2010).

II.4.4. Working memory and attention

The ability to store, maintain and retrieve items in the short-term is also linked with elements of attention (Just & Carpenter, 1992; Miyake & Shah, 1999). The digits forward, backward and
sequencing tests (Wechsler, 2008) and Symbol Digit Modalities Test (SDMT) (Smith, 2007) were used to assess working memory and attention. The SDMT is also one of the prescribed test in the UHDRS cognitive component (Huntington Study Group, 1996). Given that motor deficits in manifest HD may give a disadvantage to HD patients in the written version of SDMT, the oral version was used instead. The Ruff 2 & 7 Cancellation Test (Ruff & Allen, 1996) is a reliable measure of cognitive attention (Knight et al., 2010) thus accuracy scores from this test also contribute to the aggregated score for the working memory and attention domain.

II.4.5. Processing speed

Processing speed refers to the rate at which a person executes basic elementary processing operations (Goth-Owens et al., 2010; MacLeod, 1991; Tombaugh, 2004). Scores from Stroop – colour naming, Stroop – word reading (Delis et al., 2001), and Trail Making Test (Part A) (Reitan, 1958) were used to assess processing speed. The Ruff 2 & 7 Cancellation Test (Ruff & Allen, 1996) is a test that assesses both processing speed and visual attention (Cicerone & Azulay, 2002; Ruff et al., 1992). Speed scores from this test and scores from other processing speed oriented tests contributed to the aggregated score for the processing speed domain.

II.4.6. Learning and memory

Learning and memory are key processes involved for the acquisition of knowledge about skills and experiences. Episodic learning and memory was assessed using a verbal test and also a non-verbal test. The California Verbal Learning Test–II (CVLT–II), a verbal test, was used to measure word list acquisition and, short and delayed memory retention (Baldo et al., 2002; Delis et al., 2005). The Brief Visuospatial Memory Test–Revised (BVMT–R), which is a type of visual-graphic memory test (Benedict, 1997; Benedict et al., 1996), was used as the non-verbal test.

II.4.7. Language domain

The expression of language involves both the interpretation of speech and the internal processing of the perceived speech (Saur et al., 2010). Two tests were used to assess this domain: the Brief Boston Naming Test and the Indiana University Token Test. The Brief Boston Naming Test involves the interpretation of simple drawings and word recollection (Graves et al., 2004). The Indiana University Token Test (Token Test) requires the internal processing of speech command given by the examiner and its translation into gross motor actions by touching the tokens presented (Unverzagt et al., 1999).
II.4.8. **Visuospatial function**

Visuospatial skills enable a person to perceive spatial relationships between objects and their environment (Mervis et al., 1999). Two tests were included in this domain: (1) Judgement of Line Orientation Test (Form H), a perception and spatial thinking test (Benton et al., 1994); and (2) Rey Complex Figure Copy Test (Osterrieth, 1944; Rey, 1942), a test that evaluates visuospatial planning and construction (Lezak et al., 2004).

<table>
<thead>
<tr>
<th>Cognitive domains tested</th>
<th>Neuropsychological tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Executive function</strong></td>
<td>Letter fluency test</td>
</tr>
<tr>
<td></td>
<td>Action fluency test</td>
</tr>
<tr>
<td></td>
<td>Category fluency test</td>
</tr>
<tr>
<td></td>
<td>Category switching test</td>
</tr>
<tr>
<td></td>
<td>Trails Making Test (Part B)</td>
</tr>
<tr>
<td></td>
<td>Stroop – interference test</td>
</tr>
<tr>
<td><strong>Working memory and attention</strong></td>
<td>Digit forward, backward and sequencing tests</td>
</tr>
<tr>
<td></td>
<td>SDMT(^1)</td>
</tr>
<tr>
<td></td>
<td>Ruff 2 &amp; 7 Cancellation Test - accuracy score</td>
</tr>
<tr>
<td><strong>Processing speed</strong></td>
<td>Stroop – colour naming test</td>
</tr>
<tr>
<td></td>
<td>Stroop – word reading test</td>
</tr>
<tr>
<td></td>
<td>Trails Making Test (Part A)</td>
</tr>
<tr>
<td></td>
<td>Ruff 2 &amp; 7 Cancellation Test - speed score</td>
</tr>
<tr>
<td><strong>Learning and memory</strong></td>
<td>CVLT–II(^2)</td>
</tr>
<tr>
<td></td>
<td>BVMT–R(^3)</td>
</tr>
<tr>
<td><strong>Language domain</strong></td>
<td>Brief Boston Naming Test</td>
</tr>
<tr>
<td></td>
<td>Indiana University Token Test (Token Test)</td>
</tr>
<tr>
<td><strong>Visuospatial function</strong></td>
<td>Judgement of Line Orientation Test (Form H)</td>
</tr>
<tr>
<td></td>
<td>Rey Complex Figure Copy Test</td>
</tr>
</tbody>
</table>

\(^1\)SDMT: Symbol Digit Modalities Test; \(^2\)CVLT–II: California Verbal Learning Test–II; \(^3\)BVMT–R: Brief Visuospatial Memory Test–Revised

II.5. **Behavioural measures**

Psychiatric and behavioural symptoms such as depression, anxiety, and apathy are prevalent in manifest HD (Paulsen, 1999; Vassos et al., 2008). This study, in addition to the UHDRS behavioural component, also included Beck’s Depression Inventory–II (BDI–II), Beck’s Anxiety Inventory (BAI), and Apathy Evaluation Scale. The BDI–II is a reliable and effective screening tool for depression (Beck et al., 1988). The BAI (Beck & Steer, 1993), which has been validated to be a useful tool for screening anxiety related symptoms in outpatient settings (Steer et al., 1993), was used in this study for assessing anxiety. The AES is a scale for measuring motivation and goal directed behaviour (Marin et al., 1991). Behavioural measures were assessed at the end of each assessment session, the BDI–II and BAI in the first session, and AES in the second.
II.6. Saccadic function assessment

Saccadic function assessment consisted of six eye movement tasks: (1) reflexive; (2) self-paced; (3) temporally-cued (predictive); (4) delayed; (5) memory-guided; and (6) anti-saccade tasks. They were administered to all participants in the same order as listed above in a one-hour session in an eye movement laboratory at the NZBRI.

II.6.1. iViewX™ Hi-Speed eye tracker

A non-invasive high-speed video-based eye tracking system, the iViewX™ Hi-Speed (SMI, Teltow, Germany) was used for recording eye movement in the head-fixed tasks above. The device features high resolution [typically < 0.01°] and high accuracy [typically 0.25°- 0.50°] tracking of eye position at a sampling rate of 1250 Hz (SMI, 2010b). The hardware component of the device comprises an eye tracking column with adjustable ergonomic chin rest, a see-through glass piece and a built-in infra-red camera. A DLP projector with a resolution of 1280 x 720 pixels and a refresh rate of 100 Hz, was used to project targets (12 x 12 pixel squares) onto a screen measuring 1574 mm in width and 877 mm in height, placed 1649 mm from the eye tracker column (Figure II.1). Study subjects were seated with their chins placed on the chin rest and their foreheads against the forehead rest of the eye tracker column (Figure II.1). The eye tracking system was controlled by one PC while stimulus targets for saccadic tasks were presented by another PC using PsychoPy (Peirce, 2008), an open-source software package for stimulus presentation.

![Figure II.1](image)
II.6.2. Calibration protocols for the eye tracking system

Trial blocks were preceded by a semi-automatic calibration procedure in which the eye tracking system would match eye position data from each participant relative to known fixation positions on the screen. Participants were asked to fixate at randomly appearing targets, one at a time, at 13 pre-selected locations on the screen. The calibration targets were distributed to give good coverage over an area slightly larger than the ±15° deg (horizontal) by ±10° (vertical) field in which stimuli were presented. These targets were spread well within the maximum viewing angle of the iViewX™ Hi-Speed System which is ±30° in the horizontal direction and ±30° (upwards), -45° (downwards) in the vertical direction (SMI, 2010b). The calibration process was repeated until satisfactory gaze positions relative to the actual targets were obtained and calibration checks were constantly reviewed between trial blocks.

II.7. Eye-hand coordination assessment

Participants attempted four eye-hand coordination tasks: reflexive, self-paced, temporally-cued (predictive), and delayed tasks in a 45 min session in the MoVElab at the NZBRI. Memory-guided and anti-saccade eye-hand tasks were not assessed because of time-constraints.

II.7.1. iViewX™ HED

For the eye-hand coordination tasks, a mobile eye tracker was required to allow the participants to respond to the tasks naturally. The iViewX™ HED system (SMI, Teltow, Germany) is a mobile head-mounted video eye tracker with a manufacturer’s stated sampling rate of 200 Hz, a typical tracking resolution of < 0.01° and a typical accuracy of 0.5°–1.0° (SMI, 2010a). The system comprised of a set of lightweight eye and scene video cameras mounted on a modified baseball cap (total weight of < 80 g) connected by a USB cable to a laptop device for eye data compilation. This was used for recording eye movement in eye-hand coordination tasks (Figure II.2).

II.7.2. Modified modular virtual environment platform

The modular virtual environment platform was originally designed and developed at the New Zealand Brain Research Institute for use in movement and rehabilitation research in a virtual environment. The platform is capable of providing accurate calibration, high graphics update rate, and low latency feedback (Myall et al., 2008). The platform’s ability to perform in a wide spectrum of motion characteristics made it a suitable device for kinematic analysis in HD, in which movement impairment is prevalent (Phillips et al., 1996; Phillips et al., 1995).
The platform consisted of a 240 Hz Liberty™ electromagnetic tracker (Polhemus GMP Contract Manufacturer, Vermont, USA) that has an accuracy of 0.08 mm RMS in the X, Y, Z axes and an accuracy of 0.15° RMS for orientation (Polhemus, 2008). It was remotely operated using a software system written from open source and custom modules. The platform was modified for the eye-hand coordination tasks in order to fulfil the purpose of analysing kinematic characteristics of HD in a pseudo real-life environment. One motion sensor, attached to the tip of the index finger on the dominant hand (the hand performing the tasks), was used for motion tracking in eye-hand coordination tasks (Figure II.2).

### II.7.3. Overall MoVElab setup

Targets (20 mm x 20 mm) were displayed on a 22-inch LCD screen with a resolution of 1680 x 1050 pixels and a frequency of 120 Hz. The inferior border of the screen was placed 200 mm away from the edge of a modified desk and the screen-table angle was set at 30° (Figure II.2). Participants were seated at an arm length away from the screen during the assessment.

![Laboratory setup for eye-hand coordination assessment.](image)

**Figure II.2** Laboratory setup for eye-hand coordination assessment. The iViewX™ HED mobile eye tracker (A) and motion sensor are shown on the left and the stimuli display screen on the right.

### II.7.4. Calibration protocols in eye-hand coordination assessment

There were two parts to the calibration protocols in eye-hand coordination assessment: (1) a calibration process for the eye tracking system; and (2) a calibration process for the eye tracking system together with the motion tracking system. For the calibration process for the eye tracking system, participants were asked to fixate at five different locations on the LCD screen (the four corners and the mid-point of the screen) in a seated position and with their head resting on a chin rest. In the second calibration process (eye tracking system together with the motion
tracking system), the chin rest was removed and participants were asked to fixate and touch the targets on the LCD screen using their index finger (the one attached to a motion sensor). Calibration targets were presented at 17 pre-selected locations on the screen and the process was repeated until satisfactory gaze positions were achieved.

II.8. Experiment paradigms

II.8.1. Visually-guided reflexive tasks

II.8.1.1. Saccade-only reflexive tasks

There were two blocks of trials in the reflexive paradigm, a one dimensional (1D) block (horizontal saccades only) and a two dimensional (2D) block (horizontal and vertical saccades).

In the 1D trial block, red targets would appear, one at a time, at one of seven fixed locations (-15°, -10°, -5°, 0°, 5°, 10°, and 15° in the horizontal axis relative to the eye column tracker) for 108 trials. Three types of reflexive stimulus onsets (‘gap’, ‘step’, and ‘overlap’) were used in this task (Figure II.3) and they were randomly distributed across the trial block. Stimulus types could be differentiated by the time interval between preceding and successive targets. The onset of a new target occurred 200 ms after the offset of the previous target in ‘gap’ stimulus. In the ‘step’ condition, the new target appeared simultaneously to the offset of the previous target. The ‘overlap’ stimulus would appear 200 ms before the previous target disappeared from the screen.

![Figure II.3](image-url)

**Figure II.3** Screen transitions and timings between preceding and successive targets for the three stimulus types (‘gap’, ‘step’, and ‘overlap’) in the reflexive 1D paradigm.

The 2D trial block featured individual targets appearing in a random manner in both horizontal and vertical positions for 120 trials. There were 35 possible locations, all confined within an
area of -15° to +15° in the horizontal axis and -10° to +10° in the vertical axis from the centre point of the screen (Figure II.4). The rationale for using a 2D task rather than an all vertical saccade task in this study was because of the restricted field of vision for vertical eye movements (Walker et al., 1990) which consequentially would limit the range of target locations used for assessing vertical saccades. The use of a 2D task greatly increased the number of possible target locations in a trial block as compared to a one dimensional task. That is, in an all vertical saccade task, there are only 5 possible target locations while an all horizontal saccade task is limited to 7 possible target positions. To control for mixed movement saccade, i.e. oblique movement, all target angular displacements were relative to the previous target and were limited to either purely horizontal or vertical movement. Only ‘Step’ stimuli were used in this task.

In both reflexive protocols, subjects were instructed to fixate at the appearing target as fast and accurately as possible.

![Possible target positions in the reflexive 2D paradigm.](image)

**Figure II.4** Possible target positions in the reflexive 2D paradigm. Target positions are measured in degrees from the eye tracker column.

### II.8.1.2. Visually-guided reflexive eye-hand task

There were 60 trials of a red target alternating between a central home target and peripheral target locations in the visually-guided eye-hand task. For each trial, the home target, which was placed at a fixed position, would illuminate for a variable period between 1000 and 2000 ms whereas the peripheral target, which could appear at one of the 30 preset locations, would always be illuminated for 1500 ms. Peripheral targets were presented on three 80° arcs placed 10 cm, 15 cm, and 20 cm from the fixation target (Figure II.5). Participants were asked to look at and touch the illuminated targets as accurately as they could.
II.8.2. Rhythmical tasks

II.8.2.1. Saccade-only self-paced tasks

Self-paced tasks examined the ability to voluntarily initiate saccades and disengage from constantly illuminated targets (Winograd-Gurvich et al., 2003). Participants were given two blocks of trials, first a horizontal block and then a vertical block. Both blocks began with targets appearing at random locations 14 times as a calibration check and then two targets would simultaneously and continuously be illuminated for 30 seconds (s) at 10° left and right of the centre of the screen in the horizontal block and 10° above and below the centre point in the vertical block (Figure II.6). In these tasks, participants were asked to fixate the two targets alternately in a fast and accurate manner.

![Figure II.6](image)

**Figure II.6** Self-paced tasks. Screen display for (A) the horizontal and (B) the vertical trial blocks are shown. The red dotted arrows indicate the directions of saccadic and/or hand responses.

II.8.2.2. Combined eye-hand self-paced tasks

In the combined eye-hand self-paced tasks, participants were presented with two 30 s trial blocks, a horizontal trial block and followed by a vertical trial block. In contrast to the saccade-only tasks, the two fixation targets in the eye-hand tasks were placed at 10 cm to the left and right of the screen’s midpoint in the horizontal block and 10 cm above and below the midpoint.
in the vertical block. The visual angle between consecutive targets were typically $9.5^\circ - 10.2^\circ$ from the recorded eye depending on the distance between subject’s head and the LCD screen (typically 56 cm – 60 cm). Participants were instructed to look and touch the two concurrent illuminated targets alternately at their fastest speed for 30 s.

II.8.2.3. **Saccade-only temporally-cued (predictive) tasks**

Predictive saccades (generated in anticipation of a regularly alternating target), are known to occur in healthy controls after consecutive trials of target alternating at a constant rate (inter-stimulus interval) between two peripheral locations (Crawford et al., 1989; Smit & Van Gisbergen, 1989). Such predictive behaviour has been shown to peak at an inter-stimulus (ISI) of 625 ms and diminish in trials with longer ISIs (Isotalo et al., 2005; Lasker et al., 2006; Ventre et al., 1992). As a compromise between the peak ISI for predictive saccades and known longer saccadic latency in HD (Tian et al., 1991), an ISI of 750 ms (0.67 Hz) was chosen as the shortest ISI in this study. Three other ISIs selected were: 1000 ms (0.5 Hz), 1400 ms (0.36 Hz), and 2050 ms (0.24 Hz).

Four trial blocks were presented in a pre-determined randomised order (ISI: 1000 ms, 2050 ms, 750 ms, 1400 ms), generated from a square matrix, to protect against subjects predicting the ISI sequence. Each trial block began with a random phase and immediately followed by a predictable phase. In the random phase, targets (one at a time) would appear at random locations and intervals on the screen for 17 times. There were then 40 trials in the predictable phase, in which targets would appear alternately at two fixed target locations ($\pm 10^\circ$ target positions) on the screen (Figure II.7). In all trial blocks, participants were asked to keep their eyes to the fixation target as accurately as possible.

![Figure II.7](image.png)  
**Figure II.7**  
**Trial and timing sequences in the temporally-cued tasks.** ISI indicates the time interval (750 ms, 1000 ms, 1400 ms or 2050 ms) between the two alternating targets.
II.8.2.4. Temporally-cued (predictive) eye-hand tasks

Participants were presented with four cued trial blocks similar to the saccade-only temporally-cued tasks. The four cued trial blocks were presented in a pre-determined randomized order (ISI: 1000 ms, 2050 ms, 750 ms, 1400 ms). All four cued tasks began with a random phase, consisting of 17 reflexive trials, followed by a predictable phase that contained 40 temporally-cued trials. The temporally-cued trials comprised of a target alternating at a constant ISI between two fixed positions, ±10 cm from the centre. These targets were typically 9.5° – 10.2° from the recorded eye depending on the distance between participant’s head and the LCD screen (typically 56 cm – 60 cm). Participants were given the instruction to look and touch the targets on the screen as precisely as they could.

II.8.3. Complex movement tasks

In this study, three tasks – delayed, memory-guided, and anti-saccade – were applied to evaluate the control of complex movements. Participants were presented with all three tasks in saccade-only assessment. Only the delayed task was presented for eye-hand coordination assessment because of time constraints.

II.8.3.1. Saccade-only delayed task

A delayed saccade task evaluates the ability to initiate a saccade to a peripheral target only after a certain period of delay, when a cue is given (Curtis & D'Esposito, 2006; Everling & Fischer, 1998; Lueck et al., 1992). There was one block of 38 individual trials in the saccade-only delayed task. The trial block began with the illumination of a fixation target at 0° position. A fixation target was illuminated for a period ranging from 3100 to 3500 ms. A peripheral target would then appear at either ±5°, ±10° or ±15° horizontally from the fixation target, 600 ms before fixation target offset. Participants were asked to withhold a saccade to the peripheral target until after the fixation target was extinguished, which was accompanied by a sound cue (Figure II.8). The position of the peripheral target in the previous trial became the fixation target position for the next trial.

II.8.3.2 Combined eye-hand movements delayed task

This task was an adaptation of the saccade-only delayed task. Similarly, each participant performed a block of 38 individual trials. The task followed the same trial and timing sequences as the saccade-only delayed task except that the initial fixation target was always located at the centre of the LCD screen and peripheral targets would appear at 5 cm, 10 cm or 15 cm to the left or right of that central fixation target. Participants were asked to withhold both eye and
hand responses to the peripheral target until the fixation target was extinguished and a sound cue was given.

Figure II.8 The delayed task. Screen transitions and timing sequences in a delayed task trial block are shown. The red dotted arrow indicates the direction in which a correct saccadic response (saccade-only delayed task) or eye-hand response (combined eye-hand delayed task) should be made.

II.8.3.3. Memory-guided task

The ability to integrate sensorimotor function and working memory and attention function, which is a key process in the generation of memory-guided saccade, is compromised in diseases associated with basal ganglia and frontal lobe pathology (Keedy et al., 2006; McDowell et al., 2001). A memory-guided task involves the suppression of a saccade to a briefly-flashed peripheral target and then directing a saccade to that remembered location only after a period of delay.

Two trial blocks were presented to each participant. Each block consisted of 18 individual memory-guided saccade trials. A trial block would begin with a fixation target at 0° position and a peripheral target would flash briefly (400 ms) at 5°, 10° or 15° horizontally from that fixation target. The offset of the fixation target, accompanied by a sound cue, occurred after a delay of 1500 ms to 2500 ms. Participants were told to withhold a saccade to the briefly-flashed peripheral target and only to direct a saccade to that remembered position (position of the briefly-flashed target) when the fixation target was extinguished. The briefly-flashed peripheral target then reappeared on the screen 3150 ms after the offset of the fixation target and became the fixation target for the next trial (Figure II.9).
II.8.3.4. Anti-saccade task

The anti-saccade task, introduced by Hallett (1978), involves the decoupling of stimulus encoding and saccadic response selection (Everling & Fischer, 1998; Everling & Munoz, 2000) and is a widely-used behavioural task in saccade assessment (Munoz & Everling, 2004). Participants performed two blocks of trials, each consisting of 36 trials of anti-saccade. Each trial began with a fixation target at 0° position that was illuminated for a period ranging from 1500 ms to 2500 ms. A green peripheral target would then appear at ±5°, ±10° or ±15° horizontally from the central fixation target for 1500 ms. Participants were instructed to look at the mirror position (i.e. in the opposite direction) of that green target (Figure II.10).

Figure II.10  Screen transitions and timing sequences in the anti-saccade task. A correct response (red dotted arrow) is illustrated in ‘A’ and an incorrect response (green dotted arrow) in ‘B’.
II.9. Analysis

II.9.1. Cognitive status classification

The cognitive status – normal, mild cognitive impairment (MCI) or dementia – of HD participants was determined from the neuropsychological test battery and relevant items in the UHDRS (functional assessment scale, independence scale, and functional capacity). Criteria for mild cognitive impairment (MCI) followed that described for Parkinson’s disease by Dalrymple-Alford et al. (2011) and Litvan et al. (2012), with a requirement of two measures at below or equivalent -1.5SD of norms within a single domain. Dementia criteria followed that of Peavy et al. (2010), who defined HD dementia as having deficits in at least two areas of cognition (not limited to memory deficits) in the context of impaired everyday function, as determined using the UHDRS Functional Independence Scale.

II.9.2. Scoring system for cognitive measures

The raw scores of each test in the neuropsychological test battery were converted to a standardised z-score using test-specific norms. Domain-specific scores were the mean aggregated scores of component tests within each cognitive domain and the mean aggregated scores of all six cognitive domain determined the global cognitive z-score. MoCA scores were adjusted to participants’ education level (Nasreddine et al., 2005). The three cognitive tests in the UHDRS cognitive component were also part of the neuropsychological test battery so the mean aggregated score of these tests was used as the UHDRS cognitive score for both the HD and control groups.

II.9.3. Saccade detection and measuring techniques

All eye movements were measured individually via a semi-automatic process using the Saccade Analysis, Measurement, and Research Application (SAMARA) software, developed in-house at the NZBRI for measuring eye movement responses. The automatic saccade detection algorithm searched forward in time for any movement with a minimum velocity of 150 deg/s in the horizontal-only (1D) task and 100 deg/s in the 2D task. It then searched backwards for the first zero-crossing prior to that, which was deemed as the onset of a saccade. The system would continue to search forward and when the horizontal velocity dropped below a 5 deg/s threshold, this marked the end of a primary saccade. All saccades detected through the automated system were verified by the operator prior to being accepted for further analysis. Eye movements made towards to the left and to the right were represented as negative and positive respectively on the y-axis while upward and downward movements were positive and
negative on the y-axis of the eye movement trace. For all saccadic tasks, except the anti-saccade task, saccades that were opposite to the direction of a stimulus were excluded from the data pool.

The SAMARA software allowed the use of three cursors to mark three different time points of an eye movement response. In any given eye movement response, the onset of a response was denoted with Cursor 1 (green) and the end of the primary eye movement response was represented with Cursor 2 (blue) while Cursor 3 (maroon) demarcated the final fixation position of the eye (Figure II.11).

![Figure II.11 Measuring saccades in the SAMARA software.](image)

II.9.4. Visually-guided reflexive tasks

A reflexive saccade is defined as a ‘reactive’ eye movement made in response to randomly appearing visual targets. The time required for a visual stimulus to be perceived and processed by the visual afferent system and the onset of a saccade is estimated to be around 80 ms (Fischer et al., 1995). Therefore, any eye movement responses with latency less than 80 ms or greater than 1000 ms were excluded from the analysis as they were regarded as either an anticipatory saccade or a non target-directed eye movement. There are considerable variations in terms of maximal saccadic velocity for healthy controls, which typically range from 500 deg/s to 1000 deg/s (Baloh et al., 1975a; Baloh et al., 1975b; Boghen et al., 1974; Wright & Ward, 2008). Given that saccadic amplitude in any given tasks in this study was less than 30˚, any eye movement responses with maximal velocity greater than 810 deg/sec were removed from the data pool. Saccades were not measured if a blink occurred: (1) immediately before target onset; (2) in the period from target onset to saccade initiation; or (3) during a saccade.
The principal saccadic parameters measured in this task were: (1) saccadic latency; (2) maximal velocity; (3) primary gain; and (4) saccade count. Saccadic latency, expressed in milliseconds (ms), was defined as the delay between target onset and saccade initiation in all three types of reflexive stimuli (‘gap’, ‘step’, and ‘overlap’) (Figure II.12). The maximal speed attained in a saccadic response (peak saccadic velocity) was measured in degree per second (deg/s). Primary saccade amplitude was the distance covered (measured in degrees) by the primary saccade and was measured relative to the position of the fixation target (Figure II.12). Primary gain was the ratio of primary saccade amplitude over amplitude of the target displacement. Saccade count, defined as the number of saccades occurring between the first and last cursors, was a measure of how many saccades (primary plus corrective) made to reach the target. Upon the detection of a primary saccade, the automated system used a lower threshold (1D task: 30 deg/s; 2D task: 50 deg/s) to detect corrective saccades, which usually have a peak velocity of less than 150 deg/s. The rationale for the higher threshold for primary saccade detection was to prevent the automated saccade detection algorithm for falsely detecting small fixation saccades (i.e. non target-directed saccades) during fixation periods.

**Figure II.12**  An eye trace from the reflexive 1D task. Three types of reflexive stimuli (‘step’, ‘overlap’, and ‘gap’) are shown. The red line indicates target positions and the dark blue trace, position of the eye. The green cursor indicates the onset of primary saccade. Primary saccade amplitude, marked by a light blue cursor, is the distance made in the primary saccade and final amplitude, marked by a maroon cursor, is the distance attained in the final saccade. As illustrated, saccadic latency in the ‘gap’ stimulus is visibly the shortest and followed by a ‘step’ stimulus and an ‘overlap’ stimulus.

**II.9.4.1. Express saccades**

In ‘gap’ stimuli of the reflexive task, there is a time delay between fixation target offset and peripheral target onset. The distribution of saccadic reaction time is often described as bi-modal or tri-modal, with peaks occurring first at 100 ms after target onset, secondly at around 150 ms, and some have reported another peak at much longer latencies (Fischer et al., 1993a; Fischer & Boch, 1983; Fischer & Ramsperger, 1984; Fischer et al., 1993b; Hamm et al., 2010). The term ‘express saccades’ (saccades with very short latencies) has been used to describe the sub-population of saccades occurring at the latency around the first peak in the distribution. One
study defined express saccades as those with a latency of 90 ms to 110 ms (Wenban-Smith & Findlay, 1991) but a majority of studies use criteria of saccadic latency in the range of 90 ms to 150 ms (Clementz, 1996; Currie et al., 1993; Fischer et al., 1993b; Hamm et al., 2010).

Given that 100% of saccades with directional errors in a pro-saccadic ‘gap’ task have been found to have a latency less than 100 ms (Fischer & Boch, 1983; Fischer et al., 1993b) and saccades with a latency shorter than 75 ms were associated with greater than 20% error in amplitude (Fischer & Ramsperger, 1984), saccades with a latency less than 90 ms have been suggested to be anticipatory in nature and not under the influence of visual target. Fischer et al. (1997) reported that fast regular saccades in a pro-saccade task occurred in the range of 135 ms to 179 ms. Taking these factors into consideration, a criterion of 90 ms to 135 ms was used in this study to ensure the inclusion of express saccades and exclusion of anticipatory saccades.

II.9.4.2. Saccadic main sequence

A main sequence analysis was performed only for peak velocity achieved in response to ‘step’ stimuli in the horizontal reflexive saccade task, as peak velocity varies with cognitive involvement in a task (Chen et al., 2013; Van Gelder et al., 1997). As the maximal saccadic velocities calculated for patient S5 were unrealistically fast in comparison to other HD patients with similar clinical severity (refer Figure IV.4 and Figure IV.5), it was deemed that patient S5 was an outlier and thus data from this patient was removed in this analysis. A negative exponential curve function \[ \text{Saccadic velocity} \ (\text{Amp}) = \text{Vmax} \ (1 - e^{-\text{Amp}/\text{C}}) \] (Balogh et al., 1975b) was fitted to the data of all participants. ‘Vmax’ was the maximal saccadic velocity of which the main sequence function saturates, ‘Amp’ was the saccadic amplitude in degrees, and ‘C’ was a constant. Subject-specific maximal saccadic velocities \( \text{Vmax} \) were then fitted to a linear mixed-effect model to establish group differences and relative change after 12 months.

II.9.5. Rhythmical tasks

II.9.5.1 Self-paced tasks

Manual counting was used to determine the number of self-initiated saccades in the self-paced tasks. A saccade made from the vicinity of one target towards the opposite target was considered as one self-paced movement. Self-paced saccades were only considered to be complete if the primary amplitude of a saccade was greater than 50 percent of the total distance between the two targets. That is, a saccade must have at least crossed the centre line (x) on the eye trace (Figure II.13). Saccades that failed to meet the criterion would not contribute to the final tally.
II.9.5.2. Temporally-cued (predictive) tasks

Healthy controls are capable of generating predictive saccades when the target alternates between two fixed positions at a temporally predictable manner (Crawford et al., 1989; Isotalo et al., 2005; Zorn et al., 2007). That is, these saccades may coincide with or even occur prior to the onset of the next target (McDowell et al., 1996). Each trial block, which consisted of a random phase and a predictable phase, was further divided into three sub-phases (Phase I, Phase II, and Phase III). The random phase (i.e. the first 17 trials of a trial block with stimuli appearing at random locations and time intervals) was labelled as Phase I. Phase II consisted of the first 30 trials of the predictable phase (i.e. the stimulus alternating between two fixed positions at a constant ISI) and Phase III, the last 10 predictable trials (Figure II.14).

Any saccades in Phase I with a latency less than 80 ms were excluded from the data. Saccades with latencies greater than 1000 ms in this phase were considered outliers and were also removed from further analysis. Accepted saccades provided the mean saccadic latency in the random phase. Due to the predictable nature of stimuli in Phase II and III, saccades with a latency less than 80 ms were considered as valid responses and were included in the data. In Phase II and Phase III, a saccade was only accepted as a valid response if, relative to the target amplitude, the primary gain was greater than 0.2 and not followed by a corrective saccade in the direction opposite of the impending target (Figure II.14).

Saccadic latencies were defined as ‘positive’ if they occurred after target onset and ‘negative’ if they preceded target onset. All participants completed all four ISI trials blocks except for one stage 4 HD patient (S08) who was unable to perform some of the trial blocks. Data from this patient was consequently excluded from analysis at both assessment points.

Figure II.13 An eye trace from the self-paced task. The red lines indicate stimuli positions (-10° and +10° concurrent targets) and the dark blue trace, eye position. A saccade must have at least crossed target position 0°, labelled as ‘x’, to be considered a self-paced movement.
Saccadic latencies in the predictable phase decline rapidly over the first few trials until saccades are initiated on the basis of internal prediction of target onset (Ross & Ross, 1987). An exponential decay function \[ \text{Saccadic latency} (n) = C + A \times e^{(B \times n)} \] was fitted to the group-specific mean latencies of each trial in the predictable phase (Phase II and Phase III) to determine the group-specific learning curves in all four ISIs for the control and HD groups. ‘A’ represents the mean latency at the start of the predictable phase. ‘B’ denotes the decay rate, i.e. the rate of change in the shortening of saccadic latency. ‘C’ is the plateau (final saccadic latency in a trial block) and ‘n’, the trial number in each trial block. Ideally, analysis of the predictable phase is best assessed by examining the exponential decay function of saccade latencies in the predictable phase in each subject. However, an exponential decay function could not be fitted to the data of 18 HD patients. Therefore, saccades in the last 10 predictable trials (Phase III) were used instead for the analysis of the predictable phase as it was assumed that all participants had established a stable predictive pattern at this stage. The mean latency and proportion of predictive saccades (expressed in percentages) in the last 10 predictable trials of all four ISIs were calculated.

II.9.6. Complex movement tasks

II.9.6.1. Delayed task

Saccadic responses in the delayed task were labelled as ‘correct’ or ‘disinhibited’ based on the latency of responses (Figure II.15). As there was a 600 ms time delay between peripheral target onset and fixation target offset, only responses made more than 90 ms after fixation target offset were classified as ‘correct’. Disinhibited responses were defined as responses made between 90 ms and 690 ms after peripheral target onset. The rate of disinhibited responses was
calculated as a percentage of the total number of responses made (correct and disinhibited). Saccadic latency of correct responses was measured from fixation target offset and of disinhibited responses, from peripheral target onset.

