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Pursuit of Cognitive Biomarkers:

Longitudinal neuropsychological evaluation of

pre-symptomatic Huntington’s Disease

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This thesis is submitted in partial fulfilment of the requirements of the degree of
Doctorate of Clinical Psychology, University of Auckland 2013.
Abstract

Recent research findings have challenged the conventional view of Huntington’s Disease (HD) as a disease primarily of the basal ganglia and striatal-frontal circuits. Use of cortical thickness mapping (an automated MRI technique) has revealed significant cortical thinning in the posterior cortex even in pre-symptomatic HD (Rosas et al., 2005). Three years ago Davison (2009) found posterior cortical thinning in a pre-symptomatic HD (PreHD) sample, accompanied by poorer performance on some cognitive tasks thought to depend upon posterior brain regions, with unimpaired performance on anterior tasks, suggesting there may be functional effects of cortical changes identified by neuroimaging. The research in this thesis involves a follow-up study to Davison, involving the same PreHD (n=18) and matched Control participants (n=17). The same neuropsychological measures used in the first assessment were administered to examine cognitive and mood changes over the three years. Based on the logic that the cortical thinning identified at the first assessment was due to the HD gene, and the poorer performance on tasks selected to recruit these brain regions was a consequence of that thinning, it was predicted that poorer performance would be evident in the PreHD group on the same cognitive tasks at the second time-point. Given the PreHD participants have progressed towards clinical onset, it was also hypothesised that performance on posterior tasks would have declined, particularly in individuals closest to clinical onset. Lastly, we predicted the PreHD group would be unimpaired on tasks sensitive to anterior brain regions.

Consistent with these predictions, the pre-symptomatic group performed more poorly than Controls on three tasks sensitive to posterior brain regions (Judgement of Line Orientation Test, Roadmap test and Benton Facial Recognition). Decline was evident on two tasks (Roadmap test and Benton Facial Recognition), most pronounced for those close to clinical onset, while PreHD performance was unremarkable on anterior tasks. These findings
suggest there are functional consequences of posterior cortical thinning found in pre-symptomatic HD. The findings also reveal potential candidates for cognitive biomarkers that may be sensitive to detecting, and tracking, progression of functional changes resulting from cortical changes occurring very early in the disease.
Acknowledgements

There are many people who have contributed to this journey and made this thesis possible.

Firstly, I would like to thank my primary supervisor, Lynette Tippett, for her support and encouragement throughout this entire process. Lynette, your immense knowledge of the brain and HD is humbling, but your teaching style has encouraged me to grow in this knowledge and improve my skills. Thank you for supporting me over the past 5 years, I have been very blessed and privileged to have you as a supervisor.

Thank you to Richard Roxburgh and Virginia Hogg for your incredible support and dedication to this research project. Richard, your time was invaluable, thank you for being so flexible and making every effort to conduct all the motor assessments for this study. Virginia, thank you for being the doorway to the relationships with all the HD participants, your dedication to our HD community made recruitment and retention of participants a far easier process.

To John Davison, thank you for helping me get my head around all the different components of this study and dealing with all my questions throughout the process, and thank you for allowing all the hard work for your thesis to be the foundation for mine.

To the staff at CAMRI, thank you so much for all your help and hard work. Special thanks to Anna-Maira Lydon, for all your support and Carol for helping me schedule all the scans.

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I would like to honour my Mum and Dad, Grandparents on both sides and family in the generations before me. Poverty and hardship was not a part of my journey because they sowed seeds of hard work, determination and sacrifice with their faith in God. I have been able to accomplish so much because of the foundations they worked so hard to lay; now I, and the generations after me, can excel in life. Mum and Dad, words cannot express how thankful I am for all your practical, emotional and financial support throughout my entire studies. I could not have accomplished this without your love and prayers, and I am so grateful for all the sacrifices you have made to make my journey a successful one. One victory at a time, we did it!!

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To my precious family members who have gone to heaven during this journey, I love you and miss you more than words can say; this thesis is dedicated to you.

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# Table of Contents

Abstract .................................................................................................................. ii

Acknowledgements ................................................................................................ iv

Table of Contents ................................................................................................... vi

List of Tables ........................................................................................................... x

List of Figures ......................................................................................................... xii

List of Appendices .................................................................................................. xv

List of Abbreviations ............................................................................................... xvi

Preface ..................................................................................................................... xviii

Chapter One General Introduction ........................................................................... 1

Background Information on HD ............................................................................... 2

Epidemiology ........................................................................................................... 2

Genetics .................................................................................................................. 3

Diagnostic Criteria ................................................................................................. 5

Diagnosis and Clinical Progression ......................................................................... 6

Stages of HD ........................................................................................................... 6

Clinical Features .................................................................................................... 7

Neuropathology in HD ........................................................................................... 12

Neuroimaging in HD ............................................................................................... 15

Changes in the Striatum .......................................................................................... 15

Changes in Extra-Striatal Subcortical Structures .................................................... 17

Cortical Changes .................................................................................................... 18

White Matter Changes ............................................................................................ 24

Neuropsychological Changes in HD ...................................................................... 27
Chapter Three  Results ........................................................................................................... 95

Statistical Analysis .................................................................................................................. 95

Results ................................................................................................................................... 96

UHDRS Cognitive Tests ......................................................................................................... 96
Psychomotor Tasks ................................................................................................................... 97
Tasks Sensitive to Posterior Brain Regions .......................................................................... 98
Tasks Sensitive to Anterior Brain Regions .......................................................................... 106
Mood Assessments ................................................................................................................. 116

Proximity Group Results ....................................................................................................... 119

UHDRS Cognitive Measures ................................................................................................. 119
Psychomotor Tasks ................................................................................................................... 120
Tasks Sensitive to Posterior Brain Regions .......................................................................... 121
Tasks Sensitive to Anterior Brain Regions .......................................................................... 129
Mood Assessments ................................................................................................................. 139

Chapter 4: Discussion .............................................................................................................. 143

Significant Findings from “Posterior Cortical” Tasks .......................................................... 144
Lack of Decline on “Posterior Cortical” Tasks ...................................................................... 150
Findings from “Anterior Cortical” Tasks .............................................................................. 151
Motor Speed and Psychomotor Performance ...................................................................... 152
Findings from UHDRS Cognitive Tasks ............................................................................. 153
Findings from Mood Assessments ....................................................................................... 154
Summary of Findings ............................................................................................................. 156
Inclusion of Participants who ‘Converted’ to Symptomatic .................................................. 157
Reflection on Findings ........................................................................................................... 159
What our Findings say about Cortical Thinning in Pre-symptomatic HD ......................... 162
Could Striatal Pathology be Responsible for our Findings? ............................................... 165
List of Tables

Table 1: *Clinical characteristics of the PreHD group at T2* .................................................................65

Table 2: *Frequency of PreHD participants in each UHDRS Diagnosis Confidence Level at T1 and T2.* .................................................................................................................................66

Table 3: *Demographic characteristics for the PreHD and Control groups at T2* .........................68

Table 4: *Demographic characteristics for the PreHDclose, PreHDbad and Control groups at T2* ..................................................................................................................................70

Table 5: *Administration details of Neuropsychological tasks* .........................................................74

Table 6: *Order of test administration (variations in procedure noted and explained)* .................94

Table 7: *Mean scores and standard deviations for UHDRS cognitive tasks for PreHD and Control groups at Timepoint-2 (T2).* .................................................................................................................96

Table 8: *Mean response times (ms) and standard deviations for Motor Screening and Reaction Time tasks for PreHD and Control groups at Timepoint-1 (T1) and Timepoint-2 (T2).* ........................................................................................................................................97

Table 9: *Mean and standard deviations of accuracy scores (percentage) for the PreHD and Control groups on the Collision-Judgement test, Hooper Visual Organisation Test (HVOT) and Judgement of Lines Orientation Test (JLOT) at T1 and T2.* ........................................................................................................99

Table 10: *Accuracy scores on the Roadmap Test for the PreHD and Control groups at Timepoint-1 (T1) and Timepoint-2 (T2).* ..............................................................................................................................101

Table 11: *Overview of significant findings in the Stockings of Cambridge Analysis* ..............116

Table 12: *Means and Standard Deviations of total scores for PreHD and Control groups on the HADS Anxiety and Depression and the IDAS Inward and Outward Irritability scales at T1 and T2.* ...............................................................................................................................117

Table 13: *Percentage in abnormal range for PreHD and Control groups on the HADS Anxiety and Depression and IDAS Inward and Outward Irritability scales at T2.* ...............118
Table 14: Mean scores and standard deviations for UHDRS cognitive tasks for PreHD, Close-to Onset, Far-from Onset and Control groups at Timepoint-2 (T2).

Table 15: Mean response times (ms) and standard deviations for Motor Screening and Reaction Time tasks for PreHD and Control groups at Timepoint-1 (T1) and Timepoint-2 (T2).

Table 16: Mean and standard deviations of accuracy scores (percentage) for the PreHDClose, PreHDfar and Control groups on the Collision-Judgement test, HVOT, JLOT and Benton Facial Recognition at T1 and T2.

Table 17: Accuracy scores (combined half and full rotation) for the PreHDClose, PreHDfar and Control groups on the Roadmap Test at time-point-1 (T1) and time-point-2 (T2).

Table 18: Response times for the PreHDClose, PreHDfar and Control groups on the Roadmap Test at time-point-1 (T1) and time-point-2 (T2).

Table 19: Overview of significant findings in the Stockings of Cambridge Analysis for proximity groups.

Table 20: Means and Standard Deviations of total scores for PreHD and Control groups on the HADS Anxiety and Depression and the IDAS Inward and Outward Irritability scales at T1 and T2.

Table 21: Percentage in abnormal range for PreHD and Control groups on the HADS Anxiety and Depression and IDAS Inward and Outward Irritability scales at T2.

Table 22: Cortical regions considered crucial to mediating cognitive task in the study.
List of Figures

*Figure 1:* Displays cortical thickness map of the PreHD group (n = 19) compared with the Control group (n=19) at T1. ................................................................. 67

*Figure 2:* Displays cortical thickness map of the PreHDfar group (n=9) compared with matched Controls (n=9) and the PreHDClose group (n=10) compared with matched Controls (n=10) at T1. ................................................................. 71

*Figure 3:* Motor Confidence Diagnosis Rating Scale from Unified Huntington’s Disease Rating Scale. ...................................................................................... 72

*Figure 4:* Sample stimuli from the Judgement of Lines Orientation Test ........................................... 78

*Figure 5:* Item 22 from the HVOT. .................................................................................................. 79

*Figure 6:* Collision Judgements Task. ............................................................................................. 80

*Figure 7:* Benton Facial Recognition Test ....................................................................................... 82

*Figure 8:* Modified Roadmap Test of Direction Sense. ..................................................................... 83

*Figure 9:* Different orientations of Letter F presented to participants ........................................... 85

*Figure 10:* Different orientations Hands presented to participants ................................................. 87

*Figure 11:* Stockings of Cambridge Task .......................................................................................... 89

*Figure 12:* Accuracy scores of PreHD and Control groups on Benton Facial Recognition (Short Form) over T1 and T2. ........................................................................ 100

*Figure 13:* Mean response times for Letter F mental rotation task for the PreHD and the Control groups. .................................................................................. 104

*Figure 14:* Mean accuracy on Letter F mental rotation task for the PreHD group and the Control group at time-point 2. ........................................................................ 105

*Figure 15:* Mean response times on Hand mental rotation task for the PreHD group and the Control group. .................................................................................. 107
Figure 16: Mean accuracy on Hand mental rotation task for the PreHD group and the Control group.

Figure 17: Displays (A) Proportion of perfect solutions and (B) Mean number of excess moves across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T2.

Figure 18: Initial thinking time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2.

Figure 19: Subsequent thinking time (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2.

Figure 20: Motor initiation time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2.

Figure 21: Motor Execution time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T1 (A) and T2 (B).

Figure 22: (A) displays accuracy for PreHDClose, PreHDFar and Control groups on Roadmap test at T1; (B) displays accuracy for PreHDClose, PreHDFar and Control groups on Roadmap test at T2.

Figure 23: Mean response times for the PreHDClose, PreHDFar and Control groups on the Letter F mental rotation task.

Figure 24: Mean accuracy for the PreHDClose, PreHDFar and Control groups on the Letter F mental rotation task.

Figure 25: Mean response times for PreHDClose, PreHDFar and Control groups on the Hand mental rotation task.

Figure 26: Mean accuracy for PreHDClose, PreHDFar and Control groups on the Hand mental rotation task.
Figure 27: Proportion of perfect solutions across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T2. .................................132

Figure 28: Mean number of excess moves across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T2. .................................133

Figure 29: Initial thinking time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T1 (A) and T2 (B) .........134

Figure 30: Subsequent thinking time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2. .................................................................................................................................136

Figure 31: Motor initiation time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2. .........137

Figure 32: Motor execution time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2. .................................................................................................................................138
List of Appendices

Appendix A: Rationale for cognitive tests used in this study ........................................ 170
Appendix B: Cortical Thinning Methods ......................................................................... 176
Appendix C: Structured interview .................................................................................. 179
Appendix D: Study consent form .................................................................................... 181
Appendix E: MRI safety and consent form ..................................................................... 182
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>BDNF</td>
<td>Brain Derived Neurotropic Factor</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebro-Spinal Fluid</td>
</tr>
<tr>
<td>CVLT</td>
<td>Californian Verbal Learning Test</td>
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<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
</tr>
<tr>
<td>DRS</td>
<td>Dementia Rating Scale</td>
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<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HD</td>
<td>Huntington’s Disease</td>
</tr>
<tr>
<td>HVLT</td>
<td>Hopkins Verbal Learning Test</td>
</tr>
<tr>
<td>HVOT</td>
<td>Hooper Visual Organisation Test</td>
</tr>
<tr>
<td>ICV</td>
<td>Intracranial volume</td>
</tr>
<tr>
<td>IDAS</td>
<td>Irritability-Depression-Anxiety Scale</td>
</tr>
<tr>
<td>JLOT</td>
<td>Judgement of Line Orientation Test</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s Disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>QNE</td>
<td>Quantified Neurological Examination</td>
</tr>
<tr>
<td>ROCF</td>
<td>Rey-Ostreith Complex Figure</td>
</tr>
<tr>
<td>ROI</td>
<td>Region-of-interest</td>
</tr>
<tr>
<td>RT</td>
<td>Reaction Time</td>
</tr>
<tr>
<td>SDMT</td>
<td>Symbol Digit Modalities Test</td>
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<tr>
<td>SoC</td>
<td>SoC Stockings of Cambridge task</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>T1</td>
<td>Time-point 1</td>
</tr>
<tr>
<td>T2</td>
<td>Time-point 2</td>
</tr>
<tr>
<td>TFC</td>
<td>Total Functional Capacity Scale</td>
</tr>
<tr>
<td>TMT</td>
<td>Trail Making Test</td>
</tr>
<tr>
<td>ToL</td>
<td>Tower of London</td>
</tr>
<tr>
<td>UHDRS</td>
<td>Unified Huntington’s Disease Rating Scale</td>
</tr>
<tr>
<td>VBM</td>
<td>Voxel-Based Morphometry</td>
</tr>
<tr>
<td>VOSP</td>
<td>Visual Object and Space Perception battery</td>
</tr>
<tr>
<td>VMPFC</td>
<td>Ventromedial Prefrontal Cortex</td>
</tr>
<tr>
<td>WMS</td>
<td>Wechsler Memory Scale</td>
</tr>
<tr>
<td>WCST</td>
<td>Wisconsin Card Sorting Test</td>
</tr>
<tr>
<td>YTO</td>
<td>Estimated Years To clinical Onset</td>
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Preface

This thesis investigated longitudinal cognitive changes in pre-symptomatic HD. Various aspects of cognition were measured using specifically selected neuropsychological tasks based on previous MRI cortical thinning findings. Mood measures were also included in the investigation.

Chapter 1 provides an introduction with background information on HD and literature specific to the background of this study, including neuroimaging in HD and longitudinal findings of other pre-symptomatic HD studies before outlining the rationale and objectives for this study. Chapter 2 provides the reader with a more specific introduction to the study and then outlines the methodology. Chapter 3 presents the results and Chapter 4, the discussion and conclusions.
Chapter One  General Introduction

Huntington’s Disease (HD) is an autosomal dominant genetic disorder. This neuro-degenerative disorder is marked by a symptom triad of progressive motor, cognitive and psychological impairment, where the proportion of each of these features, its presenting severity, and progression, varies significantly in each individual (Sturrock & Leavitt, 2010). Individuals with HD frequently develop symptoms between 30 and 40 years old (Walker, 2007), but many subtle signs may be present prior to this and there is a gradual worsening in symptoms across the span of the disease (Marshall, 2004). Motor symptoms are generally the most obvious symptoms of the disease, although cognitive and psychological changes are noted to be just as debilitating (Rosenblatt, 2007).

The HD gene, identified in 1993, allows family members to undergo genetic testing prior to clinical onset (Huntingtons-Disease-Collaborative-Research-Group, 1993). Prior to this time, there was no way to determine if an individual or their offspring would develop the disease. Research to date has provided many insights into HD, from molecular to structural changes, in addition to psychological and cognitive changes and effects on family, at all stages of the disease. Genetic testing has allowed HD gene carriers who are pre-symptomatic for HD to be investigated, which, in recent years has led to insights into significant pathological changes that are occurring prior to the appearance of clinical symptoms. Regardless of the large amount of knowledge gathered to date, there is still no treatment or cure for the disease, though a number of clinical trials are currently underway (Huntington-Study-Group, 2010).

Recent research has begun focusing on studies of pre-symptomatic HD, with the understanding that treatments will need to occur in this stage if symptomatic onset is to be delayed. Magnetic resonance imaging (MRI) has become a key tool used to investigate
progression of neural pathology, but cognitive testing is also being pursued to track changes in HD. If disease pathology can be tracked with neuropsychological measures, then it serves as a more accessible and cost effective tool than MRI. With this in mind, a number of longitudinal studies tracking changes in the pre-symptomatic stages of HD, using both MRI and cognitive measures are in progress (Paulsen & Long, 2012; Paulsen et al., 2010; Tabrizi et al., 2012), with the common goal of finding bio-markers, both structural and cognitive, that can be utilised as effective outcome measures in clinical trials. The study reported in this thesis attempts to contribute to this body of knowledge by conducting a longitudinal investigation into cognitive changes in pre-symptomatic HD. The design of this study combines the knowledge that there is posterior cortical thinning in pre-symptomatic HD with the selection of tests that involve cognitive functions reliant on these regions previously shown to be thinned.

**Background Information on HD**

**Epidemiology**

HD is found in all regions of the world, but most prominently where the populations are from European decent (Harper, 1992). Although prevalence statistics exist, exact estimates of HD frequencies around the world are not established due to the vast numbers of at-risk individuals who have not undergone genetic testing and additionally, the new mutation rate, which is reported to be as high as 1-3% (Myers, Macdonald, & Gusella, 1993). In European populations, prevalence is relatively uniform ranging between 5-10 individuals per 100,000 (Bates, Harper, & Jones, 2002; Marshall, 2004). Finland, with its genetically distinct origins, is an exception at 0.5 individuals per 100,000 (Harper, 1992; Marshall, 2004). Prevalence in Asiatic countries is not well documented, however, some fragmented evidence suggests that the disorder is not infrequent in China, India, and Central Asian populations.
(Harper, 1992). Kindreds of HD exist around in different regions of the world, where the HD gene has been passed on over generations within small or geographically isolated communities (Paulsen & Mikos, 2008; Sturrock & Leavitt, 2010). Examples of this exist within Tasmania (Pridmore, 1990), Venezuela, England, Northern Sweeden and Southern Wales (see Harper, 1992). The precise prevalence of Huntington’s disease within the New Zealand population is unknown, however, it is estimated to lie somewhere within the range gathered for western populations (Walker, 2007).

Genetics

The familial nature and high penetrance of HD has been noted for decades (Gusella & Macdonald, 2004). The disease presentation was first described and reported in 1872 by George Huntington. It was to be more than a century later, however, before the location of the chromosomal abnormality was first mapped in 1983 (Gusella et al., 1983), then the causative mutation identified in 1993 (Huntingtons-Disease-Collaborative-Research-Group, 1993). The HD gene, identified as IT15, is located on the short arm of chromosome four, and consists of a variably expanded trinucleotide sequence (CAG). CAG codes for the amino acid glutamine, however, the entire gene codes for a protein 3144 amino acids in length named Huntingtin (Huntingtons-Disease-Collaborative-Research-Group, 1993). All individuals possess the IT15 gene, however, those with HD have an abnormal expansion of CAG repeats in the 5’ end of the first exon (Walker, 2007). The normal version of the gene possess CAG trinucleotide repeat lengths of between 10-29. Repeat lengths between 30-35 are considered to be mutably normal (Brinkman, Mezei, Theilmann, Almqvist, & Hayden, 1997), because there is a likelihood that expansion into the abnormal range can occur in meiotic replication (MacDonald, Gines, Gusella, & Wheeler, 2003). Those with an HD gene with complete penetrance have expanded CAG repeat lengths of 40 or greater (Ross & Tabrizi, 2011;
Incomplete penetrance is observed for CAG repeat lengths of 36-39 (Walker, 2007).

The IT15 gene is autosomally inherited in a mendelian fashion, however, the mutant IT15 gene exhibits instability in meiotic replication where repeat lengths may expand when passed to offspring (MacDonald et al., 2003). The observed high spontaneous mutation rate of 1-3% (Myers et al., 1993) is due to the expansion of repeat lengths in the mutably normal range and the disease range with incomplete penetrance (Brinkman et al., 1997). A child born to a parent with HD has a 50% chance of inheriting the disease gene, the dominant nature of the IT15 gene means that if the disease gene is inherited, the disease phenotype will likely be expressed in their lifetime (Gusella & Macdonald, 2004).

The expressed product of the IT15 gene is named ‘Huntingtin’. Huntingtin is a cytoplasmic protein widely expressed in cells all around the body and is implicated in many processes, although the exact function/s of this protein are still being determined (Gusella & Macdonald, 2004; Novak & Tabrizi, 2011). The mutant Huntingtin contains an extended poly-glutamine tract which alters the resultant molecular interactions causing abnormal folding patterns and shape of the Huntingtin protein (Gusella & Macdonald, 2004; Hersch, Rosas, & Ferrante, 2004). HD pathology and its relationship to Huntingtin is discussed in further detail under the heading Neuropathology in HD.