**Figure II.15** An eye trace from the delayed task. The red line indicates the positions of stimuli and the dark blue trace, the eye position. In the eye trace above, there are two correct responses (A) and a disinhibited response (B) that was later corrected (C). Cursor 1 (green) marks the onset of a primary saccade. Cursor 2 (light blue) denotes the end of a primary saccade and Cursor 3 (maroon), final position of the eye.

### II.9.6.2. Memory-guided task

Responses in this task were also categorised as ‘correct’ or ‘disinhibited’. They were considered ‘correct’ if they were initiated at least 80 ms after fixation target offset but prior to the reappearance of the briefly-flashed target (i.e. the fixation target for the next trial) (Figure II.16). Disinhibited responses were those made: (1) immediately towards the briefly-flashed peripheral target; (2) during the time delay, i.e. after the offset of briefly-flashed peripheral target but prior to fixation target offset; and (3) less than 80 ms after fixation target offset (Figure II.16). The proportion of disinhibited responses was calculated as a percentage of the total number of responses made (correct and disinhibited). Saccadic latency of correct responses was measured from fixation target offset.

**Figure II.16** An eye trace from the memory-guided task. The red lines indicate the positions of the stimuli and the dark blue trace, position of the eye. The first response is a disinhibited response (A) that was later ‘corrected’ (B) and the second, a correct response (C). Cursor 1 (green) marks the onset of the primary saccade and Cursor 2 (light blue), the end of the primary saccade. The onset of the corrective saccade is marked by Cursor 3 (maroon) and Cursor 4 (pink), final position of the eye for that trial.
II.9.6.3. **Anti-saccade task**

Responses made in the opposite direction to the green peripheral targets were classified as ‘correct’ and those towards the target, ‘disinhibited’. Disinhibited responses were further classified as ‘corrected’, if a corrective saccade, i.e. a saccade in the opposite direction to the green peripheral target, was made immediately after a disinhibited response, and ‘uncorrected’, if otherwise (Figure II.17). The proportion of disinhibited responses was calculated as a percentage of the total number of responses (correct and disinhibited) made. The proportion of corrected pro-saccade errors was calculated as a percentage of the total number of disinhibited responses (corrected and uncorrected) made. Latencies for correct and disinhibited responses were calculated as the time from green peripheral target onset to saccade initiation. Latency for correcting a disinhibited response (pro-saccade correction) was the time between the end of a disinhibited saccade and the onset of the first corrective saccade to that disinhibited saccade.

![Figure II.17 An eye trace from the anti-saccade task.](image)

*Figure II.17 An eye trace from the anti-saccade task.* The red lines indicate positions of fixation targets and the green, positions of green peripheral targets. The black trace denotes position of the eye. In the eye trace above, a disinhibited response (A) that was corrected (B) and two correct responses (C) are shown. The onset and the end of the primary saccade are marked by Cursor 1 (green) and Cursor 2 (light blue) respectively. The latency for correcting a disinhibited response is defined as the time between Cursor 2 (light blue) and Cursor 3 (maroon). Cursor 4 (pink) marks final position of the eye for that trial.

II.9.7. **Hand movement detection and measuring techniques**

Hand movement data were measured offline using a fully-automated movement detection system which was capable of firstly, matching the movement data to the stimuli data and secondly searching forward and backward in time for hand movements corresponding to the stimulus targets. A signal processing filter, a low-pass Butterworth filter, with a filter order of 8 and a cut-off frequency of 10 Hz was applied in both directions (forward and backward) to the movement data to reduce high-frequency noise in the recorded data. Hand velocity was defined as the absolute rate of change in hand distance travelled in the three dimensions (x, y, and z) combined over time. The time point when a velocity exceeded two percent of its peak velocity was determined as the onset of a hand movement. Hand latency was calculated from
stimulus target onset to the initiation of the matched hand movement. Several other criteria were used to minimize false detections (Figure II.18): (1) Hand movements identified had to have a latency that fell within the range of latencies specified for the given eye-hand task (Table II.4); (2) The direction of the detected movement was required to match the stimulus target direction; and (3) The movement gain, a ratio of movement amplitude over stimulus target amplitude, had to be greater than 0.2, i.e. movement amplitude had to be greater than 20% of the stimulus amplitude. Hand movements that satisfied all three criteria were accepted as valid hand responses. If there were multiple hand movements within the allowed latencies that met the required criteria, the hand movement with the largest amplitude was chosen.

Figure II.18  The automated hand movement response selection process

Table II.4  Latency ranges used for selecting valid hand responses in the movement data

<table>
<thead>
<tr>
<th>Eye-hand task</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimum</td>
</tr>
<tr>
<td>Visually-guided</td>
<td></td>
</tr>
<tr>
<td>Reaching</td>
<td>120</td>
</tr>
<tr>
<td>Return</td>
<td>- 1000</td>
</tr>
<tr>
<td>Temporally-cued</td>
<td></td>
</tr>
<tr>
<td>Random phase</td>
<td>120</td>
</tr>
<tr>
<td>Predictable phase</td>
<td>- 1200</td>
</tr>
<tr>
<td>Delayed</td>
<td>- 600</td>
</tr>
</tbody>
</table>
II.9.8. Hand movement in the visually-guided reflexive task

As reported by Schmidt et al. (2005), simple motor movements usually have a reaction time that ranges from 130 ms to more than 200 ms but a minimum reaction time of 100 ms is typically used as the conservative criterion for a reactive motor movement. There were two distinct hand responses in the visually-guided reflexive task, reaching (to randomly appearing peripheral targets) and return (to the home target) movements. After taking both the conservative criterion and the typical range of reaction time for simple motor movements, a latency of 120 ms was used as the minimum cut-off for a reactive hand response in the reflexive task and any movements with a latency of shorter than 120 ms were considered as anticipatory in nature. Anticipatory movement was accepted as a valid response only in the return movement because of the predictable nature of target location and onset for the home target. All anticipatory-type reaching movements were removed from the final data pool. The eye-hand latency interval was calculated by subtracting the mean eye latency (across trials) from the mean hand latency (across trials) of the corresponding movement for each subject. A positive latency difference indicates that the eye was leading the hand while for a negative difference, the hand led the eye.

II.9.9. Hand movement in the self-paced tasks

The number of self-initiated hand movements made in the self-paced tasks was manually counted offline. A movement made from one target to the opposite target was considered as one self-paced movement. A self-paced movement was only considered complete if its amplitude was greater than 50 percent (by visual inspection of offline data) of the movement amplitude of the preceding hand movement. The total number of self-paced hand movements for each subject was tallied for further analysis.

II.9.10. Hand responses in the temporally-cued tasks

Each trial block in the temporally-cued tasks was divided into two phases, the random phase that consisted of 17 trials of stimuli appearing at random locations and time intervals, and a predictable phase that contained 40 trials of stimuli alternating between two fixed positions and at a constant ISI. All anticipatory hand movements in the random phase (i.e. movements with latencies shorter than 120 ms) were excluded. However, due to the predictive nature of stimulus targets in the predictable phase, all reactive and anticipatory movements were deemed as valid responses. Mean hand latency was calculated for the random phase and also the last 20 trials of the predictable phase. The last 20 predictable trials, instead of the last 10 (as in the saccade-only task), were used because based on the group-level data, participants were found to already
have expressed a predictive pattern at this stage. For each subject, eye-hand latency interval was computed by subtracting mean hand latency (across trials) from mean eye latency (across trials) of the corresponding phases in the four ISI trial blocks.

II.9.11. Disinhibited hand responses in the delayed task

Hand responses in the delayed task were categorized as ‘correct’ or disinhibited’ depending on their latencies. Hand latency was calculated from fixation target offset. A disinhibited response was defined as a hand response with a latency of shorter than 120 ms while a correct response must have a latency of longer than 120 ms and must also not be preceded by a disinhibited response. The proportion of disinhibited hand responses was calculated as a percentage of the total of hand responses made (correct and disinhibited).

II.9.12. Statistical analysis

Data analysis was performed in the R software environment for statistical computing and graphics (R Development Core Team, 2012). Statistical data were plotted with the ggplot2 plotting system (Wickham, 2009).

The package lme4 (Bates et al., 2014a) was used for fitting generalized linear models (Bolker et al., 2009) for binomially distributed data and the package nlme (Pinheiro et al., 2014), for fitting linear mixed-effects models (Gelman & Hill, 2007) for continuous and discrete variables. These models take into account the correlated measurements within a participant when assessing the differences between groups and changes over time. Heteroscedasticity (i.e. when the variance of the dependent variables is not constant across the range of a predictor variable) between groups and tasks was allowed for in the models as required.

The overall effect of multi-levelled factors such as disease stage (three levels) and or task factors was assessed using linear mixed-effects models with ordered factors. Likelihood ratio tests were used to determine group and disease stage effects on binomially distributed data, for example the proportions of disinhibited saccade in complex volitional saccade tasks and the proportions of corrected pro-saccade error in the anti-saccade task. The likelihood ratio test, which compares the fit of two models, the null and the alternative models, uses likelihood ratios to calculate a critical value, and hence a $p$ value, to decide whether to reject the null model and to accept the alternative model. Results yielding a $p$ value of less than 0.05 is considered as statistically significant.
Correlation coefficients were used to determine the strength of the linear associations between two variables. Bootstrapping procedures (Efron, 1979), a statistical method involving random sampling with replacement from a dataset to measure the variability of estimates, were used to determine the statistical significance of the differences between two $r^2$ values (coefficients of determination for correlation coefficients). During the process of bootstrapping, the random sampling of data with replacement was repeated 1000 times and the resulting distribution of differences between two $r^2$ coefficients gave an indication of the mean difference and a 95% confidence interval (95% CI). In this analysis, a difference was considered statistically significant if the estimated 95% CI of the $R^2$ difference did not contain ‘0.0’.

Cohen’s $d$ was used to report effect sizes for between-group differences. Effect sizes for relative change at 12 month follow-up in the HD group in the three summary tables of Chapter VII (Table VII.1 – 3) were calculated using a modified Cohen’s $d$ formula, $d = t.c*[(2*(1-r))/n]^{0.5}$ (Dunlap et al., 1996), that takes into account the correlation between baseline and 12 month follow-up measurements. ‘$t.c$’ represents the $t$ value of the relative change at 12 month follow-up in the HD group. ‘$r$’ is the correlation coefficient for the relationship between baseline and 12 month follow-up measurements. ‘$n$’ denotes sample size. A transformation of effect sizes is essential when combining the results across independent-groups and of repeated measures designs (Morris & DeShon, 2002). For repeated measures, effect sizes must take into consideration the change over time in a measure relative to the combined sample distribution (Dunlap et al., 1996) of the control and HD groups, and hence the application of the aforementioned modified Cohen’s $d$ formula.

Due to the exploratory nature of this research, there were numerous statistical tests performed. The focus was on estimating effect sizes (both absolute and standardised) and hence, family-wise error corrections were not performed. However, if focusing on single significant results rather than the overall picture, then the results should be confirmed in future research to gain confidence that they are not just due to sampling variability.
Chapter III

Cognitive, motor, and behavioural functions

III.1. Background

HD is characterized by involuntary hyperkinetic movements, cognitive impairment, and behavioural disorders. Cognitive impairment, which may be evident even in gene-positive individuals yet to be clinically diagnosed (Blackmore et al., 1995; Duff et al., 2010; Kirkwood et al., 1999; Peavy et al., 2010), is progressive in nature and a contributing factor in the loss of everyday function (Bates et al., 2002). Subtle cognitive impairment can be overlooked by clinicians during routine follow-up (Chodosh et al., 2004), indicating the need for easily administered and yet robust tools to detect cognitive changes in HD. Comprehensive neuropsychological testing is necessary to establish cognitive status definitively. However, neuropsychological batteries are time-consuming and brief cognitive screening tools such as the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA)
are commonly used in clinical settings and in a broad range of conditions. The Unified Huntington’s Disease Rating Scale (UHDRS), a standard assessment tool for HD, also includes a brief cognitive component.

The MMSE (Folstein et al., 1975) comprises eleven questions spanning five aspects of cognitive function: executive function, language, memory function, visuospatial ability, and orientation. It has good inter-rater, test and re-test reliability in differentiating cognitive status in dementia syndromes (Tombaugh & McIntyre, 1992) and other disorders featuring cognitive impairment (Godefroy et al., 2011a). Nevertheless, it is influenced by demographic factors such as age, education, and cultural background (Scazufca et al., 2009; Tombaugh & McIntyre, 1992; Wind et al., 1997). The MoCA places greater emphasis than the MMSE on naming, attention, abstraction, and delayed recall, functions that are most likely to be compromised in the earlier stages of cognitive impairment. Unlike the MMSE, it compensates for education level (Nasreddine et al., 2005). Both the MMSE and MoCA have been employed as measures of cognitive performance in manifest HD patients (Bezdicek et al., 2013; Gluhm et al., 2013; Mickes et al., 2010; Videnovic et al., 2010). The MoCA was found to have higher sensitivity, without losing specificity, compared to the MMSE in identifying those with cognitive impairment in HD (Mickes et al., 2010). Furthermore, Bezdicek et al. (2013) demonstrated a strong correlation between MoCA scores and comprehensive neuropsychological assessment scores in manifest HD patients. The UHDRS cognitive component (Huntington Study Group, 1996) includes three tests of executive function – letter fluency test, Symbol Digit Modalities test, and Stroop test; which can be used with corrected norms to attenuate the impact of various demographic variables (O’Bryant & O’Jile, 2004; Sheridan et al., 2006).

The progressive nature of HD means that any cognitive assessments should be useful longitudinally. HD patients are routinely followed up at clinics at 6 month and 12 month intervals thus it is preferable that brief cognitive assessment tools are sensitive to changes even over relatively short time intervals. Effective yet brief cognitive tools would enable easier detection of cognitive changes in HD patients in clinic settings, compared to time-consuming comprehensive cognitive assessment. They would also assist health care providers in designing treatment and care plans aimed at improving patient’s quality of life. MMSE and MoCA have been extensively evaluated in previous cross-sectional HD studies (Glhum et al., 2013; Mickes et al., 2010; Videnovic et al., 2010) but there is a lack of longitudinal data on the utility of these brief cognitive tests, compared to the UHDRS cognitive assessment, in monitoring cognitive changes in HD patients. Therefore the objective of this study was to examine and compare the
utility of two widely used brief cognitive tests (MMSE and MoCA) and the UHDRS cognitive component, relative to a comprehensive neuropsychological test battery for monitoring cognitive changes in HD patients over an interval of 12 months. Such a direct comparison has not been previously reported.

In addition, this study also examine the longitudinal changes in behavioural aspect of HD by using commonly-used neuropsychiatric measures such as Beck Depression Inventory (BDI), BAI (Beck Anxiety Inventory), AES (Apathy Evaluation Scale), and the UHDRS behavioural component.

III.2. Methods

Please refer to Chapter II: Methods for a detailed description of study methods.

III.3. Results

III.3.1. Demographics at 12 month

Invitations were sent out to all study subjects 10 months after their initial visit, asking them to return for a follow-up assessment after 12 months. The HD group had a 100% retention rate while the controls recorded a 9% dropout rate (n=2). The two control subjects declined due to non-health related reasons. Table III.1 summarizes the demographics at 12 month follow-up.

<table>
<thead>
<tr>
<th>Demographic changes of control and HD groups</th>
<th>Control group</th>
<th>HD group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean (SD)</td>
<td>50 (16)</td>
<td>51 (15)</td>
</tr>
<tr>
<td>Follow-up interval (weeks) Mean (SD)</td>
<td>53 (3)</td>
<td>54 (4)</td>
</tr>
<tr>
<td>Gender (n)</td>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>12</td>
</tr>
<tr>
<td>Ethnicity (n)</td>
<td>NZ European</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>NZ Maori</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>South African Indian</td>
<td>0</td>
</tr>
<tr>
<td>Retention rate (%)</td>
<td>91% (n= 20)</td>
<td>100% (n = 22)</td>
</tr>
</tbody>
</table>

The disease stages of the Huntington’s disease patients ranged from stage 1 to stage 4 as determined through the scores from the FRS of the UHDRS. At baseline, there were eight patients in stage 1, eight in stage 2, five in stage 3, and one having stage 4 disease. Nine patients deteriorated in disease status at 12 month follow-up: three patients progressed from stage 1 to stage 2, four from stage 2 to stage 3, one from stage 3 to stage 4, and one from stage 2 to stage 4. However, one patient showed an improvement from stage 3 to stage 2.
III.3.2. Cognitive function

At baseline, six HD patients were classified as having normal cognition, 10 met criteria for MCI, and six had dementia (Peavy et al., 2010). All 22 controls had normal cognition. The HD group showed significantly lower scores in global cognition from the test battery and brief cognitive tests compared to controls both at baseline and at 12 month follow-up. The effect size at baseline in global cognition was $d = 2.4$ whereas in the brief cognitive tests, it ranged from $d = 1.1$ in the MMSE with ‘World’ spelled backwards to $d = 2.4$ in the UHDRS cognitive component (Figure III.1A; Table III.2). In terms of domain-specific scores, the HD group had significantly lower scores compared to controls across all cognitive domains and the effect sizes at baseline ranged from the smallest ($d = 1.4$) in the language domain to the largest ($d = 2.7$) in the executive function domain (Figure III.1B; Table III.2). Individual component test scores at

---

**Figure III.1** Change in cognitive scores over 12 months. Baseline and 12 month scores for the control and HD groups in: (A) the five cognitive measures; and (B) the six cognitive domains within the global assessment. LMEM-estimated group means, and scores for individual subjects, are shown.
baseline and 12 month follow-up and the brief cognitive tests are detailed in Figure S1 and Table S1 of the Appendix respectively.

There was an overall pattern of improvement in the control group across all cognitive tests after 12 months. In contrast, the HD group showed minimal change in global cognitive z-score and a general decline across all brief cognitive tests scores after 12 months, which was significant for the UHDRS cognitive score and MMSE (with ‘World’ spelled backwards) (Figure III.1A; Table III.2). The control group showed an improvement at 12 month in most cognitive domains, excepting the executive function and visuospatial domains. In contrast, the HD group demonstrated a decline in the executive function domain but an increase in language domain z-score 12 months later. There were no significant changes in the other cognitive domains in the HD group (Figure III.1B; Figure S1). However, relative to the change in controls, there was a significant decline in global cognition, executive function domain score, learning and memory domain score, and MMSE with ‘World’ spelled backwards in the HD group after 12 months (Table III.2).

III.3.3. Behavioural and motor functions

![Figure III.2](image-url)  
**Figure III.2**  
Change in neuropsychiatric measures and UHDRS motor scores over 12 months. Baseline and 12 month follow-up scores for control and HD groups in: (A) the BAI, BDI, and AES; and for the HD group only in (B) the UHDRS motor and behavioural components. LMEM-estimated group means, and scores for individual subjects, are shown.

Similarly, linear mixed-effect models were fitted to the neuropsychiatric measures to determine group differences at baseline and relative change after 12 months. At baseline, the HD group demonstrated poorer mean scores on all behavioural indices when compared to the controls.
The range of scores for the UHDRS motor component at baseline was 11 to 82 points. Although there was an increase in the UHDRS motor component score over time in the HD group, there was no evidence of a change in any of the behavioural indices (Figure III.2; Table III.2). In contrast to the controls, who showed no significant changes, HD group showed a significant drop in their AES scores after 12 months indicating that there was worsening of apathy in HD patients at a group level (Figure III.2; Table III.2).

Table III.2 Scores at baseline, within-group changes and group over time interactions of control and HD groups

<table>
<thead>
<tr>
<th>Measures</th>
<th>Control group</th>
<th>HD group</th>
<th>HD vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean [95%CI]</td>
<td>Change after 12 months Mean [95%CI]</td>
<td>Baseline Mean [95%CI]</td>
</tr>
<tr>
<td>Global cognitive level</td>
<td>0.4 [0.2 – 0.7]</td>
<td>0.2 [0.1 – 0.3], p &lt; 0.001</td>
<td>-1.2 [-1.4 – -0.9], p = 0.8</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.8 [0.4 – 1.2]</td>
<td>0.1 [0.04 – 0.1], p &lt; 0.001</td>
<td>-1.4 [-1.7 – -1.0], p = 0.03</td>
</tr>
<tr>
<td>Working memory &amp; attention</td>
<td>0.2 [-0.1 – 0.5]</td>
<td>0.2 [0.05 – 0.3], p = 0.01</td>
<td>-1.0 [-1.2 – -0.7], p = 0.3</td>
</tr>
<tr>
<td>Processing speed</td>
<td>0.7 [0.3 – 1.1]</td>
<td>0.1 [0.01 – 0.03], p &gt; 0.04</td>
<td>-1.4 [-1.8 – -1.0], p = 0.8</td>
</tr>
<tr>
<td>Learning &amp; memory</td>
<td>0.5 [0.1 – 0.9]</td>
<td>0.6 [0.3 – 0.9], p &lt; 0.001</td>
<td>-1.0 [-1.4 – -0.6], p = 0.8</td>
</tr>
<tr>
<td>Language</td>
<td>0.1 [-0.2 – 0.4]</td>
<td>0.3 [0.1 – 0.6], p = 0.008</td>
<td>-0.9 [-1.2 – -0.6], p = 0.01</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>0.3 [0.0 – 0.6]</td>
<td>0.0 [-0.2 – 0.2], p = 0.8</td>
<td>-1.4 [-1.7 – -1.1], p = 0.5</td>
</tr>
<tr>
<td>UHDRS cognitive score</td>
<td>0.6 [0.2 – 1.0]</td>
<td>0.06 [-0.1 – 0.2], p = 0.5</td>
<td>-1.5 [-1.9 – -1.1], p = 0.048</td>
</tr>
</tbody>
</table>

* UHDRS motor and behavioural components were assessed in the HD group only.

**Baseline and 12 month follow-up SD and ranges for all variables are detailed in the Appendix: Table S1 and score changes after 12 months in individual component tests are shown in the Appendix: Figure S1.

III.3.4. Usefulness of brief cognitive tests for measuring change over time

There are several considerations to take into account when determining which brief cognitive
Chapter III  Cognitive, motor, and behavioural functions

test has greatest utility for measuring cognition over time. This includes how well the score reflects global cognition, whether there is any ceiling effect, and how noisy (variability of score residuals) the score is after taking systematic changes into consideration.

Simple correlations confirmed that the scores of all three brief cognitive screening tests, as judged by their $r$ coefficients, were significantly correlated with the scores of the full neuropsychological test battery at baseline (Figure III.3) and 12 month follow-up (not shown). Bootstrapping procedures confirmed that there were no significant differences between the three brief cognitive screening tests in extent of correlation with global cognition (Table III.3). Thus all brief cognitive tests provided a reasonable cross-sectional measure of global cognition.

![Figure III.3](image)

**Figure III.3**  Correlations between brief cognitive screening tests scores and global cognitive z-scores at baseline. The control group is shown in the top row and the HD group in the bottom row. $r$ [95% CI] and $p$ values are shown.

**Table III.3** Differences in $r^2$ coefficients (coefficients of determination for correlations between full cognitive battery and brief cognitive tests) between the brief cognitive tests

<table>
<thead>
<tr>
<th>Differences in $r^2$ values [95% CI]</th>
<th>MMSE – WORLD</th>
<th>MMSE - Sevens</th>
<th>MoCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>UHDRS cognitive component</td>
<td>0.1 [-0.0 – 0.4]</td>
<td>0.1 [-0.1 – 0.3]</td>
<td>0.0 [-0.2 – 0.2]</td>
</tr>
<tr>
<td>MMSE – WORLD</td>
<td>-</td>
<td>-0.1 [-0.3 – 0.1]</td>
<td>-0.1 [-0.4 – 0.0]</td>
</tr>
<tr>
<td>MMSE - Sevens</td>
<td>-</td>
<td>-</td>
<td>-0.0 [-0.2 – 0.1]</td>
</tr>
</tbody>
</table>

A reliable test would have a low level of score variability over time. To determine the variability of score residuals over time, simple linear models were fitted to the baseline and 12 month
follow-up scores of the global cognition and of brief cognitive tests. The correlations of baseline and 12 month follow-up scores of the different cognitive measures were evaluated by examining the $r$ coefficients of the model fits (Figure III.4).

![Figure III.4](image)

**Figure III.4** Correlations between baseline and 12 month scores of the five cognitive measures. The control group is shown in the top row and the HD group in the bottom row. $r$ [95% CI] and $p$ values are shown.

**Table III.4** Differences in $r^2$ coefficients (coefficients of determination for correlations between baseline and 12 month scores) between the different cognitive measures

<table>
<thead>
<tr>
<th>Differences in $r^2$ coefficients [95% CI]</th>
<th>UHDRS cognitive component</th>
<th>MMSE - WORLD</th>
<th>MMSE - Sevens</th>
<th>MoCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognitive z-score</td>
<td>-0.0 [-0.1 – 0.1]</td>
<td>0.2 [0.0 – 0.4]$^*$</td>
<td>0.2 [0.0 – 0.5]$^*$</td>
<td>0.1 [-0.0 – 0.3]</td>
</tr>
<tr>
<td>UHDRS cognitive component</td>
<td>-</td>
<td>0.2 [0.0 – 0.4]$^*$</td>
<td>0.2 [0.0 – 0.4]$^*$</td>
<td>-0.1 [-0.0 – 0.4]</td>
</tr>
<tr>
<td>MMSE - WORLD</td>
<td>-</td>
<td>-</td>
<td>0.0 [-0.2 – 0.1]</td>
<td>-0.1 [-0.3 – 0.1]</td>
</tr>
<tr>
<td>MMSE - Sevens</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.1 [-0.3 – 0.2]</td>
</tr>
</tbody>
</table>

* The estimated 95% CI of $r^2$ differences contains ‘0.0’, suggesting that the difference in $r^2$ values between the two cognitive measures tested could be considered significant.

In the control group, the range of scores in MMSE and MoCA was narrow due to ceiling effects, presumably contributing to low $r$ values ($r \leq 0.60$). In contrast, the global z-score and UHDRS cognitive score showed greater utility in the control group, with a wider range of values together with small deviations from the linear fit, resulting in high $r$ values. In the HD group the baseline scores were well correlated ($r \geq 0.82$) with 12 month follow-up scores for global cognition and all three brief cognitive tests (Figure III.4). The comprehensive neuropsychological test battery and UHDRS cognitive component, as confirmed by bootstrapping procedures, had smaller deviations from linear fits (i.e. lower level of score variability after 12 months) than the two versions of the MMSE but not the MoCA (Table III.4). This finding indicates that the two
versions of MMSE had higher measurement noise (i.e. greater score variability over time), compared to global cognition and the UHDRS cognitive component after 12 months.

III.4. Discussion

Cognitive decline in HD, has been shown to assume a relatively slow course, especially in early stages of HD (Bachoud-Levi et al., 2001; Snowden et al., 2001). Although MMSE and MoCA have been extensively evaluated in previous cross-sectional HD studies (Gluhm et al., 2013; Mickes et al., 2010; Videnovic et al., 2010), there has been no longitudinal data on the utility of these brief cognitive tests compared to the UHDRS cognitive component. This study attempted to evaluate the usefulness of these two widely-used brief cognitive assessment tools and the UHDRS cognitive component over a 12 month interval by comparing them to a comprehensive neuropsychological test battery. The key findings were: (1) there was no significant change in global cognition, despite the presence of significant decline in the executive function domain in the HD group; (2) relative to the control group, which showed an increase over time in global cognitive z-score and learning and memory domain scores, the HD group demonstrated significantly less change on these scores; and (3) the UHDRS cognitive component performed the best (compared to MMSE and MoCA) as a brief cognitive assessment tool in monitoring cognitive progression in HD over 12 months.

III.4.1. Domain-specific cognitive performance

Overall, the findings of the present study were consistent with other longitudinal studies on pre-manifest and early manifest HD patients wherein, relative to a control group, cognitive changes were evident after 12 months in the HD group (Tabrizi et al., 2010). Similar conclusions were found at 24 months follow-up (Tabrizi et al., 2012). The change in apparent global cognition in the control group is consistent with practice effects, which have been reported previously in healthy controls in longitudinal studies (McCaffrey & Westervelt, 1995; Salthouse & Tucker-Drob, 2008). Practice effects are characteristic of many neuropsychological tests during serial assessments (Goldberg et al., 2015). It is hypothesized that score improvement caused by practice effects do not actually reflect a true enhancement in a person’s ability that is being measured by the neuropsychological test (Calamia et al., 2012; Reeve & Lam, 2007). Practice effects are most apparent in the early phases of repetitive testing, with performance scores tending to plateau on subsequent testing (Collie et al., 2003; Falleti et al., 2006), or after changing to low frequency testing (Bartels et al., 2010).
Several factors are thought to contribute to practice effects, such as reduced anxiety on retesting (Messick & Jungeblut, 1980), increasing familiarity with testing environment (Hausknecht et al., 2007), memory of specific test items (Kulik et al., 1984; McCaffrey et al., 2000), and enhancement of test taking strategies (Sackett et al., 1989). Practice effects, when not taken into consideration, can compromise the validity of a cognitive test or research finding. The main implication of practice effects in clinical trials and clinical practice is that it can lead to incorrect conclusions about cognitive changes over time (Calamia et al., 2012). In clinical trials, it may provide a false impression that a medical intervention is beneficial when the score improvement was in fact attributable to practice effects. In clinical practice, practice effects may mask slow deterioration in cognition during serial assessments, hence giving a false illusion of stability and no change in cognition over time. This may inadvertently lead to incorrect classification of performance and subsequently, the delay in the implementation of useful medical interventions for a patient. Therefore, taking practice effects into account, the statistically significant group-over-time interaction in the global cognitive z-score between HD and control groups likely indicates that the control group had benefited from practice effects, rather than the HD scores declining on the comprehensive neuropsychological battery.

Although practice effects are usually regarded as confounding factors, it is posited that a failure to demonstrate practice effects might be a useful prognostic marker of a patient’s cognition in the future (Duff et al., 2007a). For example, it was found that patients with mild cognitive impairment who had minimal practice effects at one week retesting had higher risk of developing cognitive decline after one year than those with larger practice effects (Duff et al., 2011). Further, practice effects are capable of differentiating longitudinal cognitive changes related to healthy ageing from changes in Alzheimer’s disease (Ivnik et al., 2000). Based on the findings from those studies, it can be inferred that the smaller practice effect-related score improvement in global cognition at 12 month follow-up in the HD group compared to controls may suggest of a concurrent or predictive indicator of cognitive deterioration.

Despite the lack of changes in the HD group in the majority of cognitive domains after 12 months, there was a significant improvement in the language domain. Perhaps, patients with early stages of HD benefited from practice effects at least in this domain, as genuine improvement is unlikely. As reported by Bachoud-Lévi et al. (Bachoud-Levi et al., 2001) in a medium- to long-term longitudinal study on disease progression in early HD, there was a significant retest effect in many neuropsychological tests in HD patients. The significant decline in executive function domain in HD is consistent with previous work that this domain is most
vulnerable to HD (Lawrence et al., 1996), with progressive impairment evident in both pre-manifest (Lemiere et al., 2004) and early stages of HD (Bachoud-Levi et al., 2001; Ho et al., 2003). Atrophy of the caudate nucleus is found in the normal aging process but when compared to healthy controls, it was demonstrated on serial radio-imaging that atrophy occurs at an expedited rate in HD patients (Roth et al., 2005; Tabrizi et al., 2012). This suggests that although patients do deteriorate over time, such changes may not be easily measurable with cognitive tests over short intervals.

The present study reaffirmed the general slow progression of cognitive deterioration in HD patients over short time interval. This inevitably, creates great difficulty in monitoring cognitive changes in HD patients on routine follow-up in clinic settings. Longitudinal monitoring of disease progression is generally conducted to evaluate potential interventions for delaying phenoconversion in HD. Therefore, it is often argued that it is more meaningful for serial evaluation of disease progression in pre-manifest HD. However, understanding short-term changes and the utility of various cognitive tools in manifest HD patients are also important for multi-disciplinary health teams in planning and modifying disease plans, which consists of pharmacological and non-pharmacological interventions aimed at improving patient’s quality of life. Findings from the current study have implications for clinical practice and research. Cognitive decline in HD appeared to be most marked in executive function, and learning and memory domains after 12 months. Therefore in the clinic, cognitive deterioration in HD should not be determined by changes in global cognitive score of comprehensive neuropsychological test battery but ideally by detailed analysis of individual cognitive domain-specific performance. Due to practice effects, it is important in short- to medium-term longitudinal clinical research to include a control group when assessing the cognition of patients.

### III.4.2. Usefulness of brief cognitive tests for longitudinal assessment

As expected, the MMSE, MoCA, and the UHDRS cognitive component scores correlated well with global z-scores of the comprehensive neuropsychological test battery in the HD group. These findings support the utility of the three brief cognitive assessment tools in cross-sectional detection of cognitive deficits in manifest HD patients. Furthermore, there were no significant differences between the three brief cognitive tests in reflecting global cognition in HD patients, providing no evidence that one test is better than the other in this respect.

However, the baseline scores of the comprehensive neuropsychological test battery (global cognition) and UHDRS cognitive component were highly correlated with themselves at 12
month follow-up, with minimal deviations from the linear fit, indicating that both had low score variability over time. The reliability of the MMSE in the HD group, though reasonable, was significantly lower than that for the full neuropsychological test battery and the UHDRS cognitive component. Deficiencies in the reliability of the MMSE were highlighted in a study by Bowie et al. (1999), who inferred that the test was inadequate in detecting small cognitive changes longitudinally. Moreover, large score variance on annual assessment was another weakness of the MMSE as shown in a study on patients with Alzheimer’s disease (Clark et al., 1999), which further limits its value in assessing disease progression. Similarly in the HD sample of the current study, the two versions of MMSE were found to have greater score variance than the comprehensive neuropsychological test battery and the UHDRS cognitive component. The large score variance in the MMSE is likely to be caused by practice effects in some HD patients. Previous studies have concluded that the MMSE is highly susceptible to practice effects, especially in the healthy older adult population (Helkala et al., 2002; Hensel et al., 2007; McCaffrey & Westervelt, 1995; Stein et al., 2012; Tombaugh, 2005). However, such effects are usually minimal or absent in those with dementia (Helkala et al., 2002). Even though the present study demonstrated that there were significant within-group changes after a 12 month period in the MMSE (with ‘World’ spelled backwards) in HD patients, its use in routine follow-up in clinical practice should be interpreted with caution because of its tendency to vary unsystematically from one assessment to the next.

On the contrary, the MoCA and UHDRS cognitive component, as judged by the differences of linear fit models, had comparable performance to the comprehensive neuropsychological battery. A likely explanation for this is the nature of short-term cognitive progression in HD, which is most marked in executive function and also the overall design of these two brief cognitive tests, which has greater emphasis on testing executive function. The MoCA, which has been claimed to have superior sensitivity for detecting MCI compared to the MMSE (Larner et al., 2013), contains more demanding tasks for assessing executive and memory functions while the UHDRS cognitive component essentially assesses the executive function domain only. However, MoCA is a multiple cognitive domain assessment tool, hence, similar to global cognitive score, short-term cognitive decline in HD patients may have been counteracted by practice effects in other domains within the test. The MoCA, like other neuropsychological tests, is also susceptible to practice effects on repeated assessment (Cooley et al., 2015). It was found in Cooley et al.’s study that there was a lack of age-expected decline in MoCA scores over a three year period in healthy older adults. In addition, there was a significant increase scores from baseline to first 12 month follow-up assessment, mainly in those who scored lower
scores at baseline assessment (Cooley et al., 2015). It is recommended that alternate form of the MoCA should be considered to minimise the effects of practice on serial assessment (Costa et al., 2012).

On the basis of the findings in the present study, it is recommended that the UHDRS cognitive component is a good brief substitute for comprehensive neuropsychological testing and a sensitive cognitive measure to assess short-term cognitive changes in manifest HD, compared to MMSE and MoCA. The MoCA and MMSE, in that order, might be considered as reasonable alternatives to the ‘gold standard’ for use in clinic setting in circumstances where the UHDRS cognitive component is unavailable. However, due a higher level of score variability over time in MMSE and issues concerning practice effects in MMSE and MoCA, short-term longitudinal results from these two brief cognitive tests shall be cautiously interpreted.

III.4.3. Behavioural measures and the UHDRS motor score

There was no significant worsening in the UHDRS behavioural score in the HD group at follow-up, similar to prior observations (Huntington Study Group, 1996). Behavioural abnormalities in HD are heterogeneous in nature and without clear temporal progression (Jauhar & Ritchie, 2010). Furthermore, psychiatric interventions are often effective in managing behavioural disturbances of HD patients (Phillips et al., 2008) so such features are less likely to exhibit progressive deterioration over time. Thus, the UHDRS behavioural index is not particularly useful as a measure of short- to medium-term disease progression in HD.

In contrast to the absence of measurable change in the behavioural measure, there was a significant increase (an average of seven points increase) in the UHDRS motor score over 12 months. This is consistent with the Huntington Study Group’s (1996) report of an average three point increase in motor score over six months in manifest HD patients. The ability to demonstrate increase in the UHDRS motor score is not exclusive to manifest HD patients, with another study on pre-manifest patients showing that while the change was minimal after one year, there was a significant increase in motor scores over five years (Rao et al., 2011). These observations combined suggest that motor changes are possibly more aggressive in the short-term than cognitive and behavioural changes in HD patients.
III.5. Chapter summary

While the HD group exhibited no clear change in global cognitive z-score after a 12 month period, a decline was observed in the executive function domain. The significant improvement in the control group’s cognitive scores, along with the language domain score in the HD group, suggested some practice effects. Such practice effects may have implications for clinic follow-up and clinical research and the inclusion of a control group is vital in serial or longitudinal research studies involving HD patients.

Finally, cognitive findings in this study provided a new perspective on the utility of two widely used brief cognitive assessment tools (MMSE and MoCA) in comparison to UHDRS cognitive component and other measures on longitudinal monitoring of cognitive changes in manifest HD patients over a 12 month period. Despite the MMSE and MoCA being effective at describing global cognition in HD patients in cross-sectional analysis, they are less useful for monitoring longitudinal cognitive changes, hence their serial test scores should be interpreted prudently. The UHDRS cognitive component, which is a relatively brief cognitive assessment tool, is sensitive to short-term cognitive changes in HD and also a more reliable brief cognitive assessment tool compared to MMSE and MoCA over 12 months.
Chapter IV

Visually-guided reflexive movement

IV.1. Background

Abnormal saccadic function is a relatively well-established deficit in cross-sectional studies in HD (Becker et al., 2009; Lasker et al., 1987; Pelsch et al., 2008; Tsai et al., 1995; Winograd-Gurvich et al., 2003). Several studies have examined longitudinal changes in reflexive and complex saccades but many of these studies are limited by the small number of saccadic variables investigated (Tabrizi et al., 2012; Tabrizi et al., 2010) or the long follow-up period between baseline and follow-up assessments (Beenen et al., 1986; Rubin et al., 1993). It was suggested by Hotson et al. (1984) that HD has greater impact on vertical saccades than horizontal saccades. Although the performance of vertical and horizontal saccades of HD patients has been compared in a cross-sectional study (Patel et al., 2012), there is no longitudinal study that compares changes in both horizontal and vertical saccades over time.

Somatomotor movement and eye-head movement coordination in HD have been well
documented (Becker et al., 2009; Berardelli et al., 1996; Georgiou-Karistianis et al., 2014; Phillips et al., 1996; Thompson et al., 1988; Thompson et al., 1986). Becker et al. (2009) concluded that eye-head coordination of HD patients was identical to that of controls and that the use of head movement to facilitate eye movement was thought to be an adaptive behaviour employed by advanced stage HD patients. However, the relationship between eye and somatomotor or more specifically eye and hand movements in HD has yet to be explored.

The present study is an attempt to examine in a novel way the longitudinal changes of horizontal and vertical saccades and also of changes in eye-hand coordination in visually-guided reflexive tasks in manifest HD over a short interval of 12 months. These movement parameters were also then compared to measures of disease status, namely the UHDRS motor score and global cognitive score.

IV.2. Methods

Please refer to Chapter II: Methods for a detailed description.

IV.3. Results

IV.3A. Reflexive saccades

IV.3A.1. Saccadic latency by stimulus type in reflexive 1D paradigm

Mean latency in the ‘gap’ stimulus condition (task) in the control group was 145 ms. In the control group, mean latencies in the ‘step’ and ‘overlap’ tasks were longer than the ‘gap’ task by 44 ms [95% CI: 33 – 54; \( p < 0.0001 \)] and 74 ms [95% CI: 64 – 85; \( p < 0.0001 \)] respectively (Figure IV.1). There was likely only a small increase in latency in the HD group in the ‘gap’ task relative to controls, with an estimated non-significant increase of 24 ms [95% CI: -3 – 52; \( p = 0.07 \)]. The ‘step’ task in HD didn't appear to be overtly affected, with an estimated 9 ms increase in latency over the increases observed in the control group ‘step’ task and HD group ‘gap’ task [95% CI: -6 – 24; \( p = 0.3 \)]. In contrast, there was a strong additional effect of the ‘overlap’ task in HD, with an additional 46 ms [95% CI: 31 – 61; \( p < 0.0001 \)] increase in latency relative to the ‘overlap’ task effect in controls and the effect of HD in ‘gap’ task (Figure IV.1). There was an effect of time, with latency increasing in the follow-up session by 24 ms across tasks and groups [95% CI: 17 – 31; \( p < 0.0001 \)] (Figure IV.1).
Chapter IV  Visually-guided reflexive movement

Figure IV.1  Saccadic latency by stimulus type (‘Gap’, ‘Step’, and ‘Overlap’). Baseline and 12 month data for controls and HD patients are shown. LMEM-estimated group means are shown in filled circles and means for individual participants, in unfilled circles.

IV.3A.2. Express saccades in HD

Figure IV.2  Latency distributions in ‘Gap’, ‘Step’, and ‘Overlap’ tasks. Baseline data only is shown for controls and HD patients. Two red dotted line mark the latency range for express saccades (70 – 135 ms). The binwidth for the histograms is 10 ms.
Express saccades are those with very short latencies (70 – 135 ms) and are commonly found in saccadic responses of healthy controls in the ‘gap’ task (Fischer & Weber, 1993; Munoz et al., 1998). The saccadic latency distributions of the three tasks, i.e. ‘gap’, ‘step’, and ‘overlap’, are shown in Figure IV.2. Although both groups had noisy unimodal distributions in all three stimulus types, the bulk of latency values in the ‘gap’ task appeared to be different to the ‘step’ and ‘overlap’ tasks. That is, in ‘gap’ task, a larger number of observations was found on the left margin of the distribution plot.

A binomial family type generalized linear mixed-effect model was fitted to the binary classification of each trial (express saccade vs. regular saccade) to determine whether there was any effect of HD on express saccades. The model showed that in both groups, the occurrence of express saccade was higher in the ‘Gap’ task than the other two tasks (Control group: \( \chi^2 = 162.7, p < 0.001 \); HD group: \( \chi^2 = 175.2, p < 0.001 \)). There were minimal differences in express saccades rate between controls and the HD group in the ‘Gap’ task (Table IV.1). Both groups in general made fewer express saccades \(( p \leq 0.01)\) in the ‘Gap’ task in the follow-up session (Table IV.1).

### Table IV.1 Express saccade percentages in ‘Gap’, ‘Step’, and ‘Overlap’ tasks

<table>
<thead>
<tr>
<th>Stimulus type</th>
<th>Control group</th>
<th>HD group</th>
<th>HD vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (SD)</td>
<td>Change after 12 months Mean (SD)</td>
<td>Baseline Mean (SD)</td>
</tr>
<tr>
<td>Gap</td>
<td>43 (22)</td>
<td>-11 (20), ( p = 0.01 )</td>
<td>33 (23)</td>
</tr>
<tr>
<td>Step</td>
<td>9 (10)</td>
<td>-8 (11), ( p &lt; 0.001 )</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Overlap</td>
<td>8 (8)</td>
<td>-6 (7), ( p &lt; 0.001 )</td>
<td>6 (10)</td>
</tr>
</tbody>
</table>

### IV.3A.3. Saccadic performance in the reflexive 2D paradigm

In the 2D task, only ‘Step’ stimuli were used. Mean latency in the control group was 191 ms for horizontal saccades and 201 ms for vertical saccades. Mean latency for vertical saccades in the HD group was longer than controls by 32 ms \( (p = 0.03) \). Both groups had longer latencies in vertical saccades than horizontal saccades \( (p \leq 0.04) \). There was possibly a small effect of time upon latency in controls, with an estimated increase of 9 ms \( (p = 0.05) \) in horizontal saccades and 11 ms \( (p = 0.03) \) in vertical saccades at follow-up (Figure IV.3A). By contrast, there was a strong additional effect of time in HD, with an additional increase of 21 ms \( (p = 0.002) \) and 24 ms \( (p = 0.003) \) over the increases observed in the control group in horizontal and vertical saccades (Figure IV.3A).
Figure IV.3  **Horizontal and vertical saccades in the reflexive 2D paradigm.** Saccadic parameters assessed are: (A) latency (ms); (B) maximal velocity (deg/s); (C) primary gain (ratio); and (D) saccade count (n). Baseline and 12 month follow-up data for controls (red) and the HD patients (blue) are shown. Filled circles are LMEM-estimated group means and unfilled circles, means for individual subjects.

Saccadic main sequences (representations of the relationship between saccadic velocity and amplitude) for horizontal (Figure IV.4) and vertical (Figure IV.5) saccades in HD patients showed a high degree of variability across subjects and amplitudes. A main sequence could not be fitted to horizontal saccades (baseline and 12 month follow-up) for HD patient S05 or vertical saccades (12 month follow-up) for HD patient S06 because the data did not obey the typical logarithmic function. For example, patient S06 had velocities that were too low to saturate and remained linear across the entire range of amplitudes. They were therefore, excluded from group-level analysis of maximal saccadic velocity. In controls, the mean...
maximal velocity achieved at baseline for horizontal and vertical saccades were 484 deg/s and 483 deg/s respectively. There was likely a slightly lower maximal velocity in the HD group, with an estimated decrease of 50 deg/s ($p = 0.2$) in horizontal saccades and 55 deg/s ($p = 0.2$) in vertical saccades (Figure IV.3B). However, it should be noted that the HD group had a larger variance in maximal velocity than controls. In both groups, there were minimal differences in maximal velocity between the two directions of saccade (Controls: -1 deg/s [95% CI: -48 deg/s – 47 deg/s]; $p = 1.0$; HD: -6 deg/s [95% CI: 53 deg/s – 42 deg/s]; $p = 0.8$). There was an effect of time upon maximal velocity in the HD group only, with an estimated decrease in maximal velocity by 50 deg/s ($p \leq 0.01$) in both directions in the follow-up session (Figure IV.3B).

There were minimal differences of 0.02 ($p = 0.4$) and 0.06 ($p = 0.05$) in primary gain (ratio) between the two groups, in the horizontal and vertical direction respectively (Figure IV.3C). In the HD group only, primary gain in vertical saccades was lower than in horizontal saccades by 0.06 ($p = 0.03$). There were minimal 12 month changes of 0.01 ($p \geq 0.7$) in primary gain in controls (Figure IV.3C). By contrast, there was a decline of 0.07 ($p = 0.005$) in horizontal saccades and 0.09 ($p = 0.001$) in vertical saccades in HD in the follow-up session, resulting in a group $\times$ time interactions ($p \leq 0.03$).

The HD group had higher saccadic count ($p \leq 0.007$) than controls in both directions (Figure IV.3D). Both groups had minimal changes in the range of -0.08 to 0.05 ($p \geq 0.1$) in saccadic count in either directions in the follow-up session.

A summary of LMEM-estimated means and 12 month changes for controls and the HD groups in the four saccadic parameters measured (latency, maximal velocity, primary gain, and saccadic count) is shown in Table IV.2 (see overpage).
Table IV.2  LMEM-estimated group means [95% CIs] and 12 month changes in saccadic parameters measured in the reflexive 2D paradigm

<table>
<thead>
<tr>
<th>Saccadic parameter</th>
<th>Control group</th>
<th>HD group</th>
<th>HD vs. Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean [95% CI]</td>
<td>Change after 12 months Mean [95% CI]</td>
<td>Baseline Mean [95% CI]</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>191 [174 – 208]</td>
<td>9 [-0.1 – 18], p = 0.05</td>
<td>208 [191 – 225]</td>
</tr>
<tr>
<td>Vertical</td>
<td>201 [180 – 221]</td>
<td>11 [0.3 – 22], p = 0.04</td>
<td>233 [213 – 253]</td>
</tr>
<tr>
<td>Maximal velocity (deg/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>484 [428 – 541]</td>
<td>16 [-24 – 57], p = 0.4</td>
<td>434 [378 – 490]</td>
</tr>
<tr>
<td>Vertical*</td>
<td>483 [429 – 537]</td>
<td>-23 [-61 – 16], p = 0.2</td>
<td>428 [374 – 482]</td>
</tr>
<tr>
<td>Primary gain (ratio)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>0.97 [0.9 – 1.0]</td>
<td>0.01 [-0.04 – -0.05], p = 0.8</td>
<td>0.95 [0.9 – 1.0]</td>
</tr>
<tr>
<td>Vertical</td>
<td>0.95 [0.9 – 1.0]</td>
<td>0.04, p = 0.7</td>
<td>0.88 [0.8 – 0.9]</td>
</tr>
<tr>
<td>Saccade count (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>1.6 [1.5 – 1.7]</td>
<td>-0.01 [-0.1 – -0.1], p = 0.8</td>
<td>1.8 [1.7 – 1.9]</td>
</tr>
<tr>
<td>Vertical</td>
<td>1.7 [1.6 – 1.8]</td>
<td>-0.08 [-0.2 – -0.02], p = 0.1</td>
<td>1.9 [1.8 – 2.0]</td>
</tr>
</tbody>
</table>

^Saccadic main sequences (horizontal saccades) for HD patient S05 at baseline and 12 month follow-up failed to fit an exponential curve function, hence this patient was removed from group-level analysis for maximal velocity in horizontal saccades. *Saccadic main sequence (vertical saccades) for HD patient S06 at 12 month follow-up failed to fit an exponential curve function, and therefore was excluded from group-level analysis for maximal velocity in vertical saccades.
Figure IV.4  Main sequences of horizontal saccades for HD patients. The red reference lines represent the mean main sequence of horizontal saccades for the control group.
Figure IV.6  **Main sequences of vertical saccades for HD patients.** The red reference lines represent the mean main sequence of vertical saccades for the control group.
IV.3A.4. Usefulness of saccadic parameters in reflecting disease severity and measuring change over time

Several issues must be considered in assessing the utility of saccadic measures for measuring disease progression over 12 months. These issues include: (1) whether there are any within-group and between-group relative changes in those measures over a 12 month period; (2) how well these measures reflect patients’ disease status; and (3) reliability of a measure, as determined by the variability of the measurements on repeated testing after taking account of 12 month systematic changes.

Three saccadic parameters – latency, maximal velocity, and primary gain – were selected to have their utility in monitoring longitudinal changes evaluated because these parameters were found to show a deterioration in the HD group and also a significant group × time interaction. The correlations between these saccadic parameters and the UHDRS motor scores, and global cognitive scores of HD patients determined how well these saccadic measures reflect HD patients’ disease status. All three saccadic parameters were found to have moderate correlations to either the UHDRS motor score or global cognitive scores at baseline (Figure IV.6) and also at follow-up (not shown).

Bootstrapping procedures (refer section II.9.12 for a detailed description) determined the differences in $r^2$ coefficients (coefficients of determination for correlations between saccadic measures and UHDRS motor scores, and global cognitive scores) of one saccadic parameter to another. This analysis provided an indication of whether all saccadic parameters were identical in reflecting the severity of motor and cognitive impairment in HD. The bootstrapping procedures showed that there were no significant differences among the three saccadic measures in terms of their relationships to the UHDRS motor scores and global cognitive scores, suggesting that all three saccadic parameters are reasonably similar in reflecting the severity of motor impairment and cognitive impairment in manifest HD.

The variability of measurement residuals in a saccadic parameter after taking account into 12 month systematic changes was determined firstly by fitting simple linear models to the baseline and 12 month measurements of that parameter and then evaluating the correlation within a parameter by assessing the $r$ coefficient from the fitted models. Baseline measurements were well correlated with 12 month measurements for all three saccadic parameters in the HD group (Figure IV.7A).
Figure IV.6 Correlations between saccadic parameters and UHDRS motor scores, and global cognitive scores in the HD group. $r$ [95% CI] and $p$ values are shown.
The variability of measurement residuals after 12 months for the three saccadic parameters (Figure IV.7A) was compared to the variability of score residuals after 12 months in UHDRS motor score (Figure IV.7B) using bootstrapping procedures. This provides an objective indication of whether saccadic measures were as reliable as the UHDRS motor component in showing a decline in HD patients over a 12 month interval. This analysis showed that there were minimal differences in terms of the variability of measurements after 12 months between the UHDRS motor component and most saccadic parameters, except for primary gain of horizontal and vertical saccades (the estimated 95% CIs of $r^2$ differences: $0.1 – 0.9$). This indicates that latency and maximal velocity showed similar profile of variability of measurements over time to the UHDRS motor component.
The combination of a significant decline in saccadic latency and maximal velocity after 12 months, high correlations of these measures to UHDRS motor and global cognitive scores, and low measurement variance across time (a consistent 12 month change among patients) indicate that latency and maximal velocity of reflexive saccades are reliable measures in reflecting disease progression in HD over a 12 month interval.

**IV.3B. Visually-guided reflexive eye-hand movement**

**IV.3B.1. Eye-hand coordination in the visually-guided reflexive task**

The visually-guided reflexive eye-hand task comprised two types of movement, reaching (towards a novel peripheral target) and return (towards a consistent home target).

**IV.3B.1.1. Latency**

![Latency Graphs](image)

**Figure IV.8** Eye and hand latencies in the visually-guided reflexive task for controls and HD patients. Baseline and 12 month data for reaching (A) and return (B) movements are shown. Filled circles are LMEM-estimated group means and unfilled circles, means of individual subjects.
In reaching towards an unpredictable target, eye latency in controls was 163 ms [95% CI: 144 – 181] and in HD, it was longer than controls by 43 ms [95% CI: 18 – 69; \( p < 0.001 \)]. In controls, hand latency was longer than the eye by 57 ms [95% CI: 43 – 71; \( p < 0.001 \)] in the reaching movement (Figure IV.8A) but 336 ms ahead of the eye in the return movement (Figure IV.8B), indicating that the eye led the hand when reaching for an unpredictable target whereas the hand preceded the eye upon returning to a known target. The HD group, despite showing a similar pattern of eye-hand movement behaviour to controls in the two movements (Figure IV.8A), had longer hand latency in the reaching movement, with the estimated latency 69 ms [95% CI: 36 – 102; \( p < 0.001 \)] longer than the hand latency of controls. It should be noted that in reaching movements, hand latency variance in the HD group was noticeably larger than amongst controls. Both groups had a minimal change in latency in the follow-up session, except for a statistically significant increase in eye latency in the reaching movement (Controls: 19 ms [95% CI: 1 ms – 36 ms]; \( p = 0.03 \); HD: 24 ms [95% CI: 13 ms – 36 ms]; \( p < 0.001 \)) (Figure IV.8A).

![Figure IV.9](image)

**Figure IV.9** Eye-hand latency interval (ms) in reaching (A) and return (B) movements for controls and the three sub-group of HD patients. Baseline and 12 month data are shown. Filled circles are LMEM-estimated group means and unfilled circles, means of individual subjects. *NB: The only stage 4 patient in this study was analysed collectively with stage 3 patients.

A linear mixed effect model fitted to eye-hand latency intervals (i.e. the time between the initiation of each eye and its corresponding hand movements) and disease stages revealed that there was a strong positive linear effect of disease stage \( (p < 0.001) \) on eye-hand latency intervals in the reaching movement (Figure IV.9A), indicating that there is progressive prolongation in the time interval between eye and hand movement initiation as disease progresses in HD. There was however, no evidence of a disease stage effect \( (p = 0.2) \) in the return movement (Figure IV.9B). The change if any for the follow-up is small in eye-hand
latency interval across disease stages in the follow-up session, with an estimated decrease of 9 ms [95% CI: -18 ms – 35 ms; \( p = 0.5 \)] in the reaching movement and an increase of 45 ms [95% CI: -166 ms – 75 ms; \( p = 0.5 \)] in the return movement.

**IV.3B.1.2. Hand velocity**

Peak hand velocity in the reflexive eye-hand task in controls was 36 cm/s for a movement amplitude of 10 cm. There was a reduction in peak hand velocity in the HD group compared to controls, with an estimated decrease of 7 cm/s [95% CI: 1 cm/s – 13 cm/s; \( p < 0.001 \)] for the same movement amplitude. Both groups showed that there was a non-linear effect of movement amplitude (\( p < 0.001 \)) on the change in velocity in the reaching movement (Figure IV.10). That is, hand velocity rises in a non-linear manner with rising movement amplitude.

In both groups, the pattern of change in velocity in the return movement (not shown) was identical to the reaching movement. In controls, there was an increase in hand velocity by 13 cm/s [95% CI: 10 cm/s – 16 cm/s; \( p < 0.001 \)] for movement amplitude of 20 cm but no increase (\( p = 0.8 \)) for 15 cm. However, in HD, there was an overt increase in hand velocity in movements of 15 cm and 20 cm in movement amplitude, with an estimated increase of hand velocity of 4 cm/s [95% CI: 1 cm/s – 8 cm/s; \( p < 0.03 \)] and 6 cm/s [95% CI: 1 cm/s – 11 cm/s; \( p = 0.03 \)] respectively over the increases observed in the control group (Figure IV.10).

**Figure IV.10** Hand velocity (cm/s) by movement amplitude in the reaching movement of the visually-guided reflexive eye-hand task. Baseline and 12 month follow-up data are shown. Filled circles are LMEM-estimated group means and unfilled circles, means for individual participants.
As there was an insufficient range of movement amplitudes to determine the absolute maximal hand velocity of individual subjects, the mean velocity at 20 cm movement amplitude (the largest movement amplitude in this task) was used instead. There was no overt effect of disease stage on maximal hand velocity \((p \geq 0.2)\) in either reaching (Figure IV.11) or return movements, indicating that maximal hand velocity in a reflexive task was relatively unchanged across disease stages in HD. There was however, an effect of time on maximal velocity in both controls and HD (Figure IV.11), with hand decreasing by about 7 cm/s [95% CI: 4 cm/s – 9 cm/s; \(p < 0.001\)] in the follow-up session for reaching and return movements.

![Figure IV.11](image)

**Figure IV.11** Maximal hand velocity (cm/s) in the reaching movement for controls and the three sub-groups of HD patients. Baseline and 12 month data are shown. Filled circles are LMEM-estimated group means and unfilled circles, means for individual subjects. **NB**: *Mean velocities in 20 cm movement amplitude were considered as maximal hand velocities. *The only stage 4 patient in this study was analysed collectively with stage 3 patients.

**IV.3B.2. Clinical correlates of eye-hand movement parameters**

To determine the relationships between eye-hand movement and disease status in HD, the eye-hand movement parameters in the reaching movement were each correlated with UHDRS motor scores and global cognitive scores using correlation tests.

Both eye and hand latencies showed moderate positive correlations \((r = 0.48, p = 0.03)\) to UHDRS motor scores and moderately strong negative correlations to global cognitive scores \((r \geq -0.66, p \leq 0.001)\) in HD (Figure IV.12). Mean eye-hand latency intervals showed moderate negative correlation \((r = -0.61, p = 0.003)\) to global cognitive scores only. Mean velocities in movement amplitude of 20 cm however, had weak correlations to the UHDRS motor scores \((r = -0.19, p = 0.4)\) and global cognitive scores \((r = 0.34, p = 0.1)\). Correlations of eye-hand
movement parameters to CAG repeat number were analysed in addition and showed that CAG repeat numbers generally had poor associations \((0 \leq r \leq 0.1, p > 0.3)\) to all parameters, thus indicating that changes in eye-hand movement performance is not related to CAG repeat size.

![Figure IV.12: Correlations between mean latency (ms) of the eye and hand and UHDRS motor scores, and global cognitive scores in the HD group at baseline.](image)

**Figure IV.12** Correlations between mean latency (ms) of the eye and hand and UHDRS motor scores, and global cognitive scores in the HD group at baseline. \(r\) [95% CIs] and \(p\) values are shown.

**IV.4. Discussion**

The key findings in the saccadic and eye-hand movement visually-guided reflexive tasks were that the HD group exhibited: (1) A stronger ‘overlap’ effect than controls; (2) A decline in saccadic performance in most saccadic parameters in the reflexive 2D task over 12 months, relative to controls; and (3) A prolongation in the time interval between eye movement and hand movement initiation compared to controls.

**IV.4A. Reflexive saccades**

**IV.4A.1. ‘Gap’ and ‘overlap’ effects in HD**

The ‘gap’ and ‘overlap’ effect on saccadic latency in the HD group reaffirms the findings of a previous study (Tian et al., 1991). Although the basal ganglia, the main sites of HD pathology, are implicated in the generation of saccades (Hikosaka et al., 2000), Keating et al. (1983) suggested that reflexive saccades in healthy controls are generally triggered by the direct
projections from the parietal cortex to the superior colliculus. Therefore, Tian et al. (1991) has ascribed the appropriate effects of the ‘gap’ and ‘overlap’ stimulus conditions on saccadic latency to the relative preservation of the parietal-superior colliculus pathways.

Further, the present study provides evidence that HD patients have similar proportions of express saccades in the ‘gap’ condition to controls. Express saccades, which is exclusive to the ‘gap’ condition, are defined as saccades with shorter than normal reaction times (Fischer & Weber, 1993). A rhesus monkey lesional study demonstrated that a defective frontal eye field did not have a noticeable effect on the production of express saccades whereas a unilateral ablation of the superior colliculus resulted in the loss of express saccades when directing saccades to the direction opposite to the side of the lesion, suggesting that the superior colliculus has a critical role in the control system of reflexive saccades (Schiller et al., 1987). Hamm et al. (2010) further demonstrated that in humans, express saccades are facilitated by priming the saccade generating circuitry in the brain stem and this process is directly associated with the enhancement of activity in the occipital-parietal network. Based on these studies, it can be deduced that the ability to generate express saccades is dependent upon an intact superior colliculus and occipital-parietal network. The finding of an identical proportion of express saccades in HD compared to controls is therefore suggestive of a relative preservation of these neural structures in manifest HD and that in HD, there is a disparity in the degenerative changes occurring within and outside the basal ganglia.

Although there were ‘gap’ and ‘overlap’ effects upon saccade latency in the HD group, the latency of saccades in the ‘overlap’ condition for the HD group was significantly greater than controls. This observation could be attributed to a HD effect on three separate neural mechanisms: (1) failure of cortical regulatory systems on fixation release; (2) delay in information processing; or (3) inefficiency in basal ganglia-regulated threshold mechanisms. As proposed by Findlay and Walker (1999), saccade generation involves the integration and resolution of competing signals from fixation and saccadic activities through a slow build-up of saccadic activity and a decline in fixation activity. This proposition was based on the physiological observation of a competitive interaction between fixation and saccade-related neurons in the superior colliculus (Dorris et al., 1997). Findlay et al. (1999) argued that the occurrence of the ‘gap’ effect was related to an automatic reduction of fixation that occurs during the blanking period between two visual stimuli, which ultimately facilitates the generation of saccades. However, the reduction in fixation activity may not be an automated process for all types of visual stimuli. In normal human development, maturation of the
subcortical system occurs earlier than the cortical regulatory systems (Johnson, 1990) leading to a normal ‘gap’ effect but longer latency in the ‘overlap’ condition in a normal human infant when compared to a healthy adult (Hood & Atkinson, 1993). These findings suggest that cortical involvement in the reduction of fixation activity is essential for saccade generation in the ‘overlap’ condition. An increased magnitude of ‘overlap’ condition effect in the HD group may therefore translate to an impairment in fixation disengagement. This might be a result of a dysfunctional cortical regulatory system caused by HD.

Nevertheless, a study comparing saccades of four hominid species in the ‘gap’ and ‘overlap’ conditions revealed that despite cross-species similarities in saccadic latencies in the ‘gap’ condition, saccadic latencies of humans subjects were significantly longer compared to other hominids in the ‘overlap’ condition (Kano et al., 2011). The authors attributed the slower response in humans in the ‘overlap’ condition to humans’ visual strategy, which favours fixation over frequent gaze shifting to enable the facilitation of internal processing of information (Kano et al., 2011). Given that information processing may be a contributing factor to the delay in saccade initiation in the ‘overlap’ condition for controls, the greater increase in time delay in the ‘overlap’ task in manifest HD may be an effect of a slower information processing system in HD, i.e. the system requires considerable longer time to internalize the new information given and to conceptualise a response. Such a deficit is likely to be caused by HD-related neurodegenerative changes in the central nervous system. Further, Schmidt et al. (2005) proposed that there are three distinct processes in a human model of information processing: (1) stimulus identification; (2) response selection; and (3) response programming. The significantly prolonged latency in the ‘overlap’ condition in manifest HD might be caused by deficits in these processes. However, the present study lacks the specific and quantitative data pertaining to these processes, hence it is not possible to determine which of these processes might have contributed to an increased magnitude of ‘overlap’ condition effect in manifest HD.

Another possible interpretation of the very strong ‘overlap’ effect in the HD group relates to the overall vitality of the basal ganglia, the main neuropathological site of HD. In another model of human saccades, it is proposed that a saccade is generated when the discharge rate in the saccade-related neurons of FEF and superior colliculus reaches a certain threshold level of activation (Brown et al., 2008; Pare & Hanes, 2003). As demonstrated via a computational accumulator model, this threshold mechanism can be adaptively tuned by the efficacy of the synapses in the cortico-basal ganglia pathway depending upon the behavioural tasks involved (Lo & Wang, 2006). Loss of anatomic integrity of the basal ganglia in HD, which clearly begins
in premanifest HD (Stoffers et al., 2010), might have altered the threshold level of saccade initiation and such deficit may become more pronounced in tasks with higher behavioural demands. In this instance, the ‘overlap’ task has the highest level of behavioural demands of the three stimulus conditions, hence the stronger ‘overlap’ effect translate to a deficiency in the basal ganglia to recalibrate this threshold mechanism to facilitate saccade initiation when presented with competing visual stimulus.

IV.4A.2. **Usefulness of saccadic measures for reflecting disease status and longitudinal assessment**

Longitudinal changes in various horizontal saccade parameters in the HD group are broadly consistent with findings in earlier studies (Abel et al., 1988; Beenen et al., 1986; Rubin et al., 1993; Tabrizi et al., 2010). In addition to the conventional measures of saccade latency and velocity used in those reports, the present study provided evidence of deterioration in the primary gain of horizontal saccades in HD over 12 months. As suggested by Leigh et al. (1983), the effect of HD might be greater on vertical saccades than horizontal saccades. Thus, longitudinal changes in vertical saccades might be a more sensitive progression marker of HD. In the present study, this hypothesis was examined by assessing both horizontal and vertical saccades. A strong group × time effect was evident in latency, primary gain, and maximal velocity of both horizontal and vertical saccades, hence suggesting that saccades in either directions are susceptible to change over a 12 month interval. Further, the strong interaction effects in those saccadic parameters suggest that a decline in the HD group is highly likely an effect of HD, rather than normal short-term ageing effect.