There is an inverse relationship between the pathogenic CAG repeat length and the age of symptom onset, whereby greater repeat lengths are associated with earlier disease onset (Langbehn, Brinkman, Falush, Paulsen, & Hayden, 2004; Langbehn, Hayden, & Paulsen, 2010). Those with CAG repeat lengths of 36-50 tend to have adult onset while those with CAG repeat lengths of 60 or more tend to have juvenile onset (Paulsen & Mikos, 2008). The CAG repeat length, however, does not specify precisely what age an individual will develop clinical onset of the disease; it only explains 50% to 70% of the variation seen in age
of onset (Gusella & Macdonald, 2004; Ross & Tabrizi, 2011). Non-CAG genetic modifiers in addition to personal and environmental factors all may contribute to the variation in age of onset (Novak & Tabrizi, 2011; Ross & Tabrizi, 2011). CAG repeat length has little relationship to symptom type or symptom progression in the disease, but it does have a significant correlation with rates of atrophy in the caudate and putamen (Aylward et al., 2012; Aylward, Nopoulos, et al., 2011)

**Diagnostic Criteria**

Genetic testing confirms whether or not an individual has the disease gene. Clinical onset of HD, however, is based on the presence of extrapyramidal motor symptoms. The most commonly used diagnostic criterion requires the assessing neurologist to be 99% confident that the motor symptoms present are not explained by any other disorder except for the Huntington’s phenotype (Huntington-Study-Group, 1996). The Unified Huntington’s Disease Rating Scale (UHDRS) motor assessment is the most frequently used assessment tool on which to base HD clinical diagnosis, involving rating the presence and severity of a constellation of classical HD motor symptoms by a neurologist (Huntington-Study-Group, 1996). The motor assessment can be performed at any stage pre-clinical onset, and based on the outcome, the examining neurologist is able to give a motor diagnosis confidence rating level ranging from 0 - 4. Clinical diagnosis requires a rating at level four on the UHDRS motor confidence rating scale. Prior to diagnosis, the term pre-symptomatic, pre-clinical, pre-manifest and prodromal are commonly used to denote an individual who is gene positive for HD but is yet to be diagnosed with clinical onset. The presence of psychiatric and cognitive disturbance is not used in the UHDRS clinical diagnosis. It is important to note, however, that cognitive and affective changes are often present before clinical diagnosis based on motor symptoms (Novak & Tabrizi, 2011; Rosas, Feigin, & Hersch, 2004; Weir, Sturrock, & Leavitt, 2011).
Diagnosis and Clinical Progression

Individuals who are pre-symptomatic for HD transition from experiencing subtle, yet still recognisable, motor, cognitive and psychiatric signs to eventually displaying symptoms strong enough to warrant a clinical HD diagnosis (Novak & Tabrizi, 2011; Sturrock & Leavitt, 2010). The average age of clinical onset for those with HD is between 30 and 40 years old (Walker, 2007), with documented onset ranging from infancy to 90 years old (Dennhardt & LeDoux, 2010; Paulsen & Mikos, 2008). A small sub-group of HD sufferers fall into the juvenile subtype, where onset occurs before age 20 (Walker, 2007). This subtype accounts for 5% - 10% of HD sufferers, and symptoms within this sub-type are reported to progress faster with death occurring within a shorter trajectory (Paulsen & Mikos, 2008). For most of the HD population who have adult onset, symptoms of HD progress more gradually. In the early stages, HD individuals usually have the capacity to maintain a normal lifestyle, however, at the late stages individuals are fully dependent, which places a large burden on families (Sturrock & Leavitt, 2010). In most cases, somewhere between 15 and 20 years after symptoms first appear, the toll of the disease or secondary complications cause death (Paulsen & Mikos, 2008; Sorensen & Fenger, 1992; Walker, 2007). The causes of death are varied, some attributable to the physical debilitation of HD (e.g. choking) and others being secondary to HD such as infection, pneumonia, cardiovascular disease (Sorensen & Fenger, 1992) and suicide (Paulsen, Hoth, Nehl, & Stierman, 2005).

Stages of HD

Variation in progression and presentation in HD makes the stages of HD difficult to define. Brain pathological grades can be determined in post-mortem studies (Vonsattel et al., 1985), but these are no use in classifying HD stages when individuals are living. The most widely used, reliable and consistent tool to classify the stages of HD is based on daily living function (Bylsma, Rothlind, Hall, Folstein, & Brandt, 1993; Kieburtz et al., 1996; Marder et
al., 2000; Nehl & Paulsen, 2004). The HD Functional Capacity Scale, which measures this, is found in the Unified Huntington’s Disease Rating Scale and is reported as the Total Functional Capacity (TFC) scale which ranges from 0-13 (Huntington-Study-Group, 1996). This scale gives an indication of a person’s ability to manage domestic duties, perform activities of daily living, and levels of care needed (Dubinsky, 2005). Stages of HD range from I – V and are based on the score of the TFC, such that higher TFC scores indicate lower stages of the disease (Dubinsky, 2005; Marder et al., 2000). The TFC seems to be sensitive to degeneration in the disease with reports of average rate of decline between 0.63 (Feigin et al., 1995) and 0.72 units/year (Marder et al., 2000). The TFC may have limited ability to assess decline in later stages because of a ‘floor effect’; similarly, in pre-symptomatic stages the TFC is of limited use because high levels of functioning result in ‘ceiling effects’ (Marder et al., 2000).

Clinical Features

HD is commonly referred to as a disorder with a triad of clinical symptoms. In effect, HD is a disorder of movement, cognition and affect.

Movement disturbance

The disturbance of normal movement is the most overt symptom in HD. Motor symptoms experienced in HD can be categorised into involuntary and voluntary movement disturbances. The involuntary movement disturbances are probably the best characterised and are initially observed as an increase in movement (Novak & Tabrizi, 2011; Walker, 2007). While these movement disturbances may start as twitching and fidgeting, they progress to choreiform motor disturbance, which is characterised as rapid, irregular and jerky movements of the limbs, often athetoid (dance-like) in nature (Walker, 2007). Involuntary motor disturbance is not constrained to the extremities of the body (such as arms and legs) but also include musculature of the larynx, pharynx and respiratory system (Marshall, 2004). As the
disease progresses, choreic movements can impair a patient’s ability to feed, sit and sleep. Patients are still able to function relatively well despite these movements in the early stages of the disease, however, neuroleptic medications are often prescribed to reduce chorea and maximise an individual’s independence (Novak & Tabrizi, 2011; Sturrock & Leavitt, 2010). A second stage of involuntary motor disturbance occurs later on in the disease where the choreiform movements decrease and are replaced by muscular rigidity (Marshall, 2004). These features are debilitating causing functional disability, immobility and skin breakdown at the advanced stages (Marshall, 2004). Significant voluntary motor abnormalities also occur and decline in a progressive nature. Bradykinesia makes the initiation and execution of tasks difficult and individuals find it difficult to control their walking gait until eventually individuals’ are no longer able to walk (Sturrock & Leavitt, 2010). Abnormalities in eye movements occur early where individuals find it difficult to control head-eye co-ordinated movements and experience saccadic bursts (Hersch et al., 2004). In addition, difficulties in swallowing and speech occur later in the disease, progressing from trouble with rhythm and pitch to unintelligible utterances and inability to swallow (Marshall, 2004). The movement symptoms are extremely physically disabling, particularly in the late stages of the disease. It is noted, however, that the cognitive and affective features of the disease can have a more devastating effect on individuals and for family (van Duijn, Kingma, & van der Mast, 2007).

**Psychiatric Disturbance**

Prevalence reports of psychiatric disturbances in HD range from 33%-76% and include symptoms of depressed mood, anxiety, apathy, obsessive compulsive symptoms and psychosis (Kirkwood et al., 2002b; Paulsen, Ready, Hamilton, Mega, & Cummings, 2001; van Duijn et al., 2007). It is hard to classify the most common psychopathology in HD because the degenerative nature of HD means there is continuous instability of psychiatric symptoms throughout the disease (Naarding, Kremer, & Zitman, 2001). Similarly,
incongruity of results between studies may exist because many have used non-standard measures (Naarding et al., 2001) and have tended to group together participants at all stages of HD. This makes results unclear as the different stages of HD have profoundly different effects on psychopathology (De Marchi & Mennella, 2000; Epping & Paulsen, 2011). Nonetheless, the research available does give a good indication of psychiatric problems in HD.

The incidence of psychiatric diseases overall in those with HD are double the rate seen in the healthy controls (Leroi et al., 2002). Diagnoses of depression and dysthymia are relatively high with reported rates ranging anywhere between 30% and 53% (De Marchi & Mennella, 2000; Duff, Paulsen, Beglinger, Langbehn, & Stout, 2007; Naarding et al., 2001; M. Smith, Mills, Epping, Westervelt, & Paulsen, 2012) and sub-clinical depression higher at 35-60% (Duff et al., 2008; Snowden, Craufurd, Griffiths, Thompson, & Neary, 2001). In concordance with trends seen in depressive disorders, suicide risk is also increased in HD (Paulsen et al., 2005).

Anxiety is not reported as frequently in the literature as a major psychiatric symptom in HD (Anderson, 2011; Novak & Tabrizi, 2011; Thompson et al., 2012). Its presence, however, is reported in both symptomatic and pre-symptomatic HD (Duff et al., 2007; Paulsen, Ready, et al., 2001), although, at sub-clinical levels in pre-symptomatic HD (Duff et al., 2007).

Irritability is widely reported in both symptomatic and pre-symptomatic HD (Duff et al., 2007; Julien et al., 2007; Kloppel et al., 2010; van Duijn et al., 2007). The significance of it presence has received more attention recently, with reports that that irritability may be one of the first detectible signs of mood changes in pre-symptomatic HD (Julien et al., 2007). Symptoms of irritability cause large amounts of distress to those who care for individuals
with HD, and high levels of irritability and resultant aggression can often determine if home care or community care is needed (Anderson, 2011).

Personality changes are also frequently reported in HD. Leroi et al. (2002) found that 46.7% of their HD sample met DSM criteria for personality change with labile, dis-inhibited, apathetic and paranoid subtypes most frequent. Anger, irritability and apathy are thought to be a cluster of symptoms that reflect disruption of frontal and sub-cortical networks, which gives rise to these symptoms (Rosenblatt, 2007). These symptoms are commonly reported by the families of HD individuals and are also reported to be present in the pre-symptomatic stages of the disease (Julien et al., 2007; Kirkwood et al., 2002a; Kloppel et al., 2010; Naarding et al., 2001; Paulsen, Ready, et al., 2001).

Psychotic disorders are apparent in HD, however, these occur in a minority of cases (Paulsen, Ready, et al., 2001). Reported prevalence rates are inconsistent, ranging from 3%-30% across selected studies (van Duijn et al., 2007). Symptoms of psychosis may be present without warranting a clinical diagnosis for psychosis; for example Paulsen, Ready et al. (2001) report rates of delusions (11.5%), aberrant behaviour (9.6%) and hallucinations (1.9%) in 52 HD participants.

Much of the psychiatric disturbance seen in HD is thought to have an organic basis, related to deterioration of cortical-striatal circuitry (Naarding et al., 2001; Rosenblatt & Leroi, 2000). Irritability is a symptom, for example, most closely aligned with the pre-frontal cortex (Rosas et al., 2002) and amygdyla in symptomatic HD (Douaud et al., 2006; Kloppel et al., 2010), however, in pre-symptomatic HD this relationship failed to show (Kloppel et al., 2010). The neural basis of depression and anxiety in HD are less clear (Unschuld et al., 2012). A lot of the affective disturbance is likely also related to the stress and life change associated with a diagnosis of HD (Rosenblatt & Leroi, 2000). The presence of psychiatric symptoms has become a greater focus of more recent research, as there are indicators that
these may be the first clinically detectible signs of HD-related pathology in pre-symptomatic HD (Duff et al., 2007; Julien et al., 2007; Unschuld et al., 2012). The two symptoms suspected to indicate these changes are depression and irritability (Julien et al., 2007; Unschuld et al., 2012). The difficulty thus far, however, is that measures currently used are suspected to not be sensitive to detecting mood changes specific to HD, as symptoms may present differently to mood disturbance in the general population, for whom these measures are designed (Vaccarino et al., 2011). As a result, a current task-force is attempting to create effective measures for detecting mood change specific to both symptomatic and pre-symptomatic HD (Vaccarino et al., 2011).

For most individuals who experience psychological disturbance, conventional medications are reported to be effective in reducing psychotic and affective symptoms (Rosenblatt, 2007), although even with medication, these disturbances do take a significant toll on HD sufferers and their families (Marshall, 2004).

**Cognitive Disturbance**

Disturbances of cognition have been widely described in HD. These impairments, just like psychological disturbances, are insidious and can often be the most frustrating and debilitating aspect of HD (Marshall, 2004). Even prior to clinical onset, groups of pre-symptomatic carriers are repeatedly shown to have modest cognitive deficits compared to control group counterparts (Brandt et al., 2008; Davison, 2009; Witjes-Ane et al., 2007). Cognitive decline in memory, executive functions, and psychomotor deficits are characteristic of HD (Shoulson, 1990), however, not everyone experiences the same difficulties and progression varies considerably (Marshall, 2004). The main trait of cognitive deficits in HD is their progressive deterioration. Not all functions, however, follow this pattern, for example, language is preserved until quite late in the disease (Sturrock & Leavitt, 2010). In the advanced stages of the disease all domains of cognition are severely affected.
which results in a global dementia state (Sturrock & Leavitt). Extensive investigations into specific cognitive domains that deteriorate in HD have been reported which will be explored later in this document under Neuropsychological Changes in HD.

Neuropathology in HD

The hallmark of neuropathology in HD is neuronal loss in the striatum, which progresses to extra-striatal regions leading to global devastation in the brain later in the disease (Ross & Margolis, 2001; Ross & Tabrizi, 2011). Changes in the striatum occur more than a decade before clinical diagnosis (Aylward et al., 2000; Aylward et al., 2004; Thieben et al., 2002). At the microscopic level, medium spiny neurons, inhibitory neurons that use GABA as their primary neurotransmitter, are the most vulnerable (Hersch et al., 2004). They make up approximately 90% of the striatal neuronal population and at the advanced stages of the disease, 90% of these neurons are lost (Vonsattel et al., 1985). In fact, immunocytochemical and biochemical studies show that changes in the levels of GABA and their relative enzymes are some of the earliest neuro-chemical changes seen in HD (Tippett et al., 2007). The pattern of neuronal loss in the striatum seems to depend on projection sites of the striatal neurons, where the degeneration of striatal cells progresses in a dorsal to ventral pattern (Kipps et al., 2005) with most reports indicating degeneration occurs with a left hemisphere bias (Kipps et al., 2005; Rosas et al., 2001; Thieben et al., 2002).

Additional to striatal loss, histological and immunocytochemical studies show reductions in gross neuronal densities in extra-striatal structures. The subthalamus shows a reduction of 25% of neurons (H. Lange, Thorner, Hopf, & Schroder, 1979), the substantia nigra experiences substantial gliosis (Ferrante, Kowall, & Richardson, 1991), the thalamus shows a 55% loss of neurons and marked astrogliosis (Heinsen et al., 1994), the hypothalamus experiences a reduction in oligodendrocytes of about 40%, and a loss of
approximately 90% of neurons in the lateral nucleus (Kremer et al., 1991) and the globus pallidus, shows a reduction of 40% of its overall neuronal population (H. Lange et al., 1979).

There is evidence, however, that the cortex also deteriorates considerably. Thu et al. (2010) report cell loss in the cortex is reported to be as high as 50%. Pyramidal cortical cells are shown to undergo morphological changes such as hypotrophy (Gutekunst et al., 1999) and an increase in neuronal support cells (glia) is also seen, indicative of pathological processes (Selemon, Rajkowska, & Goldman-Rakic, 2004). Post-mortem studies also show atrophy of the cerebral cortex (Kosinski & Landwehrmeyer, 2005), however, determining cell loss in the cortex via histological studies of post-mortem brains is labour intensive, making it difficult to quantify regional cell loss.

Changes in the cortex and striatum may be related. The structures of the basal ganglia (which include the striatum) form integral components of re-entrant neural loops. These loops progress from cortical regions to subcortical structures and back to the cortex, effectively known as cortico-subcortical-cortical circuitry (DeLong & Wichmann, 2007). Five parallel circuit loops have been identified; these loops are anatomically distinct and proposed to serve functionally different domains which are identified by the areas of the cortex from which the input originates (Gombart, Soares, & Alexander, 2004). The cortical regions involved in these circuits are predominantly in the frontal cortex (Delong & Wichmann, 2007), thus the term fronto-striatal dysfunction is often used to describe the consequences of pathology within these loops. This has been the basis for the dominant view regarding the cause of the triad of symptoms in HD. That is, the motor symptoms are due to pathology in the striatum, but the cognitive and psychiatric symptoms of HD are due to dysfunction of the fronto-striatal loops, which emerge secondary to striatal pathology. Recent evidence, however, suggests other neural changes may be independently contributing to the symptoms of HD (Paulsen, 2010; Rosas et al., 2005). The complex circuitry makes disorders of the basal
ganglia complicated, as it is difficult to ascertain for certain what pathology is due to consequential effects of disrupted cortico-subcortical-cortical loops, and what processes are independent of these (DeLong & Wichmann, 2007). For these reasons, the precise pattern of progression of neural pathology in HD has been hard to define.

The precise molecular processes and mechanisms of pathology in HD are yet to be resolved (Imarisio et al., 2008). As previously discussed, ‘Huntingtin’ is a cytoplasmic protein widely expressed in cells all around the body and is implicated in many processes. The extended poly-gluatamine tract contained in the mutant Huntingtin alters the resultant molecular interactions causing abnormal folding patterns and shape of the Huntingtin protein (Gusella & Macdonald, 2004; Hersch et al., 2004). Multiple processes eventually lead to aggregates of mutant Huntingtin forming in the nucleus of the cell (Gusella & Macdonald, 2006). The idea has held for a very long time that intranuclear aggregates of mutant Huntingtin play a significant but unknown pathogenic role in the neuronal degeneration of HD (Hersch et al., 2004). As yet, however, research has failed to show direct or causative links between mutant Huntingtin aggregates and HD neuropathology (Imarisio et al., 2008). There are a lack of significant relationships between high levels of mutant Huntingtin aggregates and areas most affected by neurodegeneration. For example, mutant Huntingtin aggregation was only found in 1-4% of striatal neurons across grades 1-4 of the disease, a population of neurons that are most vulnerable to death in HD (Gutekunst et al., 1999; Kuemmerle et al., 1999). Additionally, mutant Huntingtin aggregates in neuronal cell cultures are shown to be insufficient to cause cell death (Saudou, Finkbeiner, Devys, & Greenberg, 1998) and conversely, potentially play a role in cell survival (Arrasate, Mitra, Schweitzer, Segal, & Finkbeiner, 2004).

The loss of normal Huntingtin is thought to disrupt normal cell processes, but again these mechanisms are not clear (Hersch et al., 2004; Rosas, Salat, Lee, Zaleta, Hevelone, et
al., 2008). There is evidence that the abnormal HD gene has multiple effects (or pleiotropic properties) on pathogenic mechanisms in the cell (Gusella & MacDonald, 2007; Ross & Tabrizi, 2011). It is likely that these cause many of the pathogenic mechanisms seen in HD, such as defective axonal transport affecting mitochondria and cell metabolism, and direct and indirect excitotoxicity from pathological chemical channel and receptor activation (Hersch et al., 2004; Rosas, Salat, Lee, Zaleta, Hevelone, et al., 2008; Ross & Tabrizi, 2011). The crucial steps in the progression from compensation mechanisms, to degeneration, to death of vulnerable neuronal populations, however, remains elusive and the exact role of abnormal Huntingtin aggregates and the loss of normal Huntingtin is still being determined (Ross & Tabrizi, 2011).

**Neuroimaging in HD**

**Changes in the Striatum**

Numerous MRI studies document significant atrophy of the caudate and putamen in both clinical and pre-clinical HD (Paulsen, Magnotta, et al., 2006; Rosas et al., 2003), which is progressive (Aylward et al., 2004; Ruocco, Bonilha, Li, Lopes-Cendes, & Cendes, 2008; Ruocco, Lopes-Cendes, Li, Santos-Silva, & Cendes, 2006) and predictive of years to onset of the disease (Aylward, Nopoulos, et al., 2011; Aylward et al., 2003). In clinical HD, atrophy is consistently detected in the caudate and putamen compared to controls (Aylward et al., 2000; Aylward et al., 1997; Aylward et al., 2003; Brandt, Bylsma, Aylward, Rothlind, & Gow, 1995; Kassubek et al., 2004; Rosas et al., 2001; Ruocco et al., 2008). Most MRI studies show greater atrophy in the caudate nucleus than the putamen. Studies of clinical HD show that caudate volumes range from 37% (Rosas et al., 2003) to 47% (Rosas et al., 2001) of healthy controls while putamen volumes range from 49% (Rosas et al., 2001) to 53% (Rosas et al., 2003) of healthy controls. The largest rates of atrophy and effect sizes are seen in change for
the caudate (Aylward, Nopoulos, et al., 2011). For example, in a sample of symptomatic HD individuals over 20 months, the caudate on average lost 9.5% of its volume whereas the putamen atrophied by 6.0% (Aylward et al., 1997). Longitudinal studies have suggested that the rates of annual atrophy in the caudate in symptomatic HD range from 4.9% (Aylward et al., 2003) to 7.24% (Aylward et al., 2000) per annum.

Changes in both the caudate and putamen are noted to occur more than 10 years before estimated diagnosis (Aylward et al., 1996; Aylward, Nopoulos, et al., 2011; Aylward et al., 2004). In pre-symptomatic HD, the volume of the striatum is shown to be larger in those with no motor symptoms, suggesting a positive linear relationship between motor symptoms and striatal volume loss (Aylward et al., 2012; Paulsen, Hayden, et al., 2006). Reduced volumes have been reported in both the caudate and putamen in pre-symptomatic HD (Paulsen, Magnotta, et al., 2006; Thieben et al., 2002), with magnitude affected by years to clinical onset (Aylward et al., 1996; Davison, 2009; Paulsen et al., 2008; Paulsen, Magnotta, et al., 2006). Aylward et al. (1996) report their far-from-onset group (greater than 6 years to clinical onset) have caudate and putamen volumes that are 90% the size of gene negative controls whereas those close-to-onset (less than 6 years to clinical onset) have caudate and putamen volumes 67% the size of gene negative controls. Even when estimated years to onset are considerably longer, those in close-to onset groups (less than 15 and less than 17 years to clinical onset) show significantly smaller caudate and putamen volumes in comparison to far-from onset groups (greater than 15 and greater than 17 years to clinical onset) and controls (Davison, 2009; Paulsen et al., 2008). No differences in caudate and putamen volumes are observed when far-from onset groups are compared to controls in these studies (Davison, 2009; Paulsen et al., 2008). Paulsen et al. (2008) suggest there is little change in these structures 15-20 or more years prior to clinical onset.
Changes in Extra-Striatal Subcortical Structures

Extra-striatal subcortical structures also show significant changes in MRI studies of both clinical and pre-symptomatic HD. Changes of subcortical structures outside the striatum have not been a focus of much research but changes in many of these structures do occur, and may be a secondary response to striatal degeneration, contributing to HD symptoms. Consistent with histological and immunological findings, neuroimaging studies of symptomatic HD individuals report volume changes of the globus pallidus (41%) (Rosas et al., 2003), thalamus (Ruocco et al., 2008) and hypothalamus (Douaud et al., 2006; Kassubek, Juengling, Ecker, & Landwehrmeyer, 2005). Significant volume changes are also reported, however, to occur in the hippocampus (9%), amygdala (37%), nucleus accumbens (41%) and brainstem (Rosas et al., 2003). Changes in extra-striatal subcortical structures begin in the pre-clinical stages of HD, where there are reports of significant pathological changes in the thalamus (Paulsen, Magnotta, et al., 2006; Thieben et al., 2002) and globus pallidus (Aylward et al., 1994; Aylward et al., 1996; Paulsen, Magnotta, et al., 2006). Striatal pathology, which leads to disrupted striato-pallido-thalamo-cortical circuitry, is likely the main factor that causes the early degeneration of extra-striatal structures; and these are also likely to contribute to cognitive and psychiatric changes prior to clinical onset (Lawrence et al., 1996; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2004; Paulsen, Magnotta, et al., 2006).

Very recent MRI findings also suggest that brain development may be abnormal in HD. This is exemplified through the finding of significantly smaller intra-cranial volume (ICV) in pre-symptomatic HD males compared to controls (Nopoulos et al., 2011). The authors reason that ICV is a measure of maximal brain growth attained during developmental periods and that ICV stays stable regardless of neuropathology, thus significantly smaller ICVs compared to controls indicates differential brain development.
Cortical Changes

The clinical significance and extent of cortical pathology within HD has become a focus of research in recent times. While changes in the cerebral cortex have been noted for years, there is a new interest in its significance. The cortex, or cerebral grey matter, forms an integral beginning and endpoint for striato-pallido-thalamo-cortical circuitry, and is the most important source of glutamatergic projections to the striatum (Hersch et al., 2004). Additionally, the cortex is an important source of trophic factors to the striatum, in particular brain derived neurotrophic factor (BDNF), which plays a crucial role in supporting the neurons of the striatum (Hersch et al., 2004). Recent MRI evidence, however, shows that in addition to expected cortical changes in clinical HD, there are also changes in pre-clinical HD. These findings show posterior cortical changes occur first, before anterior cortical changes, and that these changes may be independent of striatal pathology (Paulsen et al., 2010; Rosas et al., 2005). This is striking given the dominant understanding of HD pathology is that it begins in the striatum, and also because it raises the possibility that these cortical changes may be significant in the early development of clinical symptoms (Rosas et al., 2002; Rosas, Salat, Lee, Zaleta, Pappu, et al., 2008).

In general the cortex can be described as a complex folded sheet of neuronal tissue that has functional areas arranged in a mosaic fashion (Fischl et al., 2008). The unique organisation of the cortex, in terms of its regional and topographic organisation, means it is of great interest in understanding normal brain processes and neurodegenerative processes (Fischl, Sereno, & Dale, 1999). If changes are regionally specific then it gives important information about significant factors that may be instrumental in the disease process and also indications about the progression of pathology (Fischl & Dale, 2000). The cortex, however is difficult to measure because of its complex folding (Fischl et al., 2008).
Voxel Based Morphometry (VBM) is one of the main techniques used to measure cortical changes from MRI data (Fennema-Notestine et al., 2004; Thieben et al., 2002). VBM involves a voxel-wise comparison of local concentrations of gray matter between two groups of subjects, where a voxel refers to a unit of volume existing within a theoretical three-dimensional space (Ashburner & Friston, 2000). The VBM method produces a voxel-map indicating regions where gray matter concentration may differ between groups. While this has been used in studies of HD, the use of VBM to measure precise aspects of cortical change is limited because there is a lack of knowledge about what aspect of the cortex (e.g. thickness, volume or surface area) the ‘grey matter density’ measure of VBM is assessing (Mechelli, Price, Friston, & Ashburner, 2005). The authors of this technique note their method for gray matter segmentation is not robust, as many gray matter structures ‘have image intensities that are almost indistinguishable from that of white matter’ (Ashburner & Friston, pg. 808) making the definition of gray matter in these regions less accurate (Ashburner & Friston, 2000; Mechelli et al., 2005). Additionally, the VBM model assumes all voxels contain only one tissue type, thus voxels containing boundaries between white matter and ventricles will often appear as gray matter (Ashburner & Friston, 2000).

Cortical thinning is a technique that has emerged in the last decade. Major leaps in the use of technology have allowed novel manipulations of MRI data sets that enable actual measurements of the cortex to be obtained (Fischl & Dale, 2000). The cortical thinning technique involves the collective use of automated surface reconstruction, high resolution surface averaging, co-ordinate systems, automatic parcellations, and inflation and inversion, enabling the cortical thickness at each point of the cortex to be calculated (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl et al., 2008; Fischl, Sereno, & Dale, 1999; Fischl et al., 2004). These techniques allow cortical thickness measurements to be gained in-vivo for clinical and normal populations with sub-millimetre precision (Dale et al., 1999; Fischl &
The automated components of the cortical thinning techniques are preferred over manual analysis of MRI data, which requires labor intensive efforts of trained neuro-anatomists and still results in measurement overestimates (Fischl & Dale, 2000; Fischl et al., 2004; Rosas et al., 2002). The thickness measurements derived from this technique are shown to be valid compared with manual measures on post-mortem brains (Rosas et al., 2002). Other benefits are that cortical thickness maps are not limited to the voxel resolution of the original scan images (Fischl & Dale, 2000) and the use of this technique has been shown to be reliable across different scanning variables (Dickerson et al., 2008; Han et al., 2006).

Proponents of cortical thinning thus argue that the technique is superior to VBM. VBM, for example, gives gross grey matter measurements (Mechelli et al., 2005), whereas the cortical thinning technique gives more precise information of cortical changes that are not detected with VBM methods. Nopoulos et al. (2010) contend that VBM and cortical thinning techniques may be measuring different aspects of the cortex. Winkler et al. (2010) show that cortical volume, as measured with VBM, is more closely aligned to measuring surface area rather than giving indication about the thickness of the cortex. Changes in the cortex, especially in the early disease processes, are not big enough to produce large global changes that can be detected in gross volume measures of the cortex (Rosas et al., 2002). Precise measurements at each point on the cortex are therefore required in order to be able to detect subtle cortical atrophy or hypertrophy (Fischl & Dale, 2000; Rosas et al., 2002).

Rosas et al. (2002) measured cortical thickness in 11 clinical HD individuals and found that cortical thinning was present bilaterally at all stages of the disease including the very early stages (Rosas et al., 2002). Surprisingly, in those with early HD, thinning was found to be most prominent over posterior cortical regions, namely regions of middle occipital, middle temporal, and angular and supramarginal gyri (Rosas et al., 2002).
increased disease stages, cortical thinning progressed to include more anterior cortical regions, with global thinning in the advanced stages (Rosas et al., 2002). In the sample overall, the greatest differences in cortical thickness between HD and controls was in the order of 1mm which the authors document correspond to greater than a 30% loss of thickness (Rosas et al., 2002).

In 2005, Rosas and colleagues expanded their investigation to include participants who were pre-symptomatic for HD, and found selective cortical thinning present in this group (Rosas et al., 2005). Consistent with the previous finding in clinical HD participants, thinning was most significant in posterior regions including parietal, temporal and occipital gyri (Rosas et al., 2005). To investigate the impact of striatal pathology, the results of cortical thinning were adjusted for caudate and putamen volumes; although thinning became less prominent in more anterior regions (superior temporal and posterior frontal areas), findings of thinning in posterior areas were still significant, highlighting the robustness of the finding in these areas (Rosas et al., 2005). This finding also suggests that the process of cortical change may be somewhat less dependent on the changes in the striatum (Paulsen, 2010; Paulsen et al., 2010) and is in line with other research that suggests deterioration in brain structures apart from the striatum are significant (Paulsen et al., 2010).

Rosas and colleagues further extended their investigations measuring cortical thickness in 33 diagnosed HD individuals and 22 age and sex matched controls (Rosas, Salat, Lee, Zaleta, Pappu, et al., 2008). This study sought to confirm and map the topology of regional cortical changes across the spectrum of the disease stages but particularly in early clinical HD. Their results were remarkably similar to previous studies, confirming regionally selective, progressive and heterogeneous thinning beginning in posterior regions of the cortex. They showed early HD (stage I) had average loss in thickness ranging from 5 – 15% in posterior cortical regions (e.g. visual cortex). Within stage II, Rosas, Salat, Lee, Zaleta,
Pappu, et al. (2008) report that the magnitude of cortical thinning increased to 15-20% with extension to more anterior regions. In stage III, the thinning became more severe covering ‘most of the cortex’ with only relative sparing of anterior frontal and inferior temporal cortices with thinning estimates reported to be as high as 30% (Rosas, Salat, Lee, Zaleta, Pappu, et al., 2008).

In 2009, Davison (2009) attempted to replicate Rosas et al.’s (2005) findings in pre-clinical HD. Identical MRI-based cortical thinning methods were used in the sample comprising 19 pre-symptomatic HD individuals and 19 age, sex and education-matched controls. Cortical thinning was present in posterior regions of the brain in the pre-symptomatic HD participants, most significant in the right parietal-temporal-occipital junction, extending into small portions of the posterior middle temporal gyrus, the inferior parietal cortex, and the lateral occipital cortex. Smaller areas of thinning were noted in paracentral lobule/posterior superior frontal gyrus and the pars opercularis (Davison, 2009). When the pre-symptomatic group was divided by years to estimated clinical onset, the close-to-onset group (less than 15 years to onset) showed significant cortical thinning in the right parietal-temporal-occipital junction whereas the far-from onset group (greater than 15 years to onset) did not show any cortical thinning in comparison to controls. As expected from previous findings for pre-symptomatic HD (Rosas et al., 2005), no thinning was found in the anterior regions of the cortex regardless of estimated years to clinical onset (Davison, 2009). Tabrizi et al. (2009) also report significant thinning of the cortex in their pre-symptomatic groups at baseline, with those close-to-onset (less than 10.8 years to onset) showing the most dominant thinning in the occipital, parietal and superior temporal lobes.

The most recent study to report regionally selective cortical thinning (Nopoulos et al., 2010) investigated the largest pre-symptomatic sample for cortical thinning to date (523 pre-symptomatic HD participant’s and 170 controls). Nopoulos et al. (2010) used identical
methods as previous studies (Rosas et al., 2005; Tabrizi et al., 2009) to achieve cortical thickness measures. They split their pre-symptomatic group into near- (less than 9 years to onset) mid- (9-15 years to onset) and far-from-onset (greater than 15 years to onset) groups. Their far-from-onset group did not show significant cortical thinning compared to controls, whereas their mid-to-onset and near-to-onset groups did (Nopoulos et al., 2010). The authors report an increasing pattern of progression of cortical thinning as participants are nearer to clinical onset, with cortical thinning predominantly in the lateral parietal and occipital regions of the cortex early on, then progressing to thinning over most of the cortex by the time of HD diagnosis. They note, however, that even when thinning is more global, the most affected regions remain in posterior regions of the cortex (Nopoulos et al., 2010).

Not all MRI studies support the finding of reduction of cortical grey matter in HD. In studies using VBM, both no change in gray matter (Jernigan, Salmon, Butters, & Hesselink, 1991), and a small increase in frontal gray matter volume (Aylward et al., 1998) are shown in those with symptomatic HD. In a study of pre-clinical HD, Paulsen and colleagues found a generalised significant increase in cortical grey matter volume in comparison to controls (Paulsen, Magnotta, et al., 2006). Paulsen and colleagues suggest that their finding is not unusual, and in fact, Nopoulos et al. (2007) also showed significantly thicker gyri, in pre-clinical HD, however, they also report reduced cortical volume in sulci. All these studies, however, used VBM methods. As discussed earlier, VBM give localised measures of gray matter volume rather than specifically defining the cortical thickness at precise points on the brain.

Rosas, Salat, Lee, Zaleta, Pappu, et al. (2008) using cortical thickness measurements also found thickening of the cortex within the anterior cingulate in their clinical HD sample. Similarly, Davison (2009) showed areas of significant cortical thickening in the right anterior cingulate, medial orbitofrontal cortex and within the left posterior cingulate cortex. Cortical
thickening may be indicative of pathological processes, and seems to be most present in the pre-clinical and early stages of HD (Paulsen, Magnotta, et al., 2006). Thus, localised volume measurements of VBM may be misleading, as collective thickening and thinning processes may result in overall undetectable change in neuronal volume.

Overall, Davison (2009), Rosas et al. (2005); Rosas, Salat, Lee, Zaleta, Hevelone, et al. (2008), Tabrizi et al. (2009) and Nopoulos et al. (2010) have had significant findings in thinning of cortical gray matter, most significantly in posterior cortical regions. These studies have reported selective and regional cortical thinning, and in some cases thickening, which was highly heterogeneous, meaning that apart from the areas of significance, the rest of the cortex was unremarkable in comparison to controls (Davison, 2009; Rosas et al., 2005; Rosas et al., 2002; Rosas, Salat, Lee, Zaleta, Pappu, et al., 2008). Conflicting evidence in research using different methods may exist because cortical changes are heterogeneous, regionally selective, involving pathology that results in concurrent thickening and thinning (Paulsen, Magnotta, et al., 2006; Rosas et al., 2005; Rosas et al., 2002) and both methods may measuring different characteristics of the cortex (Nopoulos et al., 2010).

In general, however, these investigations highlight that HD is far more than just a disease of the basal ganglia; in-fact cortical changes may occur as early as the changes in the striatum, suggesting a partially independent pathological process (Aylward et al., 2000; Aylward et al., 2004; Davison, 2009; Nopolous et al., 2010; Rosas et al., 2005). This evidence is highly arresting given the dominant understanding is that pathology begins in the striatum, and cortical changes occur later, perhaps secondary to the striatal pathology.

**White Matter Changes**

Diffusion tensor imaging (DTI) is a recently developed MRI technique that allows in-vivo investigation into the integrity of white matter in healthy and diseased brains (Seppi et al., 2006). The use of this technique within HD has given researchers the ability to investigate...
white matter pathology and its relationship to already known structural degeneration (Bohanna, Georgiou-Karistianis, Hannan, & Egan, 2008; Rosas et al., 2006). DTI measures the diffusion of water molecules in the nerve fibre which gives information about current integrity or composition of the white matter tract. This is most commonly reported as a measure of fractional anisotropy (FA), which ranges from 0 to 1 (Beaulieu, 2002). FA varies across white matter regions and is greater in regions with more tightly packed axons, thicker myelin sheaths, fewer obliquely oriented fibres, and different radii of individual axons (Chepuri et al., 2002).

Investigations into white matter changes in HD using diffusion techniques began in the early 2000’s, but have increased in number in recent times (Bohanna et al., 2008; Weaver et al., 2009). These studies indicate that significant white matter pathology occurs during the course of HD, including the pre-clinical stages (Reading et al., 2005; Rosas et al., 2006). Earlier studies report reductions in white matter integrity in the caudate, putamen (Mascalchi et al., 2004; Seppi et al., 2006), globus pallidus, thalamus (Seppi et al., 2006) periventricular white matter and generally in a whole brain measure (Mascalchi et al., 2004). These studies, however, only looked at regions of interest (ROI) within the basal ganglia or gross whole brain analyses (Mascalchi et al., 2004; Seppi et al., 2006). Other studies investigating white matter changes in HD have used hypothesis-based investigations into ROI’s, as well as whole brain voxel maps in order to find white matter changes that were not predicted a priori (Rosas et al., 2006). Using these techniques, degeneration in white matter has been observed in the corpus callosum (genu, body and splenium), the posterior limb of the internal capsule, cerebral peduncles, brain stem and thalamus (Rosas et al., 2006). Surprisingly, increases in white matter integrity were also reported in clinical HD in the anterior limb and left genu of the internal capsule, and bilaterally in the putamen and globus pallidus (Rosas et al., 2006). These changes are unexpected and only one other study (Mascalchi et al., 2004) has reported
increases in integrity in clinical HD, but only in the putamen. Such increases are hypothesised to be a result of pathologic processes that remodel the composition of internal fibres (e.g. microtubules, neurofilaments and neurofibrils) and cause astrocytosis (Rosas et al., 2006).

White matter changes in pre-symptomatic HD have also been reported (Kloppel et al., 2008; Reading et al., 2005; Rosas et al., 2006). Reading et al. (2005) examined regional white matter changes and found significantly decreased white matter integrity bilaterally in superior frontal, middle frontal, post-central and pre-central white matter and right occipital white matter. Reduced white matter integrity is also seen in anterior regions of the corpus callosum (Kloppel et al., 2008) and the genu and posterior limb of the internal capsule (Rosas et al., 2006). Increases in white matter integrity would be expected more in pre-clinical HD, as compensatory processes are likely to occur in the early and pre-clinical stages of HD pathology. Indeed, increases in white matter integrity are reported in pre-clinical HD in the anterior limb of the internal capsule, bilaterally in the putamen (Kloppel et al., 2008; Rosas et al., 2006), pallidum, occipital pole (Kloppel et al., 2008), thalamus, primary pulvinars, and in white matter underlying the sensory-motor and frontal cortex (Rosas et al., 2006).

The pathological reasons for decreases in the integrity of white matter in HD are still elusive and may reflect decreases in axonal densities, micro-structural changes, diminished myelination and axonal membrane changes. All authors stress that the biological causes behind the DTI findings are unclear as many factors could be contributing to the changes, and these may be disease specific (i.e. different to those occurring in other neurodegenerative diseases). Thus the interpretation of these findings is still speculative and the resultant relationship of these changes to symptomatology is even more unclear. Further investigations into these areas combined with other measures (such as cortical thinning) and neuropsychological tasks may aid in finding clearer explanations of relationships to white matter pathology and HD symptoms.
Neuropsychological Changes in HD

As indicated earlier, changes in cognition are a significant part of HD. These changes in cognition progressively deteriorate throughout the span of the disease and are thought to reflect underlying neural pathology. Cognitive changes are well documented in current research and are explored further according to specific cognitive domains below.

Motor Speed and Psychomotor Abilities

Psychomotor abilities are typically measured by timed tests that require some sort of physical response to complete the task, but also involve a cognitive component. Motor speed tasks such as finger tapping, however, only assess motor ability.

Symptomatic HD participants are shown to be slower on motor speed tasks of finger tapping (Giordani et al., 1995; Muller et al., 2002) and a computerised motor screening task compared to controls (Giordani et al., 1995; Watkins et al., 2000). Pre-symptomatic HD participants are also reported to be significantly slower on motor speed tasks such as a simple reaction time task (Davison, 2009), button tapping time (Giordani et al., 1995; Kirkwood et al., 2000) and finger tapping (Tabrizi et al., 2009).

In symptomatic HD, poorer performance is seen on psychomotor tasks such as the Symbol Digit Modalities Test (SDMT) (Brandt & Bylesma, 1993; Giordani et al., 1995; Watkins et al., 2000). Additionally, HD participants are impaired in time taken to complete both Trails A and B in the Trail Making Test (TMT) (Brandt et al., 1990; Giordani et al., 1995; Ho et al., 2003) and in a similar Number Connection task which is akin to part A of the TMT (Muller et al., 2002). Deficits in symptomatic HD are also seen on the Stroop Colour and Word trials which are measures of processing speed without a major psychomotor component (Watkins et al., 2000; Giordani et al., 1995).
In pre-symptomatic HD, findings have varied from no difference on SDMT performance (Brandt, Shpritz, Codori, Margolis, & Rosenblatt, 2002; Hahn-Barma et al., 1998) to longer completion times (Foroud et al., 1995; Gomez-Anson et al., 2007; Kirkwood et al., 1999; Paulsen, Ready, et al., 2001). Some studies also report that SMDT performance can differentiate those close-to and far-from clinical onset (Brandt et al., 2002; Hahn-Barma et al., 1998). In the TMT, there are reports of no difference in performances on either parts A or B (Brandt et al., 2002; Gomez-Anson et al., 2007; Hahn-Barma et al., 1998), more errors and longer time to complete part B but not part A (Wahlin, Lundin, & Dear, 2007) and slower performance on both part A and B (Giordani et al., 1995). Part B of the TMT, however, has a significant executive function component of shifting set, thus difficulties in part B are not necessarily reflective of poorer processing speed. Lastly, reports for pre-symptomatic performance on the Stroop are mixed, with reports of no difference in performance on the Colour and Word trials (Brandt et al., 2002; Gomez-Anson et al., 2007), worse performance on the Colour trial only (Snowden et al., 2001) and poorer performance on both Colour and Word trials (Paulsen, Zhao, et al., 2001).

Attention

The concept of attention is complex and has been described as a multi-dimensional system that has semi-dependent processes (Sohlberg & Mateer, 2001). The construct of attention consists of dimensions such as focused attention, sustained attention and divided attention, and can be measured by specific attention-modulated tasks. Attention within each of these dimensions is dependent on the type of selection participants are required to make and the intensity/complexity of the task (Muller et al., 2002)

Research indicates symptomatic HD participants are impaired on basic tests of attention span capacity such as Digit Span and Spatial Span Forward tasks (Ho et al., 2003; Snowden et al., 2001), and that their performance on these tasks shows a significant pattern of
longitudinal decline (Ho et al., 2003). In pre-symptomatic HD, for the most part no differences have been found on Digit Span Forward (van Walsem, Sundet, Retterstol, & Sundseth, 2010) or Spatial Span Forward tasks (Wolf et al., 2012). Wolf et al. (2012), however, reports worse performance in pre-symptomatic participants on the Digit Span Forward task.

Sustained attention tasks require maintaining a consistent behavioural response during continuous and repetitive activity. Reports are mixed in symptomatic HD, with sustained attention reported to be unimpaired in vigilance and sustained attention tasks (K. W. Lange, Sahakian, Quinn, Marsden, & Robbins, 1995; Sprengelmeyer, Lange, & Homberg, 1995); a more recent study, however, shows that sustained attention as measured by the Sustained Attention to Response Task (SART) is impaired even in early HD (Hart et al., 2012). In pre-symptomatic HD, performance in a tonic alertness task was not different to controls (Wolf et al., 2012).

Focused attention tasks require participants to focus their attention on either the global or local level of stimuli when multiple stimuli are present. The stimuli can be simple, such as two stimuli presented side by side, or more complex where the stimuli overlap or are embedded. Roman et al. (1998) found no difference in reaction times of symptomatic HD participants compared with age matched controls when the demands of the focused attention task were simple. Symptomatic HD participants, however, had slower response times on the complex task, and another study, using an identical task to Roman et al. (1998) found reaction times of symptomatic HD participants were impaired in both simple and complex versions (Filoteo et al., 1995). Similar to these findings, Finke et al. (2007) found symptomatic HD participants were impaired when attending to complex stimuli with overlapping layers. In pre-symptomatic HD, Wolf et al. (2012) report no difference on a task of phasic alertness compared to controls suggesting focused attention is unimpaired.
Divided attention tasks involve presentation of two streams of competing stimuli simultaneously, with participants required to attend to both. In symptomatic HD both minimal impairments (Muller et al., 2002) and severe impairments (Sprengelmeyer et al., 1995) are reported. Tsai, Lasker, and Zee (1995) report symptomatic HD participants have difficulty in inhibiting eye movements towards distraction stimuli when focusing on a central fixation point. This matches clinical information whereby patients report a difficulty in driving and listening to the radio simultaneously, or eating while trying to concentrate on a conversation (Paulsen & Mikos, 2008). In pre-symptomatic HD, Wolf et al. (2012) report no difference compared to controls on a divided attention task in which both visual and auditory information were required to be processed simultaneously. Other studies measuring divided attention through the Brief Test of Attention tests also report no difference in performance between pre-symptomatic HD and controls (Brandt et al., 2008; Brandt et al., 2002).

Changes in the posterior attention network, are likely to contribute to attention deficits in HD (Sprengelmeyer et al., 1995). Additionally, decline in dopamine signalling within cortico-striatal pathways, a known key regulatory system for modulating attention, working memory and executive functions, are contributors to attention process deficits in HD (Lawrence, Weeks, et al., 1998). In general HD patients show a particular pattern of attention deficits that suggests pathological changes in both posterior and anterior attention systems while basic arousal systems are undisturbed (Finke et al., 2007).