In line with an earlier study by Patel et al. (2012), all three saccadic parameters (mean latency, maximal velocity, and primary gain) correlated well with UHDRS motor scores and global cognitive scores. These findings suggest that saccade measurement in general was useful in reflecting disease state in manifest HD, thus supported its application for tracking disease progression. The baseline values of the UHDRS motor score, mean saccadic latency, and mean maximal velocity were highly correlated with the same measurements taken 12 months later and with minimal deviation from linear fits. These observations confirm the reliability of repeated testing, especially UHDRS motor score, saccadic latency, maximal velocity, and perhaps less so for saccadic gain. Humans are known to exhibit plasticity in the modification of saccadic gain (Deubel et al., 1986), which consists of two key processes, visual remapping and motor adjustment (Wallman & Fuchs, 1998). Albano et al. (1989) also showed that this adaptive process changes more rapidly in humans than in other hominid species. This adaptive
nature of saccadic gain modification may explain the higher variability in primary gains in the HD group after 12 months. Although primary gains of horizontal and vertical saccades in the current study showed significant deterioration in the HD group after 12 months, the larger variance in the same measurement over time limits its utility as a measure of disease progression in routine follow-up. In contrast, the reliability performance of saccade latency and also maximal velocity was comparable to the UHDRS motor component, a current gold-standard measure of disease progression, highlighting the robust nature of these saccadic parameters.

Most saccadic measures were found to be sensitive in detecting longitudinal changes in manifest HD over 12 months and also have a level of reliability that was comparable to the UHDRS motor component. These findings suggest that reflexive saccade measurement may represent a useful strategy for detecting and tracking either clinical progression or pathological changes in the basal ganglia and its associated circuits involved in the control of eye movement. Some may have reservations about this postulation, as it was demonstrated in a study by Tabrizi et al. (Tabrizi et al., 2012) that disappointingly, there were no significant saccadic changes in premanifest and early HD over a longer follow-up interval (i.e. 24 months). It should be highlighted that there are two main shortcomings in that study that unlike the present study, (1) the saccadic task was unidirectional (horizontal only); and (2) vertical saccades were not assessed. The reflexive task in the present study was bi-directional, i.e. target displacement for any given trial could occur either in the horizontal or vertical direction. This design inevitably adds another level of uncertainty (compared to a unidirectional task) to the presentation of an impending target. There is evidence to suggest that in HD, there is a dysregulation of information processing in the striatum (Miller et al., 2008). A 2D reflexive task, which is likely to place additional burden on a compromised information processing system in HD, may be better in accentuating the effect of HD on saccadic function and also the longitudinal changes of HD.

In summary, the findings of the present study suggest that saccadic latency in a reflexive 2D task appears to be a sensitive and reliable marker for short-term disease changes/progression in manifest HD, and superior to other saccadic measures. The maximal velocity of saccades also appears to be a useful short-term progression marker for HD, and may complement saccadic latency measurement.
IV.4B. Visually-guided reflexive eye-hand movement

IV.4B.1. Eye-hand coordination in HD

In the combined eye-hand task, there was a delay in hand movement initiation in the HD group compared to controls. This observation supports previous findings of prolonged latencies in somatomotor movement in other muscle groups in HD (Heftet et al., 1987; Koller & Trimble, 1985; Thompson et al., 1988).

Under normal circumstances, coordination of human eye and hand movements is tightly coupled and operates in a fixed temporal sequence, whereby hand movements typically lag eye movement (Pelz et al., 2001). In contradistinction, hand movements may precede eye movement when there is prior knowledge (i.e. spatial information) of target location (Abrams et al., 1990). The present study provides evidence that temporal sequencing of eye and hand movements is relatively preserved in manifest HD, with the eyes leading the hand in response to randomly appearing peripheral targets, and lagging the hand when returning to a fixed-positioned home target.

There was however, an abnormally long interval between eye and hand movement initiation in the visually-guided reflexive task in the HD group. Further, the duration of the interval increased with an increase in disease stages, implicating an origin in the progressive neurodegeneration of the eye-hand control pathways in HD. The medium spiny neurons, which are selectively degenerated in HD (Vonsattel et al., 2011), are important for normal information processing in the basal ganglia (Murer et al., 2002). In a mouse model of HD, reduction in basal ganglia output burst firing activity (Salinas & Sejnowski, 2001) correlated with medium spiny neuron degeneration and dysregulation of information processing (Miller et al., 2008). Thus, the longer latency in hand movement initiation in HD patients in the present study may represent an increased processing time – to select and execute the movement appropriate for the task involved – within the compromised basal ganglia.

The superior colliculus (SC), an integral structure for saccade generation (McDowell et al., 2008), is also suggested to be involved in the coordination of eye and hand movements because neuronal activity in the SC was found to be closely associated with the pattern of electromyographic activity of the musculature in the proximal limb during reaching (Stuphorn et al., 1999). Furthermore, strong interactions were found between gaze- and arm-related neurons in the SC in gaze coordinated arm movements (Lunenburger et al., 2001; Stuphorn et al., 2000). A direct inference from this is that degeneration of the basal ganglia in HD
(Berardelli et al., 1999) may interfere with the activity of the superior colliculus which is under the direct influence of basal ganglia (Hikosaka et al., 2000), resulting in an increase in the silence period between the eye and hand movements. Nevertheless, an increased firing in the SC with simultaneous eye and hand movements may not necessarily translate to a role for SC in limb control as such. Limb control is likely dependent on the combined activation of SC and motor cortex, with SC regulating the eye aspect and motor cortex controlling the hand aspect of eye-hand movement. The exact role of SC in eye-hand movement control can only be deciphered via functional neuroimaging techniques that primarily focus on SC and motor cortex activation during gaze coordinated hand movements.

An fMRI study revealed that a distributed network, involving various cortical and subcortical structures, was activated in healthy controls when performing a visually-guided task that involves eye-hand coordination (Lavrysen et al., 2007) with the highest activation peak being in the cerebellum. The cerebellum is well known to contribute to the coordination and timing of eye and hand movements in visually-guided arm movements (Miall et al., 2000; Miall & Reckess, 2002). Although the basal ganglia are the main sites of HD pathology, studies have consistently reported about the coexistence of cerebellar and striatal atrophy in manifest HD patients on routine post-mortem and neuroimaging examinations (Rub et al., 2013; Ruocco et al., 2006). Thus, some contribution to deficits in eye-hand coordination in HD might be from cerebellar neuropathology. However, as discussed above, a number of cortical brain regions are also involved in the control of voluntary movement. Visuomotor processing during a visually-guided reaching task requires the interpretation of visual information in the visual cortex, and sensorimotor transformation in the parietal lobe and the premotor areas of the frontal lobe (Ellermann et al., 1998). Progressive cortical atrophy is a well-established neuroimaging feature in premanifest and manifest HD (Tabrizi et al., 2012; Tabrizi et al., 2010; Tabrizi et al., 2013), with the sensorimotor cortex being the most affected (Rosas et al., 2008). One might propose therefore that a prolonged interval between eye and hand movement initiation in HD, as observed in the present study, results from the disruption of sensorimotor transformation processes particularly in the parieto-frontal cortex which causes a protracted delay in hand movement initiation. Neurodegeneration continues to worsen with disease progression in HD and this may translate to a concurrent deterioration of sensorimotor transformation system in HD, hence the progressive prolongation of eye-hand latency interval with higher disease stages.

**IV.4B.2. Clinical correlates of eye-hand movement parameters**

There was a significant relationship between slowness in hand movement and UHDRS motor
scores, consistent with the observations of a previous study (van Vugt et al., 2004). These findings are consistent with an origin, at least in part, in an abnormally functioning motor circuit in the basal ganglia. However, the prolongation of the interval between eye and hand movement initiation (eye-hand latency interval) in the HD group also correlated well with global cognitive level (global cognitive scores) of HD patients, suggesting cognitive processes also contribute to the control of eye-hand coordination.

The traditional model of basal ganglia physiology hypothesized the existence of multiple circuits in the basal ganglia, arranged in a parallel manner but functionally segregated from one another (Alexander et al., 1990). Later, Joel (2001) posited that these circuits are interconnected to each other at different levels so consequently, impairment at a specific site in the basal ganglia circuitry could influence neural processes in other parallel pathways. According to this hypothesis, the motor circuit of the basal ganglia connects with the associative circuit, which in turn has projections to the prefrontal cortex. A connection between the two circuits might explain a deficit in eye-hand coordination associating with both motor and cognitive impairment in HD. Alternatively, as discussed above, visuomotor processing, which involves close interaction of cognition and motor function, is integral in the control of eye-hand coordination. Therefore, the coexistence of an association between eye-hand coordination abnormality and cognitive decline may conceivably reflect an underlying deficit in visuomotor processing in HD.

IV.4B.3. 12 month changes in eye and hand movement parameters

The HD group, despite having a significant within-group deterioration in eye and hand latencies at 12 month follow-up, demonstrated minimal change in eye-hand latency interval in the visually-guided reflexive task. These findings could relate to heterogeneity in the longitudinal progression of cognitive and motor aspects of eye-hand coordination. In fact, several studies have demonstrated that the rate of change in various neural structures varies by HD clinical stage (Aylward et al., 2011; Tabrizi et al., 2012; Tabrizi et al., 2013). In addition, in comparison to the striatum, there is greater variability in cortical atrophy in early manifest HD patients (Kassubek et al., 2004). There was, rather surprisingly, comparable decline in eye-hand coordination performance in the HD and control groups. The decline in the control group was unexpected, not readily explained and may have masked a true comparative decline in the HD group. One possible postulation for this is that the paradigm used in the present study does not have as high test
reliability as envisioned. Alternatively, the absence of a decline relative to controls in the HD group might be due to a very slow rate of deterioration in HD, or a lack of uniform changes across different sub-groups of HD patients in this study over 12 months. Consistent with this postulation, Tabrizi et al. (2010) reported variation in performance changes across various tasks after 12 months in premanifest and early manifest HD. Compensatory processes might also explain a relative lack of decline in eye-hand coordination in the HD group. One piece of evidence to support this argument is that there is reorganisation of brain activation to retain motor performance in premanifest (Kloppel et al., 2009) and also manifest (Bartenstein et al., 1997) HD. However, it is necessary to take into consideration of the considerable large variance in hand latency in the HD group (refer Figure IV.8). For a group with a large variance, the group average may have inadvertently masked the true effects of HD upon changes in eye-hand coordination performance over time. The lack of a significant change in eye-hand movement in the HD group, relative to controls, does suggest that this methodology has doubtful utility for monitoring short-term disease progression in HD. On the other hand, reflexive saccades, in comparison to reflexive visually-guided somatic movement, may be a better measure for detecting disease changes over one year.

IV.5. Chapter summary

This study provides novel perspectives on 12 month changes in visually-guided reflexive saccades and eye-hand coordinated movements in manifest HD. It shows that two saccadic measures, namely latency and velocity are sensitive to 12 month longitudinal changes in HD and are as reliable as the current gold-standard measure of disease progression, the UHDRS motor component for tracking disease changes in manifest HD. However, similar 12 month longitudinal performance decline in eye-hand coordination in the HD and control groups was unexpected and possible explanations include slow and heterogeneous disease progression or a compensatory brain processes for maintaining behavioural performance. The HD group did however, show a significant 12 month decline in eye movement performance in the eye-hand variant of the visually-guided reflexive task, reinforcing the postulation that saccade measurement is a potentially useful marker of short-term disease changes and progression in manifest HD. The 2D reflexive paradigm (assessing both horizontal and vertical saccades in the same task) used in this study, which has added uncertainty in the presentation of targets, may accentuate HD effect on saccadic function. This paradigm, given that it better highlights the saccadic deficits in HD, may potentially have greater utility for tracking longitudinal changes in manifest HD.
Chapter V

Rhythmical movement

V.1. Background

Planning a motor response in advance of an upcoming change in the environment provides a distinct evolutionary advantage (Isotalo et al., 2005) because it allows motor responses with shortened reaction times. This behaviour has been shown in the human ocular motor system, with saccades initiated at or before target onset after just a few repetitions of a target alternating at a constant frequency between two predictable locations (Isotalo et al., 2005; Ross & Ross, 1987). This type of saccade is commonly known as ‘predictive’. The latency of predictive saccades is dependent upon the frequency at which the target alternates (Crawford et al., 1989; McDowell et al., 1996; Shelhamer & Joiner, 2003; Smit & Van Gisbergen, 1989). Saccades are generally reactive when stimuli are presented at low frequencies (< 0.3 Hz, i.e. at longer inter-stimulus intervals [ISIs], ≥ 1600 ms). They switch to a predictive response, i.e. with fast or even negative latencies, at higher frequencies (> 0.5 Hz, i.e. shorter ISIs, ≤ 1000 ms) (Shelhamer & Joiner, 2003). Tian and colleagues (1991) demonstrated that unlike controls, HD patients did
not show a reduction in saccadic latency in a predictive task, suggesting that individuals with HD are unable to benefit from the regular timing of stimuli.

Rhythmical saccadic movement, which includes self-paced saccades, has been evaluated in HD but the results have thus far been mixed. Winograd-Gurvich et al. (2003) reported that HD patients, in addition to increased performance variability, generate fewer horizontal self-paced saccades than controls. The authors proposed that in HD, degeneration in the cortico-striatal loops indirectly degrades the normal functioning of the supplementary motor area, a region involved in regulating voluntary and rhythmical saccades. Despite there is evidence suggesting vertical reflexive saccades in HD are more affected than horizontal saccades (Leigh et al., 1983) and that deficits in vertical saccades are closely associated with neuroimaging changes on MRI (Rupp et al., 2012), vertical self-paced saccades in HD are yet to be examined.

The studies of Tian et al. (1991) and Winograd-Gurvich et al. (2003) were cross-sectional so questions on longitudinal changes in self-paced and predictive saccades, and the sensitivity of these saccade types to disease progression of HD, remain largely unanswered. In their study of predictive saccades in HD, Tian et al. (1991) examined saccadic performance of manifest HD patients using only stimuli at a fixed frequency of 0.5 Hz. Assessing a wider spectrum of saccadic behaviour, driven by a range of alternating target frequencies (i.e. ISIs) might provide greater insight into the effect of HD on neurophysiological processes. Therefore, one of the objectives of this study was to extend current findings on rhythmical saccadic movement in HD, determining its relationship to disease status and 12 month longitudinal changes.

Studies of Parkinson’s disease, which is also a basal ganglia disorder, suggested that deficits in predictive and rhythmical hand movements are associated with degenerative changes in the basal ganglia (O’Boyle et al., 1996). In HD, repetitive hand tapping rate, in addition to being well correlated with the current functional status of manifest HD patients, also showed a progressive decline in performance rate over time (Collins et al., 2014). However, another longitudinal study showed that hand tapping performance of HD patients declined significantly less than the systematic prolongation of reflexive saccade latencies in HD patients over a period of three years (Antoniades et al., 2010), suggesting that saccadic deficits may potentially be more sensitive than somatomotor changes to underlying disease progression in HD. Eye movement, in normal circumstances, is essential in the coordination of somatomotor movement. Although it is well established that rhythmical movement is impaired in HD, previous works were restricted to investigating the performance of the eye and hand separately.
(Antoniades et al., 2010; Delmaire et al., 2010; Michell et al., 2008; Winograd-Gurvich et al., 2003). This study, in addition to assessing rhythmical saccades, also examined the combined behaviour of the eye and hand in rhythmical movements using self-paced tasks (horizontal and vertical) and temporally-cued tasks with different ISIs.

V.2. Methods

Please refer to Chapter II: Methods for a detailed description of methods used for assessing rhythmical movement.

V.3. Results

V.3A. Rhythmical saccades

V.3A.1. Self-paced tasks

The mean number of self-paced saccades made in 30 s by controls was 64 [95% CI: 57 – 70] in the horizontal task and 63 [95% CI: 56 – 70] in the vertical task. The HD group made 29 [95% CI: 20 – 38; \( p < 0.001 \)] fewer self-paced saccades than controls in the horizontal task and 28 [95% CI: 18 – 38; \( p < 0.001 \)] fewer saccades in the vertical task. The effect size for the between-group differences was \( d = 1.9 \) for both tasks. Both groups showed that there were minimal differences (\( d \leq 0.1, p \geq 0.5 \)) between tasks (horizontal vs. vertical), in terms of the number of self-paced saccades made.

There was a strong negative linear effect of disease stage (\( p < 0.001 \)) in the horizontal and vertical tasks, indicating that there is a linear progressive decline in the number of self-paced horizontal and vertical saccades made across disease stages in HD (Figure V.1). The data also revealed that this decline in performance is evident even in Stage 1 HD (Figure V.1), with the estimated number of horizontal and vertical saccades made being 13 [95% CI: 3 – 23; \( p \leq 0.01 \)] fewer than controls.

Controls showed no relative change in the number of self-paced saccades made in the two tasks at follow-up (0.001 < \( d \leq 0.05 \), \( p \geq 0.8 \)). In general, there was no apparent effect of time in self-paced saccades in the HD group (0.04 < \( d \leq 0.05 \), \( p \geq 0.2 \)) at follow-up (Figure V.1).
Figure V.1  Number of self-paced saccades made in 30 s by controls and patients in the three stages of HD at baseline and at 12 month follow-up. Data from the horizontal task is shown in the left panel and vertical, in the right panel.
*NB: There was only one stage 4 patient and this patient was analysed with the stage 3 patients in the self-paced tasks.

V.3A.2. Temporally-cued tasks
V.3A.2.1. Random phase

In the random phase, the LMEM-estimated mean latency was 174 ms [95% CI: 134 ms – 214 ms] in controls. There was likely a minimal prolongation of latency in the HD group compared to controls, with an estimated prolongation of 20 ms [95% CI: -3 ms – 44 ms; \( p = 0.1 \)] in the HD group. There was an effect of time on latency, with an estimated increase of 15 ms [95% CI: 9 ms – 21 ms; \( p < 0.001 \)] in controls. In the HD group, relative to controls, there was an estimated additional increase of 15 ms [95% CI: 3 ms – 26 ms; \( p = 0.02 \)] in latency at follow-up.

V.3A.2.2. Predictable phase

A generalised linear mixed-effect model showed that in controls, there was a strong negative linear effect of ISI \( (p < 0.001) \) on the proportion of predictive saccades in the last 10 trials of the predictable phase (Figure V.2). That is, the occurrence of predictive saccades was highest in the shortest ISI (750 ms) and gradually reduced with increasing ISI. This effect was not evident in the HD group \( (p = 0.4) \), with the proportion of predictive saccades being relatively similar across all ISIs (Figure V.2). There was no evidence of a time effect \( (p = 0.5) \) on the proportion of predictive saccades in the last 10 trials across ISIs in either groups.
Saccadic latencies appeared fairly consistent across trials in the random phase but there was a progressive reduction in latencies after the change to predictable target motion (Figure V.3A). In controls, latencies in the last 10 predictable trials were less than the random phase by 226 ms [95% CI: 187 ms – 265 ms; $p < 0.001$] at the 750 ms ISI and 59 ms [95% CI: 24 ms – 93 ms; $p < 0.001$] at the 2050 ms ISI. There was likely only a small reduction in latency in the HD group, with an estimated reduction of 12 ms [95% CI: -27 ms – 51 ms; $p = 0.6$] at the 750 ms ISI and 43 ms [95% CI: 10 ms – 77 ms; $p = 0.01$] at the 2050 ms ISI.

In controls, there was a strong linear effect of ISI ($p < 0.001$) on saccadic latency in the predictable phase (Figure V.3B). There was a steep reduction in saccadic latency from the random phase to the predictable phase with the shortest ISI (750 ms) but there was less reduction in latency with increasing ISI. That is, saccadic latency in the predictable phase increases with increasing ISI. By contrast, latency was not affected by the change in ISI ($p = 0.2$) in the entire HD group. That is, the reduction in saccadic latency in the predictable phase was relatively similar across all ISIs. There was a weak ISI effect across all disease stages of HD, with the effect being the weakest in the highest disease stage (Figure V.3B)

There was in general, a global increase in latency at follow-up with no additional effect of ISI on latency in the predictable phase in either group (Figure V.3A).
Figure V.3  Saccadic latency in the saccade-only temporally-cued tasks. (A) Mean saccadic latency by trial number for the four ISIs (750 ms, 1000 ms, 1400 ms, and 2050 ms) in the control group (left panel) and HD group (right panel). There were 17 trials in the random phase, indicated by negative trial numbers (-16 to 0), and 40 in the predictable phase (1 to 40). The dotted vertical line in each plot indicates the end of the random phase and the start of the predictable phase. The exponential decay curves model the change in mean latency by trial number at baseline (red lines) and at 12 month follow-up (blue lines). (B) Mean latency of the random phase and of the last 10 predictable trials for the four ISIs (750 ms, 1000 ms, 1400 ms, and 2050 ms) in controls and the three sub-groups of HD patients. Filled points represents the LMEM-estimated group means and unfilled points, means for individual participants.
V.3A.3. Correlations between saccadic measures and disease measures

Saccadic parameters were correlated against UHDRS motor scores and global cognitive z-scores at baseline in the HD group.

Correlation tests showed that the number of self-paced horizontal and vertical saccades made was strongly positively associated with UHDRS motor score ($r = 0.8$, $p < 0.001$) and negatively with global cognition ($r = -0.8$, $p < 0.001$) (Figure V.4).

![Figure V.4 Correlations between the number of self-paced horizontal and vertical saccades made in 30 seconds and UHDRS motor scores, and global cognitive z-scores. $r$ [95% CIs] and $p$ values are shown.](image)

In all trial blocks, the mean saccadic latencies of the last 10 trials of the predictable phase correlated positively with the UHDRS motor scores ($0.44 \leq r \leq 0.59$, $0.005 \leq p \leq 0.04$) and negatively with global cognitive z-scores ($-0.57 \leq r \leq -0.40$, $0.007 \leq p \leq 0.07$) (Figure V.5). This indicates that a reduction in saccade prediction in the temporally-cued tasks is associated with a higher UHDRS motor score and lower cognitive level.
V.3B. Rhythmical eye-hand movement

V.3B.1. Eye-hand coordination in the self-paced tasks

Analysis of eye-hand movement data of individual participants revealed that self-paced hand movements could be made in the absence of a corresponding eye movement. In controls, the number of hand movements (Horizontal: 81 [95% CI: 73 – 88]; Vertical: 83 [95% CI: 76 – 91]) made was more than the eye (Vertical: 78 [95% CI: 72 – 85]) in the vertical task (Difference: 5 [95% CI: 1 – 9; p = 0.01]) but relatively identical to the eye (Horizontal: 81 [95% CI: 73 – 88]) in the horizontal task (Difference: 1 [95% CI: -1 – 3]; p = 0.4).
The HD group however, had minimal differences in the number of self-paced movements between the eye (Horizontal: 50 [95% CI: 43 – 57]; Vertical: 49 [95% CI: 43 – 56]) and the hand (Horizontal: 50 [95% CI: 42 – 57]; Vertical: 52 [95% CI: 44 – 59]) in both tasks (Horizontal difference: -1 [95% CI: -3 – 2], p = 0.5; Vertical difference: 2 [95% CI: -2 – 6], p = 0.2).

At baseline, the entire HD group generally made fewer self-paced eye and hand movements than controls in either tasks. In the horizontal task, it was estimated that the HD group made 29 [95% CI: 19 – 39; p < 0.001] less eye movements and 31 [95% CI: 21 – 41; p < 0.001] less hand movements than controls. In the vertical task, the estimated reduction was by 29 [95% CI: 19 – 39; p < 0.001] movements in the eye and in the hand, 32 [95% CI: 21 – 42; p < 0.001] movements. The effect sizes for the between-group differences were $d \geq 1.9$.

![Figure V.6](image.png)

**Figure V.6** Number of eye-hand movement made in 30 s by controls and patients in the three* HD stages in the self-paced tasks. Horizontal tasks are shown in the top panel and vertical tasks in the bottom panel. Bars in light grey indicate baseline performance while dark grey bars are 12 month performance. Error bars shown are means and 95% CIs. *NB: The sole stage 4 patient was analysed collectively with stage 3 patients in disease stage-specific analysis.

There was a very strong linear effect ($z \geq -2.2$, $p < 0.001$) of disease stage on the number of self-paced eye and hand movements made in the horizontal and vertical tasks (Figure V.6). This
indicates that the number of self-paced eye and hand movements made in both tasks reduces in a linear manner with disease progression in HD. It was also revealed that even at stage 1, HD patients made significantly fewer number of self-paced eye ($p \leq 0.01$) and hand movements ($p \leq 0.007$) than controls in both the horizontal and vertical tasks (Figure V.6).

Controls in general showed minimal changes in the number of self-paced eye and hand movements made in the two tasks in the follow-up session (Figure V.6). There was however, relative to controls, a strong effect of time in the entire HD group across most movements and tasks at 12 month follow-up. In the horizontal task, relative to controls, the number of self-paced movement in HD reduced by 8 [95% CI: 1 – 16; $p = 0.03$] in the eye and by 11 [95% CI: 1 – 20; $p = 0.03$] in the hand. In the vertical task, relative to controls, there was a reduction of 8 movements [95% CI: 2 – 14; $p = 0.01$] in the eye and likely a small reduction of 4 movements [95% CI: -3 – 12; $p = 0.3$] in the hand in the HD group. There was however, no significant disease stage × time effect ($p \geq 0.06$) across movements and tasks, indicating that there was a similar trend of decline in number of self-paced eye and hand movements made in the two tasks across all disease stages in HD at follow-up (Figure V.6).

**V.3B.2. Correlations between self-paced eye and hand movements, and disease measures**

![Figure V.7](image)

Correlations between number of self-paced horizontal and vertical eye-hand movements made and UHDRS motor scores of HD patients. $r$ [95% CIs] and $p$ values are shown.
Simple correlations were used to establish the relationship between self-paced movements and disease status, as measured using UHDRS motor scores and global cognitive scores in the HD group at baseline.

The number of self-paced eye and hand movements in both tasks (horizontal and vertical) showed strong negative correlations \((r \leq -0.7, p < 0.001)\) with the UHDRS motor scores (Figure V.7), indicating that a higher UHDRS motor score is associated with a smaller number of eye and hand movements made in either direction.

In contrast, global cognitive scores showed strong positive correlations \((r \geq 0.7, p < 0.001)\) with the number of self-paced eye and hand movements in either direction (Figure V.8). That is, a lower global cognitive score is associated with a smaller number of self-paced movements made.

![Figure V.8](image_url)

**Figure V.8** Correlations between number of self-paced horizontal and vertical eye-hand movements made and global cognitive scores of HD patients. \(r\) [95% CIs] and \(p\) values are shown.

The UHDRS motor component contains two test items for rapidly alternating hand movement (Item 6: finger tapping and Item 7: hand pronating/supinating) for each hand (Huntington Study Group, 1996). The number of self-paced eye-hand movement and the aggregated scores of the two items (a maximum score of four in each hand for each item, leading to a maximum total score of 16 for both hands) of each of the HD patients were fitted by simple linear models. Both eye and hand movements demonstrated moderately strong but statistically significant negative
correlations to the aggregated score (Figure V.9), suggesting that a decline in the number of self-paced movement made corresponds to a decline in the score in those two items in the UHDRS motor component.

Figure V.9  Correlations between number of self-paced horizontal and vertical eye-hand movements made and aggregated scores of HD patients for test items 6 and 7 (items containing rapidly alternating hand movement) in the UHDRS motor component. $r$ [95% CIs] and $p$ values are shown.

V.3B.3.  Eye-hand coordination in temporally-cued tasks

One of the objectives of this study was to examine eye-hand coordination in a temporally-cued tasks and any changes in eye-hand coordination performance after 12 months. However, due to unforeseen technical issues related to the software used for recording hand movement in this task, raw data for some subjects in certain cued trials were incomplete at baseline and corrupted for many subjects at 12 month assessment. This issue was only discovered after the completion of data collection at 12 month. Given the circumstances, it was decided that only the baseline data of the temporally-cued eye-hand tasks would be analysed.

There were two phases in the temporally-cued tasks, the random and predictable phases. Subjects had to reach for the target on the screen with their fingertip while having their eye movement recorded. Eye and hand latencies of individual subjects in the four temporally-cued tasks are illustrated in Figure S3 – S10 of the Appendix. Six distinct behavioural strategies were identified in the 2050 ms ISI temporally-cued task in the control (Figure S6) and HD groups (Figure S10): (1) very ‘early’ saccades with ‘early’ hand movements, in which ‘early’ means
responses were made in advance of target onset; (2) ‘reactive-type’ eye and hand movement responses, i.e. responses were made after target onset; (3) ‘early’ saccades with alternating ‘early’ and reactive-type hand responses, i.e. ‘reactive-type’ hand responses interspersed with ‘early’ hand responses; (4) concurrent ‘early’ eye and hand movements, i.e. both eye and hand responses were made in advance of target onset; and (5) a mixture of ‘early’ and ‘reactive-type’ eye and hand responses.

Approximately 50% of controls exhibited a strategy involving very ‘early’ saccades with ‘early’ (but slower than the eye) hand responses in the 2050 ms ISI block. In contrast to controls, only three HD patients (two ‘Stage 1’ patients and one ‘Stage 3’ patient) utilised this strategy. Fifty percent of HD patients (n = 11) were found to show a ‘reactive-type’ response in eye and hand movements, compared to three controls who used this strategy in the same trial block.

**V.3B.3.1. Random phase**

In the random phase, the LMEM-estimated mean eye latency was 156 ms [95% CI: 98 ms – 215 ms] in controls and 195 ms [95% CI: 135 ms – 225 ms] in the HD group. Hand latency was longer than the eye by 79 ms [95% CI: 65 ms – 92 ms; p < 0.001] in controls and 109 ms [95% CI: 95 ms – 125 ms; p < 0.001] in the HD group, indicating that the eye leads the hand when reaching for a novel and unpredictable target.

**V.3B.3.2. Predictable phase**

Figure V.10A shows that in both groups, eye and hand latencies were fairly consistent across trials in the random phase but there was a progressive reduction in latencies following the change to predictable target motion.

In controls, the LMEM-estimated reduction in eye latencies in the last 20 predictable trials, compared to the random phase, ranged from 308 ms at the 750 ms ISI to 683 ms at the 2050 ms ISI. There was a more modest reduction in eye latency in HD, with an estimated reduction of 145 ms at the 750 ms ISI and 237 ms at the 2050 ms ISI. Reduction in hand latencies in controls ranged from 124 ms at the 2050 ms ISI to 402 ms at the 750 ms ISI whereas in HD, it ranged from 164 ms at the 2050 ms ISI to 251 ms at the 750 ms ISI. For eye-hand latency intervals (i.e. the time between the initiation of each eye and its corresponding hand movements) for the control group, they ranged from -16 ms (i.e. the hand preceded the eye) at the 750ms ISI to 698 ms at the 2050 ms ISI. In the HD group, eye-hand latency intervals ranged from -2 ms at the 750 ms ISI to 185 ms at the 2050 ms ISI.
Figure V.10  Eye and hand latencies in the temporally-cued tasks. (A) Mean eye and hand latencies in the random and predictable phases of the four ISI trial blocks (750 ms, 1000 ms, 1400 ms, and 2050 ms) by trial number. There were 17 trials in the random phase, indicated by negative trial numbers (-16 to 0), and 40, in the predictable phase (1 to 40). The dotted vertical line in each plot indicates the end of the random phase and the start of the predictable phase. The exponential decay curves model the change in mean eye latency (red lines) and hand latency (blue lines) by trial number. (B) Mean saccadic latency of the random phase and the last 20 predictable trials of the four ISIs (750 ms, 1000 ms, 1400 ms, and 2050 ms) in controls and the three sub-groups of HD patients. Filled circles are the LMEM-estimated group means and unfilled circles, means for individual subjects.
In controls, ISI had a strong but diverging effect in eye \((p < 0.001)\) and hand \((p = 0.02)\) latencies in the predictable phase (Figure V.10B). In the eye, there was progressive reduction in eye latency with increasing ISI, with the greatest latency reduction at the 2050 ms ISI. That is, controls initiated an eye movement well in advance of an appearing target when the target was alternating at the slowest speed. This is a directly opposite to the effect of ISI on eye latency in the saccade-only temporally-cued task, in which the greatest reduction in latency was found at the shortest ISI (refer section V.3A.2, Figure V.3). By contrast, the reduction in hand latency was greatest at the shortest ISI and the reduction in latency progressively diminished with the prolongation of ISI. There was also a strong ISI effect \((p < 0.001)\) in eye-hand latency interval. That is, eye-latency interval was the shortest at the shortest ISI and gradually increased with increasing ISI. These findings in combination indicate a disparity in eye and hand behaviour in different ISIs.

The effect of ISI was however, not apparent in the entire HD group in either the eye \((p = 0.07)\) or the hand \((p = 0.2)\), suggesting that reduction in eye and hand latencies was not affected by the length of ISI. When analysed by disease stage, it appears that there was a weak ISI effect across all disease stages in HD (Figure V.10B). By contrast, there was an effect of ISI \((p = 0.03)\) on eye-hand latency interval in the entire HD group. That is, there was a slight reduction in eye-hand latency interval at the shortest ISI and this gradually increased (albeit smaller compared to controls) as ISI increased.

**V.3B.4. Correlations between temporally-cued eye and hand movements, and disease measures**

The relationships between performance in the temporally-cued tasks and disease status in the HD group was determined by separately correlating mean eye and hand latencies in the last 20 trials of the predictable phase of all four ISIs with the UHDRS motor scores and global cognitive scores of HD patients.

Mean eye latencies in the last 20 trials of predictable phase of all ISIs, except for 1400 ms ISI, showed weak to moderate positive correlations \((0.31 \leq r \leq 0.42, p \leq 0.04)\) with UHDRS motor scores (Figure V.11A) and moderate negative correlations \((-0.45 \leq r \leq -0.36, p \leq 0.02)\) with global cognitive scores (Figure V.11B). This translates to a prolongation of latency in last 20 trials of predictable tasks is associated with an increase in UHDRS motor scores and a decrease in global cognitive function. In contrast, mean hand latencies in the last 20 trials of all ISIs
generally showed weak and insignificant correlations to either the UHDRS motor scores or global cognitive scores (Figure V.11).

Correlation analyses of CAG repeat number and eye-hand parameters, which was performed in an addition, showed that CAG repeat number was poorly associated ($0 \leq r \leq 0.2, p > 0.1$) with any parameters measured in these tasks.

![Correlation diagram](image)

**Figure V.11** Correlations between eye-hand movement latencies in the last 20 predictable trials and (A) the UHDRS motor scores, and (B) global cognitive scores of HD patients for the four ISIs (750 ms, 1000 ms, 1400 ms, and 2050 ms). $r$ [95% CIs] and $p$ values are shown.
V.4. Discussion

V.4A. Rhythmical saccades

Rhythmical saccades of HD participants were evaluated and the relationships of their saccadic performance to measures of disease severity were examined. The main findings in rhythmical saccades were that: (1) In the HD group, the number of self-paced saccades made decreased with worsening HD disease severity; (2) There was a lack of prediction in the HD group irrespective of inter-stimulus interval (ISI), unlike controls, in whom there was greater prediction at shorter ISIs; (3) Saccadic characteristics of HD patients in the self-paced and temporally-cued tasks correlated with UHDRS motor scores and global cognitive level; and (4) There was, in general, a global slowing of saccadic latency in HD patients after 12 months.

V.4A.1. Self-paced saccades

The finding that HD patients made significantly fewer saccades than did healthy controls confirms a previous study of horizontal self-paced saccades (Winograd-Gurvich et al., 2003). However, in contrary to the view that vertical reflexive saccades are more affected than horizontal reflexive saccades in HD (Leigh et al., 1983; Rupp et al., 2012), the present study revealed that there was no difference between the horizontal and vertical tasks in the number of self-paced saccades generated.

Several regions in the cerebral cortex, particularly the frontal eye-field (FEF) and supplementary eye field (SEF), have been implicated in the control of self-paced and internally-generated saccades. Neurophysiological evidence suggests that neurons in the FEF are involved in saccade fixation and disengagement (Everling & Munoz, 2000) whereas the SEF has a preparatory role in self-initiated oculomotor movement (Goldberg, 1985). The observations of increasingly impaired self-paced saccade generation with increasing HD disease severity in the present study suggest that the severity of FEF and SEF dysfunction is associated with HD pathophysiology and degeneration (Selemon et al., 2004). In addition to cortical structures, the basal ganglia are also involved in voluntary saccade production (Alexander et al., 1990). Neurdegeneration of the basal ganglia, which is evident in premanifest HD (Tabrizi et al., 2009) and worsens with disease progression (Aylward et al., 1997; Tabrizi et al., 2010), may also contribute to the decline in the number of self-paced saccades made in HD.
V.4A.2. Predictive saccades

Controls had the highest proportions of predictive saccades and lowest saccadic latencies in the predictable phase of trial blocks with the shortest ISIs (i.e. 750 ms and 1000 ms). This is consistent with previous work which showed that short ISIs (less than 1000 ms) promote the generation of predictive saccades (Isotalo et al., 2005; Shelhamer & Joiner, 2003). Predictive saccades in HD were first explored by Tian et al. (1991), who reported less saccadic prediction in HD patients than controls, when a target alternated between two fixed locations at a constant frequency of 0.5 Hz. The current study extended this work by examining a range of ISIs. In contrast to controls, who demonstrated a clear transition between strongest predictive behaviour a shorter ISIs (e.g. 750 ms) to weaker saccadic prediction at longer ISIs (e.g. 2050 ms), there was no strong evidence of such a transition, regardless of clinical severity, in our HD patients (Figure V.2), suggesting an abnormality in the predictive system in manifest HD.

Everling & Munoz (2000) demonstrated (in a non-human primate study) that in volitional saccades, saccadic latency is negatively correlated with pre-saccadic activity in the saccade-related neurons in the FEF (i.e. shorter latency is related to increased activity in those neurons). A number of frontal cortical and basal ganglia regions are important in the generation of predictive saccades. A functional MRI study of healthy human subjects demonstrated that advanced knowledge of spatial and temporal information, which is the key factor for predictive saccade generation (Ross & Ross, 1981), was associated with increased brain activation in the FEF, SEF, dorsolateral prefrontal cortex, and basal ganglia (Gagnon et al., 2002). Gagnon et al. (2002) also found that there was greater activation of caudate nucleus with advanced spatial information and greater activity in the lentiform nucleus with advanced temporal information, indicating that there is different activation of basal ganglia with different types of advance information. In HD, there is atrophy of various cortical structures, the FEF included, and also degeneration of the basal ganglia (Reiner et al., 2011). Degenerative changes in these structures may ultimately affect the handling of advanced spatial and temporal information in HD, which consequently hamper the ability to generate predictive saccades in HD, as observed in this study.

Humans are capable of achieving a high degree of synchronisation to external stimuli in repetitive rhythmic movement tasks, leading to the proposal that such behaviour is mediated by an ‘internal clock’ mechanism (Rao et al., 1997; Semjen et al., 2000). Joiner & Shelhamer (2006) postulated that predictive saccades, which can be established even after only two successive equal target intervals in healthy controls, are also under the influence of an ‘internal
clock’. The cerebellum and basal ganglia are thought to be integral to the internal representation of temporal information (Buhusi & Meck, 2005; Ivry, 1996). This notion is supported by the observation that patients with cerebellar (Spencer et al., 2003) and basal ganglia lesions (O’Boyle et al., 1996) exhibit deficits and increased variability in timed movements. Concurrent activation in the FEF and cerebellum during predictive saccades suggests that neural circuits between the FEF and cerebellum are critical in their generation (O’Driscoll et al., 2000). Pertinently, in addition to striatal atrophy in HD, recent evidence indicates that cerebellar degeneration begins relatively early in HD and is independent of the neurodegenerative changes in the striatum (Rub et al., 2013).

Reduced saccadic prediction in HD might also be a consequence of a disrupted error monitoring system. Timing errors from the current saccade during a temporally-cued task are thought to expedite the neural command for the subsequent saccade via a feed-forward programming system (Shelhamer, 2005). In contrast to controls, who showed a distinct pattern of event-related brain potentials to correct and erroneous responses, there were relatively minimal differences in event-related brain potentials between the two type of responses in patients with basal ganglia and prefrontal cortex lesions (Ullsperger & von Cramon, 2006), suggesting that dysfunctional fronto-striatal circuits can affect performance monitoring. Based on these observations, one can draw a parallel between patients with basal ganglia lesions and HD patients, who also suffer from basal ganglia degeneration. Therefore, in HD, inefficient fronto-striatal circuits may compromise the performance monitoring system, which in this task results in a reduction in saccadic prediction. The reduction in motor prediction as a consequence of an impaired performance monitoring system may have implications on HD patients in their activities of daily living.

Additional mechanisms may however, also be involved in the generation of predictive saccades. Zorn et al. (2007) demonstrated that in addition to motor actions, sensory information such as visual and auditory cues can also be used to develop predictive mechanisms in human saccades. These observations suggest that saccade prediction impairment in HD may not be explained solely by the degeneration of fronto-striatal circuits but may be a result of a multi-site and multi-system degeneration in the central nervous system.

An alternative explanation for impaired saccadic prediction in HD might be a tendency of HD patients to favour reactive over predictive responses due to relative preservation of the parietal lobe-superior colliculus network (Tian et al., 1991). This is however, unlikely to be a
contributing factor to the present findings. Firstly, the HD group exhibited predictive saccades in the last 10 trials of the predictable phase at all four ISIs (Figure V.3). Besides, the time series of reactive saccade latency (i.e. saccade latencies by trial number) is relatively flat whereas in predictive mode, the latency series decayed as a function of frequency in an exponential fashion (Shelhamer & Joiner, 2003). Group analysis of saccade latencies in the predictable trials of the HD group in the present study did show evidence of an exponential decay in saccadic latency by trial number at all four ISIs, albeit to a much lesser degree than controls. These findings did not support the idea that in HD there is a preference for reactive to predictive responses, but rather, there is a deficit in the predictive mechanism itself. Taken together, the evidence discussed above suggests that impairment in predictive saccades in HD likely has a basis in neurodegeneration involving particularly the cerebellum, the basal ganglia – especially the lentiform nuclei – and the frontal oculomotor control centres, resulting in a faulty predictive process.

V.4A.3. Clinical correlates of rhythmical saccades

In the present study, the relationships between saccadic parameters and CAG repeat number, the UHDRS motor score, and global cognitive score were examined to determine if deficits in rhythmical saccades are associated with the genetic load, motor or cognitive status in HD.

As expected, self-paced and predictive saccade impairments were poorly correlated with CAG repeat number. This is because CAG repeat number only provides prognostic information pertaining to disease onset and also speed of disease progression but not disease status at any one point in time (Penney et al., 1997). Saccadic performance in the HD group did however, correlate with current UHDRS motor scores. The UHDRS motor component contains mostly items of voluntary movements which are governed by the frontal-striatal circuits (Groenewegen, 2003). Therefore, the significant correlation between the two variables suggests that in HD, a decline in rhythmical saccades and motor scores may reflect the pathological process in the frontal-striatal circuits. Shabbott et al. (2013) however, argued that caution should be taken when correlating kinematic data to disease severity scales due to the fact that clinical severity of HD patients, as determined by various rating scales, on their last assessment prior to their death, showed poor correlations with the degree of striatal degeneration at autopsy (Pillai et al., 2012).

Cognitive function has been suggested to have an influential role in the control of saccadic movement (Anderson & MacAskill, 2013; Hutton, 2008; Isotalo et al., 2005). There were
significant correlations between nearly all saccadic parameters (in the self-paced and temporally-cued tasks) and global cognition in HD patients. Thus, these findings support the conclusion that both motor and cognitive decline is associated with deterioration in rhythmical saccade performance in HD patients.

V.4A.4. **Short-term longitudinal changes in rhythmical saccades**

There was in general, no obvious effect of time in self-paced saccades in either direction in the HD group over a period of 12 months. Based on this, it might be argued that performance in self-paced saccades is independent of the neuropathological changes in HD. However, the close association of self-paced saccade performance with UHDRS motor scores and global cognitive score in our HD patients suggested otherwise. Therefore, the parsimonious interpretation of this lack of change is that regions involved in the control of self-paced saccades, at least over short-term (i.e. 12 months), are relatively spared from the effect of HD. It would also seem that self-paced saccade measurement is useful for reflecting current disease status but not a sensitive progression marker for tracking 12 month disease changes in HD.

It was found that there was an increase in saccadic latency in both the HD and control groups in the random phase, suggesting that an age effect might have contributed to this change after 12 months. However, this study also revealed that at follow-up, there was a greater increase in latency in the HD group compared to controls. This indicates that the increase in latency in the HD group is not solely contributed by ageing effect but also caused by the effect of HD. The presence of an additional HD effect on normal ageing effect in latency in the random phase of temporally-cued tasks reaffirms the postulation that measurement of saccadic latency may potentially be a useful short-term progression marker for HD.

There was however, no additional HD effect on the increase in saccadic latency in the predictable phase of all ISI trial blocks over time. It is unlikely that changes in predictive behaviour of saccades are not linked to the underlying pathology in HD as it was found in this study that in the patient group, the mean saccadic latencies of the last 10 predictable trials (a measure of saccade predictive behaviour) showed moderate to strong correlations with UHDRS motor scores and global cognitive level. Therefore, it is hypothesized that in HD, there was a global deterioration in saccadic latency over time with a relative preservation of saccade predictive behaviour over a short follow-up period. Such a hypothesis is supported by our finding of a relatively stable proportion of predictive saccades in the HD group after 12 months (refer to Figure V.2). Based on these findings, it appears that the measurement of predictive
saccades in a temporally-cued task is useful for reflecting patients’ current disease status but has limited utility as a HD progression marker for detecting or tracking short-term longitudinal disease changes.

V.4B. Rhythmical eye-hand movement

The current study extended previous studies, which examined either the rhythmical movement of the eye or the hand in manifest HD, by investigating coordinated eye-hand movement in manifest HD in a self-paced task and a temporally-cued task. The main findings were: (1) in HD, there were significant 12 month declines in self-paced eye and hand movements in contrast to a minimal change in performance in controls over time; (2) in contrast to the saccade-only temporally-cued tasks, in which the HD group had little reduction in eye latencies (a measure of saccade prediction), there was a greater reduction of eye latencies (albeit smaller compared to controls) in the eye-hand variants of the same task; and (3) there were striking differences between controls and the HD group in terms of the predictive behaviour of the eye and hand across the four ISIs. In controls, the reduction in eye latency was greatest at longer ISIs whereas there was initially a shortening of hand latency, which progressively became longer with longer ISI. By contrast, in the HD group, the predictive behaviour of the eye and the hand movements were relatively similar across ISIs.

V.4B.1. Eye and hand movements in the self-paced task

Overall, the findings of a reduction in the number of rhythmical eye and hand movements in the HD group in a self-paced task compared to controls on cross-sectional analysis were in line with previous studies (Andrich et al., 2007; Antoniades et al., 2010; Collins et al., 2014; Delmaire et al., 2010; Michell et al., 2008; Winograd-Gurvich et al., 2003). Such findings were not unexpected because the basal ganglia, which house the motor circuitry for the control of oculomotor and somatic movements (Alexander, 1994), are the primary site of HD pathology. The selective degeneration of the striatum in the basal ganglia might have in general, affected the functionality of the motor circuits, resulting in a reduced ability to generate self-paced rhythmical movements in HD. It is well-established that there is a greater loss of striatal neurons in the indirect (inhibitory) pathway of the basal ganglia than the direct (excitatory) pathway in early HD (Albin et al., 1990; Reiner et al., 1988). Based on this, it can be speculated that movement initiation should be relatively preserved in early HD. Conversely, the findings of the current study showed that relative to controls, there was a reduction in the number of self-paced rhythmical eye and hand movements even in patients with early HD. This implies that a decline
in self-paced rhythmical movements might not be directly related to the degenerative changes of the striatum in HD.

The posterior parietal cortex has been implicated as a key communicating and processing centre for spatial and temporal information in the control of eye and hand movements (Hwang et al., 2014; Vesia et al., 2010; Yttri et al., 2013). Several overlapping but functionally distinct areas within the posterior parietal cortex have been identified to have specific roles in the control of eye and hand movements (Vesia et al., 2010). Nevertheless, the different regions were found to interact with each other to support the coupling and decoupling of eye-hand movement (Battaglia-Mayer et al., 2006; Dean et al., 2012). Besides, the posterior parietal cortex is also involved in the control of attention (Colby & Goldberg, 1999). Thinning of the cerebral cortex, which is progressive in nature and occurs relatively early in HD (Rosas et al., 2002), is also a neuropathological hallmark of HD (Rosas et al., 2005; Tabrizi et al., 2009). Rosas et al. (2002) also showed that in comparison to other cortical regions, cortical thinning was most significant in the sensorimotor (parietal) region of the cortex. These findings might therefore explain the reduction in performance level in self-paced rhythmical eye-hand movement in early HD. Recent neuroimaging studies also found that there was a significant reduction in connections between the caudate nucleus of the basal ganglia and the posterior parietal cortex in HD compared to controls (Marrakchi-Kacem et al., 2013) and also a generalised loss of the region in the caudate nucleus specific for receiving neural inputs from the posterior parietal cortex (Bohanna et al., 2011). Taken together, these findings suggest that impairment in self-paced rhythmical eye and hand movements in HD patients can be attributed to HD pathology both in and outside the basal ganglia, thus explaining the marked reduction of self-paced eye and hand movements made in Stage 1 patients, as compared to controls. Given the number of self-paced eye-hand movements made decreases with increasing clinical severity in HD, a measurement of self-paced eye-hand movements may provide a useful global indication of underlying neuropathological changes in HD and also a progression marker for this disease.

It is also noteworthy that both groups appeared to have made more self-paced eye movements in the eye-hand task than in the saccade-only task (refer to section V.3A.1). Such a finding might conceivably be explained by the physiological interactions between the neural mechanisms for the control of eye and hand movements. It has been consistently reported that in healthy controls, there is an improvement in oculomotor performance when eye movement is executed simultaneously with hand movement (Gauthier et al., 1988; Leist et al., 1987). Based on suggestions that the oculomotor control system relies on visual feedback (Lewis et
and the somatomotor control system is dependent on proprioceptive feedback (Barnes & Grealy, 1992). Barnes and Marsden (2002) posited that such an effect was likely to be contributed by a cross-modality transfer of feedback information between the two motor controls systems which resulted in the reinforcement of the behaviour of the oculomotor control system. The increase in the number of self-paced rhythmical eye movement in the HD group when eye movement is executed together with the hand implied that the cross-modality of transfer of feedback information appeared be relatively spared by the disease process in HD. The effective control of gaze behaviour is essential in monitoring and changing direction during locomotion (Hollands et al., 2002). There is evidence to support that the performance of locomotor movement can be improved with training of eye movement (Azulay et al., 1999; Crowdy et al., 2002). Taken together, it can therefore be speculated that the relatively intact ability to use multi-modal feedback information in HD might potentially be useful to improve motor control in HD patients.

V.4B.2. Clinical correlates of eye and hand movements in the self-paced tasks

In the current study, the results corroborated previous studies which showed that the performance level of hand movement was strongly correlated with the UHDRS motor scores of HD patients (Andrich et al., 2007; Michell et al., 2008; Saft et al., 2006). This was expected, as the UHDRS motor component primarily assesses the control of voluntary movement in HD. In addition to the hand, the performance of the eye in the eye-hand task was well correlated with UHDRS motor scores in HD. According to Saft et al. (2006), the change in performance level in a hand tapping task was also related to the extent of caudate atrophy in HD patients. These findings show that self-paced rhythmical eye and hand movement might not only be a good indicator of the severity of motor impairment in HD but also of the underlying neuropathological changes in HD patients.

Saft et al. (2006) showed that the reduction in hand tapping rate of HD patients was also associated with decline in performance in the cognitive tests of the UHDRS. However, it is known that the UHDRS cognitive component primarily provides a measure of executive function domain rather than global cognitive functioning (Toh et al., 2014). Therefore, I extended their work (Saft et al., 2006) by comparing the performance level of eye and hand movements to the global cognitive function of HD patients. Interestingly, it was revealed that the ability to generate self-paced rhythmical eye and hand movements was significantly correlated with the global cognitive scores of HD patients. This suggested that a decline in the ability to control self-paced rhythmical eye and hand movements in HD reflects an overall
deterioration of cognition. As discussed before, the control of eye and hand movements is dependent on the functional interactions between cortical and subcortical structures. Therefore, cerebral degeneration, which is a direct attribute of cognitive deterioration in HD (Rosas et al., 2005), can also affect the control of self-paced rhythmical eye-hand movement in HD patients. Based on these findings, it can be suggested that the performance level in self-paced rhythmical eye and hand movements, in addition to having the potential to be a global disease progression marker, might also be an effective tool in providing an overall measure of motor disability and cognitive decline in HD.

**V.4B.3. 12 month changes in self-paced rhythmical eye-hand movement**

It is well-established that there is a systematic decline in hand tapping rate in HD over time (Andrich et al., 2007; Antoniades et al., 2010; Collins et al., 2014; Michell et al., 2008). However, there is conflicting evidence in terms of the annual changes in hand tapping rate in manifest HD, as Collins et al. (2014) demonstrated a decline in task performance after a year while others claimed that a change was only apparent after considerably longer follow-up intervals (Andrich et al., 2007; Antoniades et al., 2010; Michell et al., 2008). It is also noteworthy that many of these studies made the assumption of a systematic decline in the HD group in the absence of a control group. In contradistinction to the studies by Andrich et al. (2007) and Antoniades et al. (2010), in which they revealed that there were relatively negligible annual changes in rhythmical somatomotor movement, the present study demonstrated that relative to controls (who had negligible performance changes after 12 months), there was a significant decline in rhythmical self-paced eye and hand movements over time in all HD stages. Taken together, these findings suggest that there was a generalised and systematic decline in self-paced rhythmical movement across all stages of HD and that such a decline was measurable over a relatively short period of 12 months.

Nevertheless, one might argue that the finding of a significant decline in the performance of the eye in the eye-hand task contradicted the finding of a minimal change in the number of self-paced saccades generated after 12 months in the saccade-only task reported earlier in this chapter (refer to section V.3A.1). However, the neural pathways for the control of saccades made in isolation and those made during coordinated eye-hand movements, though sharing a similar fundamental neural circuit, involve different regions of cerebral cortex. The neural circuitry involved in the generation of self-paced saccades was discussed in detail in section V.4A.1. In contrast to the neural pathway for self-paced saccades, which primarily receives inputs from the frontal eye field and the supplementary eye field in the frontal cortex, the key
cortical area involved in the control of coordinated eye-hand movements is the posterior parietal cortex (Dean et al., 2012; Hwang et al., 2014; Vesia et al., 2010). Progressive degeneration of the cerebral cortex (Rosas et al., 2008; Tabrizi et al., 2010) in HD might have affected the functionality of the frontal and posterior parietal cortices and contributed to the poor performance of HD patients in the two variants of the rhythmical self-paced tasks when compared to controls. However, Rosas et al. (2008) demonstrated that there was great heterogeneity in terms of cortical degeneration in HD patients over time. These findings might conceivably explain the differences in the rate of decline in the performance level of the HD group in the two rhythmical self-paced tasks after 12 months. Rosas et al. (2002) reported that the sensorimotor region of the cortex was the most affected of all cortical regions. Taken together, it can be postulated that the neural control system for rhythmical self-paced eye and hand movements might be more susceptible to HD pathology than the neural system for controlling self-paced saccades over a relatively brief period of time and thus, making it an appealing tool for measuring short-term disease progression in HD.

V.4B.4. Eye-hand movement prediction in the temporally-cued tasks

The data of the control group in the present study can be compared with the results of Barnes and Marsden (2002), who studied the characteristics of eye-hand movement of healthy controls in tasks with repeated presentation of a target stimuli at a constant inter-stimulus interval (ISI). Barnes and Marsden (2002) reported that there was a progressive shortening of latency in the eye and the hand with increasing ISI from an ISI value of 480 ms up to 910 ms. However, it was shown that in contrast to the eye, which continued to show further reduction in latency in trials at the longest ISI (3740 ms), there was a gradual reversal of movement prediction in the hand beyond an ISI value of 910 ms (Barnes & Marsden, 2002). Despite variation in the ISIs used in the present study and the study by Barnes and Marsden (2002), the control group of the current study also demonstrated that there were differences in the predictive behaviour of the eye and hand movements with increasing ISI. That is, the latency of the eye was progressively reduced with longer ISIs, whereas the latency of the hand reduced initially and progressively increased as the ISI increased. The pattern of predictive behaviour of the hand in controls is consistent with the fact that humans, in general, are capable of instigating predictive somatomotor movement at an ISI value of 100 ms (Jeeves, 1961). However, such predictive behaviour would tend to cease when the ISI is longer than 2000 ms (Mates et al., 1994), which coincides with the increase in hand latency in the control group at the 2050 ms ISI in the present study.
Based on a review by Gross et al. (1999), predictive behaviour in the somatomotor system – referred to by the authors as sensorimotor prediction – is controlled by two partially distinct but parallel neural network loops, the cortico-basal ganglionic and cortico-cerebellar loops. The posterior parietal cortex, a key centre for integrating sensory information (Vesia et al., 2010), is thought to provide the secondary motor areas (the premotor cortex and supplementary motor area) with visual representations of the body in relation to the environment in real-time and also in a predicted state (i.e. if an anticipatory movement was to be performed) (Kosslyn & Sussman, 1994). The secondary motor areas are actively involved in motor planning and these regions are thought to participate in sensorimotor prediction by constructing hypothetical movements based on associative memories and visual representations supplied by the posterior parietal cortex (Tsunoda et al., 1996). These hypothetical movements would then be projected to the striatum of basal ganglia for further processing. It was postulated that the striatal neurons of the basal ganglia are capable of selecting these suggested movements via an internal process that evaluates the sensory situations and the outcomes of these motor commands based on past experiences (Gross et al., 1999). There is compelling evidence to suggest that the cerebellum plays a significant role in the control of predictive behaviour (Barrera, 2010). As stated by Gross et al. (1999), the cerebellum uses sensory context from the sensory cortex to predict the sensory outcomes of the proposed motor commands from the secondary motor areas. Sensory prediction is then projected back to the primary motor areas via the thalamus to enable the suggested actions to be performed (Gross et al., 1999).

Consistent with the findings in the saccade-only temporally-cued tasks (please refer section V.3A.2), in which there was minimal predictive behaviour in the eye in HD, the HD group, relative to controls, showed significantly less prediction in eye-hand movements. These findings suggest that there is a generalised change in the predictive behaviour in manifest HD. As previously discussed (refer section V.4A.2), in HD, there is strong evidence of progressive degenerative changes in various neural structures implicated in the control of predictive behaviour (Aylward et al., 1997; Aylward et al., 2011; Rosas et al., 2001; Rosas et al., 2008; Rub et al., 2013; Tabrizi et al., 2013). Taken together, it can be speculated that HD pathology in the cortical and subcortical structures might have in general, affected the normal functioning of neural systems involved in controlling predictive behaviour of motor movements. The finding of an altered predictive behaviour in stage 1 HD patients compared to controls in the present study is consistent with these neuropathological changes being evident even in early HD (Kipps et al., 2005; Rosas et al., 2005; Stoffers et al., 2010; Tabrizi et al., 2009).
V.4B.5. Differences in the predictive behaviour of the eye in the saccade-only and eye-hand variants of the temporally-cued tasks

It is interesting to compare the results of the saccade-only (refer section V.3A.2 for a detailed description) and eye-hand variants of the temporally-cued tasks (refer section V.3B.3). The present study revealed that in controls, when saccades are performed in isolation in the temporally-cued tasks, the strength of prediction is inversely related to the length of the ISIs. That is, saccade prediction was found to be the strongest in trials with the shortest ISI and decreased with increasing ISI. Conversely, this relationship was reversed in the eye-hand variants of the same task. It is to be noted that the HD group, which failed to demonstrate significant saccade prediction in the saccade-only temporally-cued task, was found to exhibit certain degree of movement prediction in the eye and the hand in the eye-hand variants of temporally-cued tasks. Based on this, it can be speculated that the predictive behaviour of the oculomotor system could be enhanced when oculomotor movement is executed concurrent with somatomotor movement. Consistent with this interpretation is the fact that in healthy volunteers, ocular pursuit was found to be improved when ocular tracking was accompanied with hand tracking (Gauthier et al., 1988; Leist et al., 1987).

There are several possible mechanisms by which hand movement may enhance the predictive behaviour of the eye. According to Barnes and Marsden (2002), the central initiation of hand movement might have the ability to accentuate the expectancy level of the central system, leading to the facilitation of eye movement execution. Based on the postulation that there is a constant exchange of information between the eye and the hand systems when executing coordinated eye-hand movements (Gauthier et al., 1988), Barnes and Marsden (2002) claimed that in the process of initiating the hand movement, the somatomotor control system might have provided the immediate kinematic information of the intended hand movement to the oculomotor system, thus eliminating the need for the oculomotor system to access the internally-stored information required to generate a predictive saccade.

Feedback control systems may also have a role in strengthening the predictive behaviour of the eye in the temporally-cued eye-hand tasks. Lewis et al. (1994) demonstrated that visual feedback is the main form of feedback mechanism for the oculomotor system because proprioceptive feedback from the extraocular muscles primarily contributes to long-term (i.e. over several weeks or months) regulation of eye movement. By contrast, the somatomotor control system has the advantage of concurrently utilising both visual and proprioceptive feedback mechanisms (Barnes & Grealy, 1992). The availability of visual and proprioceptive
feedback information during a coordinated eye-hand movement might have provided additional feedback information for the oculomotor system to assess the eye performance, resulting in stronger predictive behaviour of the eye in the temporally-cued eye-hand tasks, as observed in both groups in the present study.

The ability for the motor system to express predictive behaviour in motor planning and execution is integral to a smooth and efficient control of motor movement (Wexler & Klam, 2001). This is because sensorimotor prediction enables the motor system to minimise reaction time delays by preparing the desired response well in advance of the anticipated situations (Schmidt, 1968). The finding that there was a synergistic effect in sensorimotor prediction in temporally-cued eye-hand movement in HD suggests that this effect may have utility in managing their motor symptoms. HD patients might benefit from motor training techniques that make use of one movement to facilitate the execution of another movement, i.e. using the eye to assist in the initiation of limb movement or vice versa, when performing self-paced or temporally-cued rhythmical movements.

**V.4B.6. ISI effect on the difference between eye and hand latencies in the temporally-cued tasks**

The presence of a significant ISI effect in the difference between eye and hand latencies (eye-hand latency interval) in the control group (i.e. mean eye-hand latency interval was shorter than at the random phase at the shortest ISI and this progressively increased to being longer at longer ISIs) suggests that there is no strict temporal sequentiality in the coordination of eye and hand movement in a temporally-cued task. That is, in eye-hand coordinated movements, the eye does not necessarily have to lead or precede the hand movement. Consistent with this idea is the fact that the pattern of human eye-hand coordination in a natural environment can vary according to the task in context (Pelz et al., 2001). The current study also showed that there was a significant effect of ISI in eye-hand latency interval in the HD group. That is, eye-hand latency interval changes in the HD group, albeit smaller in magnitude than controls, when target motion becomes predictable. This indicates that in a temporally-cued task, HD patients could accordingly adjust the temporal sequencing of eye-hand coordination to meet the demand of the task, suggesting a relative preservation of flexibility in the temporal sequentiality of eye-hand movements in manifest HD.

It is however, important to highlight that there was a greater increase in eye-hand latency interval, i.e. eye movement was initiated well in advance of the hand, in controls compared to
the HD group with increasing ISI. Based on these findings, it is tempting to suggest that HD patients might have a more efficient control of temporal coordination of the eye and hand movement in a temporally-cued task, because there was a reduced period of dormancy between the initiation of eye and hand movements. This may, however, not be the case. It is well-established that there are two distinct types of fixation in naturalistic tasks, ‘guiding’ fixation and ‘look-ahead’ fixation (Lehtonen et al., 2013; Mennie et al., 2007; Pelz et al., 2001). It was suggested that ‘guiding’ fixations are closely coupled to the ongoing movement whereas ‘look-ahead’ fixations aim at objects that are relevant in the future but not in the current ongoing subtask (Lehtonen et al., 2013). Khan et al. (2011) posited that the rationale for directing fixation to locations relevant for future actions is to enable the motor system to process the properties of the objects that will be manipulated for setting internal goals for future motor actions. Mennie and colleagues (2007) provided evidence to support that look-ahead fixations are indeed involved in gathering spatial and temporal information relevant for future actions and have direct influences on the accuracy of subsequent motor actions. Taken together, the findings in the present study might possibly suggest that in controls, there was a greater flexibility in selecting gaze strategies for motor planning which might be reduced in the HD group.

It can be speculated that in HD, the reduced flexibility in the selection of gaze strategy is related to a greater reliance on visual guidance in movement execution in HD. An increased reliance upon visual cues to guide movement in HD was reported in a study by Georgiou et al. (1995), in which they showed that HD patients had difficulty in executing sequential responses with the reduction of advanced visual information in a button pressing task. The authors postulated that an increased reliance on external cues is likely an effect of HD. Given that the basal ganglia provide internal cues for movement generation, the degeneration of basal ganglia in HD might have affected the ability of HD patients to use internal cues to control their movements (Georgiou et al., 1995). Besides, Pelz and colleagues (2001) demonstrated that hand movements in healthy controls are usually initiated close to or concurrently with the eye, in tasks that require high level of visual guidance. They also posited that this strategy of eye-hand coordination eliminates the need for the motor control system to separately initiate the eye and the hand movement at different times (Pelz et al., 2001). Based on this evidence, it can be posited that manifest HD patients have likely selected a gaze strategy with relatively constant eye-hand latency interval, because this ensures that the eye is always available or near to the hand for guiding the movement. Further, such a strategy does not place additional burden on an already compromised motor control system.
In summary, the findings in the temporally-cued tasks conceivably suggest that in HD, there was greater reliance on visual guidance in movement control and having a relatively fixed temporal coupling of eye-hand coordination (compared to controls) ensures that the eye can be readily called upon to guide the hand during movement execution.