**Executive Functions**

Executive functions refer to higher cognitive functions with multilevel components in which the task cannot be carried out by activation of one brain region alone (Lawrence, Sahakian, & Robbins, 1998). It enables independent, purposeful, self-serving behaviour (Lezak, Howieson, & Loring, 2004) and thus recruits multiple neural circuits to complete such a task (Lawrence, Sahakian, et al., 1998). In HD, executive function deficits are seen in
varying severities throughout the disease. These changes may be due to cortical pathology, a result of disrupted striatal-frontal circuits due to striatal pathology or more likely a combination of both (Alexander & Crutcher, 1990).

**Cognitive flexibility & attention set shifting**

Cognitive flexibility is the ability to generate alternative responses/solutions when presented with a given problem situation (Hanes, Andrewes, & Pantelis, 1995). Defects in cognitive flexibility are often seen in difficulty shifting set and in rigid approaches to problem solving (Lezak et al., 2004). This type of skill is usually mediated by the prefrontal cortex and striatal structures and is most commonly measured by the Wisconsin Card Sort Test (WCST) (Savage, 1997), the interference trial of the Stroop (Paulsen et al., 1995) and other tools such as the initiation and perseveration subtest of the Dementia Rating Scale (Paulsen & Mikos, 2008).

In symptomatic HD, deficits in performance on the WCST are documented across numerous studies (Savage, 1997; Snowden et al., 2001; Snowden, Craufurd, Thompson, & Neary, 2002; Ward et al., 2006; Zakzanis, 1998). When broken down, it seems HD participants are impaired in set-shifting, resulting in perseverative errors rather than any difficulty in forming or maintaining their set of responses (Lawrence et al., 1996; Snowden et al., 2001; Sprengelmeyer et al., 1995). Deficits in cognitive set-shifting are also exemplified using other tasks. In a task of response flexibility, HD participants made significantly more errors in the set-shifting condition compared with the ‘fixed’ condition that did not require set-shifting (Sprengelmeyer et al., 1995). Additionally, difficulties in set-shifting were reported as a discriminating factor between HD and Parkinson’s Disease (PD) participants in a complex word finding task (Hanes et al., 1995).

Individuals pre-symptomatic for HD perform significantly better than their symptomatic HD counterparts on the WCST (Snowden et al., 2002). One study has shown a
trend towards pre-symptomatic HD performing worse than gene negative controls (Wahlin et al., 2007). In general, however, performance on this task has been unremarkable in pre-symptomatic HD (Blackmore, Simpson, & Crawford, 1995; Brandt et al., 2002; Campodonico, Codori, & Brandt, 1996; de Boo et al., 1997; Snowden et al., 2002; Witjes-Ane, Vegter-van der Vlis, van Vugt, Lanser, et al., 2003).

On the interference trial of the Stroop test, which requires inhibition of the automatic reading response in order to name the colour ink of the printed word, symptomatic HD participants perform worse than controls (Giordani et al., 1995; Ho et al., 2003; Snowden et al., 2001; Ward et al., 2006; Watkins et al., 2000). In pre-symptomatic HD, however, only one study has shown poorer performance on the interference trial than controls (Witjes-Ane et al., 2007), while others report no distinguishable difference in performance (Brandt et al., 2002; Campodonico et al., 1996; Witjes-Ane, Vegter-van der Vlis, van Vugt, Hermans, et al., 2003).

**Planning & decision making**

Planning and decision making refer to the ability to identify and organise a series of steps in order to carry out a goal driven task. It requires an individual to weigh options and make choices in both a sequential and hierarchical fashion (Lezak et al., 2004). Planning and decision-making abilities require attention and working memory functions as well as impulse control (Lezak et al., 2004). Tasks commonly used to measure these dimensions include the Tower of London (ToL) and the Iowa gambling task as well as less pure measures such as Picture Arrangement and Block Design (Lezak et al., 2004).

Two recently developed computerised versions of the ToL task that use a touch sensitive screen have been commonly used. One is the modified ToL and the other, the one-touch ToL (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Owen, Sahakian, Semple, Polkey, & Robbins, 1995). In the modified ToL, participants are required to sequentially
move balls that hang in ‘stockings’ within a minimum number of moves in order to solve the task. The ‘one-touch’ ToL task (Owen et al., 1995) alternatively requires participants to carry out the sequential planning in their mind for the same tasks, but respond to a multi-choice option on the screen regarding the minimum number of moves required to complete the task. This task in particular is thought to be sensitive to detecting change in HD due to its heavy reliance on dorsolateral prefrontal cortex (DLPFC) which may deteriorate early in HD from dysfunctional cortico-striatal loops (Owen, Doyon, Petrides, & Evans, 1996).

On the modified ToL, early HD patients are significantly worse in generating ‘perfect solutions’ for all problem difficulties of the task (K. W. Lange et al., 1995; Lawrence et al., 1996) and show more ‘excess moves’ to achieve a correct solution than controls, but only in the more difficult five-move problems (Lawrence et al., 1996). Similarly, on the one-touch ToL, HD participants are less able to generate perfect solutions (Lawrence, Weeks, et al., 1998; Watkins et al., 2000) and tend to choose options with greater numbers of excess moves (Lawrence, Weeks, et al., 1998). In the modified ToL, HD participants also show slower initial and subsequent thinking times after correction for motor slowing, likely highlighting the bradyphrenia present in early HD (Lawrence et al., 1996). This is also shown in the one-touch ToL; Watkins et al. (2000) report the HD group were significantly slower at making their first response and showed a trend towards taking longer on the more difficult problem levels.

In pre-symptomatic HD, results on this task are less clear. Lawrence, Weeks et al. (1998) report their pre-symptomatic HD group showed significantly fewer first-time correct solutions and required significantly more response time overall on the one-touch ToL. Another study by Lawrence, Hodges, et al. (1998), however, using the same one-touch ToL found no distinguishable difference between pre-symptomatic and controls on task performance. Davison (2009) used a computerised Stockings of Cambridge task, identical to
the computerised modified ToL. Performance of the pre-symptomatic HD participants was no different from age- and gender-matched controls in measures of perfect solutions, excess number of moves or initial and subsequent thinking times. These results were unchanged when the pre-symptomatic group were split into close-to and far-from estimated onset groups (Davison, 2009).

Impairment in decision-making abilities are often associated with frontal lobe injury (A.R. Damasio, 1996). Tasks that examine decision-making capacity over planning ability are known to recruit the ventromedial prefrontal cortex (VMPFC) (Yechiam, Veinott, Busemeyer, & Stout, 2007). Patients with VMPFC lesions tend to make choices based on short-term reward rather than consideration of long-term punishment (i.e. large gains but also large losses) (Watkins et al., 2000; Yechiam et al., 2007). According to Watkins et al. (2000) damage in DLPFC, the area highly involved in problem-solving planning (such as the ToL), does not affect performance in decision-making tasks like this.

In a study comparing symptomatic HD, PD and Control participants, HD participants performed worse overall on the Iowa gambling task than PD participants who were matched for dementia-severity, and age-education matched normal controls (Stout, Rodawalt, & Siemers, 2001). HD participants made fewer advantageous selections compared to the control and PD group. Similarly, another study showed HD participants made fewer selections from advantageous blocks, and even shifted to make a greater number of disadvantageous selections in the last trial (Campbell, Stout, & Finn, 2004). Watkins et al. (2000) show a different pattern in their HD sample using a computerised decision-making task, where HD patients showed their decision making abilities were relatively unimpaired compared to controls, although their response times were slower. This task operates on the same principles as the Iowa gambling task, however, seems to activate the orbito-frontal cortex differentially
Davison (2009) found no significant differences in performance of pre-symptomatic HD participants compared to controls in the number of advantageous selections in any stage of the Iowa gambling task. 31.6% of the pre-symptomatic HD participants, however, selected 50 or greater disadvantageous cards compared to 11.1% of controls who did the same, although, this difference was not statistically significant. Results were unchanged even when the pre-symptomatic HD group was split into close-to (less than 15 years to onset) and far-from-onset (greater than 15 years to onset) (Davison, 2009).

**Working memory**

Working memory refers to the ability to temporarily store and manipulate information in order to carry out a cognitive task. Working memory can be measured by the Spatial Span backward, Digits Span backward, Letter Number Sequencing and Arithmetic subtests of the WAIS or Wechsler Memory Scale (WMS).

Performance on both Arithmetic (Giordani et al., 1995) and Digit Span backward are impaired in symptomatic HD patients compared to controls (Giordani et al., 1995; Snowden et al., 2001). Working memory deficits in symptomatic HD have been shown in a coding and scanning task (Lawrence et al., 1996; Wahlin et al., 2007), a spatial working memory task (K. W. Lange et al., 1995; Lawrence, Watkins, Sahakian, Hodges, & Robbins, 2000; Watkins et al., 2000) and computerised spatial working memory task (Ho et al., 2003; Owen et al., 1990). In contrast, symptomatic HD patients were relatively unimpaired on a visual object working memory task sensitive to temporal lobe rather than frontal lobe lesions (Lawrence et al., 2000; Watkins et al., 2000).

In pre-symptomatic HD, the Digit Span backward and Arithmetic subtests of working memory from the WAIS and WMS are generally not impaired (Foroud et al., 1995; Giordani
Verbal fluency

Tests of verbal fluency are designed to capture both phonemic and semantic aspects of word generation. Semantic fluency tasks assess ability to name as many words within a specified category whereas phonemic fluency tests ability to generate words beginning with a specified letter (Henry, Crawford, & Phillips, 2005). Significant deficits in both phonemic and semantic fluency are evident in clinical HD (Snowden et al., 2001; Ward et al., 2006; Zakzanis, 1998) and these deficits have been shown to deteriorate over a one year and four year period (Ward et al., 2006). Mostly, deficits in phonemic and semantic fluency are equal, however, a meta analytic review across studies that assessed either phonemic or semantic fluency suggests that semantic deficits are the larger of the two (Henry et al., 2005).

In pre-clinical HD, findings range from no deficit to minimal deficits on verbal fluency tasks (Blackmore et al., 1995; Lawrence, Hodges, et al., 1998; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2002; Paulsen, Zhao, et al., 2001). Witjes-Ane et al. (2007) report better performance over time on the verbal fluency task, however, authors note this is indicative of practice effects. A meta-analytic review shows evidence of a ‘slight deficit’ in verbal fluency across numerous studies of pre-symptomatic HD, although they highlight the small magnitude of the effect size (Henry et al., 2005).

Insight & awareness of deficits

Paulsen and Mikos (2008) highlight that denial of illness symptomatology and its consequences are a frequent complaint from family members of those with HD. While this could be an unwillingness to accept the disease, serving as a coping mechanism, some findings suggest that this denial is neurologically based (Deckel & Morrison, 1996; Snowden, Thompson, Craufurd, & Neary, 1998). There is evidence, for example, of symptom denial in
patients with sub-cortical damage in the internal capsule, globus pallidus, caudate nucleus and putamen (Caplan et al., 1990). Symptomatic HD patients who rated their level of difficulties in an eight-item self-report questionnaire, had significantly different ratings than staff and inaccurate ratings relative to neuropsychological test findings (Deckel & Morrison, 1996). Vitale et al. (2001) asked HD patients to complete subjective questionnaires of dyskinesia after performing a series of motor tasks. Seven out of the nine HD participants were unaware of their own dyskinesias despite clear observation of dyskinesia by both the clinician and patients’ caregivers. Lastly, Ho, Robbins, and Barker (2006) assessed both HD patients and caregivers’ perceptions of ‘dysexecutive behaviour’ and found symptomatic HD participants underrated the extent of their own dysexecutive behaviours by 26%. Percentage differences from patient and caregiver ratings in the HD sample were nearly double that of identical measurements in elderly patients with no neurodegenerative disease and their caregivers (Ho et al., 2006). Overall this suggests that those with symptomatic HD have a significant deficit in aptly perceiving the degree of their deficits in both motor and behaviour domains, and that these deficits are likely to be linked to sub-cortical deterioration and resultant disruption of circuits involving the prefrontal cortex.

Memory

Memory refers to the ability to encode and store new information, retain, then retrieve this information when needed. Memory is a complex concept with multiple facets each involving the basic processes above, but each facet having unique characteristics (Montoya, Pelletier, et al., 2006). Difficulties in memory can stem from any point in the course of memory development, such as trouble encoding the initial information, failure to consolidate the information into long-term stores and difficulties in retrieving the stored information (Montoya, Pelletier, et al., 2006).
In symptomatic HD, memory impairments are frequently reported in empirical studies of memory, from complaints of family members of HD patients and HD patients themselves (Paulsen & Mikos, 2008; Montoya, Pelletier, et al., 2006; Zakzanis, 1998). A meta-analytic review found that symptomatic HD patients show a large impairment in acquisition of new memories (Zakzanis, 1998). Performances of symptomatic HD participants on memory acquisition tasks were able to differentiate 93% of HD participants from controls. Due to the complexity of other neuropsychological deficits in symptomatic HD, such as deficits of attention and executive functioning, memory acquisition may be somewhat impaired due to the impact of these deficits (Montoya, Pelletier, et al., 2006). This may be why the storage of memory is reported to be relatively unimpaired in symptomatic HD individuals. HD participants are able to retain information over delay periods, suggesting that they do not have a higher rate of information loss or forgetting in comparison to controls (Delis, Massman, Salmon, Cermak, & Kramer, 1991). Lawrence et al. (2000) also found no significant temporal decline in memory retention in their HD group compared to controls. These reports appear contradictory to the findings of poor memory acquisition in HD. It may be that while symptomatic HD participants perform more poorly on tests of memory, more is laid down in their memory stores than is measured by the memory test itself, particularly because of executive functions that impact their ability to perform in these tasks.

The large debate in research is the extent of impairment in recall and recognition. In a meta-analytic review Zakzanis (1998) showed their largest effect size in delayed recall tasks compared to tests of memory acquisition and other cognitive abilities. There are a number of reports of symptomatic HD patients having difficulties in recall but no difficulties in recognition (Butters, Wolfe, Granholm, & Martone, 1986; Jacobson et al., 1999; Lundervold, Reinvang, & Lundervold, 1994). A recent meta-analytic review, however, found no statistical difference in effect sizes for recall, cued recall or recognition memory across 48 published
studies and when testing recognition and recall within the same sample, these authors report
deficits in both domains to be similar (Montoya, Pelletier, et al., 2006). Indeed other studies
support this, showing that recognition is far from spared in HD (Lawrence et al., 2000;
Sprengelmeyer et al., 1995). One study showed that HD patients did not improve on memory
relative to controls when moving from a recall task to a recognition task (Lang, Majer, Balan,
& Reischies, 2000). Conversely, Montoya, Pelletier, et al. (2006) found larger disturbances in
recall compared to recognition when split into severity of dementia ratings, and in a table of
recall-recognition effects, they found a greater skew towards a deficit in recall (Montoya,
Pelletier, et al., 2006). Lawrence et al. (2000) suggest that the pattern of performance seen in
recognition tasks for symptomatic HD suggests a processing deficit, such as attention or
selection that hinder recognition ability, rather than a problem in recognition memory per se.

Memory impairments in pre-symptomatic HD are small (Montoya, Pelletier, et al.,
2006). Diamond et al. (1992) found deficits in delayed verbal memory and learning, however,
others have found no impairment in tasks of spatial, verbal and visual memory (Brandt et al.,
2002; de Boo et al., 1997; Lawrence, Hodges, et al., 1998).

In summary, studies suggest that while memory acquisition seems to be impaired in
symptomatic HD, it is possible that these shortfalls are affected by deficits in attention and
executive processes (Montoya, Pelletier, et al., 2006). Imaging, however, has revealed
pathology in the hippocampus (Rosas et al., 2003), thus difficulties with memory acquisition
may result from this later in the disease when this pathology is present. Additionally, there
are impairments in memory recall, while recognition deficits are debated as it may be
attention or selection processes that hinder these abilities (Lawrence et al., 2000; Montoya,
Pelletier, et al., 2006; Montoya, Price, Menear, & Lepage, 2006). Thus the ability to
systematically retrieve information may be impaired in symptomatic HD because of deficits
in executive functions and attention systems, more so than difficulties in acquiring or storing
information (See Montoya, Pelletier, et al., 2006). Generally, there are minimal, if any, impairments of memory in pre-symptomatic HD.

**Visual Functions**

Visual functions include visual perception, perceptual organisation, attention to detail and the translation from visual perception to construction abilities. Such abilities are commonly measured in tasks such as the copy of the Rey-Osterieth Complex Figure (ROCF), Judgement of Line Orientation Task (JLOT), Hooper Visual Organisation Task (HVOT), the Money’s Road Map Test of Directional Sense, Mental Rotation tasks and the Block Design, Picture Arrangement, Picture Completion and Object Assembly subtests of the WAIS batteries (Lezak et al., 2004). Many of these tests, however, are not pure measures of visual function. They also require other abilities such as non-verbal reasoning or problem solving, which taps into executive functions or processing speed.

Symptomatic HD participants are generally impaired in performance on the Block Design subtest of the WAIS (Backman, Robins-Wahlin, Lundin, Ginovart, & Farde, 1997; Ho et al., 2003; Mohr et al., 1991). Performance on Block Design is reported to show a large effect size discriminating 71% of HD patients from controls (Zakzanis, 1998). Mohr et al. (1991) found that HD participants were impaired on Picture Arrangement, Picture Completion and Object Assembly, with Zakzanis (1998) reporting that these subtests have effect sizes that discriminate 65% of HD patients from controls. As indicated earlier, tasks such as Block Design and Picture Arrangement, are not pure tests of visual function. This means that poor performance on these tasks may not always reflect difficulties in visuo-spatial function, as the executive functions and motor skills required to complete the tasks may be contributing to the impairment. Additionally, the Block Design task is timed, and bradyphrenia in symptomatic HD may also contribute to impairments, especially with the more difficult designs.
Symptomatic HD participants have difficulties copying the ROCF (Jacobs, Shuren, & Heilman, 1995; Mohr et al., 1991) and completing clock-drawing tasks (Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992). Lezak et al. (2004), however argue that visuo-spatial abilities in symptomatic HD are not as impaired as they might appear on such tasks. Rather, poor performance is said to be due to executive function deficits of visual scanning and planning. This was exemplified in a case study of a 59 year-old HD patient who was greatly impaired on his initial copy of the ROCF but was able to produce an ‘organised and spatially accurate’ representation of the figure after realisation that his drawing was highly distorted (Lezak et al., 2004). Rouleau et al. (1992) report that their symptomatic HD group displayed graphic (i.e., inaccurate size replication) and planning-related (i.e., inability to fore-plan the spatial layout of numbers) difficulties on the clock-drawing task, which they also suggest were due to motor and fronto-striatal deficits. Basic visuo-perceptual deficits, however, could equally be responsible for this pattern of performance, and may be playing a significant role in the difficulties described for symptomatic HD participants.

Symptomatic HD participants, also perform poorly on tasks without motor components such as the Judgement of Lines Test (JLOT), which assess angle judgement (Lezak et al., 2004; Lineweaver, Salmon, Eberson-Shumate, & Corey-Bloom, 1999; Soliveri et al., 2002), the figure matching test (Lineweaver et al., 1999) and on a non-motor, untimed perceptual task (Mohr et al., 1991). HD participants have also been found to be impaired on a task of map reading (Mohr, Claus, & Brouwers, 1997) and on tasks that require egocentric directional judgements such as the Money’s Roadmap Test of Directional Sense (Bylsma, Brandt, & Strauss, 1992; Lineweaver et al., 1999; Snowden et al., 2001) and a similar street map test (Mohr et al., 1991; Mohr et al., 1997). Even after controlling for motor response time, HD participants still performed significantly less accurately on the Moneys Roadmap test of Directional Sense indicating the deficit is robust against motor slowing (Snowden et
Additionally, those with symptomatic HD are shown to misjudge the distance of themselves self in relation to other objects (Mohr et al., 1997). Symptomatic HD participants, however, are not impaired on tests of extra-personal rotation (Lineweaver, Salmon, Bondi, & Corey-Bloom, 2005; Lineweaver et al., 1999), although they do tend to be slower (Lineweaver et al., 2005). Lastly, the perception of unfamiliar faces as tested by the Benton Facial Recognition test is shown to be disturbed in symptomatic HD (Henley et al., 2008; Jacobs et al., 1995).

Pre-symptomatic HD patients are generally unimpaired on the Block Design, Picture Arrangement and Object Assembly subtests of the WAIS batteries (Brandt et al., 2002; Campodonico et al., 1996; Foroud et al., 1995; Kirkwood et al., 1999). Brandt et al. however, did find that those close-to onset performed worse on Block Design compared with those far-from onset. Davison (2009) found performance on the JLOT was significantly impaired in a pre-symptomatic HD group compared to controls, and when broken into proximity groups, only those close-to-onset performed more poorly than controls (Davison, 2009). Other studies, however, report no differences in pre-symptomatic HD performance compared to controls on this task (Blackmore et al., 1995; Soliveri et al., 2002). Wahlin et al. (2007) found that pre-symptomatic HD participants performed slightly worse than controls in the copy of the ROCF, however, this difference only approached significance. The close-to-onset (less than 15 years to onset) subgroup, however, performed significantly worse on the ROCF than controls.

Performance on non-motor tasks involving egocentric rotation, such as the Roadmap test of Directional Sense, indicate that in general those who are pre-symptomatic for HD are not impaired (Brandt et al., 2008; Brandt et al., 2002; Bylsma et al., 1992; Campodonico et al., 1996; Davison, 2009), although, reaction times may be slower (Brandt et al., 2008) or show a trend towards being slower compared to controls (Davison, 2009). When participants
are split into proximity groups, however, close-to-onset groups are either impaired (Brandt et al., 2002; Snowden et al., 2002) or show a trend towards impairment (Davison, 2009) on both accuracy and timed components of a modified Roadmap test of Directional Sense compared to those far-from onset. Deficits of reaction time have also been reported in a route-walking test in pre-symptomatic HD (Campodonico et al., 1996). Conversely, Davison (2009) investigated performance on a letter mental rotation task and found that the pre-symptomatic participants performed remarkably similarly to controls, with no differences in the rates of rotation. Similarly, in a mental rotation task using a hand as the stimulus, pre-symptomatic participants were no different compared to controls on measures of reaction time and accuracy (Davison, 2009). Lastly, the perception of unfamiliar faces as tested by the Benton Facial Recognition test has been shown to be generally un-disturbed in pre-symptomatic HD (Aviezer et al., 2009; Davison, 2009; Diamond et al., 1992; Sprengelmeyer, Schroeder, Young, & Epplen, 2006; Witjes-Ane et al., 2007). A more recent investigation, however, found that pre-symptomatic HD participants performance on the Benton Facial Recognition test were significantly impaired in the near-to-onset (less than 9 years) and mid-to-onset (9-15 years) groups, but not the far-from-onset group (greater than 15 years) (Stout et al., 2011).

**Emotion recognition**

While the recognition of facial emotions requires perception of emotions on faces, it is also considered to be a fundamental component of social cognition. Thus while it is examined here under visual functions, it is not a purely visuo-perceptual ability.

Facial emotion recognition is impaired in symptomatic HD. Early findings suggested that HD patients where only impaired on recognition of disgust (Sprengelmeyer, Young, Calder, Karnat, & et al., 1996; Sprengelmeyer et al., 1997; K. Wang, Hoosain, Yang, Meng, & Wang, 2003). Further research, however, has identified that recognition of other negative
emotions, such as fear and anger, are also impaired (Henley et al., 2008; Milders, Crawford, Lamb, & Simpson, 2003; Snowden et al., 2008). Snowden et al. (2008) found their symptomatic HD group was more impaired overall in recognising facial emotions than controls but not as impaired as a fronto-temporal dementia group. Henley et al. (2008) showed that HD participants were impaired at recognising surprise which is considered a positive emotion, a finding not revealed in previous studies, and is contrary to the notion that HD patients are only impaired in recognising negative emotions. Deficits in recognising sadness are also reported in some studies (Johnson et al., 2007; Milders et al., 2003; Sprengelmeyer et al., 1996), while others report no deficit in recognition of sadness (Henley et al., 2008). Detailed analysis of the performance of HD subjects found that those who performed more poorly on facial recognition tasks attended to features of the face in isolation, such as the eyes and then the mouth, and consequently made judgements on the type of expression based on singular features rather than integrating the different aspects of the face to get a coherent picture of the emotional expression (Henley et al., 2008).

In pre-symptomatic HD, findings have been variable, ranging from no deficits in emotion recognition (Milders et al., 2003), to deficits in recognition of fear, sadness, anger (Johnson et al., 2007) and disgust (Henley et al., 2008; Johnson et al., 2007; Milders et al., 2003; Sprengelmeyer et al., 2006; Tippett, Samorow, Bruneau-Herman, Hogg, & Roxburgh, 2011) Henley et al. also found that pre-symptomatic HD participants were impaired in recognising happiness compared to controls. Tippett et al. (2011) found that recognition of disgust was mediated by mood states of anxiety and irritability, with higher levels of anxiety and irritability predicting better performance on disgust recognition.

**Language Abilities**

Language ability is one function that tends to be relatively spared in HD until the late stages of the disease (Sturrock & Leavitt, 2010). There are, however, reports of difficulties in
language comprehension and production in symptomatic HD (Murray, 2000; Murray & Lenz, 2001; Murray & Stout, 1999). Those with symptomatic HD, for example, are shown to make fewer grammatically complete utterances (Murray, 2000; Murray & Lenz, 2001) and tend to produce a larger proportion of simple sentences with fewer words per sentence compared to age matched controls (Murray, 2000). The number of utterances, however, was not significantly different meaning that HD patients spoke just as many times as their age-matched counterparts (Murray, 2000). Thus it may be that motor difficulties prevent HD patients from speaking more complex sentences with more words, rather than there being a language deficit. While HD patients can understand the main information supplied in a conversation, they find it difficult to comprehend complex information or themes/information that are implied (Murray & Stout, 1999). The authors suggest that this is due to attention processing and working memory deficits as comprehension difficulties are correlated with sustained attention abilities, memory capacity and dementia severity (Murray & Stout, 1999). Relentless difficulties in communication result later in the disease as speech production becomes severely impaired, resulting in the use of communication aids such as computer devices, alphabet boards and picture cards (Paulsen & Mikos, 2008). In these late stages, comprehension becomes dependent on sentence complexity and length, as poor attention and working memory in late stages impairs their ability to cohesively join the sequence of sentences and comprehend information simultaneously (Paulsen & Mikos, 2008).

Longitudinal Research and HD

Specific characteristics of HD, such as the single identifiable gene that is almost fully penetrant and the typically long period of time before symptoms are manifest, enable longitudinal studies to track and determine rates of change. Ultimately, the results of longitudinal studies will help establish optimal points for therapeutic intervention (Tabrizi et al., 2012). Longitudinal study designs look at the same cohort of participants across time on
identical measures in order to establish effects or changes over a period of time. In the past
decade, longitudinal studies have focused on individuals pre-symptomatic for HD because
there is evidence that significant changes occur prior to clinical onset of HD (see Paulsen,
2010). The hope is that these studies will provide insight into the progression of the disease
leading up to clinical onset, and help establish effective biomarkers of these changes to use in
clinical trials (Paulsen, 2010; Weir et al., 2011).

**Longitudinal Neuroimaging in Pre-Symptomatic HD**

The overall objective of longitudinal neuroimaging studies in pre-symptomatic HD is
to detect rates of change in structures of the brain that suggest neuronal loss or atrophy
indicative of disease processes. The objective is to gain greater understanding of measurable
neural changes that are occurring as individuals’ progress towards clinical onset and what
changes are thus indicative of close proximity to clinical onset.

**Striatal Changes**

Rates of atrophy in individual striatal structures, as well as the striatum as a whole,
are consistently reported to be significant in the pre-symptomatic stages of HD. Aylward,
Nopoulos, et al. (2011) found that total striatum volume decreased at a faster rate in all pre-
symptomatic HD groups (near, mid, far) compared to controls over a 24-month period.
Similarly, over a 24 month period, both pre-symptomatic carriers close-to-onset (less than
10.8 years to onset) and far-from-onset (greater than 10.8 years to onset) showed gray matter
loss in the striatum (Tabrizi et al., 2012).

Caudate atrophy rates are significantly greater in close-to and far-from-onset groups
compared to controls over 12 months (Tabrizi et al., 2011), and 24 months (Tabrizi et al.,
2012). Similarly, increasing rates of atrophy are seen in near and mid (but not far) proximity
groups over 24 months (Aylward et al., 2011) and in a pre-symptomatic sample not stratified
into proximity groups over 36 months (Aylward et al., 2000). Caudate volumes are reported to decline at 0.24 cm$^3$ per year (Aylward et al., 2004), with Tabrizi et al. (2011) reporting a rate of 0.22cm$^3$ in those close-to-onset and 0.17cm$^3$ in those far-from-onset over 12 months. Caudate atrophy becomes prominent 11 years before clinical onset, changing at 4.3% per year until clinical onset (Aylward et al., 2004). Aylward et al. (2004) found caudate volume predicted those who would become pre-symptomatic within 2 years with 100% accuracy. In a 24 month longitudinal study, caudate atrophy rates show the largest effect size compared with all other brain measures (Tabrizi et al., 2012).

Increasing rates of atrophy are seen in the putamen in pre-symptomatic HD individuals close-to-onset (less than 10.8 years to onset) and far-from-onset (greater than 10.8 years to onset) over a 12-month (Tabrizi et al., 2011), and 24-month period (Tabrizi et al., 2012). Aylward et al. (2004) report volume loss in the putamen to be 0.035cm$^3$ per year in those far-from-onset increasing to 0.23cm$^3$ (3.1% loss) per year at approximately nine years from clinical onset. Similarly, Tabrizi et al. (2011) report a 3.09% decline in putamen volume in those close-to-onset (less than 10.8 years to onset) over 12 months while those far-from-onset (greater than 10.8 years) show a 1.51% decline.

**Subcortical Gray Matter Changes**

Only one study has reported change over time in sub-cortical structures outside the striatum, where gray matter volume loss was shown in the globus pallidus and an area in the ventral midbrain consistent with the location of substantia nigra, over a 24 month period (Kipps et al., 2005).

**Gray Matter Changes**

Whole brain gray matter volume as measured by VBM is reported to significantly decrease over a 24 month period in the pre-symptomatic stages in subjects that did not show any soft-motor signs (Squitieri et al., 2009). Tabrizi et al. (2011) report whole brain gray
matter atrophy in those close-to-onset (less than 10.8 years to onset) over a 24 month period. Conversely, Aylward et al. (2011) found gray matter volume did not change over a 24 month period in pre-symptomatic carriers in any proximity groups (near, mid and far), however, their measure looked at cortical gray matter change rather than whole brain gray matter change as the other studies report. Aylward et al.’s (2011) finding is consistent with Hobbs et al. (2010), who found pre-symptomatic participants had no change in gray matter volume over 24 months. The pre-symptomatic participants in Hobbs et al.’s (2010) study, however, were on average more than 18 years away from clinical onset, thus less likely to show any gray matter change. Longitudinal gray matter changes measured by cortical thinning in pre-symptomatic HD are yet to be published. Tabrizi et al. (2009) set out using both VBM and cortical thinning methods at baseline, however at 12- and 24-month follow up publications (Tabrizi et al., 2011; Tabrizi et al., 2012) the authors do not report longitudinal data on the cortical thinning, but only use longitudinal VBM in their analysis. Given the previously mentioned potential weaknesses in VBM measures, longitudinal investigations into cortical thinning would be of great importance to give greater detail of changes in the cortex in pre-symptomatic HD. If cortical thinning measures are to be considered as effective bio-markers in HD, then longitudinal data in this area are needed (Wier et al., 2011).

**White Matter Changes**

Longitudinal decreases in white-matter are reported in pre-symptomatic carriers who are close-to-onset, when symptomatic conversion is close (Squitieri et al., 2009). Tabrizi et al. (2011) similarly showed white matter loss over a 12 month period in those close-to-onset (less than 10.8 years to onset) with extensive white matter reduction in both anterior and posterior white matter tracts, while those far-from onset (greater than 10.8 years to onset) showed restricted loss in white matter surrounding the caudate and putamen only. At a 24-month follow-up, Tabrizi et al. (2012) found reductions in white matter expanded to
extensive white matter loss throughout the brain in those close-to-onset while those far from onset had progression of white matter loss to include the corpus callosum and posterior white matter tract. Aylward et al. (2011) found that white matter decreased in all proximity groups (near, mid and far) over a 24-month period, with the most significant reductions in frontal, parietal and temporal lobes, particularly in the frontal regions. They found no significant changes, however, in the white matter of the occipital and sub-cortical areas. Conversely, Hobbs et al. (2010) found no significant loss in white matter over a 24-month period for a group of pre-symptomatic participants, however, again, this study had participants who were much further from clinical onset (greater than 18 years on average), which may have made differences hard to detect in their small pre-symptomatic sample of 17. Overall, findings suggest that decreases in white matter begin early in pre-symptomatic HD, however, most significant changes occur in those close to clinical onset.

**Measures of Whole Brain Change**

Change in the volume of cerebro-spinal fluid (CSF) volumes is one way in which researchers have sought to measure whole-brain volume changes. Increases in the volume of CSF indicate global brain atrophy. Squitieri et al. (2009) found CSF significantly increased over 2 years in pre-symptomatic HD indicating significant brain atrophy. The authors note that increases in CSF proved to be the best predictor of disease progression in pre-symptomatic HD compared to other brain measures, as the pattern of change in CSF showed a linear progression towards clinical onset (Squitieri et al., 2009). Increases in CSF volumes are also reported over a 24-month period in pre-symptomatic participants in ‘mid’ and ‘near’ to onset groups but not in the ‘far’ from onset group (Aylward et al., 2011).

Tabrizi et al. (2011) report that whole-brain atrophy, as measured by percentage of baseline whole-brain volume, was significantly greater in the close-to-onset group (less than 10.8 years to onset) than in controls at a 12-month follow-up. At a 24-month follow-up,
whole-brain atrophy was significant in both the close-to and far-from-onset groups (Tabrizi et al., 2012). Aylward et al. (2011) also report whole brain volume loss in their pre-symptomatic proximity groups (near-, mid- and far-from-onset) over a 24-month period (Aylward et al., 2011). Contrary to these findings, a study by Henley et al. (2009) found that pre-symptomatic carriers actually showed a trend towards less whole brain atrophy compared to controls after adjusting for age and gender over a 12-month period.

**Longitudinal Neuropsychological Changes in Pre-symptomatic HD**

Tracking cognitive decline in HD has been done for decades; however as with structural change investigations, a recent increase in interest of cognitive changes in pre-symptomatic HD has arisen. Pre-symptomatic participants tend to be relatively robust in their cognitive abilities; however, subtle yet significant changes in certain cognitive domains are certainly evident. Research has begun to focus on finding tests sensitive enough to detect cognitive decline indicative of disease pathology and its progression in pre-symptomatic HD (Paulsen, 2010).

**Motor Speed and Psychomotor Changes**

Reports of pre-symptomatic decline in motor speed and psychomotor tasks are mixed. Pre-symptomatic HD individuals have been shown to decline at faster rates on a button tapping task over a 10-year period in comparison to age and education-matched controls (Solomon et al., 2008). Within this, those who were closer to their estimated onset of HD showed greater rates of decline (Solomon et al., 2008). Tabrizi et al. (2011), however, show no change in a speed tapping task over a 12-month period.

The Grooved Pegboard Test, which assesses motor dexterity and complex coordination, has shown to decline in pre-symptomatic participants who were followed to clinical onset (Maroof, Gross, & Brandt, 2011); however, in another study pre-symptomatic
participants did not show decline on the Grooved Pegboard Test over a 4-year period (Giordani et al., 1995), or when followed to symptomatic conversion (median 8.62 years) (Brandt et al., 2008). Pre-symptomatic HD participants also showed decline on an Auditory Reaction Time and Visual Reaction Time task over 10 years compared to controls (Solomon et al., 2008).

Pre-symptomatic participants’ performance on the SDMT showed no detectible decline over 12 months (Lemiere et al., 2002; Tabrizi et al., 2011), 18 months (Witjes-Ane et al., 2007), 2 years (Campodonico et al., 1996; Tabrizi et al., 2012) or 3 years (Witjes-Ane et al., 2007). Other studies with longer trajectories, however, report decline on SDMT performance over 3.7 years (Kirkwood et al., 1999), 10 years (Solomon et al., 2008) and over 21 years (Maroof et al., 2011). It seems studies with longer follow-up periods tend to detect changes on the SDMT because they track participants for long enough that pre-symptomatic participants come close to, or reach, clinical onset, which is not surprising given onset is associated with motor symptoms. When Solomon et al. (2008) split their sample into those who had converted to symptomatic stages of the disease (converters) and those who had not (non-converters), they found that converters showed more rapid decline on the SDMT task. Similarly, Maroof et al. (2011) report that performance on the SDMT changes over time, moving from linear decline in those greater than 10 years to onset to accelerated decline 5-10 years prior to clinical onset, with the greatest acceleration seen in the last 5 years.

Maroof et al. (2011) report a decline in performance on both part A and B of the TMT over a 21-year period relative to controls. This group report that rates of decline on the TMT (A and B) were associated with time to clinical onset, with faster rates of decline seen as participants approached clinical onset (Maroof et al., 2011). The majority of studies, however, report no significant change in pre-symptomatic performance on the TMT (A and
B) over 12 months (Lemiere et al., 2002), 18 months (Witjes-Ane et al., 2007) and 4 years (Giordani et al., 1995).

While pre-symptomatic participants can often present with no deficits on reaction time tasks, the changes on these tasks are subtle and proximity to disease onset plays an important role in being able to distinguish these changes (van Walsem et al., 2010). These findings fit with the determination of symptomatic onset of HD by motor symptoms. In other words, it is not surprising that decline in motor speed and psychomotor abilities is closely associated with estimated time till symptomatic diagnosis of HD. Findings suggest that rather than a steady rate of decline as individuals’ progress towards symptomatic onset, rates of decline in motor speed and psychomotor abilities take on a more exponential decline closer to onset (Maroof et al., 2011; Solomon et al., 2008)

**Attention**

Performance on digit span forward in pre-symptomatic HD does not appear to decline over 2- (Lemiere et al., 2002; Wolf et al., 2011) or 3-year periods (Witjes-Ane et al., 2007). Similarly, pre-symptomatic performance on Spatial Span did not decline over 2 years (Lemiere et al., 2002; Wolf et al., 2011). Additionally, Wolf et al. (2011) report their pre-symptomatic group did not decline over 2 years on three specific attention tasks (Tonic alertness, Phasic alertness and Divided attention), and Brandt et al. (2008) report no decline on the Brief Test of Attention, which measures divided attention, when following pre-symptomatic participants to conversion.

**Executive Function**

*Cognitive flexibility & attention set-shifting*

Longitudinal data shows pre-symptomatic performance on the WCST does not deteriorate over 2-year (Wolf et al., 2011; Campodonico et al., 1996) or 3-year periods (Witjes-Ane et al., 2007). Brandt et al. (2008), however, showed performance on the WCST
did differentiate the converters and non-converters when following pre-symptomatic participants to clinical onset, where the median time to onset was 8.62 years.

Overall, research findings indicate there is no significant change in pre-symptomatic performance on the Stroop interference task over 12 months (Lemiere et al., 2002; Tabrizi et al., 2011), 18 months (Witjes-Ane et al., 2007), 2 years (Campodonico et al., 1996), 4 years (Giordani et al., 1995) or when following participants to symptomatic conversion (Brandt et al., 2008; Maroof et al., 2011). Maroof et al. (2011) found that decline in performance on the Stroop only occurred in the Colour and Word trials, while the Stroop Interference trial, showed a flat trajectory indicating little change even as participants approached clinical onset. In other words, Stroop performance does not decline in a way that suggests frontal changes (i.e. mental flexibility), but rather reflects general cognitive slowing. This is because pre-symptomatic HD participants show most change on the less demanding conditions which do not require inhibition (Colour and Word) and only small changes on the more demanding condition (Interference) which measures executive function (Campodonico et al., 1996; Lemiere et al., 2002; Witjes-Ane et al., 2007).

**Verbal fluency**

Verbal fluency in pre-symptomatic participants improved over a 3-year period, but this was also seen in controls and likely to be a practice effect (Witjes-Ane et al., 2007). Similarly, Lemiere et al. (2002) showed both pre-symptomatic and control participants improved over a 1-year period in letter fluency, but remained unchanged in category fluency.

**Working memory**

Pre-symptomatic performance on the Digit Span backward task showed no decline over a 2-year (Lemiere et al., 2002; Wolf et al., 2011), 3-year (Witjes-Ane et al., 2007) or average 3.7-year period (Kirkwood et al., 1999). Similarly, Wolf et al. (2011) report no decline in their pre-symptomatic group on the Spatial Span backward task. Kirkwood et al.
(1999) report a trend towards longitudinal decline in pre-symptomatic HD on the Arithmetic subtest of the WAIS while other studies show no decline in the pre-symptomatic group on the Arithmetic subtest over a 3-year (Witjes-Ane et al., 2007), 4-year (Giordani et al., 1995) or 10-year period (Solomon et al., 2008). A visual working memory task (Spot the Change), chosen because it significantly differentiated between pre-symptomatic and controls in a cross-sectional baseline study (Paulsen, Hayden, et al., 2006), showed no longitudinal decline in a pre-symptomatic group over a 12-month period (Tabrizi et al., 2011).

**Memory**

In longitudinal studies involving pre-clinical HD participants, memory performance has shown both no decline (Lemiere et al., 2004) and significant decline over time (Campodonico et al., 1996). While deficits in memory are not as evident in preclinical HD, Snowden et al. (2002) suggest that memory performance shows a ‘precipitous decline that occurs around the time of clinical onset’. In contrast to this, the findings of several studies were of no change on the Hopkins Verbal Learning Test over 12 months (Lemiere et al., 2002), 2 years (Campodonico, Codori & Brandt., 1996) or when following participants to conversion (Brandt et al., 2008). Witjes-Ane et al. (2007) conducted all subtests of the Weschler Memory Scale (WMS), Word Lists, the California Verbal Learning Test (CVLT), and the Benton Visual Retention test, but none of these tasks showed longitudinal change that was different from controls over either an 18 month or three-year period. Similarly, no significant changes were observed for the pre-symptomatic group on any subtests of the WMS over a four-year follow up period (Giordani et al., 1995). Lemiere et al (2002), however, report their pre-symptomatic group showed a significant decline over a 12-month period in performance on the Block Span task which assesses immediate recall of visually presented sequences. Six other memory tests which were conducted, however, did not show decline over 12 months (Lemiere et al., 2002).
Visual Functions

Evidence of longitudinal decline on visual tasks is mixed. Pre-symptomatic participants show a significant decline over 12 months on their performance of the Cube Analysis task of the Visual Object and Space Perception battery (VOSP) which assesses visuo-spatial function, while eight other visuo-spatial tasks from the VOSP showed no significant decline (Liemere et al., 2002). It must be noted, however, that the Cube Analysis task of the VOSP may also recruit problem-solving abilities, thus poorer performance on this task may be attributable to deficits of executive functions rather than purely visuo-spatial difficulty. At 12-month follow-up, Tabrizi et al., (2011) found significant decline on a circle tracing task, which required visuomotor integration and planning, however, this was not significant at the 24-month follow-up (Tabrizi et al., 2012). Solomon et al (2008), however, found significantly faster rates of decline in their pre-symptomatic group compared to controls on the Picture Arrangement test of the WAIS-R over a 10 year period. This task, however, additionally involves executive functions of sequencing and social cognition, and thus is also not a pure visuo-spatial measure. Campodonico et al. (1996) found the pre-symptomatic group did not significantly change in their performance on a route-walking test which assesses extra-personal orientation in comparison to controls over a 2-year period. Similarly, no longitudinal change was found for the pre-symptomatic group on the Roadmap test of Directional Sense over two years (Campodonico et al., 1996) or when following participants to conversion (Brandt et al., 2008).

An emotion recognition task chosen for significantly differentiating between pre-symptomatic and controls in a cross-sectional baseline study (Paulsen, Hayden, et al., 2006), was unable to detect changes longitudinally in a pre-symptomatic group over 12 months (Tabrizi et al., 2011).
Language

In general, it seems language function remains stable in pre-symptomatic HD. No significant changes in the pre-symptomatic group have been found in the Vocabulary subtest of the WAIS-R over 2 years (Campodonico et al., 1996), 3 years (Wijes-Ane et al., 2007) or 4 years (Giordani et al., 1995) or on the Boston Naming Test over 1 year (Lemiere et al., 2002) and 3 years (Witjes-Ane et al., 2007).

Conclusions of Longitudinal Research and Future Directions

One current difficulty in interpreting longitudinal research is that some studies do not report ‘years-to-onset’ of their groups (e.g. Kipps et al., 2005; Henley et al., 2009). This would significantly enhance interpretation of findings as it is possible studies that do not find changes in their pre-symptomatic groups may be studying individuals who are significantly further from clinical onset than studies that do report declines. More recent studies investigating both structural and cognitive changes have tended to stratify subjects based on their estimated years to onset. These studies tend to find more definitive changes and greater rates of change in groups closer to clinical onset of the disease than those further from onset (Aylward, Nopoulos, et al., 2011; Brandt et al., 2008; Maroof et al., 2011; Solomon et al., 2008; Squitieri et al., 2009). Stratifying subjects based on proximity to onset enables greater comparability among research and greater insight into beginnings of changes and rates of changes through the pre-symptomatic stage of HD.

Sample size is another factor that significantly affects findings as some studies have smaller sample sizes, making them at higher risk of statistical errors (Weir et al., 2011). Thus, when comparing findings, not all results can be weighted equally. Two recent studies in particular are noteworthy of specific mention. The largest longitudinal studies in HD and pre-symptomatic HD to date have begun within the last few years, namely the TRACK-HD and PREDICT-HD studies (Paulsen, Hayden, et al., 2006; Paulsen et al., 2008; Paulsen & Long,
These studies have both used international multicentre data collection methods allowing participant numbers of 366 in TRACK-HD and 449 HD carriers at baseline (not including controls) in PREDICT-HD, to be obtained (Paulsen et al., 2008; Tabrizi et al., 2009). Both these studies have also used multiple techniques to measure different aspects of the disease, including neuroimaging, biological tests and clinical measures (cognitive, psychiatric and motor assessment). The international collaboration involved in these studies and precision in choosing of measures reflects a move towards finding effective biomarkers (Paulsen, 2010). Thus, these studies are weighted more in the current body of research, and have set high standards for contributing information that is non-redundant (Paulsen, 2010). As a result, a wave of current publications has emerged from the wealth of information gained from these large studies (Aylward et al., 2012; Downing et al., 2012; Nopoulos et al., 2010; Paulsen & Long, 2012; Paulsen et al., 2010; Say et al., 2011; Stout et al., 2012; Stout et al., 2011)

The other noted disparity within this area of research is the number of years in which participants are followed up, and the frequency of follow ups. Some have shorter follow-up periods (one to two years) (Talbrizi et al., 2011; Lemiere et al., 2002) which are less likely to show significant changes, while others have follow-up periods until clinical onset (e.g. Brandt et al., 2008; Maroof et al., 2011). Having this disparity has enabled us to establish that certain changes occur much closer to clinical onset, but has made results harder to compare given some findings are only evident in studies with longer follow-up periods.