V.4B.7. **Clinical correlates of eye and hand movements in the temporally-cued tasks**

The current study revealed that in the HD group, eye-hand movement parameters in the temporally-cued tasks were weakly correlated with UHDRS motor scores and global cognitive scores (Figure V.8). These findings suggest that eye-hand coordination performance in the temporally-cued tasks in general, do not closely reflect the disease status of HD patients. One possible explanation for the weak associations was that the UHDRS motor component primarily assesses motor movements that are under the direct influence of the cortico-basal ganglia pathway. As discussed previously, the predictive behaviour of the human motor system is governed by two partially distinct neural pathways, the cortico-basal ganglia and the cortico-cerebellar neural loops (refer to section V.4A.2 for a detailed discussion). Although the degeneration of the basal ganglia co-exists with cerebellar atrophy in HD, the extent of cell loss in the basal ganglia was independent of the atrophic changes in the cerebellum (Rub et al., 2013). Given the disparity in the degeneration of the two neural structures, it can be implied that there might be a non-uniform decline in the normal function of the two neural pathways involved in the control of sensorimotor prediction in HD. This results in deficits in sensorimotor prediction being unrelated to the clinical severity of HD patients, in terms of the degree of motor or cognitive impairment. These findings though valuable for understanding the behaviour of eye-hand movements in manifest HD, diminish the value of eye-hand movement measurement in a temporally-cued task as a potential disease biomarker for HD.

V.5. **Chapter summary**

In summary, the present study extended the current literature on the characteristics of rhythmical saccades in HD (Tian et al., 1991; Winograd-Gurvich et al., 2003) to show that deficits in rhythmical saccades – self-paced and predictive – were evident in early manifest HD and worsened with increasing disease severity, as measured using HD clinical staging, UHDRS motor component, and global cognitive level. In addition, there was demonstrable short-term progression in saccadic latency but not in the number of self-paced saccades or predictive
behaviour of the eye in the temporally-cued tasks after 12 months. It is therefore proposed that for saccade assessment, the measurement of reactive saccadic latency might be useful progression marker for following short-term disease changes, i.e. over 12 months, in manifest HD whereas rhythmical self-paced and predictive saccade paradigms may be valuable for longer-term follow-up. Given the close association between the main pathological site of HD and the neural circuits for eye movement control, and the evidence of objectively measured longitudinal changes in saccades, the use of saccadic measures in general might be helpful adjuncts for monitoring the effects of putative neuroprotective therapies in both manifest and premanifest HD. An improvement, or stable saccade measurement, would potentially translate to the therapy as having an effective neuroprotective effect.

Despite having a small sample, data from the present study provided compelling evidence of a longitudinal decline in rhythmical eye-hand movement in a self-paced task and also of a change in the predictive behaviour of eye-hand movement in HD patients, compared to controls. Findings in rhythmical saccadic and eye-hand movements were discussed in relation to the neuropathological changes in HD. The presence of a significant decline in rhythmical eye-hand movement in the self-paced tasks over a brief period of 12 months substantiated previous claims (Andrich et al., 2007; Antoniades et al., 2010; Saft et al., 2006) that a simple motor task might be more effective than complex tasks in demonstrating disease progression in HD over time. This also indicates that the measurement of concurrent self-paced eye and hand movements may potentially be useful progression marker of HD for monitoring short-term longitudinal disease changes. Given the relative simplicity of the task, it can be easily translated for use in research trials or clinical practice.

In addition, concurrent control of the eye and hand movements in the temporally-cued tasks appeared to have strengthened the predictive behaviour of the eye in the HD group. Future study is warranted to examine if concurrent control of multiple motor control systems is beneficial for the improvement of motor control in manifest HD. If this claim is substantiated by a larger study, motor training that focusses on using one movement to guide another may serve as another treatment avenue for managing motor symptoms in manifest HD.
Chapter VI

Complex movement

VI.1. Background

In general, human saccades can be broadly categorised as either visually-guided or complex volitional saccades. The execution of visually-guided saccades is dependent on an external cue and some relatively simple sensorimotor transformation processes in the saccade generating system (McDowell et al., 2008). By contrast, complex volitional saccades, which are generated based on contextual cues and instructions, often require the concurrent inhibition of a reflexive saccade and involvement of various complex cognitive processes in multiple cortical regions (McDowell et al., 2008; Munoz & Everling, 2004; Pierrot-Deseilligny, 1991; Pierrot-Deseilligny et al., 2004). Despite the differences, both type of saccades share a final common motor pathway for saccade generation (Leigh & Zee, 2006).

Complex volitional saccades have been widely-used in the study of various behavioural and
neurological disorders (Anderson & MacAskill, 2013; Landgraf et al., 2008; van Stockum et al., 2012). Memory-guided saccade and anti-saccade tasks are the most commonly used complex volitional saccade paradigms in functional neuroimaging studies (McDowell et al., 2008). Although there are slight variations in the complex volitional saccade paradigms used across studies, all of them consisted of pro-saccade inhibition and a spatial working memory processing component. In a memory-guided saccade task, for example, participants should remember the location of a briefly presented target without making a saccade to it, and a saccade should only be made to that remembered location after a brief delay. Meanwhile, in an anti-saccade task, a saccade should be directed to the mirror – opposite – location of a peripheral target upon fixation target offset.

The hallmarks in HD are involuntary hyperkinetic movements, saccadic function abnormalities (Anderson & MacAskill, 2013; Lasker & Zee, 1997) and cognitive impairment (Paulsen, 2011). Complex volitional saccades have been extensively studied in previous cross-sectional studies, in which it was found that there was a significantly increased saccade disinhibition in HD patients and authors have suggested that performance in complex volitional saccades may potentially reflect the underlying neuropathology in HD (Becker et al., 2009; Blekher et al., 2009b; Lasker et al., 1987; Peltsch et al., 2008; Tabrizi et al., 2009; Tsai et al., 1995). Despite the findings of cross-sectional studies, there has, however, been conflicting evidence of the utility of various types of complex volitional saccade tasks in the longitudinal monitoring of disease progression in HD (Rupp et al., 2010; Tabrizi et al., 2010).

The control of somatic movement calls upon the concerted interactions of a schema (a control system that specifies the current tasks and plans the overall sequence of actions), gaze, visual, and motor systems (Land, 2009). In manifest HD, there was evidence of a stronger reliance of visual guidance in the control of motor performance (Georgiou et al., 1995). It was also suggested that in HD, there are great similarities between eye and arm movement abnormalities (Berardelli et al., 1999). Despite that, there is no literature on a direct comparison of the longitudinal changes in saccadic and eye-hand coordination performance in various complex movement tasks in HD. Wolf et al. (2008) found that in premanifest HD, there was a stronger disease effect on the functional abnormalities of motor control in tasks with higher cognitive load, i.e. complex movement tasks. Therefore, one of the objectives of the present study was to examine and compare the utility of various complex movement tasks for monitoring 12 month disease progression in HD and also to probe the eye-hand coordination of HD patients in complex volitional movements.
VI.2. Methods

Please refer to Chapter II for a detailed description of study procedures.

VI.3. Results

VI.3A. Complex volitional saccades (Delayed, memory-guided, and anti-saccades)

VI.3A.1. Saccade disinhibition and pro-saccade correction

Between-group differences, group-by-time interactions, and disease stage effect on saccadic disinhibition in the three voluntary saccadic tasks were determined by fitting generalised linear mixed-effect models for binary data to the number of disinhibited saccades and the total number of saccadic responses made.

The HD group (Baseline Mean % [SD] : Delayed: 46.1 [32.4]; Memory-guided: 55.8 [30.3]; Anti-saccade: 71.5 [30.7]) had a significantly higher proportion of disinhibited saccadic response than controls (Baseline Mean % [SD] : Delayed: 6.9 [11.0]; Memory-guided: 9.7 [9.0]; Anti-saccade: 19.7 [11.3]) in all three complex movement tasks ($z > 6.0, p \leq 0.003$) at baseline and at 12 month follow-up. The mean effect sizes ranged from $d = 1.6$ in the delayed task to $d = 2.0$ in the anti-saccade task. There were no significant differences between the two groups, in terms of the proportion of pro-saccade correction (proportion of saccades made to the peripheral target which were subsequently corrected to the mirror position of that target) in the anti-saccade task ($z = -1.8, p = 0.09$).

There was a strong linear effect ($z \geq 6.3, p \leq 0.001$) of disease stage on the rate of disinhibited saccadic response in the delayed and anti-saccade tasks and a strong non-linear disease stage effect ($z = -2.9, p \leq 0.001$) in the memory-guided task. That is, in all three tasks, saccadic disinhibition increased with worsening disease severity in HD (Figure VI.1). The corrected pro-saccade error rate in the anti-saccade task ($z = -2.5, p = 0.01$) was relatively high from controls through Stage 1 and 2, with a substantial decline observed in Stage 3 HD (Figure VI.1).

There was a significant group × time interaction in the memory-guided task ($z = 3.0, p = 0.002$) and the anti-saccade ($z = 2.5, p = 0.01$) task. This was contributed by a significant improvement in performance (i.e. reduction in disinhibited saccades) by controls in the presence of a minimal change in HD patients in these complex saccade tasks. This interaction however, was not striking when the HD group was broken up by disease stage (Figure VI.1).
VI.3A.2. Saccade disinhibition in the memory-guided task

A linear mixed effect model was fitted to the differences between the proportions of disinhibited saccade at peripheral target (flash) offset and at fixation target offset to determine if there were any changes in the proportions of disinhibited saccade between the two time points in all three fixation intervals (1500 ms, 2000 ms, and 2500 ms) in the memory-guided task. In both the control and the HD groups, there was about an 8% increase in the proportion of disinhibited
saccade from fixation target offset to peripheral target offset in trials with the shortest fixation interval (1500 ms). The increase in the proportion of disinhibited saccades during fixation period (peripheral target offset and fixation target offset) was relatively stable across the three fixation intervals in either group ($p \geq 0.1$) (Figure VI.2). There was no overt HD effect ($p = 0.3$) on the increase in the proportion of disinhibited saccades between the two time points across the three fixation intervals.

![Figure VI.2](image)

**Figure VI.2** The cumulative frequencies of saccadic latencies in memory-guided trials with 1500 ms, 2000 ms, and 2500 ms fixation intervals. The green lines indicate the peripheral target (flash) offset time (400 ms) and the green dotted lines are the fixation target offset times (1900 ms, 2400 ms, and 2900 ms). The duration of the fixation interval is shaded in pink in each panel. Changes in the proportions of disinhibited saccade during fixation period are the differences between the proportions of disinhibited saccade at peripheral target offset and at fixation target offset.

### VI.3A.3. Saccadic latency of correct and corrected responses

Linear mixed-effect models were fitted to saccadic latencies in the ‘Step’ condition of the reflexive 1D (horizontal only) paradigm (refer section IV.3A.1) and latencies of correct saccadic responses in the three complex movement tasks to determine between-task and between-group differences, and the longitudinal changes within each complex task.

In the control group, the delayed, memory-guided, and anti-saccade tasks had longer latencies than the reflexive task by 137 ms [95% CI: 112 ms – 161 ms; $p < 0.001$], 145 ms [95% CI: 123 ms – 166 ms; $p < 0.001$], and 157 ms [95% CI: 138 ms – 175 ms; $p < 0.001$], respectively (Figure VI.3). There was no evidence of a group effect ($p \geq 0.6$) on the increase in eye latencies in complex tasks in relative to the reflexive task (Figure VI.3), suggesting both control and HD groups shared a similar profile of increase in eye latency in complex movement tasks. The HD group, however had a significantly longer latency ($t = 4.6, p < 0.001$) than controls for prosaccade correction in the anti-saccade task (Control: Mean = 196 ms, SD = 61 ms; HD: Mean = 360 ms, SD = 140 ms).
In controls, there were no significant changes ($p \geq 0.3$) in latency in all three complex tasks at 12 month follow-up. There was however, an overt time effect in latency in the memory guided and anti-saccade tasks in the HD group, in which there was an estimated increase of latency by 67 ms [95% CI: 13 ms – 121 ms; $p = 0.02$] and 51 ms [95% CI: 12 ms – 90 ms; $p = 0.01$], respectively in the follow-up session (Figure VI.3). A significant group × time interaction was observed in the memory guided task only ($p = 0.04$).

![Figure VI.3](image)

**Figure VI.3** Mean saccadic latencies in the reflexive (‘Step’ task) and complex movement tasks for controls and the HD group at baseline and at 12 month follow-up. Filled circles are the LMEM-estimated group mean latencies and unfilled circles, means for individual subjects.

### VI.3A.4. Clinical correlates of saccades in the complex movement tasks

#### VI.3A.4.1. Saccade disinhibition and corrected pro-saccade error rates

It was revealed that in general linear regressions did not provide a good fit for the relationships between the proportions of disinhibited saccade and corrected pro-saccade error, and current disease status (UHDRS motor scores and working memory domain z-scores). Thus, nonlinear regressions were used to assess the relationships (Figure VI.4).

The proportion of disinhibited saccades in all three complex tasks generally increased with an increase in UHDRS motor scores (Figure VI.4A) and decrease in working memory domain z-scores (Figure VI.4B). There was a much smaller range of pro-saccade correction rate in the anti-saccade task and a decline in pro-saccade correction rate was observed in participants with either a very high motor score (Figure VI.4A) or a very poor working memory domain z-score (Figure VI.4B)
VI.3A.4.2.  **Saccadic latency of correct and corrected responses**

Simple correlations were used to examine the relationships between mean latencies of correct saccadic responses and pro-saccade correction in the complex tasks, and UHDRS motor scores, and working memory domain scores.

Large deviations from a linear fit resulted in low $r$ values in the relationships between mean latencies of correct saccadic response in all three tasks and UHDRS motor scores (Figure VI.5A), and working memory domain scores (Figure VI.5B). Mean latencies of corrected pro-saccade errors, however, showed strong positive correlation ($r = 0.8, p < 0.001$) with the UHDRS motor scores (Figure VI.5A) and strong negative correlation ($r = -0.6, p = 0.007$) with working memory domain scores (Figure VI.5B), suggesting that an increase in corrected pro-saccade error latency is associated with higher motor scores and lower working memory domain scores. Further, bootstrapping procedure revealed that latencies for corrected pro-saccade errors had greater association with UHDRS motor scores than the scores pertaining to working memory function (Differences in $r$ [95% CI]: 0.4 [0.02 – 0.6]).
Saccadic parameters in all three complex tasks showed weak correlations ($0 < r < 0.3$, $p > 0.2$) to CAG repeat number, indicating that changes in saccadic performance are progressive and not related to CAG repeat size.

![Figure VI.5 Correlations between saccade latencies in the three complex tasks and (A) UHDRS motor scores, and (B) working memory domain z-scores. $r$ [95% CIs] and $p$ values are shown.]

**VI.3B. Eye-hand coordination in the delayed task**

**V.3B.1 Movement disinhibition**

Latency distributions from the combined eye-hand delayed task are shown in Figure VI.6. In contrast to controls, who showed a unimodal eye latency distribution, the HD group demonstrated a bimodal distribution, at baseline and at 12 month follow-up assessments (Figure VI.6A). That is, the HD group had an increased eye movement disinhibition rate in the delayed task. For hand movement, the HD group had a much wider latency distribution compared to controls, indicating a high variability in hand latencies (Figure VI.6B).

A binomial family generalized linear mixed-effect model was fitted to the number of disinhibited responses and total number of responses made, to establish the between-group differences and the effect of time on eye and hand disinhibited responses. At baseline, there was a significant increase ($p < 0.001$) in disinhibited eye and hand responses in the HD group.
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compared to controls (Table VI.1). There was an effect of time in eye movement disinhibition in both groups, with the disinhibited eye response rate dropping by 5% ($p < 0.005$) in controls and increasing by 10% ($p < 0.03$) in the HD group in the follow-up session. These contrasting effects in the two groups contributed to a strong group × time interaction ($z = 3.5, p < 0.001$). By contrast, there was no overt time effect in hand movement disinhibition in either group ($p \geq 0.1$) and also no group × time interaction ($p = 0.2$).

![Figure VI.6](image)

**Figure VI.6**  Latency distribution of the eye (A) and hand (B) in controls and the HD group in the combined eye-hand movement delayed task. The blue dashed lines indicate fixation target offset while the red dashed lines are the cut-off times (Eye: 80 ms; and hand: 120 ms) for correct responses. Disinhibited responses are responses made in the time frame shaded in ‘light blue’. The bin-width for the histograms is 25 ms.
Table VI.1  Mean rate (SD) of disinhibited eye and hand responses in the combined eye-hand movement delayed task

<table>
<thead>
<tr>
<th></th>
<th>Rate of disinhibited responses (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Control group</td>
<td>HD group</td>
<td>HD vs. Control</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Baseline</td>
<td>Change after 12 months</td>
<td>Baseline</td>
<td>Change after 12 months</td>
<td>Difference</td>
</tr>
<tr>
<td>Eye</td>
<td>vs. Control</td>
<td></td>
<td>vs. Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8 (14)</td>
<td>-5 (11), 0.005</td>
<td>43 (35)</td>
<td>10 (23), 0.03</td>
<td>-3.5, 0.001</td>
</tr>
<tr>
<td>Change after 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand</td>
<td>2 (5)</td>
<td>-1 (4), 0.4</td>
<td>8 (11)</td>
<td>5 (18), 0.1</td>
<td>2.6, 0.001</td>
</tr>
</tbody>
</table>

A linear mixed effect model was fitted to the proportions of disinhibited eye and hand responses at fixation offset to determine if there is any differences in the percentages of disinhibited responses between the eye and hand at fixation offset. In controls, the proportion of disinhibited responses in the eye was not significantly higher than the hand at fixation offset (10% vs. 3%), with an estimated increase of 7% [95% CI: -1% – 15%; 0.07]. The HD group, relative to controls, showed a significantly higher response disinhibition in the eye than the hand (40% vs. 17%), with an estimated increase of 23% [95% CI: 12% – 35%; 0.001] greater than the increase observed in the control group. Despite there being no evidence of a time effect in controls (0.1), the HD group demonstrated an additional increase of 9% [95% CI: 0.3% – 18%; 0.04] in disinhibited eye response compared to the hand in the follow-up session, which resulted in a significant group × time interaction (t = 2.3, 0.03).

Figure VI.7  Disinhibited response rates in controls and the three sub-groups of HD patients in the delayed task.

Error bars shown are 95% CIs. *NB: The only stage 4 patient (S08) was analysed together with the stage 3 patients.

Figure VI.7 shows the disinhibited response rate of the eye and hand for controls and the three sub-groups of HD patients in the combined eye-hand delayed task. There was a significant linear effect of disease stage on the disinhibited response rate of the eye (p < 0.001) and also
the hand \((p < 0.001)\), suggesting that the proportion of disinhibited eye and hand responses increased with increasing disease stage in HD. There was a strong disease stage \(\times\) time effect in eye movement disinhibition \((\chi^2 = 13.4, p < 0.001)\) but this effect was not significant in the hand \((\chi^2 = 6.2, p = 0.2)\). That is, there was a significant increase in disinhibition rate across disease stages in the eye but not the hand in HD in the follow-up session.

### VI.3B.2. Eye and hand latencies: Delayed task vs. reflexive task

![Eye and hand latencies in the visually-guided reflexive task and delayed task.](image)

Figure VI.8  **Eye and hand latencies in the visually-guided reflexive task and delayed task.** Filled circles are the LMEM-estimated group means and unfilled circles, mean latencies for individual subjects.

Linear mixed effect models were fitted to eye and hand latencies of the visually-guided reflexive and of the delayed task to determine the differences in latencies across tasks and the effect of time on latency. In controls, eye and hand latencies were longer by 187 ms [95% CI: 167 ms – 207 ms; \(p < 0.001\)] and 313 ms [95% CI: 270 ms – 356 ms; \(p < 0.001\)] respectively in the delayed task than in the reflexive task (Figure VI.8A). The HD group, in general
demonstrated similar profile of latency changes (Eye: Mean = 209 ms; 95% CI: 166 ms – 252 ms; p < 0.001; Hand: Mean = 225; 95% CI: 185 ms – 264 ms; p < 0.001) in the delayed task as controls (Figure VI.8B) with the exception of a lesser increase in hand latency by 88 ms [95% CI: 29 ms – 146 ms; p = 0.004] than controls (Figure VI.8B). In general, there was an effect of time on eye latency across tasks, with an estimated increase of 19 ms in the follow-up session (p < 0.001). Such effect was however, not apparent in the hand (p = 0.1).

VI.3B.3. **Eye-hand latency interval: Delayed task vs. reflexive task**

A linear mixed effect model was fitted to eye-hand latency intervals (time intervals between the initiation of eye and hand movements when reaching for a target) in the visually-guided reflexive task and in the delayed task to assess the behavioural pattern of the two movements in different eye-hand tasks.

In controls, eye-hand latency interval in the delayed task was larger than the reflexive task by 76 ms [95% CI: 24 ms – 127 ms; p = 0.005]. By contrast, in the HD group, there was no significant increase in eye-hand latency interval in the delayed task, with the estimated eye-hand difference in the delayed task likely being 3 ms [95% CI: -61 ms – 68 ms; p = 0.9] longer than the reflexive task (Figure VI.9).

There was an effect of time on eye-hand latency interval across tasks in controls, with an estimated increase of 104 ms [95% CI: 26 ms – 179 ms; p = 0.007] in the delayed task over the change in the reflexive task in the follow-up session (Figure VI.9). This effect was however, not apparent in the HD group as there was likely only a small increase of 25 ms [95% CI: -66
ms – 117 ms; \( p = 0.6 \) in eye-hand latency interval in the delayed task over the change in the reflexive task at follow-up.

**VI.3B.4. Clinical correlates of eye-hand parameters in the delayed task**

Simple correlations were used to determine if eye-hand coordination performance is associated with changes in motor and cognitive functioning of HD patients.

Disinhibited response rates of the eye showed strong positive correlations \(( p < 0.001)\) with UHDRS motor scores and strong negative correlations \(( p < 0.001)\) with working memory domain scores of HD patients (Figure VI.11), indicating that higher proportions of disinhibited eye responses are associated with higher motor scores and lower scores of working memory domain. In contrast to the disinhibited response rates of the eye, there was a much smaller range of disinhibited hand response rates. The disinhibited hand response rates showed moderation correlations to the two clinical measures of HD (Figure VI.11).

Mean latencies of correct eye and hand responses showed statistically significant positive correlations to UHDRS motor scores (Figure V.12, \( p < 0.001 \)) and not working memory domain scores \(( p = 0.2 \)). This provides the impression that an increase in eye and hand latencies in the delayed task is associated with an increase of motor scores only.
VI.4. Discussion

The present study provided novel findings on 12 month longitudinal changes in manifest HD in three types of complex movement task – delayed, memory-guided, and anti-saccade tasks – and also the relationships between eye-hand measurements in complex tasks and disease status of HD patients. The key findings in this section were: (1) HD patients, irrespective of disease stage, had an increased saccade disinhibition in all three saccade-only complex tasks, whereas impairment of anti-saccade error correction was only evident in advanced HD; (2) The HD group, relative to controls, had a prolonged latency for initiating complex volitional saccades; (3) Saccade inhibition (but not saccadic latency) was in general associated with clinical severity of HD patients, as measured using the UHDRS motor component and working memory domain testing; (4) Despite there was a reduction in saccade disinhibition in controls at follow-up, the proportion of disinhibited saccades in the HD group was relatively unchanged. The HD group, unlike controls who showed minimal 12 month changes in saccade latency across tasks, demonstrated an increase in latency in the memory-guided and anti-saccade tasks at follow-up; and (5) In terms of eye-hand movement measurements, the HD group had higher proportions of disinhibited eye and hand response than controls at baseline but there was only an overt increase in eye movement disinhibition in the follow-up session.
VI.4A. Complex volitional saccades (Delayed, memory-guided, and anti-saccades)

VI.4A.1. Saccadic performance in complex tasks

The findings in this study (refer Figure VI.1) were consistent with previous studies which demonstrated that in HD, there is increased saccade disinhibition in complex tasks (Lasker & Zee, 1997; Lasker et al., 1987; Tabrizi et al., 2009). It is well-established that the frontal cortex and the basal ganglia, via their direct projections to the superior colliculus, contribute to the planning and generation of volitional saccades (Hikosaka et al., 2000; McDowell et al., 2008; Pierrot-Deseilligny et al., 2004; Pierrot-Deseilligny et al., 2005). An increase in saccade disinhibition in HD is therefore posited to be associated with neurodegenerative changes in the indirect pathway of the basal ganglia and also degeneration of the frontal cortex, which in combination results in an impairment in saccadic activity control by the superior colliculus (Lasker & Zee, 1997; Lasker et al., 1987). In addition to increased saccade disinhibition, the present study showed that saccade disinhibition increased with worsening of UHDRS motor scores and working memory domain scores, and an increase in disease stage (refer Figure VI.1). Given that there were close associations between saccade disinhibition and clinical progression in HD, findings from the present study reaffirm the hypothesis from previous studies that performance in volitional saccades can potentially be a marker of disease progression in HD (Blekher et al., 2009a; Blekher et al., 2004; Turner et al., 2011).

However, it can be argued that the increased saccade disinhibition in the HD group may simply indicate the failure of HD patients to understand the task demands of the complex movement tasks. The present study provided evidence to refute such an argument. Subjects were given practice trials for each of the complex task to gauge their understanding of the tasks and actual trials were initiated only if they were able to perform the task during the practice trials. All subjects showed that they were capable of performing all three complex saccade tasks during practice trials.

The current study also revealed that in manifest HD, there was an inverse relationship between corrected pro-saccade errors and disease stage, such that the proportion of corrected errors declined with an increase in disease stage. Two processes – failure of inhibition (termed as ‘weakness in the fixation control system’ in several previous studies) and deficits in working memory function – have been linked to cause pro-saccade errors (corrected and uncorrected) in an anti-saccade task (Barton et al., 2008; Bowling et al., 2012; Unsworth et al., 2011). As discussed above, the main trigger for corrected and uncorrected errors is a failure of the movement gating mechanism in the basal ganglia, which results in the impairment of movement...
inhibition. However, intact working memory functioning, which is responsible for maintaining task goals, facilitates rapid correction of errors (Bowling et al., 2012). Uncorrected errors are closely associated with the level of cognition and are primarily caused by the failure to maintain the task goal in working memory (Fischer et al., 2000). In line with this argument is that uncorrected errors are commonly observed in individuals with dementing conditions or with frontal lobe lesions (Bowling et al., 2012).

Taken together, it can therefore be concluded that in early HD, the high proportion of corrected errors is driven primarily by weakness in the basal ganglia movement inhibitory network. On the other hand, an increase in uncorrected errors in higher disease stages is linked to a decline in working memory capacity. These findings are consistent with the underlying pathological changes in HD. In early HD, there is selective degeneration of the indirect pathway of the basal ganglia (Albin et al., 1992; Glass et al., 2000; Reiner et al., 1988). This results in an increased GPe inhibition on downstream structures, and in turn leads to a reduction of inhibitory signals from the SNr to the saccade generating neurons in the superior colliculus (Galvan et al., 2012). An outcome of this cascade of events is a generalised impairment of the movement gating mechanism of the basal ganglia, which in this study, translated to increased saccade disinhibition. However, the relative preservation of working memory function in early HD (Papoutsi et al., 2014; Scheller et al., 2014) enabled the task goal to be maintained in working memory and thus, most errors were corrected in early disease stages (refer Figure VI.1). The progressive deterioration in cognitive functioning in HD (Lemiere et al., 2004; Peavy et al., 2010; Stout et al., 2012) would eventually lead to an impairment in working memory function, and hence, a decrease in corrected errors in patients in the highest disease stage (Figure VI.1). However, it is worth noting that in the HD group, the decline in the proportion of corrected prosaccade errors was not in tandem with the decline in working memory function score (Figure VI.4B). That is, there was an overt decline in corrected prosaccade errors only in participants having the lowest working memory scores. This suggests that the ability to correct prosaccade errors, though influenced by working memory capacity, appeared to be maintained in the HD group until there was a severe impairment in the working memory function.

Previous studies attributed the high saccade disinhibition in HD to a deficit in the fixation control system (Bollen et al., 1986; Lasker et al., 1987; Rubin et al., 1993). In the present study, fixation control in HD was assessed in the memory-guided tasks, which comprised of trials with varying-duration fixation intervals (1500 ms, 2000 ms, and 2500 ms). The HD group, despite having higher proportions of disinhibited saccade than controls at peripheral target offset,
demonstrated a similar increase in the proportions of disinhibited saccade during the fixation interval (i.e. from peripheral target offset to fixation target offset) to controls in all three fixation intervals. As proposed by Munoz et al. (2003), there are two components – exogenous and endogenous – in the control of fixation. In exogenous control of fixation, the presence of an exogenous fixation target leads to a greater activation of fixation neurons and concurrently the inhibition of saccade generating neurons in the superior colliculus and FEF. Given that the fixation target was illuminated throughout the fixation period in the memory-guided task, it can be concluded that exogenous control of fixation is preserved in manifest HD. The dlPFC and the SNr, which have direct inhibitory influence on saccade generating neurons in the superior colliculus and FEF (Hikosaka & Wurtz, 1983), are the two key neural structures implicated in the endogenous control of fixation (Funahashi et al., 1993; Hikosaka & Wurtz, 1983). In HD, impairment in the indirect pathway of the basal ganglia (Galvan et al., 2012) and progressive thinning of the dlPFC (Rosas et al., 2002; Selemon et al., 2004; Sotrel et al., 1991) may disrupt the neurophysiology of the SNr and dlPFC, and subsequently result in a deficit in endogenous control of fixation. The fixation control system may well have a role in saccade inhibition. However, the relative preservation of exogenous fixation control in manifest HD suggests that increased saccade disinhibition in HD is not a generalised failure of the fixation control system per se but rather a poor control over the endogenous component of fixation, caused by a dysfunctional frontal-striatal network.

In summary, in early HD, high saccade disinhibition, with a correction rate that was comparable to controls, is suggestive of a weakness in saccade inhibition, caused by a failure in the basal ganglia movement gating mechanism. However, as disease progresses, there is progressive decline in cognitive functioning, which consequently affects the cognitive aspect of movement control, especially the task goal maintenance aspect of working memory function, resulting in high proportion of uncorrected errors in the anti-saccade task in advanced HD.

VI.4A.2. 12 month changes in saccade disinhibition in complex tasks

The 12 month data in the volitional saccade tasks of the present study confirmed and extended the finding of a multi-modality study that investigated longitudinal changes of various potential disease markers in premanifest and early HD (Tabrizi et al., 2010). The Tabrizi et al. study, which assessed only the proportions of disinhibited saccade in the anti-saccade task, showed that there were minimal changes in premanifest and early HD in terms of the proportions of disinhibited saccade after 12 months and hence suggested that there was no apparent worsening of saccade disinhibition in these sub-groups of HD patients over time. In spite of a step-wise
increase in saccade disinhibition with increasing disease severity in HD in the anti-saccade task at baseline (refer Figure VI.1), the present study demonstrated that there was relatively no change in saccade disinhibition in the delayed and memory-guided tasks at 12 month visit. One postulation for these contrasting results, albeit unlikely, is that there are negligible neuropathological changes in HD over a short time interval of 12 months. A more compelling explanation for this would be that saccade disinhibition does deteriorate with disease progression in HD, but a measurement of saccade disinhibition is not sensitive to short-term disease changes, such as over 12 months. Nevertheless, the lack of 12 month changes in saccade disinhibition would certainly limit the utility of this measure as a potential short-term progression marker or pharmacodynamics marker for HD.

Another possible explanation for the minimal change in saccade disinhibition is that neural plasticity could have temporarily compensated for short-term neuroanatomical degeneration changes in HD. A study on brain activity during performance monitoring showed that in patients with basal ganglia and cortical lesions, despite the abnormal electrophysiological findings, these patients were still capable of monitoring their performance level (Ullsperger & von Cramon, 2006). A functional MRI (fMRI) study reported that in Tourette’s syndrome, a disease that is caused by abnormalities in the fronto-striatal circuits, normal performance in self-regulatory tasks was achieved by increasing the activation of fronto-striatal circuits (Marsh et al., 2009). It was also shown that neural circuits within the motor cortex can be modified by corticostriatal signals to facilitate movement control (Nudo et al., 1996). Together, these findings indicate that brain plasticity may potentially have subserved short-term compensatory mechanisms to counteract for the neuropathological damages in HD. One implication of this argument is that short-term disease changes in HD, at least over a 12 month period, may not be reflected in changes in the saccade disinhibition in the complex movement tasks.

An interesting finding revealed in this study was that, in contrast to the HD group (which had relatively no change in saccade disinhibition after 12 months) the control group demonstrated significant improvement – i.e. decline – in saccade disinhibition over time. Earlier studies have revealed that cognitive strategies and experience can influence eye movement performance (Nodine et al., 1996; Yarbus, 1967). As described in a review by Schall et al. (1999), visual strategies, which can be influenced with prior training, can modify the neural selection process in the FEF during a visual search task. The authors based their hypothesis on a report that macaques, previously trained to ignore a distractor by exposing a specific type of visual search array, could suppress the activation of visually-guided cells in the FEF to the learned distractor.
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The authors further posited that the ability to alter the efficacy of inter-synaptic communications in the brain is likely the key neural mechanism in the modulation of neural selection process in the FEF (Schall & Thompson, 1999). Based on their findings, it can be implied that in the present study, controls had in general developed effective visual strategies on repeated testing of the same volitional saccade tasks, resulting in an improvement in their performance in those tasks. Several imaging studies showed that degenerative changes in the connectivity and structural integrity of white matter in various regions of the brain, which are evident in premanifest HD, continue to occur in manifest HD (Novak et al., 2014; Poudel et al., 2014; Rosas et al., 2010). Abnormalities in the connectivity and structural integrity of the white matter networks may interfere with the selection processes in the FEF and thus, affecting the ability of HD patients to develop effective visual strategies to improve their performance in saccade inhibition in the follow-up session.