Within the area of neuroimaging, results of longitudinal studies have revealed that structural neuroimaging techniques are strong contenders for effective biomarkers given their ability to detect early neurodegeneration (Weir et al., 2011) with large effect sizes (Tabrizi et al., 2012) and the capacity to predict age of onset, as is the case with striatal volumes and white matter (Aylward, 2005; Aylward et al., 2012; Aylward, Mills, et al., 2011; Aylward et
One notable area of difficulty within this approach is the use of differing imaging techniques. This factor results in discrepancies in research findings as some techniques are more sensitive to detecting small changes (Weir et al., 2011). There are also important techniques, such as cortical thinning, which are yet to be investigated longitudinally in pre-symptomatic HD that could well be strong contenders for detecting early change. Thus further research is still needed in order to reveal the most effective methods sensitive enough to detect subtle but significant structural changes in the pre-symptomatic HD brain.

Cognitive measures have been able to differentiate between pre-symptomatic HD and controls in cross-sectional studies (Papp, Kaplan, & Snyder, 2011). With this, longitudinal studies have endeavoured to track cognitive change, and thus establish cognitive tests that are able to effectively track progression of the disease, in the hope to discover biomarkers (Paulsen, 2010). Unfortunately, the success of these have been limited, and while tasks are effective at differentiating pre-symptomatic samples from controls in cross-sectional investigations, they have been unable to detect decline over time (Papp et al., 2011; Stout et al., 2012; Tabrizi et al., 2012). One difficulty with cognitive testing is that it is difficult to ascertain what the findings, or lack of findings are attributable to at a neural and structural level. Tabrizi et al. (2009), for example, set up a large longitudinal study which selected cognitive tasks shown to be effective in detecting cross-sectional differences (Paulsen, Hayden, et al., 2006) between pre-symptomatic and control participants. After 2 years of follow-up, however, they note they have been unable to yield cognitive outcome measures sensitive enough to track disease progression in the pre-symptomatic stages (Tabrizi et al., 2012). These authors speculate that the lack of change findings in their cognitive longitudinal data may be due to functional reorganisation of networks or neural plasticity. This seems to be the most likely answer, as MRI data for these participants show significant structural brain
changes, and thus lack of pathology is certainly not attributable as the reason for lack of
measureable cognitive change (Talbrizi et al., 2012). Tabrizi et al. (2012) suggest that neural
plasticity protects against functional deficits in pre-symptomatic HD, until the rate of
neurodegeneration exceeds the rate at which the brain can compensate with other intact
neural networks. This is in line with longitudinal research findings that show the rate of
change in many cognitive tasks accelerates close to disease onset (Maroof et al., 2011;
Solomon et al., 2008). Paulsen (2010) notes that tasks sensitive to longitudinal change in pre-
symptomatic HD are those that require rapid motor processing. Likewise, tasks that are
commonly reported to detect differences in pre-symptomatic HD are psychomotor, or
attention/working memory tasks (Papp et al., 2011).

Within longitudinal cognitive research, studies have tended to use small numbers of
cognitive tests (4-5 on average) (Tabrizi et al., 2010; Maroof et al., 2011; Solomon et al.,
2008). While this is not a downfall if the tests selected are sensitive to detecting changes in
pre-symptomatic HD, the use of small batteries (such as the UHDRS cognitive measures) that
do not assess functions of areas known to deteriorate in pre-symptomatic HD, fail to tap into
changes that are occurring. Studies with larger numbers of tests, however, frequently use
large batteries without consideration of the specificity or sensitivity to detect change in pre-
symptomatic HD (Lemiere et al., 2002; Campodonico et al., 1996; Witjes-Ane et al., 2007).
As a result, not many studies find tasks that differentiate their pre-symptomatic samples from
controls (Papp et al., 2011). As Paulsen (2010) documents, this field is ready to start
producing research that puts more specificity into recruitment of cognitive tasks that are
sensitive to pre-symptomatic HD, rather than just employing a large battery of tasks in a hit-
and-miss fashion of detecting changes.

From the findings of available longitudinal studies, it seems that future longitudinal
studies need to include longer follow up periods that ideally track individuals to onset and use
cognitive tasks that are sensitive to areas known to deteriorate in the pre-symptomatic stages, as shown from longitudinal MRI data. This is to be the way forward if cognitive tasks are likely to be discovered as effective biomarkers in pre-symptomatic disease progression.

Present Study

In 2009 John Davison’s doctoral research sought to replicate the findings of cortical thinning in pre-symptomatic HD reported by Rosas et al. (2005). The novel contribution of Davison’s study was to combine measurement of cortical thinning with neuropsychological testing that targeted functions known to recruit those posterior regions of the brain previously identified as thinning in pre-symptomatic HD. The objective was to compare performance on these tasks with performance on tasks that recruit anterior brain functions, which appear not to show cortical thinning in pre-symptomatic HD (Rosas et al., 2005). Davison’s (2009) findings confirmed the presence of posterior cortical thinning, and also showed that pre-symptomatic participants performed worse on some of the tasks for which posterior brain regions are known to be crucial. Additionally, pre-symptomatic HD participants performed unremarkably compared to controls on tasks known to be sensitive to anterior cortical function.

The current literature highlights the need for non-redundant investigations of cognitive changes in pre-symptomatic HD. Cognitive investigations need to contribute new insights into the earliest pathological changes in pre-symptomatic HD which can be detected through functional change. A follow up study of Davison’s (2009) work has the potential to meet these criteria, which led to the research described in the rest of this thesis.
Chapter Two  Study Introduction and Method

The cognitive and psychological changes that accompany HD, including in the pre-symptomatic stages, have been reported in a number of studies (Paulsen, 2010). More information is needed, however, about which cognitive changes are sensitive to early pathology and are capable of tracking the progression of the pathology to the point of clinical onset in pre-symptomatic HD (Tabrizi et al., 2012). The finding that posterior cortical thinning occurs in pre-symptomatic HD and the early stages of symptomatic HD (Rosas et al., 2002; Rosas et al., 2005) led to the pursuit of a novel idea at T1; to investigate if performance on selected cognitive tests would be sensitive to early changes that appear to occur in the posterior cortex. Additionally, the investigation at T1 sought to identify if the changes detected on tests, selected because of evidence that they are dependent upon regions in the posterior cortex, would appear prior to changes on tests linked primarily with anterior cortical regions, regions that appear to not thin in the pre-symptomatic stages of HD. Although there is no cognitive test on which performance recruits a single brain region, some cognitive tests involve fewer brain regions than others. Similarly, there is almost no task that measures a single construct or component of cognition. Some tests, however, are more pure, in that they involve fewer cognitive processes or components of cognition than others, which alternatively involve many other cognitive, perceptual and motor domains in order to complete the task (Davison, 2009).

When tasks were selected at T1, the identification of important regions required for task completion came from both functional MRI (fMRI) and lesion studies. fMRI studies allow identification of brain regions that are uniquely activated during a task compared to a control task, while lesion studies can reveal differential deficits in task performance
following brain damage to relatively specific brain regions. Based on converging evidence where possible, cognitive tests were selected at T1 that require involvement of posterior cortical regions previously shown to thin in pre-symptomatic HD (Rosas et al., 2005). Additionally, a set of cognitive tasks shown to primarily recruit anterior cortical regions were selected to provide comparison (Davison, 2009). The specific rationale that was used to select each cognitive task is detailed in Appendix A, derived from the thesis of Davison (2009). Other factors were also considered in the test selection at T1. Tests selected needed to be independent of the speed of motor responses in order to reduce confounds of slowing in HD. Tests were also required to be relatively short in duration and have concepts that were relatively easy to understand, in order to reduce the impact of further confounding factors such as fatigue and intellectual capacity (Davison, 2009). Mood measures were also included because of their significance in HD.

At T1, six tasks were included that were judged to be sensitive to posterior cortical regions. Of these, the pre-symptomatic HD group performed significantly worse on the Judgement of Line Orientation Task (JLOT), and showed a trend towards worse performance on the Hooper Visual Organisation Test (HVOT) compared to age, gender and education matched Controls. Additionally, the close-to-onset pre-symptomatic HD group performed significantly less accurately on the Roadmap Test than the far-from-onset and control groups. As predicted, the pre-symptomatic HD group showed an unremarkable performance in comparison to controls on tasks that recruited anterior regions of the brain. In line with previous findings of cortical thinning (Rosas et al., 2005), MRI findings for this pre-symptomatic group showed posterior cortical changes, predominantly in the right hemisphere (Davison, 2009).

If the cortical thinning detected at Time-point 1 (T1) reflected cortical changes occurring as a result of the HD gene, and if the test findings at T1 were indications of the
functional consequences of this thinning, then in a follow-up study the pattern of test findings should at least be replicated and possibly also show further decline if underlying cortical changes have progressed with time. The main objectives of the following study were therefore to (i) investigate whether the neuropsychological findings at T1 persisted over time until T2, thus providing evidence as to whether or not the findings at T1 reflected genuine differences between the groups; (ii) investigate whether there was evidence of decline in performance on these, and other posterior tasks, over the 3 year period since the original testing. This could provide some insight into the functional significance of posterior cortical changes seen in pre-symptomatic HD and whether progressive changes in these regions can be reliably tracked with cognitive testing.

It was hypothesised that the pre-symptomatic HD sample would perform more poorly on tasks sensitive to dysfunction of posterior cortical regions than matched controls, particularly on tasks where the pre-symptomatic group performed more poorly at T1 (JLOT, Roadmap test and possibly the HVOT); but would not perform more poorly on tasks sensitive to anterior cortical regions. Additionally, we expected to see decline on these tasks from T1 to Time-point 2 (T2) in the pre-symptomatic HD group that is greater than any changes seen in the control group and is most pronounced in those close to clinical onset. We also hypothesised that there would be poorer performance of the pre-symptomatic HD participants on other tasks sensitive to posterior regions given they have progressed towards clinical onset and assuming posterior cortical thinning will also have progressed. And lastly, we hypothesised that the pre-symptomatic HD group would not show deficits on tasks sensitive to anterior brain regions compared to controls.
Method

Participants

As this was the second time-point in a longitudinal study, all participants were recruited from the original cohort of participants who had taken part in the study at T1. Participants were originally recruited into one of two groups at T1: PreHD or Control (Davison, 2009). Participants in both groups were required to be over 18 years of age, speak fluent English and be able to give full informed consent. Exclusion criteria included a history of neurological conditions or events other than HD (e.g., stroke, head injury), history of significant alcohol or drug abuse, current psychiatric disorder and contraindications to MRI scanning (e.g. claustrophobia). All participants met these criteria at the initial recruitment at T1. At T2, all participants were re-evaluated with regards to these eligibility criteria and excluded if they no longer met these.

Pre-symptomatic HD (PreHD) Group

All participants recruited into the PreHD group at T1 had tested positive for the HD gene and had been assessed and diagnosed by a neurologist as being in the pre-symptomatic stages of the disease. All participants in the present study were re-assessed by the same neurologist (Dr Richard Roxburgh, R.R). As we were interested in the longitudinal follow up of the original sample, all were eligible to participate regardless of their current diagnosis.

The PreHD group at T2 comprised 18 of the original 19 participants included in the study at T1. The one PreHD participant who did not participate at T2 was a female who lived overseas and was unable to come back to the country. The PreHD group consisted of 11 males and seven females with a mean age of 46.39 years. Their HD CAG repeat lengths ranged from 38 to 45 (see Table 1). On this occasion the Unified Huntington’s Disease Rating Scale (UHDRS) Total Motor Scores of the group ranged from 1 to 26 with a mean of
6.11. For the UHDRS Diagnosis scores, two participants received a score of “4”, indicating symptomatic onset of the disease. Thus two participants who were pre-symptomatic at T1 progressed into the symptomatic stages at T2. All other participants were still classified as pre-symptomatic (see Table 2 for frequencies of diagnostic confidence scores).

TFC scores of the PreHD group at T2 ranged from 10 to 13. One participant had a score of 10, two participants had scores of 11 and two had scores of 12. The remaining 13 PreHD participants received the maximum score of 13 on the TFC. This is in contrast to T1 where 18 of the 19 PreHD participants had a TFC score of 13, and the remaining participant had a score of 12. At T2, the two symptomatic participants had scores of 10 and 13 respectively, thus the symptomatic participants were not the only contributors to the changes seen from T1 to T2. A repeated-measures ANOVA comparing TFC scores at T1 and T2 indicates that TFC scores at T2 were significantly lower compared to TFC scores at T1, $F(1, 33) = 3.96, p = 0.05$.

Ethnicity data shows 100% of PreHD participants identified themselves as New Zealand European. The representation of European in the PreHD sample is reflective of the genetic origins of the disease; however, is not reflective of the other cultures, including Maori, who suffer from this disease in NZ.

**Table 1**

*Clinical characteristics of the PreHD group at T2*

<table>
<thead>
<tr>
<th></th>
<th>Median (Interquartile Range)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of CAG repeats</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant Gene</td>
<td>41.00 (3.00)</td>
<td>38-45</td>
</tr>
<tr>
<td>Normal Gene</td>
<td>18.50 (3.00)</td>
<td>16-25</td>
</tr>
<tr>
<td><strong>UHDRS Diagnostic Confidence Level (0-4)</strong></td>
<td>1.00 (1.25)</td>
<td>0-4</td>
</tr>
<tr>
<td><strong>UHDRS Total Motor Score (0-124)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic participants included</td>
<td>4.50 (4.25)</td>
<td>1-26</td>
</tr>
</tbody>
</table>
Table 2

Frequency of PreHD participants in each UHDRS Diagnosis Confidence Level at T1 and T2.

<table>
<thead>
<tr>
<th>Diagnosis Confidence Level Category</th>
<th>Frequency of PreHD participants at T2</th>
<th>Frequency of PreHD participants at T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Cortical Thinning Profile – PreHD Group

Both PreHD and Control samples underwent MRI scanning at T1, approximately three years ago, to investigate if cortical thinning was evident in the PreHD group and to observe the distribution of this thinning. The analysis of MRI data was conducted by collaborators Rosas and colleagues in Boston, using identical automated MRI segmentation techniques to their previous studies (Rosas et al., 2005; Rosas et al., 2008). The details of scan acquisition and analyses used are provided in Appendix B.

The cortical thinning map for the PreHD sample at T1 is presented in Figure 1. The PreHD group showed thinning in specific regions of the cortex, most prominently in the right parietal-temporal-occipital junction extending into small portions of the posterior middle temporal gyrus, inferior parietal cortex and lateral occipital cortex (approximate Brodmann’s Areas [BA] 37, 39, 19). Smaller regions of thinning were also evident within the paracentral lobule/posterior superior frontal gyrus and the pars opercularis (approximate BA 44). The group also displayed significant cortical thickening in the right anterior cingulate, right medial orbitofrontal cortex (BA 12, 25 and 32) and within the left posterior cingulate (BA 23). All the cortical changes evidenced at T1 were at a significance level of p< 0.05.
Figure 1. Displays cortical thickness map of the PreHD group ($n=19$) compared with the Control group ($n=19$) at T1. The cortical thickness map is presented on a semi-inflated cortical surface of an average brain. The colour scale displays the measure of thickness change with corresponding statistical values, transitioning from $p<0.05$ to $p<0.01$. Red-Yellow corresponds to significant cortical thinning and blue/white corresponds to significant thickening compared with the Control group.

Control Group

Participants recruited into the Control group at T1 consisted of individuals with no family history of HD who were age and education-matched to the PreHD participants. The Control group at T2 comprised of 18 of the original 19 participants included in the study at T1. The one Control participant unable to recruited at T2 was a male who, due to work and family commitments, was unable to participate. The Control group consisted of 10 males and eight females, with a mean age was 47.00 years. All control participants had a TFC score of 13. Ethnicity in the control group comprised mainly of NZ Europeans. Cultural variation was seen in the control group with one participant who identified as an Israeli, and one who identified as a Pacific Islander.
The data of one Control participant was excluded from the neuropsychological component of the study because she presented with psychological distress due to life events occurring at the time, which significantly affected her ability to complete the neuropsychological tasks.

Table 3

Demographic characteristics for the PreHD and Control groups at T2

<table>
<thead>
<tr>
<th></th>
<th>PreHD (n=18)</th>
<th>Control (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male: Female (%male: %female)</td>
<td>11: 7 (61.1%; 38.9%)</td>
<td>10: 8 (55.6%; 44.4%)</td>
</tr>
<tr>
<td>Age: Mean± SD; [Range]</td>
<td>46.39± 12.19; [26-66]</td>
<td>47.00 ± 12.20; [26-67]</td>
</tr>
<tr>
<td>Years of Education: Mean± SD; [Range]</td>
<td>13.47 ± 2.03; [10-17]</td>
<td>13.53 ± 1.96; [10-17]</td>
</tr>
<tr>
<td>Handedness: Right (%)</td>
<td>17 (94.4%)</td>
<td>13 (72.2%)</td>
</tr>
</tbody>
</table>

Tests for differences between PreHD and Control groups at T2

Table 3 shows the demographic characteristics of the PreHD and Control groups. Although the sample was no longer as perfectly matched for gender and age as it was at T1, there were no significant differences between the two groups on any matching variables, including age, \( t(34) = -0.15, p = 0.88 \), years of education, \( t(34) = -0.08, p = 0.75 \), or gender, \( X^2(1, n = 36) = 0.11, p = 0.74 \). Additionally, there was no significant difference between groups on handedness \( X^2(1, n = 36) = 1.80, p = 0.18 \).

Proximity to Onset Subgroups

Indivduals pre-symptomatic for HD who are closer to clinical onset of the disease are more likely to show significant clinical changes (both structural and cognitive) (Tabrizi et al., 2012). To investigate whether proximity to disease onset affected cognitive changes in our sample, PreHD participants were split into two groups defined by the estimated Years To Onset (YTO) of the disease, using an online calculator.
This calculator is based upon data from Langbehn et al.’s (2004) research and uses the variables CAG repeat length and age to calculate an estimate of years to clinical onset. Clinical use of the calculations is not recommended, however, it is useful as a research tool.

The median YTO was used to divide the PreHD group into close-to-onset (PreHDClose) and far-from-onset (PreHDFar) groups. For the two HD participants now diagnosed as symptomatic (based upon motor presentation), the calculator tool was not used, instead these participants were given a YTO of zero years and were included in the close-to-onset proximity group consistent with the practice of other longitudinal HD studies (e.g. Tabrizi et al., 2011; Tabrizi et al., 2012). The YTO of the PreHD group ranged from 0 years (those already symptomatic) to 40.96 years, with a median of 11.70 years. Consequently, the PreHDClose group had an estimated YTO of less than 12 years and the PreHDFar group had an estimated YTO of greater than or equal to 12 years.

One-way ANOVAs showed no significant differences between the PreHDClose, PreHDFar and Control groups for age, \( F (2, 34) = 0.64, p = 0.53 \), or years of education, \( F (2, 34) = 0.17, p = 0.85 \). There were also no significant differences between the three groups on gender \( X^2 (2, n = 36) = 0.34, p = 0.84 \) or handedness, \( X^2 (2, n = 36) = 3.60, p = 0.17 \). The PreHDClose group did show significantly higher CAG repeats compared to the PreHDFar group, \( t (17) = 4.80, p = .04 \), which was expected. Table 4 shows the demographic characteristics for the PreHDClose, PreHDFar and Control groups.
Table 4

Demographic characteristics for the PreHDClose, PreHDFar and Control groups at T2

<table>
<thead>
<tr>
<th></th>
<th>PreHDClose (n=9)</th>
<th>PreHDFar (n=9)</th>
<th>Control (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender: Male: Female</td>
<td>5: 4</td>
<td>6: 3</td>
<td>10: 8</td>
</tr>
<tr>
<td>Age: mean±SD (Range)</td>
<td>49.67±11.7 (35-66)</td>
<td>43.11±12.42 (26-65)</td>
<td>47.00±12.20 (26-67)</td>
</tr>
<tr>
<td>Years of Education: mean±SD (Range)</td>
<td>13.28±2.22 (10-17)</td>
<td>13.67±1.94 (10-16)</td>
<td>13.53±1.96 (10-17)</td>
</tr>
<tr>
<td>Handedness: Right (%)</td>
<td>8 (88.9%)</td>
<td>9 (100%)</td>
<td>13 (72.2%)</td>
</tr>
<tr>
<td>CAG repeats: mean±SD (Range)</td>
<td>42.33±4.75 (39-45)</td>
<td>40.33±1.66 (38-42)</td>
<td>N/A</td>
</tr>
<tr>
<td>Total Function score (0-13)</td>
<td>12.22±1.09 (10-13)</td>
<td>12.78±0.67 (11-13)</td>
<td>N/A</td>
</tr>
<tr>
<td>UHDRS Total Motor Score (0-124)</td>
<td>7.89±7.69 (2-26)</td>
<td>4.33±2.92 (1-10)</td>
<td>N/A</td>
</tr>
<tr>
<td>UHDRS Diagnostic Level (0-4)</td>
<td>1.67±1.5 (0-4)</td>
<td>1.00±0.71 (0-2)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Cortical Thinning Profile – PreHDClose and PreHDFar Groups

Cortical thinning maps comparing the PreHDClose and Control group and PreHDFar and Control group at T1 are displayed in Figure 2. Analyses at T1 indicated the PreHDClose group showed significant thinning in the right parieto-temporal-occipital junction, with a smaller region of thinning in the pars opercula. Cortical thickening was also present within the right medial orbitofrontal cortex, anterior and isthmus cingulate cortices (approximate BA 12, 25 and 32) and left posterior cingulate cortex (approximate BA 23). The PreHDFar group, however, showed no cortical thinning compared to the Control group at T1, but did show significant cortical thickening in the right medial orbitofrontal cortex. Again, all the cortical changes evidenced at T1 were at a significance level of p< 0.05.
Figure 2. Displays cortical thickness map of the PreHDfar group (n=9) compared with matched Controls (n=9) and the PreHDclose group (n=10) compared with matched Controls (n=10) at T1. The colour scale displays the measure of thickness change with corresponding statistical values, transitioning from p < 0.05 to p < 0.01. Red-Yellow corresponds to significant cortical thinning and blue/white corresponds to significant thickening.
Screening Test Descriptions

**UHDRS Total Motor score**

The UHDRS motor assessment (Kieburtz et al., 1996) is used as a measure to assess motor abnormalities in HD. It assesses key motor areas that are known to be significantly affected in HD. This includes standardised ratings of ocular-motor function, dysarthria, chorea, dystonia, gait and postural stability. Each item is assessed in an examination by a trained neurologist then rated from 0 – 4 (normal – severely impaired). There are 31 items altogether, with the total score that one can receive ranging from 0 – 124, where higher scores are associated with increased motor symptoms.

**UHDRS Diagnosis**

Based on the UHDRS motor assessment, a neurologist can provide a UHDRS Diagnosis Confidence Level, based upon motor abnormalities that are present and to what degree. The UHDRS Diagnosis Confidence Level ranges from 0 – 4 (see Figure 3) and communicates the degree that the assessed individual shows motor abnormalities that are indicative of HD, where 0 = normal, and 4 = motor abnormalities that are unequivocal signs of HD. Scores of two or lower are considered pre-symptomatic.

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**Figure 3.** Motor Confidence Diagnosis Rating Scale from Unified Huntington’s Disease Rating Scale.
**Total Functional Capacity**

The Total Functional Capacity (TFC) (Shoulson & Fahn, 1979), also in the UHDRS, is used to assess the functional capacity of individuals in the PreHD group. This scale measures an individual’s capacity to function in selective domains, including employment, domestic duties and self-care. The scale is clinician-rated, based on the clinician’s assessment of their capacity, rather than actual performance. The TFC is relatively linear in its progression in the disease; with scores progressively decreasing the longer an individual has been symptomatic (Dubinsky, 2005). The TFC is used to classify individuals into stages of the disease once symptomatic, and ranges from 0 – 13, with higher scores indicating higher function. In the recruitment phase of T1, participants were only included if they had a TFC score within Stage One, between 11 and 13.

**Neuropsychological Test Selection and Changes**

As described earlier, the majority of cognitive tasks used in this study were selected by the principle investigator (J.D) at T1. Some additions and changes, however, were made in the present study. The Unified Huntington’s Disease Rating Scale (UHDRS) cognitive tasks were added to the battery because they are used in the majority of HD neuropsychological studies and thus including them enables comparison of our sample to samples in other HD studies. Also, although the Iowa Gambling task was included in the data collection phase of this study, due to a technical issue the data output was lost for approximately 70% of participants and thus could not be analysed. It is listed in the order of administration table at the end of the chapter (Table 6) as it was administered to all participants; however, due to its absence in the results, it will not be described further.
Table 5  
*Administration details of Neuropsychological tasks*

<table>
<thead>
<tr>
<th>Task</th>
<th>Mode of Administration</th>
<th>Mode of Response</th>
<th>Timed Yes/No</th>
<th>Performance measure Accuracy/Reaction Time (RT)</th>
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<td>Written</td>
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<td>Yes</td>
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*Neuropsychological Test Descriptions*

Altogether 14 neuropsychological tasks were completed for each participant, these included the three tasks of the UHDRS cognitive measures, two tasks that measured psychomotor speed, six tasks thought to be sensitive to posterior regions of cortical function...
and two tasks sensitive to anterior cortical function. Six tasks were computerised and seven required verbal or written response to visual stimuli.

The tasks and their performance measures are described below under the following sections; UHDRS cognitive tasks, psychomotor tasks, tasks sensitive to posterior cortical regions, tasks sensitive to anterior cortical regions and psychological measures. A summary of all neuropsychological tasks administered in this study and their relevant details can be found in Table 5.

**UHDRS Cognitive Assessment**

These tasks were administered in accordance to the UHDRS guidelines.

**Controlled Oral Word Association (Benton & Hamsher, 1989)**

The Controlled Oral Word Association Test (also known as verbal fluency) assesses naming and word generation strategy. It consists of three trials using the letters F, A and S. In the task participants are asked to name as many words as they can that begin with the given letter of the alphabet. Participants are instructed not to give proper nouns, plurals or repeat words already given and to give as many words as they can until they are stopped.

The words generated in response to each letter are recorded by the tester until 60 seconds is completed. The scoring is based on the number of words given by the participant for the particular letter within 60 seconds (minus any that violated the rules e.g. proper nouns, plurals and repetitions). Higher scores equal better performance.

**Symbol Digit Modalities Test (A. Smith, 1982)**

The Symbol Digit Modalities Test (SDMT) is a widely used test to assess complex scanning and visual tracking as well as assessing psychomotor speed.

Participants are shown a sheet of paper with nine symbols each with a digit (1-9) below, located at the top of the page. Below this are rows of the exactly the same format, except there are no corresponding digits below the symbols (spaces are blank). Participants
are instructed to write the corresponding number under each symbol in the blank space. Once
the examples are completed and the participant is clear on how to carry out the task, they are
instructed to begin from the test start point and continue the task sequentially, without
skipping over any, until they are instructed to stop. Participants are timed for 90 seconds. The
numbers of correct responses’ are recorded. Higher final scores suggest better performance in
the task.

**Stroop Interference Test (Stroop, 1935)**

The Stroop Interference Test is a well-known test used to assess attention and set-
shifting abilities (Lezak et al., 2004). The Stroop has three different trials: Colour, Word and
Colour-Word Interference trials. Its effect is based on the premise that participants will take
longer on the Colour-Word Interference trial of the test, as it requires inhibition of an
automatic reading response in order to name the colour ink the word is typed in. The three
trials are described below.

**Colour trial:** Participants are shown an A4 card with rows of colour rectangles, either
blue, green or red, presented in random order. They are asked to name the colours of the
blocks, from left to right, row after row, until they are told to stop. They are instructed to start
again at the top if they complete the sheet before they are asked to stop. Participants are timed
for 45 seconds.

**Word trial:** Participants are shown an A4 card with rows of colour words (blue, green
red) in random order printed in black ink. They are instructed exactly the same as in the
Colour trial except this time to read the names of words out loud until they are told to stop.
Participants are timed for 45 seconds.

**Colour-word interference trial:** Participants are shown an A4 card with rows of
colour word (blue, red, green) printed in a different colour ink to the name of the colour (e.g.
the word Red is printed in blue ink). Participants are instructed to name the colour of the ink,
as opposed to reading the word. Other instructions are identical to the other trials and participants are timed for 45 seconds. In all trials, higher scores equal better performance.

**Psychomotor Speed Tasks**

*Motor Control Task (Lawrence et al., 1996)*

The motor control task was included at T1 to familiarise participants with the process of using the touch screen and to allow opportunity for clarification of any difficulties (Davison, 2009). It also assesses basic motor reaction speeds in the two groups. A flashing yellow and pink X appears on a black background and participants are instructed to touch the cross as quickly as they can when it appears on the screen. When the cross is touched, it disappears then re-appears somewhere else on the screen, where participants repeat the process. Reaction time is measured by the computer.

*Simple Reaction Time (Lawrence et al., 1996)*

This task was included in the testing procedure at T1 to provide a basic measure of reaction time in both groups (Davison, 2009). Given motor abnormalities are significant in HD, it was important to assess the reaction time baselines for both groups as a number of the neuropsychological variables were measured by response time. This task measures simple reaction time and involves two components. In the first component a small pale yellow oval appears in the middle of a larger yellow lined circle on a black screen. Participants are instructed to touch the yellow oval as quickly as possible when it appears. The oval quickly disappears then reappears at varying random intervals, and participants need to be prepared to respond. The second portion of the task has five circles in which the yellow oval can appear. One circle is at the centre and four circles are placed around the centre circle. The yellow oval can appear in any one of these circles, requiring the participant to touch the oval when it appears as quickly as possible. Response times are recorded by the computer.
Task Sensitive to Posterior Cortical Regions

*Benton Judgement of Line Orientation Test (Benton, Varney, & Hamsher, 1978)*

The Judgement of Line Orientation Test (JLOT) is a test that assesses visual-spatial perception as the participants are required to judge the angles of the lines presented in the stimulus and select a match to these from a selection of lines at graded orientations.

![Sample stimuli from the Judgement of Lines Orientation Test](image)

*Figure 4. Sample stimuli from the Judgement of Lines Orientation Test*

The test (see *Figure 4*) is presented in a booklet consisting of 35 stimuli (5 practice and 30 test items). The spiral bound booklet opens to an A4 size with the stimuli of two lines at different angles appearing in the upper part of the booklet and a selection of multiple choice response options labelled 1-11 in the lower portion. The five practice items display two lines that are identical reproductions of the response choice lines, however, the test stimuli displays two lines that are partial segments of the response choices. Each partial line displays either the distal (high), middle or proximal (low) segment of the response choice line. Each test item is either a homogenous or heterogeneous combination of the partial line types.

The booklet is placed flat in front of the participant, and positioned for easy viewing of both the stimulus and response choices. Participants are instructed to give the numbers of
the two lines in the response section that are in exactly the same position/angle as the two lines in the stimulus section. Feedback is given in the practice but not the test items. There are no time restrictions on this task.

**Hooper Visual Organisation Test (Hooper, 1983)**

The Hooper Visual Organisation Test (HVOT) requires participants to mentally integrate the fragmented pieces of a line drawing of an ordinary object in order to identify the object and name it. It requires the cognitive process of visual integration (putting the pieces of the picture together), object recognition and naming.

![Figure 5. Item 22 from the HVOT. Correct response is a mouse.](image)

Participants are shown a small (A5 when open) spiral bound booklet consisting of 30 line drawings. Each line drawing represents a particular common object, however, the drawing is fragmented into pieces on the page (see *Figure 5*). The booklet is placed in front of the participant, who is instructed to view the drawing and identify the object that is represented in the line drawing without rotating the booklet or their head. If participants are undecided between options or cannot identify the object, they are asked to choose their best answer. Responses are recorded verbatim by the tester. Full credit responses are given when responses match the right answer, half credit when they are in the category of response, and no credit for the wrong answer. There are no time restrictions on this task.
Collision Judgements Task (Assmus et al., 2003)

The Collision Judgements task requires participants to judge whether two dots will collide behind the white box if they continue to move at the exact same speed and angle they are shown to be travelling on the screen. This requires integration of both spatial orientation and motion information.

Figure 6. Collision Judgements Task. Figure shows snapshot of black dots moving towards white box.

Stimuli for this task are presented on a computer screen, and responses are provided by the participant by clicking either the left or right button on the mouse, indicating a miss or collide response respectively. The task is presented using Presentation software (Neurobehavioural Systems, CA, USA). Participants see two boxes, one larger box, and a smaller box inside it on a white background (see Figure 6). Two black dots (presented at different sizes throughout the trials) move towards the white box in the centre of the screen at different angles and different speeds. The speed and angle of each dot at the outset of the trial remains constant for that trial. After the black dots disappear behind the middle box, participants are required to decide if the two dots would collide or miss each other if they continued at the same speed and angle.

For each trial the dots are visible for about 1600ms (depending on the speed of the dots), and subsequently only the white box in the middle is visible. A time limit of 20
seconds per trial is in place, if participants do not respond in this time, the next trial begins and no response is recorded. Participants are instructed to make their best guess if they are unsure of the response. Performance is assessed as the percentage of correct judgments made. In total, 90 trials are presented with an equal share of ‘collide’ and ‘miss’ scenarios.

**Benton Facial Recognition Test - Short Form (Benton, van Allen, Hamsher, & Levin, 1973)**

The Benton Facial Recognition test requires the abilities of visual perception and facial recognition of unfamiliar faces in order to identify and discriminate between unfamiliar human faces.

Participants are presented with a stimulus booklet approximately A4 size. For all items the top portion of the booklet contains the stimulus face and the bottom portion contains six multiple choice options of faces (see Figure 7). For the first 6 stimuli, the participant is asked to verbally identify the exact replica of the stimulus face in the multiple choice response pictures. This portion of the task assesses matching frontal view pictures of faces. From item 7 on, the participant is asked to identify three of the six multiple choice pictures that represent the face in the stimulus picture. This portion of the task assesses matching frontal view faces with three quarter view photographs and photographs under different lighting conditions. This task is not timed.


**Figure 7.** Benton Facial Recognition Test. Shows item where participants were asked to select three faces from the multiple choice response that represent the face in the stimulus picture

*Modified Roadmap Test of Direction Sense (Davison, 2009; Money, Alexander, & Walker, 1965)*

The Roadmap test requires participants to mentally navigate oneself through a diagrammatic map. This requires discrimination of left and right in addition to egocentric mental rotation (i.e. mentally rotating direction around the centre point of oneself). At T1 this task was slightly modified from the original version (Money et al., 1965) by providing an additional mirror version of the map. This controls for disproportionate numbers of left and right turns in the original form and provides an increase in the number of trials, which is likely to increase sensitivity in the data and allow comparisons between turn-types (Davison, 2009).

Participants are shown two diagrammatic roadmaps, one being an exact copy of the original roadmap (Money et al., 1965), and the other being an inverted or ‘mirror image’ of
the original map (see Figure 8). Thus two versions of the task are administered; one after the other with 50% of participants, randomly selected, administered the normal version first and the other 50% administered the mirror version first.

Figure 8. Modified Roadmap test of Direction Sense. Shows both the original and inverted maps shown to participants.

Visually, the map consists of paths through rectangular and triangular shapes, with the main path indicated by a dashed line through the map (see Figure 8). The map is placed at a centred and upright position in front of participants with the examiner sitting opposite. Participants are required to navigate themselves mentally through the map along the main path of the dotted-line. The examiner traces along the dotted-line path (with index finger or end of pen) until a turn is reached, at which point the participant needs to instruct the examiner whether a left or right turn is needed in order to continue along the path of the dotted-line. The examiner records the responses by pressing a key on the computer that corresponds to either ‘right’ or ‘left’, the computer then records the right/left decision and the
response time. During the task, the dotted-line path moves away from the participant, requiring participants to proceed forward along the path mentally and only requiring a left/right judgement at the turn. These turns constitute an ‘un-rotated turn’ [No Rotation, NR]. At other times, the dotted-line path moves at 90 degree angles from the participant or towards the participant (i.e. walking back toward themselves) which then requires both egocentric mental rotation and left/right judgement to give a correct response. These turn types constitute ‘half-rotated’ [Half Rotation, HR] and ‘full rotated’ [Full Rotation, FR] turns respectively.

Participants are given a practice trial before the test trials begin. This consists of another dotted-line path on the top of the map allowing practice of three turns to ensure the task is understood. All the turns in the practice task are ‘No Rotation’ turns and errors are corrected; no feedback, however, is given during the test route. The test route consists of 64 turns in total, 18 of these are NR turns, 26 turns are HR turns and 20 turns are FR turns (Vingerhoets, Lannoo, & Bauwens, 1996).

Throughout the task the map remains in a fixed position, and participants are instructed not to move their body position in order to make left and right judgements. Also, given the experimenter is tracing the map, participants’ body parts do not aid in the left/right discrimination. Performance is assessed through accuracy (percentage of correct turns for each of the three conditions) and a coarse measure of response time (average time taken in each of the three conditions).


**Modified Letter Mental Rotation task – Alpha F (Cooper & Shepard, 1973; Davison, 2009)**

The Letter Mental Rotation task requires participants to mentally rotate the letter F to an upright position before judging whether it is a normal, forward facing letter F, or a mirror image, backward F. It requires extra-personal mental rotation to complete the task, that is, rotate the letter F mentally, outside oneself.

![Figure 9. Different orientations of Letter F presented to participants. Both Mirror and Normal stimuli are shown. Each letter was presented separately and in random order.](image)

The original alphanumeric mental rotation task by Cooper and Shepard (1973) included multiple letters and numbers, however, this task uses only a single letter (F) in order to reduce the confounds of set shifting, which is reliant on frontal region activity (Davison, 2009). This computerised task was conducted using E-prime software. Participants respond with a mouse indicating if the letter is a forward or backward representation of the letter F. Participants are shown an introductory screen illustrating the progression from a rotated F to a upright letter F, to explain what is required in the task. Participants are informed they will...
see presentations of the letter F at rotations about 360 degrees, requiring them to rotate the letter F in their mind to an upright position in order to judge if it is a forward or backward letter F. Instructions are given not to flip or invert the letters and not to rotate their heads or the screens.

A practice sample is given to participants with a series of 3 letter F’s presented at different angles, where participants gain verbal feedback. A practice of block of 12 trials is then presented with visual feedback (Correct, Incorrect). The test trials do not provide feedback.

On test trials, a fixation cross appears for one second followed by the stimulus which remains until the participant responds, or for a maximum of 10 seconds. Participants are asked to respond as quickly as they can. There are 120 test trials with each trial showing a letter F presented in one of six different two-dimensional orientations (0°, 60°, 120°, 180°, 240°, 300°) (See Figure 9). The six orientations are each shown 20 times with equal representation of forward and backward ‘F’s in each orientation, presented in random order. Dependent variables are accuracy and reaction time. Reaction times that are less than 200ms are not included as they are regarded as anticipatory responses (Davison, 2009).

**Cognitive Tasks Sensitive to Anterior Cortical Regions**

*Modified Hand Mental Rotation Task (Davison, 2009; Ganis, Keenan, Kosslyn, & Pascual-Leone, 2000)*

The Hand Mental Rotation task requires participants to mentally rotate an image of a human hand to an upright position before discriminating if it is a left or right hand.
Figure 10. Different orientations Hands presented to participants. Both Mirror and Normal stimuli are shown. Each was presented separately and in random order.

This task was designed and administered using E-prime software. To provide a comparable task to the Modified Letter Mental Rotation, the original task (Ganis et al., 2000) was modified to the same design as the Letter Mental Rotation task (Davison, 2009). This was done in order to assess differences in Hand Mental Rotation (recruiting frontal and parietal cortical regions) and Letter Mental Rotation (recruiting parietal cortical regions only).

Identical to the Letter Mental Rotation task, stimuli are presented on a computer screen and participants are required to respond with a mouse. Participants are shown an introductory screen illustrating the progression from a rotated hand to an upright hand, to explain what is required in the task. Participants are informed they will see images of left and right hands at rotations about 360 degrees, requiring them to rotate the image in their mind to
an upright position in order to differentiate whether it is a left or right hand. Instructions are
given not to flip or invert the image or rotate their heads or screens.

A practice sample is given where three hands are presented at different angles, and
participants gain verbal feedback. A 12 trial practice block then begins where visual feedback
(Correct, Incorrect) is provided. The test trials do not provide feedback. For the test trials, a
fixation cross appears for one second followed by the stimulus which remains until the
participant responds or for a maximum of 10 seconds. Participants are asked to respond as
quickly as they can. There are 120 test trials, each trial showing images of left and right
hands presented in one of six different two-dimensional orientations (0°, 60°, 120°, 180°,
240°, 300°) (see Figure 10). The six orientations are each shown 20 times with equal
representation of right and left hands, in random order. Accuracy and reaction time for trials
answered correctly are the dependent variables. Reaction times that are less than 200ms are
not included as they are regarded as anticipatory responses (Davison, 2009).

**Computerised Stockings of Cambridge Task (Owen et al., 1995)**

The computerised Stockings of Cambridge (SoC) task assesses problem solving and
forward spatial planning, a task closely related to the ToL task.

The SoC is administered via a computer touch screen with responses made by the
participant directly on the screen. Participants are presented with a split screen, in which the
top half displays three ‘stockings’ with three coloured balls distributed in a particular
arrangement (see Figure 11). The bottom half also displays three coloured balls, but in a
different arrangement (see Figure 11). Participants are required to move the balls between the
stockings in the bottom half of the screen in order to replicate the arrangement of the balls in
the top half of the screen. Participants are instructed how to move the balls using the touch
screen and are explained that the task functions as if there are real balls suspended in
stockings (meaning balls cannot be suspended in air, they need balls in the bottom first, and
likewise balls in the bottom cannot be removed before the top balls are removed). Participants are made aware that the number on the right hand side of the screen represents the minimum number of moves required to solve the task, but each trial allows more moves than the minimum.

Figure 11. Stockings of Cambridge Task. Figure shows the stimulus sample in the top half of the screen and the working portion at the bottom of the screen where participants had to move to balls to copy the stimulus picture. A four-move problem is shown.

Participants practice the first six trials (4 one-move problems and 2 two-move problems) where the examiner provides feedback, ensuring the task is understood. The experimental trials consist of two each of two- and three-move problems and four each of four- and five-move problems, totalling twelve problem trials.

Following the experiment trials, participants complete a Motor Control task where the participant’s sequence of moves for each experimental trial has been stored in the computer memory. Participants see the same split screen but the computer displays the moves to be carried out on the top half of the screen. Participants then copy each move on the bottom half of the screen. The computer shows one move at a time, to which the participant copies the
move before the computer displays the next, therefore requiring no memory of previous
moves for the participant. The Motor Control task also consists of 12 trials.

The Stockings of Cambridge Task has two categories of outcome measures; accuracy
and latency. There are two accuracy measures, ‘perfect solutions’ and the number of ‘excess
moves’. ‘Perfect solutions’ refers to the number of problems that are solved in the minimum
moves and ‘excess moves’ refers to the number of moves taken to solve the problem that is
above the minimum. These are measured in the experimental trials.

There are also four latency measures, two for planning/thinking time, and two for
initiation/execution. The former being measured in the experimental trials of the SoC and the
latter being measured in the Motor Control trials. The latency measures are defined in greater
detail below.

**Planning/thinking time measures**

*Initial thinking time:* time between the presentation of the problem and time to
respond with a ball selection *minus* the time taken to make a ball selection for that problem in
the motor control task (the latter which does not require problem solving thinking time).

*Subsequent thinking time:* time between the first move and problem completion *minus*
the same measure on the identical trial in the motor control. As this will vary with increasing
complexity of the problems, this measure is divided by the number of the moves in the
problem to give an average thinking time per move. ‘All negative values produced by this
subtraction were reduced to zero, assuming minimal thinking time. In this way, pure
estimates of initial and subsequent thinking times were derived, un-confounded by motor
initiation or execution times’ (Davison, 2009 pg. 84).

**Initiation and execution measures**

*Motor initiation:* time between the presentation of the problem and time to complete
the first move (i.e., correct touch of the required ball).
*Motor execution*: time between the first move and completion. ‘The measure for total execution time was divided by the number of moves for that problem in order to provide an estimate of the average movement time per move in each problem’ (Davison, 2009, pg. 84).

**Psychological Measures**

*Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983)*

The Hospital Anxiety and Depression Scale (HADS) was selected as a psychological measure of anxiety and depression because it excludes somatic symptoms associated with these psychiatric disorders such as insomnia, fatigue etc. (Davison, 2009). This is pertinent in this study because HD has significant physical manifestations which could confound the measurement of psychological disturbance, which is also well known in HD. Two sub-scales make up the HADS self-report questionnaire of 14 items, 7 measuring symptoms of anxiety (HADS-A) and 7 measuring symptoms of depression (HADS-D). Participants rate their responses on a four-point Likert scale (0 – 3) with definitions of each point on the response form. Thus both the HADS-A and HADS-D have a score range of 0-21, which can then be categorised into severity measures [Normal (0-7), Mild (8-10), Moderate (11-14) and Severe (15-21)].

*Irritability-Depression-Anxiety Scale (Snaith, Constantopoulos, Jardine, & McGuffin, 1978)*

The Irritability-Depression-Anxiety Scale (IDAS) was included primarily because of the sub-scales of Inward Irritability and Outward Irritability (Davison, 2009). The presence of irritability is well known in HD and this tool enabled a measure of this construct. The IDAS measure of irritability looks at both external manifestations of irritability such as verbal or behavioural outbursts, and also internal manifestations such as irritable mood without overt manifestation (Snaith & Taylor, 1985). Snaith and Taylor (1985) have demonstrated that the
Inward Irritability items are not homogeneous, meaning that the questions attempting to measure this construct may also tap into measures of other constructs. Thus, caution must be used when interpreting results on the Inward Irritability scale (Davison, 2009). The scale is measured on a four point (0-3) Likert scale with definitions of each point on the response form for each question. The overall score in each scale ranges from 0-12 and can be classed into severity categories [Normal (0 - 4), Borderline (5 - 7), and Morbid (8 - 12)].