Although saccadic performance in complex volitional tasks deteriorated as clinical severity worsened on cross-sectional analyses, longitudinal changes in complex volitional saccades may assume a slow course, and not be revealed over the relatively short period of 12 months. The involvement of various cognitive and sensorimotor processes in the generation of complex volitional saccades, the heterogeneous nature of neurodegeneration in HD, and also short-term neurophysiological compensations, may have implications for the utility of behavioural performance for monitoring disease progression in HD, especially over short time intervals. However, these inferences are made in the absence of neurophysiological and imaging studies comparing complex volitional saccade performance and brain activity in HD patients. Studies with parallel approaches – i.e. concurrent saccade and neural activity measurements, and brain imaging – may enlighten the understanding of short-term disease changes in HD and also their effects on the performance in complex volitional saccade.

VI.4A.3.  Saccadic latency in complex tasks

The present study extended previous ones (Becker et al., 2009; Lasker et al., 1987) that have investigated the latency of correct saccadic responses in complex tasks. A major distinction between this study and previous ones was that here, mean latencies for complex saccades in the HD group [memory-guided saccade mean = 384 ms; anti-saccade mean = 376 ms] appeared to be shorter than in previous studies [memory-guided saccade mean = 491 ms (Lasker et al., 1987); anti-saccade mean = 461 ms (Becker et al., 2009)]. This disparity in mean latencies could be attributed to experimental design and technical variations in eye movement assessment between studies. Nevertheless, the present study revealed that similar to controls, there was a
task effect in saccade latency in complex movement tasks in the HD group. That is, latencies for complex volitional saccades were significantly longer than visually-guided saccades. The longer latencies in complex volitional saccades represent the additional time taken to modify the neural activity in the basic saccade circuitry and also to recruit additional cortical regions which are generally in idle mode during reflexive saccade execution (Everling & Fischer, 1998; McDowell et al., 2008; Sweeney et al., 2007). In contrast to controls, who demonstrated minimal change in latencies of complex volitional saccades over time, the HD group had significant prolongation in latencies in the memory-guided and anti-saccade tasks after 12 months. This suggests that a measurement of complex saccade latencies might be a sensitive marker of disease progression in manifest HD over a relatively short time interval.

In the current study, it was found that latencies of corrected pro-saccade errors in the anti-saccade task were significantly correlated with the UHDRS motor scores and working memory domain scores (Figure VI.5). As discussed in section VI.4A.1, uncorrected errors are caused by a failure in movement inhibition and also an impairment in working memory function. Given that the UHDRS motor component primarily provides an assessment of impairment in voluntary movement, this may explain the close association between latencies of corrected pro-saccade errors and UHDRS motor scores. Unsworth et al. (2004) posited that working memory capacity is reciprocally associated with disinhibition rates and latencies in an anti-saccade task because cognitive factors are the basis in the maintenance of task goals in complex tasks hence, the significant correlation between the latencies of corrected pro-saccade error and working memory capacity in manifest HD.

It was also revealed in this study that the correlation of corrected pro-saccade error latency with the UHDRS motor score was actually stronger than with the working memory function score. This is perhaps linked to a two-step sequential process involved in the correction of pro-saccade errors. That is, the first step involves recognising the pro-saccade error via the working memory function and the second, relates to the saccadic system initiating the anti-saccade. Although the latency of corrected pro-saccade errors is likely an overall temporal representation of the two events – error recognition and anti-saccade initiation – in the two-step process, the motor component might contribute more than the cognitive component to the overall latency. Therefore, changes in the latency of corrected pro-saccade errors were more closely associated with changes in the UHDRS motor scores than the working memory function scores. This hypothesis can only be validated with electrophysiological data of the separate events, which were not measured in this study. The close associations between latency of corrected pro-
saccade errors and cognitive and motor impairment in HD suggest that this measure is useful for reflecting patients’ current disease status and might potentially also be helpful for tracking longitudinal disease changes. However, the longitudinal utility of this measure could not be assessed because it was an additional parameter measured at 12 month follow-up, and not at baseline. An assessment of the utility of this measure as a biomarker of HD is definitely warranted in future studies.

In the HD group, despite mean latencies of pro-saccade error correction in the anti-saccade task being well-correlated with two standard measures of disease status (UHDRS motor component and working memory domain testing), mean latencies of correct saccadic response in the three tasks showed poor correlations to UHDRS motor scores and also working memory domain scores (refer Figure VI.5). As described earlier, the control of complex volitional saccades consists of a multitude of complex motor and cognitive processes (McDowell et al., 2008). It is likely that in the control of correct complex volitional saccades, the motor and cognitive processes involved occur in parallel to one another. Thus, the latency of correct responses in a complex task is directly related to neither the severity of motor nor cognitive impairment in HD. It can be concluded that the latency of correct responses in complex tasks is not a sensitive indicator of the current disease status of HD patients. However, there is evidence of progression in the latency of complex volitional saccades (memory-guided and anti-saccades) over a brief interval of 12 months. This suggests that latency measurement in complex tasks may potentially still be considered as a global marker for HD (i.e. provide an indication of overall disease progression).

VI.4B. Eye-hand coordination in the delayed task

VI.4B.1. Eye and hand movements in the delayed task

The finding of a high eye movement disinhibition rate in the eye-hand delayed task complemented the finding in the saccade-only delayed task (refer section VI.3A.1). In HD, a higher hand movement disinhibition rate compared to controls (refer Figure VI.7), was in line with previous studies, in which it was shown that both premanifest and manifest HD had poorer upper limb somatomotor response inhibition compared to controls in masked prime responses (Aron et al., 2003) and ‘Go/ No go’ tasks (Beste et al., 2011; Beste et al., 2008; Beste et al., 2010).

It is well-established that the basal ganglia act as a gating mechanism to minimise the
interference of competing motor mechanisms during the execution of a desired movement (Mink, 2003). In an fMRI study by Aron and colleagues (2003), it was shown in healthy controls that there was a significant deactivation of the caudate and thalamus during response inhibition. Aron and colleagues (2003) suggested that the deactivation of the caudate and thalamus is consistent with an accepted model of the basal ganglia thalamocortical circuitry in which a reduction in neural activity within the caudate leads to a reduced suppression of the globus pallidus interna via the direct pathway and in turn results in an enhancement of inhibition on the thalamus. In HD, there is progressive degeneration of the striatum (Rosas et al., 2001; Vonsattel et al., 2011). Degenerative changes in the striatum may compromise the basal ganglia in suppressing unwanted saccadic and somatic movements alike, contributing to a generalised impairment of movement inhibition in HD, which in the present study results in an increase in disinhibition rates in the eye and hand.

Another possible mechanism for the higher rate of somatic movement disinhibition in the delayed task in HD could be a deficit in information integration in the basal ganglia. Neural synchronisation processes are processes related to action selection and they are heavily dependent on the inter-connectivity of neurons (Kitano & Fukai, 2004; Lago-Fernandez et al., 2001). It has been suggested that neurodegeneration in the striatum, which is evident even in premanifest HD (Tabrizi et al., 2009), has an impact on the functional connectivity of the striatal medium spiny neurons (Cepeda et al., 2007; Mitchell et al., 1999). In an EEG study, Beste et al. (2011) demonstrated that deficits in response inhibition in premanifest HD patients became progressively more apparent as the complexity of action selection increases. The authors attributed such findings to failure of a functionally-compromised striatum at integrating conflicting contextual information and sensory inputs to inhibit undesired responses. It may appear that there are two distinct mechanisms affecting somatic movement disinhibition in HD but these two processes are unlikely to be separable in a real life situation. This is because the basis of movement control that involves conditional responding (such as in the present study) is comprised of motor inhibition and also a cognitive component. Therefore, it may be posited that both impaired inhibition and impaired cognitive integration in the basal ganglia have roles in influencing movement inhibition in HD.

The control of movement inhibition also involves the participation of various cortical structures, which provide cognitive influences upon the limb control system. In healthy controls, several fMRI studies have shown that there is concurrent activation of various cortical structures, such as the rostral supplementary motor area and the right inferior frontal gyrus, during response
inhibition (Aron & Poldrack, 2006; Rao et al., 2014). Further, these cortical structures were found on a diffusion tensor imaging study to be structurally connected to each other and also to the basal ganglia (Aron et al., 2007). Several theories of action control posited that the rostral supplementary motor area and the right inferior frontal gyrus have distinct roles in attentional monitoring and the preparation of inhibitory responses (Rushworth et al., 2004; Swann et al., 2009; Swann et al., 2012). Therefore, it appears that the implementation of inhibitory control is dependent upon a concerted effort of basal ganglia and cortical structures, with different structures contributing to different aspects of movement inhibition control.

In line with this, Rao and colleagues (2014) found in an fMRI study that, relative to controls, there was significant reduction in brain activation in various cortical inhibition centres, such as left angular/supra-marginal and right superior/middle temporal gyri, in premanifest HD during somatic movement inhibition. The authors also revealed that these changes were closely related to response inhibition in premanifest HD (Rao et al., 2014). In addition, other studies (Bartenstein et al., 1997; Beste et al., 2008) showed that in manifest HD, there was an association between a decline in movement inhibition and a decline in neural activity in the anterior cingulate cortex, a cortical area involved in rational cognitive function (Botvinick et al., 2004). Based on these findings, it can therefore be hypothesised that similar to saccade inhibition (refer section VI.4A.1), there are also two components – motor inhibition and task-goal maintenance by working memory function – in somatic movement inhibition. Therefore, increased movement in inhibition in HD appears to be caused by two sources of error: (1) poor movement inhibition, an outcome of a deficit in movement gating mechanism in the basal ganglia; and (2) a decline in working memory capacity, which compromises task goal maintenance ability. Naturally, a question arising from such a hypothesis is which source of errors has a greater influence in causing somatic movement disinhibition in HD. Unfortunately, the measurement of movement disinhibition is the combined outcome of impairment in movement inhibition and impairment in cognitive integration. Thus, without neurophysiological data, it is difficult to determine if one mechanism contributes more than the other in causing movement disinhibition.

It is clear that a decline in somatic movement disinhibition in HD is a consequence of impairment in motor and cognitive components of the limb control system caused by HD effects on subcortical and cortical structures. Therefore, a measurement of somatic movement inhibition may potentially be a useful HD global biomarker, i.e. it monitors the global changes in subcortical and cortical structures functioning in HD.
VI.4B.2. Differences in eye and hand movement disinhibition rates

The current study extended the findings of previous studies, which investigated either only saccadic (Becker et al., 2009; Blekher et al., 2006; Tabrizi et al., 2009) or only somatomotor (Beste et al., 2011; Beste et al., 2008; Rao et al., 2014) movement in complex movement tasks, by comparing the behavioural performance of both eye and hand movements simultaneously in a complex (delayed) task. Intriguingly, relative to controls, who demonstrated minimal differences in movement disinhibition between the eye and hand movement in the delayed task, the HD group demonstrated a significantly higher disinhibition rate in the eye compared to the hand (refer Figure VI.7). An intuitive explanation of this finding was that there was a greater reliance on visual information for coordinating somatic movements in HD compared to controls. Indeed, this was demonstrated in a study by Georgiou and colleagues (1995), who found that a reduction in advanced visual information had an effect on motor performance in a sequential button-pressing task in manifest HD but not in controls. Similar findings of a greater reliance on visual information in somatomotor movement control were also reported in Parkinson’s disease, another degenerative disease of the basal ganglia (Georgiou et al., 1994; Jones et al., 1992), thus supporting the postulation that visual reliance is influenced by the overall integrity of basal ganglia. Basal ganglia and supplementary motor areas are integral in providing internal cues for the motor system especially during the execution of motor sequences (Brotchie et al., 1991a, 1991b). Georgiou et al. (1995) posited that in HD, degeneration of the basal ganglia and supplementary motor areas may affect the internal representation of movement and to overcome this, patients would have to constantly update the internal mapping system by using externally-derived information, i.e. visual information. This compensatory mechanism, likely to have developed to preserve somatomotor movement control, might lead to the eye being more susceptible to making a disinhibited response than the hand in manifest HD.

The conventional concept of the basal ganglia-thalamocortical circuitry in the control of motor movement describes the basal ganglia as intermediaries for the cortical association areas, in which they integrate inputs from various cortical association areas to the motor cortex (Allen & Tsukahara, 1974). Subsequent physiological and anatomical evidence suggested that the basal ganglia-thalamocortical circuitry can be segregated into two distinct pathways, i.e. a ‘motor’ loop, which transmits the influences from the sensorimotor cortex to the premotor areas, and an ‘association’ loop that projects influences of the association areas to the prefrontal cortex (Alexander et al., 1986). In addition to the two neural loops, Alexander et al. (1986) posited that there are additional circuits, one of them identified as the ‘oculomotor’ loop for the
control of eye movement, in the basal ganglia and all these neural circuits are organised in parallel with the ‘motor’ loop. The authors argued that the circuits are not completely separated per se, as the structures within the circuits may receive inputs and send outputs to the same cortical and subcortical structures but certain portions of each circuit engage with specific regions of the cortex or structures in the basal ganglia that are not shared by other circuits (Alexander et al., 1986). Their argument was supported by the findings in a later review by Joel et al. (1994). The key difference between ‘motor’ and ‘oculomotor’ loops is that the cortical terminus of the former circuit is the supplementary motor area (Kunzle, 1978) whereas the latter engages with the frontal and supplementary eye fields of the cortex (Kunzle, 1977). Due to the segregated functional pathways in the control of somatic and oculomotor movements, the presence of a significantly higher rate of disinhibited eye movement compared to the hand in the delayed task might indicate that the ‘oculomotor’ loop might be more susceptible to HD pathology than the ‘motor’ loop.

The supplementary motor area and the supplementary eye field are part of the supplementary motor complex of the cortex and that the boundaries of the two areas are defined only in relative terms (Nachev et al., 2008). Further, it was found in a non-human primate study (Fujii et al., 2002) that the supplementary eye field contains neurons involved in the control of saccades and also non-effector specific neurons that could influence hand movement in eye-hand coupled reaching tasks. These findings appear to refute the arguments that the ‘oculomotor’ and ‘motor’ loops are mutually exclusive and that HD pathology may have different effects on the two loops. Despite the findings in primates, human case reports suggest otherwise. In one case report, it was shown that a patient with a highly discrete lesion of the supplementary eye field showed great difficulty in learning to associate a novel stimulus and the required response in eye movement but not in somatomotor movement (Parton et al., 2007). It was demonstrated in another case report that a patient with a lesion of the pre-supplementary area, it was the hand movement rather than the eye that was affected (Nachev et al., 2007). These findings suggested that although there are no definitive boundaries between these subregions, they are functionally distinct from one another. Besides, the fact that there was evidence of a heterogeneous decline within the same gyrus in the cerebral cortex in manifest HD (Rosas et al., 2008), this indicates that the cortical terminus of the two basal-ganglia thalamocortical pathways, though located in close proximity to one another, might show heterogeneity in degenerative changes in HD. This might therefore translate to a disparity in movement disinhibition rate between the eye and the hand in manifest HD in the delayed task.
VI.4B.3. Differences in eye and hand movement latencies across tasks

In healthy controls, eye and hand latencies increases in tandem with the complexity of the task (de Boer et al., 2013; Sailer et al., 2000). The delay in the initiation of the eye and hand movements in complex tasks is a representation, measured in time duration, of underlying synchronising processes involved in coordination the two movements (de Boer et al., 2013; Sailer et al., 2000). Given that movement synchronising might be a factor in delaying movement initiation, one might expect that HD patients would show a greater delay in movement initiation than controls. However, this was not supported by the findings in the present study, in which it was shown that in terms of the relative increase in eye and hand latencies from reflexive task to delayed task, there were minimal differences between the HD and control groups (Relative differences in latencies (ms) across tasks between the control and HD groups: Eye: 28 [95% CI: -38 – 95]; Hand: -49 [95% CI: -131 – 33]). That is, both groups demonstrated similar increase in eye and hand latencies across tasks. It is tempting to speculate based on this finding that the movement synchronising processing in HD is as efficient as in controls. However, there is evidence to discredit such an argument. Previous reports showed that HD had poorer performance in bimanual movements than in unimanual movement (Brown et al., 1993; Thompson et al., 2010). That is, HD patients had greater difficulty in performing a task with both hands simultaneously than with one hand. This suggests that there is indeed impairment in the automisation and synchronisation of movements in HD. The minimal difference in eye-hand latency interval between groups may therefore be explained by the relative simplicity of the delayed task used in the current study which was not challenging enough to reveal deficits in movement automisation and synchronisation in manifest HD. This finding is undoubtedly going to limit the utility of eye-hand movement measurement in the delayed task as a potential progression marker in HD.

It is well-established that human motor processes can be influenced by how the sensory information is perceived. Sensory information can lead to two potential outcomes: (1) provide triggers or guide an action; or (2) result in perception (Neumann, 1990). It was posited by Neuman that sensory information that is subconsciously perceived, can influence the motor system through a process called the ‘direct parameter specification’. That is, there are tendencies for the direct parameter specification mode of sensorimotor control, which are not under voluntary control, to partially activate the signal for motor responses. However, to prevent the activation of motor responses instigated by the direct parameter specification, an inhibitory process, called the ‘activation-followed-by-inhibition’ process would have to be activated to reverse this response tendencies (Eimer & Schlaghecken, 1998). Based on this
model of perceptuo-motor interactions, it could be posited that in the delayed task, although the participants were asked not to respond to the peripheral targets while the fixation target was illuminated, these targets would still be identified subconsciously by the sensory system. In order to maintain the behaviour in context (i.e. to maintain fixation at fixation target), the ‘activation-followed-by-inhibition’ process would have to be activated to inhibit a response to the peripheral target. However, the main implication of this ‘activation-followed-by-inhibition’ process is that a longer reaction time is required for triggering a response that is already subjected to inhibition by the system (Eimer, 1999; Eimer & Schlaghecken, 1998). Hence, the prolongation of latencies in controls across tasks (visually-guided reflexive vs. delayed task) might conceivably reflect the extra time needed to terminate this ‘activation-followed-by-inhibition’ process. As previously discussed in section VI.4A.1, response disinhibition is a hallmark of HD. Given this, it can be speculated that there might also be an impairment in the ‘activation-by-inhibition’ process in HD, which inadvertently reduces the reaction time needed to trigger a response that was initially inhibited. It is possible that in the delayed task, the duration for movement synchronising in HD was indeed longer than controls. However, in the delayed task, the longer duration in movement synchronising might have been counteracted by the reduced reaction time for triggering a response that was initially inhibited. Hence, there were minimal between-group differences in the prolongation of eye and hand latencies across tasks.

Another possible explanation for this finding might be related to HD pathology in the supplementary motor area. The supplementary motor area has been implicated to be involved in movement planning and the coordination of complex movements (Deiber et al., 1991; Halsband et al., 1993). Chen et al. (2010) suggested that the state of responsiveness in the motor system, which is constantly being adjusted by an internal control mechanism, is integral in determining the reaction time of any motor response. The authors provided evidence that the supplementary motor area, possibly together with an extended neural network, modulates the state of responsiveness by setting the response threshold in the primary motor cortex, which ultimately generate the output signals for movement initiation (Chen et al., 2010). Due to there being neurodegeneration of the supplementary motor area in manifest HD (Rosas et al., 2008), this may affect the level of motor readiness of the primary motor cortex resulting in bradykinesia in HD. Taken together, it could be proposed that slower reactions in the visually-guided task in HD patients was contributed to by a reduced motor responsiveness. However, given that there were similar increase in latencies across tasks (visually-guided reflexive vs. delayed) between the two groups, this suggests that HD patients might be able to utilise the
delay in the delayed task to allow the disease-compromised supplementary motor cortex to elevate the level of motor readiness in the primary cortex to initiate the movement. Besides, it has been demonstrated by Phillips et al. (1994) that movement execution was relatively preserved in the presence of motor programming deficits in manifest HD. If this is proven to be true, this might potentially be useful in the management of motor symptoms in HD, in which patients might be able to capitalise on this effect to improve their motor performance in activities of daily life. That is, to overcome deficits in motor programming, HD patients can be taught specific motor training techniques to allow them to thoroughly plan the desired movement by focusing on the goal of the movement rather than the speed of movement initiation.

Interestingly, the HD group, unlike controls who demonstrated longer eye-hand latency interval in the delayed task than in the visually-guided task, had minimal differences in the eye-hand latency intervals between the two tasks. Visuomotor control in human, which involves the intricate interactions of cognition, perception, and motor processes, is highly adaptable (Sims et al., 2011). In the present study, the finding of a longer time delay in hand movement initiation in the delayed task in controls corroborated previous studies that showed timings in eye and hand movement initiation vary according to the cognitive demand of the task involved (Deconinck et al., 2011; Land et al., 1999; Pelz et al., 2001). It was postulated that by prolonging the interval between the initiation of the eye and hand movements, this allows the visuomotor control system to plan a specific movement (Pelz et al., 2001). Besides, personal goals can influence the temporal sequentiality of movements (Wu et al., 2009; Yarbus, 1967). In the study by Wu et al. (2009), healthy controls were found to slow down the execution of movement sequences when accuracy in motor performance was awarded with incentives. This suggests that in the present study, the longer delay in hand movement initiation in the delayed task in controls is indicative of a greater demand for task accuracy, which may be lacking in the HD group. However, as task accuracy was not measured in the current study, there was no quantitative data to support this claim.

On the other hand, the minimal change in eye-hand latency intervals across tasks in the HD group may reflect a deficit in the adaptability of visuomotor coupling in HD. Previous works have consistently reported that HD patients were found to have poor ability at developing movement strategies and manipulating hand forces based on task demands (Gordon et al., 2000; Quinn et al., 2001; Serrien et al., 2002). The integrity of white matter microstructure has been found to be crucial in the control of condition-based visuomotor somatic movement (Reuter-
In HD, there is evidence to support that white matter atrophy is linked to the disturbances in the white matter connections of the sensorimotor cortex (Dumas et al., 2012). A direct consequence of this is the interference in the control of condition-based visuomotor somatic movement, which sequentially restricts the ability of HD patients to efficiently adjust the underlying visuomotor control mechanisms for modifying visuomotor performance based on task demands. Hence, this may explain for the HD group having relative stable eye-hand latency intervals across tasks with different level of task demands in the present study.

VI.4B.4. Clinical correlates of eye-hand movement parameters in the delayed task

The strong correlation between UHDRS motor scores and eye movement disinhibition rates was in line with the current understanding that normal functioning of motor control centres is integral in the control of inhibition (Aron et al., 2003). However, a lower r value between motor scores and hand movement disinhibition rates in HD was likely to be contributed to by the restricted range of disinhibition rates in the hand compared to the eye. Response disinhibition rates of the eye and the hand in HD were found to be strongly correlated with the working memory domain scores, thus supporting the argument posited by McDowell et al. (2008) that working memory is required to maintain contextual cues in complex tasks. Response inhibition is often argued to be a component of executive function (Barkley, 1997; Miyake et al., 2000) but it has been demonstrated in a hypothetical model of cognitive processes that there is a close relationship between working memory and executive functions (Miyake & Shah, 1999). Nevertheless, these findings suggest that eye and hand movement disinhibition rates in general reflect patients’ current disease status, more specifically, the level of motor and cognitive impairment in HD patients.

The present study also revealed that mean latencies of the two movements were significantly correlated with the UHDRS motor scores but not with the working memory domain scores. These findings are likely to be explained by the fact that bradykinesia is a direct effect of HD pathology on the motor system (Berardelli et al., 1999). In addition, the UHDRS motor score is a direct measure of voluntary movement capability in HD (Huntington Study Group, 1996), thus it is expected that the scores of such a measure would be closely associated with the latencies of the eye and the hand. Despite the moderately strong correlations between latencies and the clinical severity of motor impairment, there was large within-group variability in motor performance in manifest HD (refer Figure VI.12). Therefore, mean latencies may not
necessarily provide an accurate estimation of the level of motor and cognitive impairment in HD. Due to this, mean eye and hand latencies in a complex task might have limited utility as an assessment tool for determining the current disease status of HD patients. However, given that in HD, there is prolongation of eye and hand latencies over time, the measurement of eye and hand latencies may still be a valuable long-term progression marker for HD.

In addition, the current study demonstrated that the time intervals between the initiation of eye and hand movements were weakly correlated with the working memory domain scores and the UHDRS motor scores. As discussed in sections VI.4B.1 to VI.4B.3, several factors – cognitive, motor, and motivational – are involved in the temporal sequencing of eye and hand movements in complex tasks. Hence, eye-hand latency interval is not a direct measure of either motor or cognitive impairment in HD.

**VI.4B.5. 12 month changes in eye and hand movements in the delayed task**

In terms of the 12 month longitudinal changes in eye and hand movements in the delayed task, controls had a significant improvement (i.e. reduction) in eye and hand disinhibition rates in the follow-up session. These findings support the earlier argument that after 12 months, controls might have developed effective strategies to improve movement inhibition on repeated testing of the same task (refer section VI.4A.2 for a detailed discussion). As stated earlier, motor performance can be influenced by individual goals and motivation (refer section VI.4B.3). These factors might have also contributed to a generalised improvement in movement inhibition in controls at 12 month follow-up.

The present study also revealed that in HD, there was a significant worsening of movement inhibition control (i.e. an increase in movement disinhibition) in the eye but not the hand in the follow-up session. It could be argued that these findings contradict the finding of a relatively stable saccade disinhibition in the saccade-only delayed task at one year follow-up (refer section VI.3A.1). It could however, be posited that these findings are instead complementary to each other. As shown by Kloppel et al. (2009), there were minimal differences, in terms of motor performance in a paced button pressing task, between premanifest HD patients and controls. The authors attributed this to a complex pattern of motor compensation through the modulation of brain activity in various cortical regions. In an fMRI study, Wolf et al. (2008) found that in premanifest HD, the functional connectivity of the prefrontal cortex was abnormal when performing a task with high cognitive demand. The key difference between the saccade-only delayed task and the combined eye-hand delayed task was that the latter required the
participants to control eye movement in synchrony with the hand. As discussed before, the control of visuomotor somatic movement involves the interactions of multiple processes. Concurrent control of eye and hand movements might therefore imposed extra burden on the already compromised visuomotor control system in HD, resulting in a decline in task performance in the eye in the eye-hand delayed task but not in the saccade-only variants.

Innate compensatory mechanisms, as discussed previously, might have protected the functionality of the saccadic system in complex tasks (refer section VI.4A.2) from short-term neurodegenerative changes in HD, when the system is operated in isolation. However, these mechanisms may be inefficient in supporting concurrent operations of multiple control systems (i.e. saccadic, somatomotor, and cognition). These findings have implications for short-term longitudinal research studies. Due to compensatory mechanisms, movement inhibition performance in saccade-only complex tasks of HD patients over short-time intervals might be relatively preserved when the oculomotor control system is operated in isolation. Therefore, to better highlight the underlying short-term changes in HD patients, it is recommended for short-to medium-term longitudinal studies to include motor tasks that involve simultaneous control of multiple motor and cognitive processes. It is also worth mentioning that there was a significant worsening of eye movement inhibition compared to the hand at fixation target offset in the delayed task at 12 month follow-up. This suggests that the oculomotor control system, comparatively, might be more susceptible to HD pathology than the somatomotor control system over a short-time interval.

Interestingly, latencies of the eye and hand, and the temporal coordination of eye and hand movements (eye-hand latency interval) of HD patients in the delayed task were relatively stable after 12 months. There are several possible explanations for such findings. Rao et al. (2014) suggested that the successful implementation of somatomotor response inhibition is dependent on the interactions of the classic inhibition network, ventral attention network, and motor control system. The authors demonstrated that functional changes were observed in all three networks in premanifest HD. Although functional changes in the inhibitory control and the ventral attention networks were found to be associated with the level of genetic exposure of premanifest HD patients, reduction in the flexibility of the motor control network was not (Rao et al., 2014). Besides, neurodegenerative changes in the cortex of manifest HD patients were found to be regionally specific but heterogeneous (Rosas et al., 2002). Taken together, it can be postulated that the three neural networks, at least over a 12 month period, showed heterogeneity in longitudinal deterioration which likely results in a greater deterioration in the inhibitory
control and ventral attention networks than the motor control network over a short-time interval. Heterogeneity in the degenerative changes of the various neural networks may account for the mixed results of an overt decline in movement inhibition control and minimal changes in the kinematics of eye and hand movements in the delayed task at follow-up assessment.

The effects of motor compensation might also have contributed to the relative stability of eye and hand movement latencies and of the temporal coupling of eye and hand movements in HD in the follow-up session. It is well-established that the human brain can potentiate compensatory mechanisms by recruiting additional brain areas when faced with cognitive challenges (Stern, 2009). There is evidence to support that compensatory mechanisms can also be activated in the somatomotor control system. In HD, Bartenstein et al. (1997) demonstrated that there was enhanced activation of the parietal cortex of HD patients compared to controls when performing motor tasks. They found that patients with higher levels of parietal cortex activation had better performance than those with lower level of activation. Besides parietal cortex, increased activations in caudal and dorsal parts of the supplementary motor area were also observed in different HD stages (premanifest and manifest) and these changes in brain activation were postulated to contribute to the preservation of somatomotor performance in HD (Gavazzi et al., 2007; Kloppel et al., 2009; Rao et al., 2014). These findings suggested that multiple compensatory mechanisms could be activated in HD to maintain motor performance of HD patients, leading to the relative stability of eye-hand movement performance in HD at 12 month follow-up. Although it has been claimed that motor compensation in HD is likely to weaken with disease progression (Beste et al., 2007; Rao et al., 2014), the presence of various compensatory mechanisms would undoubtedly pose a challenge to the utility of measured kinematics of eye-hand movement as progression or pharmacodynamics markers for HD, especially over a short follow-up period.

In addition, it should be highlighted that measurement of hand movement latency is filled with difficulty because a simple reaching movement is a concerted effort of a variety of muscles in the upper limb and the trunk (Lacquaniti & Soechting, 1982) and also multiple factors may influence how the movement is performed (Georgopoulos, 1986). These factors may be significant confounders in recording of hand movement and may have an effect upon 12 month longitudinal changes on hand movement in HD patients and controls. A more accurate measure of latency would derive from rectified EMG activity recorded from agonist and antagonist muscles. These factors may not be as significant confounders in measurement of eye movement because of its relative simplicity, which is dictated by the reduced degrees of freedom to move.
and also the relative inconsequentiality of the elastic force in the orbit compared with inertia in the hand.

**VI.5. Chapter summary**

Despite a strong disease-stage effect in saccade disinhibition and saccadic latency in the saccade-only complex tasks, there were measurable 12 month longitudinal changes in HD only in the latency of memory-guided saccades and of anti-saccades. Study findings were discussed in relation to the complexity of complex movement control, short-term neural compensation, and heterogeneity in longitudinal neural degenerative changes in HD.

However, the present study revealed that there was significant worsening of inhibitory control (i.e. increase in movement disinhibition rate) in the eye and hand in the eye-hand delayed task after 12 months. These findings perhaps highlighted the inadequacy of short-term compensatory mechanisms for assisting an already disease-compromised motor control system in the concurrent operations of multiple motor and cognitive processes. Motor tasks that assess only a specific motor control system (e.g. oculomotor) might not be effective in detecting short-term longitudinal disease changes in HD. Therefore, it is recommended for short- to medium-term longitudinal studies to include complex movement tasks that involve the simultaneous control of multiple motor systems.

Minimal changes in the kinematics of the eye-hand movement in manifest HD over a 12 month period suggest that these measures might have limited utility for detecting short-term disease changes in HD and thus, not useful as short-term progression markers. However, given the progressive nature of eye and hand latencies, these measures may still be useful as long-term progression markers for HD. Nevertheless, further studies on the usefulness of complex eye-hand coordination task as a progression marker of HD over longer follow-up periods are definitely warranted.
Chapter VII

Concluding remarks

VII.1. Study highlights

In this study, the utility of saccadic and eye-hand movement measures in detecting short-term disease progression in HD was evaluated, concurrently with existing standard disease measures. Novel findings on 12 month longitudinal changes in HD patients in saccadic and eye-hand measures, and also predictive behaviour of saccadic and eye-hand movements, were revealed. There were large effect sizes of HD on all of the cognitive measures, and saccadic and eye-hand parameters on cross-sectional analysis (i.e. baseline). The decline over 12 months in HD patients was confined to a more limited number of parameters, such as measurement of reflexive saccades and measurement of rhythmical eye and hand movements.

VII.1.1. Cognitive, motor, and behavioural measures

Table VII.1 provides a summary of the effect sizes (reported in Cohen’s $d$ values) for between-
group differences, relative changes in the HD group as compared to controls at 12 month follow-up, and 12 month within-HD group changes for cognitive, motor, and behavioural measures. On cognitive measures, those that assess executive function were the most sensitive to 12 month disease progression. That is, there is within-HD group and relative to controls decline at 12 month follow-up. Global cognition and the learning and memory domain meanwhile, showed modest deterioration only when compared to controls (i.e. there is a significant relative to controls decline but no significant within-HD group changes in score at 12 month follow-up). The three brief cognitive tests (MMSE, MoCA, and the UHDRS cognitive component) were similarly useful in cross-sectional analysis but the UHDRS cognitive component was superior in documenting cognitive decline in HD over 12 months. Motor function, as measured using the UHDRS motor component, deteriorated over 12 months but no change was observed in most behavioural measures (except for the AES, in which there was a decline after 12 months).

Table VII.1 Cohen’s d effect sizes for baseline difference and change at 12 month follow-up in cognitive, motor, and behavioural measures

<table>
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<tr>
<th>Cognitive/ Motor/ Behavioural measures</th>
<th>Magnitude of Cohen’s d</th>
<th>HD vs. Control</th>
<th>HD within-group change at 12 month follow-up</th>
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<td>Baseline</td>
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<tr>
<td>Global cognition</td>
<td>2.4</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Executive function domain</td>
<td>2.7</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Working memory domain</td>
<td>1.8</td>
<td>0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>Processing speed domain</td>
<td>2.4</td>
<td>0.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Learning &amp; memory domain</td>
<td>1.5</td>
<td>0.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Language domain</td>
<td>1.4</td>
<td>0.02</td>
<td>0.4</td>
</tr>
<tr>
<td>Visuospatial domain</td>
<td>2.4</td>
<td>0.03</td>
<td>0.08</td>
</tr>
<tr>
<td>MMSE</td>
<td>1.2</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>MoCA</td>
<td>1.8</td>
<td>0.1</td>
<td>0.09</td>
</tr>
<tr>
<td>UHDRS cognitive score</td>
<td>2.4</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>UHDRS motor score</td>
<td>-</td>
<td>-</td>
<td>0.4</td>
</tr>
<tr>
<td>UHDRS behavioural measures</td>
<td>-</td>
<td>-</td>
<td>0.04</td>
</tr>
<tr>
<td>BAI</td>
<td>0.8</td>
<td>0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>BDI</td>
<td>1.0</td>
<td>0.003</td>
<td>0.1</td>
</tr>
<tr>
<td>AES</td>
<td>1.6</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Legends: The magnitude of Cohen’s d and r effect sizes (Cohen, 1988) are colour-coded: (1) ‘green’ indicates a small effect size (0.2 ≤ d < 0.5); (2) ‘blue’ indicates a medium effect size (0.5 ≤ d < 0.8); (3) ‘purple’ indicates a large effect size (0.8 ≤ d < 1.5); and (4) ‘red’ indicates a very large effect size (d ≥ 1.5). Parameters that were not assessed are marked with ‘-’.

VII.1.2. Saccadic measures

A summary of the effect sizes for baseline differences, relative changes in the HD group as compared to controls at 12 month follow-up and 12 month longitudinal changes in the HD group is shown in Table VII.2 together with the correlations (reported in r correlation coefficients) between saccadic parameters and clinical measures of disease status (cognitive scores and UHDRS motor scores). The HD group generally showed deficits in reflexive,
rhythmical (self-paced and temporally-cued), and complex volitional saccades. Most saccadic measures – especially rhythmical and complex saccades – showed strong correlations to the disease status of HD patients. However, only reflexive saccade measures showed overt 12 month longitudinal changes (within-HD group and relative to controls decline) in the follow-up session. One explanation for this is the superior within-group consistency and lower variability of measurements after 12 months in this relatively simple saccadic task compared to the more complex tasks, which require the involvement of multiple cognitive processes and various neural networks.

Table VII.2  
Cohen’s $d$ effect sizes for baseline difference and relative change at 12 month follow-up, and of $r$ effect sizes for clinical correlates of saccadic parameters

<table>
<thead>
<tr>
<th>Saccadic measures</th>
<th>HD vs. Control</th>
<th>HD</th>
<th>Within-HD Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflexive (2D)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency</td>
<td>0.5</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Peak velocity</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Primary gain</td>
<td>0.4</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Saccade count</td>
<td>1.1</td>
<td>0.002</td>
<td>0.02</td>
</tr>
<tr>
<td>Vertical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latency</td>
<td>0.7</td>
<td>0.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Peak velocity</td>
<td>0.4</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Primary gain</td>
<td>0.6</td>
<td>0.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Saccade count</td>
<td>0.7</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Rhythmical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-paced</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal</td>
<td>2.0</td>
<td>0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>Vertical</td>
<td>2.0</td>
<td>0.09</td>
<td>0.05</td>
</tr>
<tr>
<td>Temporally-cued</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predictive saccade</td>
<td>1.9</td>
<td>0.07</td>
<td>0.3</td>
</tr>
<tr>
<td>Reduction in saccadic latency in the predictable phase</td>
<td>1.8</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Complex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed</td>
<td>1.6</td>
<td>0.07</td>
<td>0.2</td>
</tr>
<tr>
<td>Memory-guided</td>
<td>1.8</td>
<td>0.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Anti-saccade</td>
<td>2.0</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Correction rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-saccade</td>
<td>0.7</td>
<td>0.07</td>
<td>0.1</td>
</tr>
<tr>
<td>Latency: correct response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed</td>
<td>0.3</td>
<td>0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Memory-guided</td>
<td>0.6</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Anti-saccade</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Legends: The magnitude of Cohen’s $d$ and $r$ effect sizes (Cohen, 1988) are colour-coded: (1) ‘green’ indicates a small effect size ($0.2 \leq d < 0.5; 0.1 \leq r < 0.3$); (2) ‘blue’ indicates a medium effect size ($0.5 \leq d < 0.8; 0.3 \leq r < 0.5$); (3) ‘purple’ indicates a large effect size ($0.8 \leq d < 1.5; 0.5 \leq r < 0.8$); and (4) ‘red’ indicates a very large effect size ($d \geq 1.5; r \geq 0.8$). Parameters that were not assessed are marked with ‘-’.

VII.1.3. Eye-hand movement parameters

Key findings (reported in Cohen’s $d$ and $r$ effect sizes) in eye-hand movement parameters are summarised in Table VII.3. One unexpected and particularly interesting finding was an
increased number of self-paced eye movements generated when eye movements were made concurrently with the hand (i.e. in the eye-hand self-paced task), in controls (saccade-only horizontal self-paced task: 64; eye-hand horizontal self-paced task: 80) and HD (saccade-only horizontal self-paced task: 35; eye-hand horizontal self-paced task: 50). The HD group, relative to controls, showed reduced predictive behaviour in oculomotor and somatomotor movements. Further, in HD, oculomotor prediction in the temporally-cued tasks was different when eye movements were performed in isolation (i.e. in the saccade-only variants) compared to when performed in synchrony with the hand (i.e. in the eye-hand variants). Despite a strong disease effect and correlations to disease status in most eye-hand measures on cross-sectional analysis, only self-paced rhythmical eye-hand movements and eye movement disinhibition rate in the eye-hand delayed task were sensitive to a 12 month progression.

Table VII.3 Cohen’s $d$ effect sizes for baseline difference and relative change at 12 month follow-up, and $r$ effect sizes for clinical correlates of eye-hand movement parameters

<table>
<thead>
<tr>
<th>Eye-hand movement measures</th>
<th>Magnitude of Cohen’s $d$</th>
<th>Magnitude of $r$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD vs. Control</td>
<td>Relative change at 12 month follow-up</td>
</tr>
<tr>
<td><strong>Reflexive movement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaching: Latency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>1.2</td>
<td>0.07</td>
</tr>
<tr>
<td>Hand</td>
<td>1.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Return: Latency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>1.5</td>
<td>0.05</td>
</tr>
<tr>
<td>Hand</td>
<td>1.4</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Eye-hand latency interval</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaching</td>
<td>1.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Return</td>
<td>0.5</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Rhythmical movement</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-paced</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye: Horizontal</td>
<td>1.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Eye: Vertical</td>
<td>1.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Hand: Horizontal</td>
<td>1.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Hand: Vertical</td>
<td>2.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Temporally-cued</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye-hand latency interval</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Reduction in eye latency in the predictable phase</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Reduction in hand latency in the predictable phase</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Complex movement (Delayed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Hand</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Latency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye</td>
<td>0.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Hand</td>
<td>0.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Legends: The magnitude of Cohen’s $d$ and $r$ effect sizes (Cohen, 1988) are colour-coded: (1) ‘green’ indicates a small effect size ($0.2 \leq d < 0.5; 0.1 \leq r < 0.3$); (2) ‘blue’ indicates a medium effect size ($0.5 \leq d < 0.8; 0.3 \leq r < 0.5$); (3) ‘purple’ indicates a large effect size ($0.8 \leq d < 1.5; 0.5 \leq r < 0.8$); and (4) ‘red’ indicates a very large effect size ($d \geq 1.5; r \geq 0.8$). Parameters that were not assessed are marked with ‘-’. 

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VII.2. Study implications

Findings in this study have implications for longitudinal clinical research HD studies, especially those of short- to medium-term, and also for clinical practice.

VII.2.1. Cognitive measures and UHDRS

There was clear evidence in the control group of some practice effects on repeated assessment of cognitive tests. Such practice effects have implications for comparative assessments of a HD group. The conclusions from repeat-testing of the HD group alone would have been different (i.e. an apparently lower degree of deterioration over 12 months) if there had been no control group. It is therefore, important to include a control group in short- to medium-term longitudinal HD research studies involving cognitive measures to assess longitudinal changes in cognition in manifest HD.

In line with previous studies (Bachoud-Levi et al., 2001; Snowden et al., 2001), the executive function domain was found to be the most sensitive cognitive domain to short-term (i.e. 12 month) longitudinal decline in HD. This finding implies that cognitive function monitoring of HD in health care settings – especially during routine clinic follow-ups – should emphasize, or at minimum include, testing of executive function. Further, the results of the study suggest that the UHDRS cognitive component is the most appropriate brief assessment tool – superior to the MoCA and MMSE – for monitoring 12 month cognitive changes of HD patients in the clinic. Although the UHDRS has been criticized for its subjectivity (Weir et al., 2011), data from the present study indicates that its motor and cognitive components are actually sensitive tools for demonstrating disease progression in the short-term. This reaffirms the utility of the UHDRS, especially the motor and cognitive components, as useful markers of progression in HD, at least over a short follow-up interval of 12 months.

VII.2.2. Measurement of reflexive movements

Based on the results herein, the measurement of reflexive saccades, especially in a 2D (horizontal and vertical) task, may provide an objective and sensitive marker for detecting and tracking longitudinal HD disease changes in research and clinical treatment trials. Given the magnitude of 12 month longitudinal changes in reflexive saccades was unlikely to be detected through conventional clinical examination, the utility of this disease monitoring technique in clinics is debatable. It is however, noteworthy to mention that a portable eye-tracking system like the saccadometer, which is capable of providing automated and immediate analysis of
saccade measurements, is commercially available, suggesting that saccade measurement can be easily translated for use in clinics. In addition, the saccadometer was found to be a reliable tool for saccade measurement in HD (Turner et al., 2011).

**VII.2.3. Measurement of rhythmical movements**

There was a strong disease stage effect on the number of self-paced saccades. That is, self-paced saccade performance diminished with increasing clinical severity. This indicates that this eye movement measure might be the most useful saccadic markers for objective assessment of disease status. The absence of significant deterioration in self-paced saccade generation after 12 months suggests, however, that this measure is not a sensitive marker of short-term disease progression in HD.

There was a significant 12 month decline in self-paced rhythmical eye-hand performance in the HD group. This underscores the proposal that simple movement tasks (such as this) might be better for monitoring HD progression than tasks involving complex movement (Collins et al., 2014). The results indicate that the measurement of self-paced eye-hand movement would be very appropriate for objectively measuring HD motor status and short- to medium-term progression in clinical research and treatment trials. In the temporally-cued tasks, there were differences in the predictive control of eye movement, both when performed in isolation (saccade-only) and when executed in combination with hand movement. The HD group did not reduce saccadic latency as much as controls in the predictable phase, indicating that in HD, there is impairment (though not abolition) of predictive mechanisms, as noted by Tian et al. (1991).

**VII.2.4. Measurement of complex movements**

The application of cognitive strategies by controls might have led to their improvement in saccade inhibition in complex volitional saccade tasks at 12 month follow-up. Similar to cognitive testing, this had implications for the comparative assessment of the HD group. Therefore, with the measurement of saccade disinhibition as a measure of disease progression, it is essential to include a control group especially in short- to medium-term longitudinal HD research studies. Another interesting finding in complex saccades was that there was overt longitudinal increase in latency in HD over 12 months, suggesting that the measurement of complex saccade latency is potentially useful for tracking disease changes in HD. Nevertheless, a recommendation for this measure should be reserved until a longitudinal study with larger
sample size and longer follow-up interval is conducted to further assess the utility of this measurement.

In the delayed task, there was a significant deterioration in eye movement inhibition in the eye-hand, but not the saccade-only, variants of the task. These findings have implications for the longitudinal assessment of changes in behavioural performance of HD patients, such that the assessment of a specific movement in isolation in a task may not provide the full picture of the underlying pathological effect in HD, and that more ‘naturalistic’ paradigms combining eye and hand movements may be more rewarding. These findings highlight one unique strength of the present study; that is, it involved the investigation of eye movement performance in both saccade-only and eye-hand variants of both simple and complex movement tasks.

There is currently insufficient evidence to support the use of physical therapies for improving motor performance of HD patients (Bilney et al., 2003). However, the results herein, showing differences in oculomotor prediction between the saccade-only and eye-hand variants of the temporally-cued tasks, suggest that it might be productive to explore whether one could induce positive transference of movement performance (e.g. movement prediction) from the combined eye-hand task to the saccade-only task with repetitive training in HD. A positive finding might open up a novel therapeutic avenue for improving motor performance in HD.

**VII.2.5. An emerging theme from this study**

The present study has revealed that though performance in complex movement tasks is significantly associated with the disease status of patients, many of these tasks did not appear to be sensitive in tracking or detecting short-term longitudinal disease changes in manifest HD. By contrast, there were quantifiable longitudinal changes over a 12 month period in simple movement tasks, such as reflexive saccades and rhythmical eye-hand movement. It is clear that there is an emerging theme from this study. That is, contrary to the belief that “complex might be better”, simple movement measurements may potentially have greater as progression biomarkers for HD, especially for short-term disease monitoring.

As discussed in previous chapters, complex movement control often comprises of: (1) a motor component, that controls movement inhibition and initiation; and (2) a cognitive component, that provides cognitive influences, such as task-goal maintenance and prediction. These components are regulated by various subcortical structures and higher cortical centres in the central nervous system. The commonly used measurements in complex movement tasks, such
as disinhibition rate and latency of correct responses, are the combined outcomes of all the components in the complex movement control system. Without supporting neurophysiological data, it is difficult to determine if one component plays a greater role than another in influencing the control system.

In HD, there is heterogeneity in the longitudinal progression of structural pathology, i.e. one neural structure may not degenerate at the same rate as another over time. This may inadvertently result in an unsynchronised decline in the functioning of the different components involved in the control of complex movement. In addition, the human brain is capable of neural compensation. Therefore, it can be hypothesised that a deficit in one component, e.g. the motor component in the complex movement control system, might be counteracted, albeit temporarily, by the cognitive component, thus resulting in no measurable changes in complex movements over a short 12 month follow-up period. In line with this, the present study found overt changes in UHDRS motor scores in the presence of subtle changes in global cognition in the HD group at 12 month follow-up. This reaffirms the hypothesis that in manifest HD, motor function declines at a faster rate than global cognition over 12 months.

By contrast, the control systems for simple movements and rhythmical movements are usually dependent on the motor component only and involve less active participation of the cognitive component. It is likely that due to the relative simplicity of the simple movement control system, it is more susceptible to HD effects (because there is perhaps less involvement of compensatory mechanisms than the complex movement control system) over a short period of time and hence the measurable changes in simple movements at 12 month follow-up. Despite this, one should not consider the measurement of complex movement as obsolete. This is because the effect of neural compensation is not permanent and, with time, a decline in cognition will eventually lead to the collapse of such compensatory mechanisms (Papoutsi et al., 2014) and subsequently a measurable performance decline in complex movement.

Based on these findings, it can therefore be hypothesised that the measurements of simple movement and complex movement have different utility in monitoring disease progression in HD. Simple movement measurement that appears to be more susceptible to short-term HD effects, may potentially be a sensitive progression marker for HD. By contrast, there are motor and cognitive components to the control of complex movement, and thus measurement of complex movement may be a useful global marker (i.e. provides an overview of global disease changes) for HD in long-term disease monitoring.
VII.3. Study limitations

The relatively small sample size is a key limitation of this study. I initially intended to have at least 25 HD patients but due to the limited patient population in the Canterbury region of New Zealand and that many potential patients failed to meet the inclusion criteria, only 22 patients were recruited. Nevertheless, the study was still able to demonstrate significant disease effects at baseline and also 12 month changes in the HD group in a majority of the measures evaluated. It is both a strength and weakness of this study that patients at various stages of HD were included. Whilst on one hand, this allowed disease stage-specific analyses to be performed, it also resulted in an increased variance in the HD group, weakening the statistical power of the study and increasing the chance of Type II errors (i.e. failing to reject the null hypothesis when it was not true).

Normal aging effects are unlikely to be a contributing factor for the decline in performance in the control group, especially when the follow-up interval was just 12 months. It is often suggested that ‘healthy’ controls may not always be completely normal as hoped for, which can affect the interpretation of results in the patient group. The main criterion used for control selection was the absence of neurological disorder on recruitment. Cardiovascular status and other medical problems, such as musculoskeletal disorders, were not considered during selection process and may have affected the motor performance of controls. This may have led to unexpected deterioration in certain measures (particularly in reflexive eye-hand movement). A more stringent protocol for health evaluation in controls might reduce such confounding factors.

The loss of 12 month data in the temporally-cued eye-hand movement task, due to an unforeseen software error, prevented the determination of the utility of this measure in monitoring changes over 12 months. It would also have been desirable to assess eye-hand movement in the memory-guided and anti-saccade/reaching tasks but these were not included due to time constraints for the patients (i.e. so as to avoid excessive participant fatigue). Finally, from a statistical point of view, it would have been better to counterbalance the order of the four ISI trial blocks in the temporally-cued tasks to minimize ‘order effect’ but at least this was consistent across both patient and control groups.

The measurement of hand latency is undoubtedly fraught with difficulty and multiple confounders may have interfered with data interpretation. A more accurate measure of hand
latency would derive from a measurement of rectified EMG activity in the agonist and antagonist muscles involved in reaching movements. This is not as significant a confounder in eye movement recording, as eye movement is relatively simple, due to the reduced degrees of freedom to move and also relative inconsequentiality of the elastic force in the orbit as compared to the inertia of the hand.

**VII.4. Recommendations for future research**

This study has established a strong foundation for the utility of cognitive, saccadic, and eye-hand movement measures for monitoring 12 month changes in HD patients. A more extended longitudinal assessment would be warranted to characterize the medium- and long-term changes of these measures over a more prolonged follow-up period. A larger sample, with patients of various HD stages (premanifest and manifest), would enable wider inferences of the longitudinal changes of the various measures evaluated in the present study to be made and might permit the identification of disease measures that are sensitive to changes specific to a particular disease stage in HD. As discussed in earlier sections on neuroimaging, there is evidence of global longitudinal changes on cortical and subcortical structures in premanifest and manifest HD. Therefore, correlation of longitudinal changes in saccades with neuroimaging progression might be an aspect worth investigating for future studies.

It would also be of considerable value to examine the performance of eye and hand movements in the temporally-cued task to discern the longitudinal changes in sensorimotor prediction in HD patients. Similarly, a logical extension of the present study would be the investigation of eye-hand movement in a memory-guided and anti-saccade/reaching task in order to better understand the relationship of the eye and the hand in tasks that require greater cognitive demand. A rectified EMG recording of opposing muscles provides a more objective measurement of hand latency and could potentially eliminate some of the confounding factors in the present study.

A previous study by Khan et al. (2011) showed that combined eye-hand performance in healthy controls is considerably different from separate eye and hand only movements. The present study showed that in the HD group, eye movement performance in the rhythmical tasks (self-paced and temporally-cued) was different when eye movement was performed in isolation (i.e. the saccade-only variants of the task) and concurrently with the hand (i.e. the eye-hand variants
of the task). A detailed study to investigate the performance of the eye and the hand in isolation and in combination would be relevant and might possibly extend the findings in the present study. Findings from such a study could then be extended to determine whether in HD, repetitive training of one movement (e.g. eye) has a positive transference effect on improving movement of another (e.g. the hand) in a multi-movement task.

Innate compensatory mechanisms might contribute to the short-term preservation of behavioural performance in HD in the face of true underlying pathological progression. As there is evidence to support preclinical neural compensation in premanifest HD (Kloppel et al., 2009; Scheller et al., 2013; Scheller et al., 2014), it would be useful to perform a longitudinal functional MRI or neurophysiological study to examine how these compensatory mechanisms may evolve over time to cope with the burden of pathology in premanifest and manifest HD, when performing complex tasks. Such knowledge may potentially lead to the use of enrichment or other brain function enhancement therapies as an intervention to maintain motor performance or as an adjunct to future disease-modifying treatments in HD.

**VII.5. Chapter summary**

The lack of sensitive disease markers poses a challenge for monitoring disease progression in HD. Neuroimaging studies are thus far the most sensitive in showing longitudinal changes in HD. However, such techniques may not be practical for use in clinical practice where medical resources are limited. This study has identified several potentially useful, relatively cheap and safe progression markers for monitoring HD changes over 12 months that could be easily adapted for use in research studies and clinical trials. Eye-hand movement assessment in this study has provided novel perspectives on eye-hand coordination in HD and could be a springboard for the design of motor training therapies to improve motor performance in manifest HD in the future.
Appendix
A. Supplementary tables
Table S1  Scores (mean, SD, and range) in the control and HD groups at baseline and 12 month follow-up assessments. Neuropsychological tests raw scores were converted to standard z-scores using test-specific norms. Global cognitive and domain scores were shown in z-scores. The MMSE and MoCA were scored out of 30 points. The UHDRS motor and behavioural components were scored in points while individual tests within the cognitive component were reported in z-scores.

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<th>Measures</th>
<th>Control group</th>
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<td>-0.2 – 1.1</td>
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<td>0.8 (0.6)</td>
<td>-0.3 – 2.1</td>
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<tr>
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<td>-0.5 – 0.7</td>
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* The UHDRS motor and behavioural components were assessed in the HD group only.
### Table S2

Mean (SD) standardised z-scores for the six cognitive domains and neuropsychological battery component tests in the control and HD groups at baseline and 12 month follow-up.

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<th>Mean (SD)</th>
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<td>-1.3 (1.3)</td>
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<td>-0.5 (0.9)</td>
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### Table S3

Mean (SD) standardised z-scores for global cognitive level and the six cognitive domains in controls and the three sub-groups of HD patients at baseline and 12 month follow-up.

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<td>Baseline</td>
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<td>Executive function</td>
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<td>0.2 (0.6)</td>
</tr>
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</tr>
<tr>
<td>Processing speed</td>
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<td>-0.03 (0.9)</td>
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<td>Language</td>
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<td>0.5 (0.4)</td>
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B. Supplementary figures
Figure S1  Change in neuropsychological battery component tests scores over 12 months. Baseline and 12 month scores for control (circle) and HD (triangle) groups in overall executive domain score (Overall: Ex); letter fluency (LF); action fluency (AF); category switching (CS); Trail Making Test – Part B (Trl.B); Stroop-Interference test (Strp.I); overall working memory domain (Overall: WM); digit forward, backward and sequencing combined score (DF.B.Sq); digit backward (DB); digit sequencing (Dsq); Symbol Digit Modalities Test (SDMT); Ruff 2 & 7 Cancellation Test – Accuracy (R27.TotA); overall processing speed domain score (Overall: PS); Stroop –Reading test (Strp.WR); Stroop – Naming test (Strp.CN); Trail Making Test – Part A (Trl.A); Ruff 2 & 7 Cancellation Test – Speed (R27.TotS); overall learning memory & attention domain score (Overall: LM); CVLT - Recall score (CV.Recall); CVLT - Long delayed score (CV.LongD); BVMT – Learning score (BVMT.Learn); BVMT – Delayed recall score (BVMT.Delayd); overall visuospatial domain score (Overall: Vs); Judgement of line (JOL); Rey complex figure copying test (RCF.Copy); overall language domain score (Overall: La); Brief Boston Naming Test (BNT); and Indiana University Token Test (IUTT). Group means and SDs are shown.
Figure S3  Eye and hand latencies by stimulus number in controls at the 750 ms ISI trial block. Missing data points for either movements are due to unforeseen technical failure with the motion tracker system that was discovered during data analysis.
**Figure S4**  Eye and hand latencies by stimulus number in controls at the 1000 ms ISI trial block. Missing data points for either movements are due to unforeseen technical failure with the motion tracker system that was discovered during data analysis.
Figure S5  Eye and hand latencies by stimulus number in controls at the 1400 ms ISI trial block. Missing data points for either movements are due to unforeseen technical failure with the motion tracker system that was discovered during data analysis.
Figure S6  Eye and hand latencies by stimulus number in controls at the 2050 ms ISI trial block. Missing data points for either movements are due to unforeseen technical failure with the motion tracker system that was discovered during data analysis.
Figure S7  Eye and hand latencies by stimulus number in the HD group at the 750 ms ISI trial block. Missing data points for either movements are due to unforeseen technical failure with the motion tracker system that was discovered during data analysis.
Figure S8   Eye and hand latencies by stimulus number in the HD group at the 1000 ms ISI trial block. Missing data points for either movements are due to unforeseen technical failure with the motion tracker system that was discovered during data analysis.
Figure S9  Eye and hand latencies by stimulus number in the HD group at the 1400 ms ISI trial block. Missing data points for either movements are due to unforeseen technical failure with the motion tracker system that was discovered during data analysis.
Figure S10  Eye and hand latencies by stimulus number in the HD group at the 2050 ms ISI trial block. Missing data points for either movements are due to unforeseen technical failure with the motion tracker system that was discovered during data analysis.
C. Supplementary data
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Abbreviations: HD (HD group); Ctrl (Control group); Edu. (Years of formal education); Eth. (Ethnicity - EU: NZ European; MO: NZ Maori; SA: South African Indian); CAG (CAG repeat size); FRS (Shoulson-Fahn staging system); Motor (UHDRS motor score); Behav. (UHDRS behavioural score); Func. (UHDRS functional score); Indp. (UHDRS independence score); TFC (UHDRS total functional capacity score); Cog (Cognitive status: HD-N, HD-Normal; HD-M, HD – Mild cognitive impairment; and HD-D, HD-Dementia); “?” indicates unconfirmed but likely mode of HD inheritance.
### Spreadsheet B

**Patient medication list at baseline**

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<td>Venlafaxine</td>
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<td>HD</td>
<td>Y0</td>
<td>Citalopram</td>
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<td>HD</td>
<td>Y0</td>
<td>Venlafaxine; Verapamil</td>
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</tr>
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### Spreadsheet C

**Patient medication list at 12 month follow-up**

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D. Study approval and permission letters
30 March 2011

Mr Eng Ann Toh
Van der Veer Institute for Parkinson's and Brain Research
66 Stewart Street
Christchurch 8011

Dear Mr Eng Ann Toh

Re: Ethics ref: URB/11/02/006 (please quote in all correspondence)
Study title: Eye-hand coordination and relationship to cognition in Huntington's disease
Investigators: Mr Eng Ann Toh, Professor Tim Anderson, Dr Michael MacAskill, Dr Daniel Myall

This study was given ethical approval by the Upper South B Regional Ethics Committee on 30 March 2011. A list of members of the Committee is attached.

Approved Documents
— Consent Form for Control Participants version 2 dated 16 February 2011
— Participant Consent Form version 2 dated 16 February 2011
— Information Sheet for Controls version 2 dated 16 February 2011
— Information Sheet for Participants version 2 dated 16 February 2011

This approval is valid until 31 December 2011, provided that Annual Progress Reports are submitted (see below).

Amendments and Protocol Deviations
All significant amendments to this proposal must receive prior approval from the Committee.
Significant amendments include (but are not limited to) changes to:
— the researcher responsible for the conduct of the study at a study site
— the addition of an extra study site
— the design or duration of the study
— the method of recruitment
— information sheets and informed consent procedures.

Significant deviations from the approved protocol must be reported to the Committee as soon as possible.

Annual Progress Reports and Final Reports
The first Annual Progress Report for this study is due to the Committee by 31 December 2011. The Annual Report Form that should be used is available at www.ethicscommittees.health.govt.nz. Please note that if you do not provide a progress report by this date, ethical approval may be withdrawn.

A Final Report is also required at the conclusion of the study. The Final Report Form is also available at www.ethicscommittees.health.govt.nz.

Requirements for the Reporting of Serious Adverse Events (SAEs)
For the purposes of the individual reporting of SAEs occurring in this study, the Committee is satisfied that the study’s monitoring arrangements are appropriate.

SAEs occurring in this study must be individually reported to the Committee within 7-15 days only where they:
- are unexpected because they are not outlined in the investigator’s brochure, and
- are not defined study end-points (e.g. death or hospitalisation), and
- occur in patients located in New Zealand, and
- if the study involves blinding, result in a decision to break the study code.

There is no requirement for the individual reporting to ethics committees of SAEs that do not meet all of these criteria. However, if your study is overseen by a data monitoring committee, copies of its letters of recommendation to the Principal Investigator should be forwarded to the Committee as soon as possible.

Please see www.ethicscommittees.health.govt.nz for more information on the reporting of SAEs, and to download the SAE Report Form.

The Committee forwards the following suggestion which does not affect ethical approval:

- Please remove the statement in the HD Project Consent Form for Controls: “I agree to my GP or other current provider being informed of my participation in this study/ the results of my participation in this study”.

We wish you all the best with your study.

Yours sincerely

Diana J. Whipp

Mrs Diana Whipp
Administrator Upper South B Regional Ethics Committee
Email: uppersouthb_ethicscommittee@moh.govt.nz
6 March 2012

Mr Eng Ann Toh
New Zealand Brain Research Institute
66 Stewart Street
Christchurch 8011

Dear Mr Toh

Ethics ref: URB/12/EXP/011 (please quote in all correspondence)
Study title: Eye-hand coordination and relationship to cognition in Huntingdon's disease - One year follow up study
Principal Investigator: Mr Eng Ann Toh

The above study has been given ethical approval by the Chairperson and Deputy Chairperson of the Upper South B Regional Ethics Committee.

Approved Documents
Study Protocol 2 March 2012
Information Sheet for Patients version 3 dated 5 March 2012
Information Sheet for Controls version 3 dated 5 March 2012
Consent Form for Controls version 3 dated 5 March 2012
Consent Form for Participants version 3 dated 5 March 2012
Maori Consultation

Final Report
The study is approved until 1 May 2013. A final report is required at the end of the study and a report form to assist with this is available at http://www.newhealth.govt.nz/ethicscommittees. If the study will not be completed as advised, please forward a report form and an application for extension of ethical approval one month before the above date.

Amendments
It is also a condition of approval that the Committee is advised if the study does not commence, or is altered in any way, including all documentation eg advertisements, letters to prospective participants.

Please quote the above ethics committee reference number in all correspondence.
It should be noted that Ethics Committee approval does not imply any resource commitment or administrative facilitation by any healthcare provider within whose facility the research is to be carried out. The organisation may specify their own processes regarding notification or approval.

On behalf of the committee, I would like to take this opportunity to wish you all the best with your research.

Yours sincerely

Diana T. Whipp

Mrs Diana Whipp
Administrator Upper South B Regional Ethics Committee
Email: Diana_Whipp@moh.govt.nz
January 26, 2011

Eng Ann Toh, MBChB/BMedSc(Hons)
Student University of Otago
Christchurch School of Medicine and Health Sciences
Van Der Veer Institute for Parkinson's and Brain
Research 66 Stewart Street
Christchurch 8011 New Zealand

Re: Use of Unified Huntington Disease Rating Scale (UHDRS)

Dear Mr. Toh,

The Huntington Study Group (HSG) has received your request to use the Unified Huntington Disease Rating Scale (UHDRS) for the assessment of patients with Huntington disease for your thesis entitled “Eye-hand Coordination and Relationship to Cognition in Huntington’s Disease.” We are writing to confirm that the University of Rochester (Department of Neurology), on behalf of the HSG, has granted approval for you to use the UHDRS for this purpose until the conclusion of your study in December 2011. This authorization does not include permission to use the UHDRS for any commercially sponsored studies or other commercial purpose.

Please note that we are only granting permission to the portions of the UHDRS created by members of the Huntington Study Group. As you may know, there are certain scales incorporated within the UHDRS that are not the intellectual property of the HSG, and therefore, you will be required to seek and obtain separate permissions from the owners of these scales. This includes the following:

☐ Symbol Digit Modalities Test – Western Psychological Services owns this test. The testing form based on the original SMDT manuscript must be purchased for use. If an alternative version of the SMDT is used, permission must be obtained from WPS and a fee for use must be paid to WPS.

☐ Stroop and Verbal Fluency-these scales as included in our formal UHDRS materials appear to be in the public domain. However, there are certain versions of the Stroop test which do require purchase from the publisher prior to use (e.g. versions sold by Psychological Assessment Resources, Inc.(PAR) and Western Psychological Services (WPS)).

☐ TFC – Permission for use is needed for this assessment tool. However, since Ira Shoulson is the author, this was grandfathered in with the UHDRS permission.
In addition, by signing below you acknowledge that this permission extends only to the use specified above. In addition, you hereby agree that any modification, extension or amendment of this request should be discussed with Shari Kinel, JD, Executive Director of the Huntington Study Group (585.275.1935, shari_kinel@ctcc.rochester.edu). You further agree to ensure that the clinicians who use the UHDRS will understand the obligations contained herein including that the copyright designations on the UHDRS remain in its current format.

I trust this letter is responsive to your inquiry. Please do not hesitate to contact me if you have any questions.

Sincerely yours,

Ira Shoulson MD
Chair, Executive Committee
Huntington Study Group

AGREED AND ACCEPTED:

(Signature)

Printed Name: ENG ANN TOH
Title: MBChB / BMedSc (Hons) Student
Institution: UNIVERSITY OF OTAGO, NEW ZEALAND
Date: 27th JANUARY 2011


randomized controlled trials. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 1*(1), 103-111.


References


References