For both the HADS and IDAS, participants are instructed to think back to the last week of their life and respond to the questions based on this period. They are also encouraged to respond with the answer that comes quickest to them, rather than a long thought-out response, as the former is likely to be more accurate. Participants completed these questionnaires prior to neuropsychological testing to reduce any affective effects resulting from the testing process.

**Study Design**

This study involved data collection at the second time-point of a longitudinal study which was conducted within an average of three years of the original data collection at T1. The measures used and procedure followed are virtually identical to that used in the original study at T1, reported in the doctoral dissertation entitled: Cortical thinning and neuropsychological changes in pre-symptomatic Huntington’s Disease (Davison, 2009).

**General Procedure and Study Components**

This study was approved by the Northern Y Regional Ethics Committee (NTY_09_09_085) and fully informed consent was gained from each participant who agreed to take part in the study prior to testing and scanning (see Appendix D and Appendix E). Participants were informed by the principle investigator at T1 (J.D) of the possibility of a follow-up study prior to the onset of the present study. Participants in the control group were contacted by telephone by the principle investigator at T2, Sasha Bruneau-Herman (S.BH).
They were given information regarding the study verbally and via the Participant information sheet prior to written consent being gained at the first face-face appointment. Contact with the PreHD group was made initially by Virginia Hogg (V.H), an HD researcher who had previous contact with each of the PreHD participants. In most cases, an initial appointment was set with the HD researcher (V.H) and the principle investigator (S.BH). Each PreHD participant was given a Participant Information Sheet and verbal information regarding the study and its components in this meeting. Further contact for testing was made after this visit.

**Testing Procedure**

All neuropsychological testing was conducted either in the participants’ home or in a testing room at the University of Auckland. The computerised tests were conducted on a Dell Latitude E6400 laptop with windows XP operating software which was linked to a Toshiba touch screen monitor with a 15” screen.

At all times tasks were conducted in a quiet, distraction-free environment with opportunities for rests and toilet breaks. A general testing introduction was given at the outset of the session, explaining the nature of the testing session, varying difficulty of tasks, and that instructions would be outlined at the beginning of each task with opportunity to ask questions or have instructions re-explained. Participants were told that there were scheduled breaks, but if rest breaks or breaks to go to the toilet were needed before the scheduled one, they were free to ask for it. Regular inquiries were made about energy levels to monitor the need for extra breaks.

Altogether, the testing component lasted between 2-2.5 hours and this was completed in one, two or three separate sessions, depending on the practical and psychological needs of the participant. The session began with a brief structured interview (see Appendix C) followed by the UHDRS functional capacity rating and a mental wellbeing questionnaire, completed by participants. The neuropsychological tests were then carried out in the order outlined in Table
6. In addition to the neuropsychological testing, PreHD participants also completed the UHDRS motor assessment performed by R.R in a separate session.

**Order of Administration of Tests**

The order of administration of the main neuropsychological tests was identical to that at T1 except for the addition of the three UHDRS cognitive tasks (see Table 6). The UHDRS cognitive tasks and Mental Rotation tasks were alternated in their point of administration. All tests were administered in the same order for all participants.

**Table 6**

*Order of test administration (variations in procedure noted and explained)*

<table>
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<tr>
<th>Test</th>
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<tr>
<td>Interview using structured questionnaire</td>
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<td>Hospital Anxiety and Depression Scale</td>
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<td>Irritability-Depression-Anxiety Scale</td>
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<td>Total Functional Capacity Scale</td>
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<td>UHDRS*</td>
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<td>Reaction Time Test</td>
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<td>Stockings of Cambridge</td>
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<tr>
<td>Iowa Gambling Task ***</td>
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<td>Collision Judgements Task</td>
</tr>
<tr>
<td>Mental Rotation 1**</td>
</tr>
<tr>
<td>Roadmap Test</td>
</tr>
<tr>
<td>Judgements of Lines Orientation Test</td>
</tr>
<tr>
<td>Hooper Visual Organisation Test</td>
</tr>
<tr>
<td>Facial Recognition Test (Short Form)</td>
</tr>
<tr>
<td>Mental Rotation 2**</td>
</tr>
<tr>
<td>UHDRS*</td>
</tr>
</tbody>
</table>

Note: * The UHDRS refers to the Verbal Fluency, Digit Symbol and Stroop tasks. The tasks were administered in this order, however, were randomly alternated in their point of administration. **Mental Rotation 1 and 2 refer to the Hand and Letter mental rotation tasks which were randomly alternated in their administration. ***The Iowa Gambling task was administered to all participants, but not included in the analysis of this document due to loss of data.*
Chapter Three  Results

Statistical Analysis

All analyses were performed using the statistical software package IBM SPSS 17.0 for Windows. All data were examined and corrected for possible outliers due to incorrect data entry. If outliers were accurate data then they were included in the analysis. If there were data missing at T2 or T1, then cases were dropped on a variable by variable basis.

To test for differences between groups on the UHDRS cognitive measures, the data were analysed using separate one-way Analyses of Variance (ANOVA). If the Levene’s test of homogeneity of variances was violated, then the Welch Robust test of equality of means was applied.

In order to determine if differences exist between the PreHD and Control groups on the cognitive variables tested and whether these have changed from T1, data collected at T1 and T2 were analysed using split-plot ANOVAs with Time (Timepoint-1 [T1] and Timepoint-2 [T2]) a within-subjects factor, and Group the between-subjects factor. A separate set of identical analyses were conducted to test for differences between the PreHDClose, PreHDfar and Control groups and to investigate changes since T1. If the Mauchly’s test of sphericity was violated in the repeated-measures ANOVA analysis, then the Greenhouse Geiser correction was used to report statistical values. More detailed descriptions of analysis for some tasks are described before the results are reported under the task heading. Non parametric tests were used for variables with non-normalised distributions. For categorical variables, Pearson’s Chi-Square tests were conducted. If the minimum expected cell frequency assumption was violated, the Fisher Exact Test value is reported.

A significance level of $p < 0.05$ was applied for all analyses. Although this significance level is liberal, therefore inflating the risk of Type-I errors, it was used to increase sensitivity for detecting subtle cognitive changes in pre-symptomatic participants.
All p-values reported are exact to two decimal places unless the p-value is less than 0.001, in which case it is reported as p <.001. All significance levels reported are two-tailed unless otherwise stated in the text, and all post-hoc comparisons are conducted using the Bonferroni correction.

**Results**

**UHDRS Cognitive Tests**

Table 7 provides the means and standard deviations of three UHDRS cognitive tasks (Verbal Fluency, Symbol Digit Modalities Test (SDMT) and the Stroop) administered at T2 for both the PreHD and Control groups. There was no significant difference in Verbal Fluency scores between the PreHD and Control group, $F(1, 33) = 1.34$, $p = 0.26$, nor in SDMT scores, $F(1, 33) = 1.56$, $p = 0.22$. For the Stroop task, there were no significant differences between the PreHD and Control group in Stroop scores for any of the three trials, Colour, $F(1, 33) = 0.51$, $p = 0.48$, Word, $F(1, 33) = 0.77$, $p = 0.39$, or Interference, $F(1, 33) = 0.08$, $p = 0.78$.

**Table 7**

*Mean scores and standard deviations for UHDRS cognitive tasks for PreHD and Control groups at Timepoint-2 (T2).*

<table>
<thead>
<tr>
<th>UHDRS cognitive task</th>
<th>PreHD Mean (SD)</th>
<th>Control Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency</td>
<td>44.44 (11.74)</td>
<td>40.12 (10.24)</td>
</tr>
<tr>
<td>SDMT</td>
<td>51.11 (12.27)</td>
<td>55.59 (8.50)</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour</td>
<td>73.39 (14.17)</td>
<td>76.47 (11.06)</td>
</tr>
<tr>
<td>Word</td>
<td>93.17 (19.07)</td>
<td>98.59 (17.35)</td>
</tr>
<tr>
<td>Interference</td>
<td>42.50 (12.76)</td>
<td>43.53 (8.81)</td>
</tr>
</tbody>
</table>
Psychomotor Tasks

Table 8 displays the means and standard deviations for the motor control and reaction time tasks for the PreHD and Control groups at T1 and T2.

Table 8

| Mean response times (ms) and standard deviations for Motor Screening and Reaction Time tasks for PreHD and Control groups at Timepoint-1 (T1) and Timepoint-2 (T2). |
|---|---|---|
| **Group** | **T1** Mean (SD) | **T2** Mean (SD) |
| Motor Control | PreHD \((n=18)\) | 1230.69 (337.79) | 1011.80 (258.54) |
| | Control \((n=17)\) | 989.58 (259.41) | 941.94 (210.79) |
| Reaction Time | PreHD \((n=17)\) | 498.57 (128.43) | 729.10 (131.03) |
| | Control \((n=16)\) | 445.06 (88.83) | 666.16 (115.70) |

**Motor Screening**

The analysis revealed the main effect of Group was marginally significant, \(F (1, 33) = 4.01, p = 0.05\) with the PreHD group having slower response times overall (\(M=1121.25, SE=54.11\)) compared with the Control group (\(M=965.76, SE=55.68\)). There was a significant main effect of time, \(F (1, 33) = 7.40, p = 0.01\) with faster response times at T2 (\(M=976.87, SE=40.0\)) compared with T1 (\(M=1110.14, SE=51.13\)). There was, however, no significant interaction between time and group, \(F (1, 33) = 3.05, p = 0.09\), although this showed a trend towards significance, with greater improvement in the PreHD from T1 to T2 relative to Controls.

**Reaction Time**

There was no significant main effect of group, \(F (1, 31) = 2.72, p = 0.11\), indicating that the PreHD and Control groups did not differ significantly in their speed of response in this task. There was a significant main effect of time, \(F (1, 31) = 118.44, p < .001\) with responses slower at T2 (\(M=697.63, SE=21.57\)) compared with T1 (\(M=471.82, SE=19.34\)), but there was no significant interaction between time and group, \(F (1, 31) = 0.05, p = 0.82\).
Tasks Sensitive to Posterior Brain Regions

Table 9 displays the mean and standard deviations of accuracy scores (percentage) for four tasks administered that are sensitive to posterior parts of the brain (Collision-Judgement test, Hooper Visual Organisation Tests (HVOT), Judgement of Lines Orientation Test (JLOT) and the Benton Facial Recognition Test). Analyses of the Collision Judgements task revealed no significant main effect of group, $F(1, 33) = 0.12, p = 0.73$, indicating that there was no significant difference between the accuracy of the PreHD and Control groups on this task. There was also no significant main effect of time, $F(1, 33) = 2.17, p = 0.15$ and no significant interaction between time and group $F(1, 33) = 0.68, p = 0.42$. On the Hooper Visual Organisation Test, there was a trend towards a significant main effect of group, $F(1, 33) = 3.71, p = 0.06$, with the PreHD ($M=89.35, SE=1.35$) group showing lowered accuracy overall compared to the Control group ($M=93.09, SE=1.39$) on this task. There was no significant main effect of time, $F(1, 33) = 0.97, p = 0.76$ and no significant interaction between time and group, $F(1, 33) = 0.05, p = 0.83$.

Analyses of performance on the Judgement of Lines Orientation Task revealed a significant main effect of group, $F(1, 33) = 4.97, p = 0.03$ with the PreHD group ($M=84.91, SE=2.55$) significantly less accurate overall at correctly judging the angle of the lines than Controls ($M=93.09, SE=2.63$). The main effect of time, $F(1, 33) = 4.05, p = 0.05$, was marginally significant with performance less accurate at T2 ($M=87.54, SE=1.92$) than T1 ($M=90.46, SE=2.02$). There was, however, no significant interaction between time and group, $F(1, 33) = 0.12, p = 0.73$, indicating that although the PreHD group were less accurate overall, they did not perform differentially more poorly at T2.

For the Benton Facial Recognition task (short form), there was no significant main effect of group on this measure, $F(1, 33) = 2.23 p = 0.15$, and no significant main effect of time, $F(1, 33) = 0.90, p = 0.35$. Importantly, however, there was a significant interaction
between time and group, $F (1, 33) = 6.35, p = 0.02$. As can be seen in Figure 12, the PreHD group performed differentially more poorly at identifying faces at T2. Analyses were performed to check whether results were sustained using the long form score conversions; results obtained in these analyses were essentially identical.

**Table 9**

*Mean and standard deviations of accuracy scores (percentage) for the PreHD and Control groups on the Collision-Judgement test, Hooper Visual Organisation Test (HVOT) and Judgement of Lines Orientation Test (JLOT) at T1 and T2.*

<table>
<thead>
<tr>
<th>Cognitive Task</th>
<th>Group</th>
<th>T1 Mean (SD) [Range]</th>
<th>T2 Mean (SD) [Range]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collision</td>
<td>PreHD (n=18)</td>
<td>82.22 (6.76) [66-93]</td>
<td>81.17 (6.20) [67-89]</td>
</tr>
<tr>
<td></td>
<td>Control (n=17)</td>
<td>84.05 (5.96) [68-94]</td>
<td>82.35 (5.19) [70-91]</td>
</tr>
<tr>
<td>HVOT</td>
<td>PreHD</td>
<td>89.07 (8.20) [73-100]</td>
<td>89.63 (7.20) [73-100]</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>93.04 (4.65) [83-98]</td>
<td>93.14 (5.23) [82-100]</td>
</tr>
<tr>
<td>JLOT</td>
<td>PreHD</td>
<td>86.11 (13.49) [53-100]</td>
<td>83.70 (12.30) [57-100]</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>94.80 (10.06) [63-100]</td>
<td>91.37 (10.28) [63-100]</td>
</tr>
<tr>
<td>Benton Facial</td>
<td>PreHD</td>
<td>88.27 (6.51) [67-96]</td>
<td>83.95 (7.83) [72-96]</td>
</tr>
<tr>
<td>Recognition</td>
<td>Control</td>
<td>88.23 (7.20) [78-96]</td>
<td>90.20 (7.04) [80-100]</td>
</tr>
</tbody>
</table>
Figure 12. Accuracy scores of PreHD and Control groups on Benton Facial Recognition (Short Form) over T1 and T2. Error bars indicate standard error of the mean.

Roadmap Test

Table 10 shows accuracy scores and reaction times on the Roadmap test for the PreHD and Control groups at both time-points. Analysis of accuracy and response time were conducted separately using repeated measures ANOVA. In each analysis, group was the between-subjects factor with turn-type (.turns requiring half rotation [HR], full rotation [FR] and no rotation [NR]) and time (T1 and T2) within-subjects factors. Separate analyses were also conducted in which FR and HR turns were merged, thus comparing turns requiring rotation of any degree (half rotation and full rotation), with no rotation turns.

Accuracy: There were no significant main effects of group, $F(1, 33) = 1.50, p = 0.23$, or time, $F(1, 33) = 0.25, p = 0.62$, nor a significant interaction between time and group, $F(1, 33) = 0.17, p = 0.68$. As expected, there was a significant main effect of turn-type, $F(1.15, 38), 19.84, p < .001$, with pair-wise comparisons revealing decreasing accuracy on turns requiring increasing amounts of rotation (all p-values < 0.05). There were no significant
interactions between turn-type and group, \( F (1.15, 38) = 0.35, p = 0.59 \), or time and turn-type, \( F (1.54, 50.93) = 1.00, p = 0.36 \). There was, however, a significant three-way interaction between time, turn-type and group, \( F (1.54, 50.93) = 5.61, p = 0.01 \). Pair-wise comparisons revealed that the PreHD group was significantly less accurate on NR turns compared to the Control group but only at T1 (\( p = 0.04 \)).

**Table 10**

*Accuracy scores on the Roadmap Test for the PreHD and Control groups at Time-point-1 (T1) and Time-point-2 (T2)*

<table>
<thead>
<tr>
<th></th>
<th>T1 Mean (SD)</th>
<th>T2 Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Accuracy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Rotation [NR]</td>
<td>95.43 (6.38)</td>
<td>95.56 (9.70)</td>
</tr>
<tr>
<td>Half Rotation [HR]</td>
<td>89.76 (14.98)</td>
<td>91.50 (12.70)</td>
</tr>
<tr>
<td>Full Rotation [FR]</td>
<td>86.83 (17.69)</td>
<td>81.11 (21.25)</td>
</tr>
<tr>
<td>Half &amp; Full Rotation [HR+FR]</td>
<td>88.30 (15.99)</td>
<td>86.50 (16.88)</td>
</tr>
<tr>
<td><strong>Reaction Time</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Rotation [NR]</td>
<td>1806.33 (998.86)</td>
<td>2028.61 (696.86)</td>
</tr>
<tr>
<td>Half Rotation [HR]</td>
<td>2367.38 (1181.36)</td>
<td>2481.02 (1110.43)</td>
</tr>
<tr>
<td>Full Rotation [FR]</td>
<td>3341.00 (2145.80)</td>
<td>2879.20 (1530.18)</td>
</tr>
<tr>
<td>Half &amp; Full Rotation [HR+FR]</td>
<td>2854.20 (1628.45)</td>
<td>2680.11 (1268.63)</td>
</tr>
</tbody>
</table>

When turns requiring rotation were combined analysis revealed similar results. There was no significant main effect of group, \( F (1, 33) = 1.71, p = 0.20 \), or time, \( F (1, 33) = 0.23, p = 0.63 \) and no significant interaction between time and group, \( F (1, 33) = 0.02, p = 0.89 \).
Again, there was a significant main effect of turn-type, $F(1, 33) = 14.90, p < .001$, with both 
groups performing less accurately when turns required rotation. There were no significant 
interactions between turn-type and group, $F(1, 33) = 0.46, p = 0.50$, time and turn-type, $F(1, 
33) = 0.12, p = 0.73$, or time, turn-type and group, $F(1, 33) 3.47, p = 0.07$, although this did 
approach significance.

**Reaction Time:** Analysis for the reaction times for the Roadmap test revealed there 
was no significant main effect of group, $F(1, 32) = 1.91, p = 0.18$, no significant main effect 
of time, $F(1, 32) = 0.35, p = 0.56$ and no significant interaction between time and group, $F 
(1, 32) = 0.91, p = 0.35$. There was a significant main effect of turn-type, $F(1.26, 40.40) = 
33.57, p < .001$. Pair-wise comparisons revealed both groups were significantly slower at FR 
and HR turns compared to NR turns (all $p$ values < 0.05). There was also a significant 
interaction between time and turn-type, $F(1.89, 60.35) = 19.04, p < .001$, with pairwise 
comparisons revealing both groups were slower on NR and FR turns at T2 compared with T1 
and faster on HR turns at T2 compared with T1 (all $p$-values < 0.05). There was no 
significant interaction between turn-type and group, $F(1.26, 40.40) = 0.82, p = 0.40$ or 
between time and turn-type and group, $F(1.89, 60.35) = 0.44, p = 0.64$.

Similarly when turns requiring rotation were combined, analysis of reaction times 
revealed no significant main effect of group, $F(1, 32) = 1.87, p = 0.18$, or time, $F(1, 32) = 
1.23, p = 0.28$ and no significant interaction between time and group, $F(1, 32) = 0.80, p = 
0.38$. As expected, there was a significant main effect of turn-type, $F(1, 32) = 44.61, p < .001$, 
with slower reactions times for turns requiring rotation ($p < .001$). There was also a significant 
interaction between time and turn-type, $F(1, 32) = 13.70, p = < .001$, demonstrating 
significantly slower reaction times on turns requiring rotation (HR+FR) at T1 ($p = 0.01$) but 
not at T2. There were no significant interactions between turn-type and group, $F(1, 32) = 
1.55, p = 0.22$ or between time, turn-type and group, $F(1, 32) = 0.63, p = 0.43$. 

102
**Mental Rotation Tasks (Letter and Hand)**

Separate three-way ANOVAs were used to analyse the mean response time and mean accuracy measures for both rotation tasks. Orientation (6 [6 angles of rotation about 360°]), and condition (mirror, normal for the Letter task and left, right for the Hand task) were within subjects factors, and Group (2) the between subjects factor. In keeping with the previous studies (e.g. Hamm, Johnson, & Corballis, 2004; Shepard & Metzler, 1971) and analyses done at T1 (Davison, 2009), data were collapsed across angles that required the same amount of rotation regardless of whether it was in a clockwise or anticlockwise direction. After the data were collapsed about the 180 degrees, planned contrasts were used to test for linear, quadratic and cubic trend components. Again, as in the study analyses conducted at T1 (Davison, 2009), the contrasts involving linear trend component were of primary interest as they indicate differences in rate of rotation. Where no significant contrast effects emerged, only the linear contrast is reported. Note that due to the complexity of the analysis, time was not included as a variable, thus only cross-sectional analyses of the mental rotation tasks are presented.

**Letter Mental Rotation**

*Figure 13* shows that the response time performance of the PreHD and Control groups on the letter mental rotation task exhibits a curvilinear pattern of response times across the degrees of rotation similar to that which has been described in previous studies of mental rotation (e.g. Hamm, Johnson, & Corballis, 2004; Shepard & Metzler, 1971), and to what was demonstrated at T1 (Davison, 2009). Reaction time increases in a curvilinear fashion as the angle of rotation increases from 0 degrees to 180 degrees. The data points for 0 and 360 degrees are identical; however, they were not entered twice in analysis.
Figure 13. Mean response times for Letter F mental rotation task for the PreHD and the Control groups. Error bars indicate the standard error of the mean.

Response time: Analysis of mean response time for the Letter Mental Rotation task revealed there was no significant main effect of group, $F(1, 33) = 0.48, p = 0.49$. There was a significant main effect of condition, $F(1, 33) = 26.69, p < .001$, with both groups taking longer to respond on the mirror condition ($M = 1175.75$, $SE = 67.50$) compared with the normal condition ($M = 1031.59$, $SE = 56.91$). There was, however, no interaction between condition and group, $F(1, 33) = 0.95, p = 0.34$, indicating that the PreHD group was not preferentially slower on either condition compared with the Control group. There was a significant main effect of orientation, both linear, $F(1, 33) = 94.05, p < .001$, and quadratic, $F(1, 33) = 20.53, p < .001$ with pairwise comparisons revealing reaction times increased as a greater degree of mental rotation was required (all $p$-values $< 0.05$). There was, however, no significant interaction between orientation and group, $F(1, 33) = 1.11, p = 0.30$. Analysis revealed a marginally significant interaction between condition and orientation of a quadratic nature, $F(1, 33) = 4.23, p = 0.05$, with pair-wise comparisons indicating reaction times for the mirror
condition were significantly slower than the normal condition on orientations of 0 degrees ($p = 0.01$), 60 degrees ($p = 0.01$), 240 degrees ($p < 0.001$) and 300 degrees ($p < 0.001$) but not orientations of 120 or 180 degrees ($p > 0.05$). There was no significant interaction between condition and orientation and group, $F(1, 33) = 1.59, p = 0.96$.

Figure 14: Mean accuracy on Letter F mental rotation task for the PreHD group and the Control group at time-point 2. Error bars indicate the standard error of the mean.

**Accuracy:** Figure 14 displays mean accuracy on Letter F mental rotation task for the PreHD group and the Control group at each orientation. There was a significant main effect of group, $F(1, 33) = 4.59, p = 0.04$, with the PreHD group ($M= 95.8$, $SE=1.0$) performing significantly less accurately than the Control group ($M= 98.9$, $SE=1.0$). There was a significant main effect of condition, $F(1, 33) = 9.90, p = 0.003$, with performance significantly less accurate when rotating normal stimuli ($M= 96.1$, $SE=1.1$) than when rotating mirror stimuli ($M= 98.6$, $SE=0.4$). The significant interaction between condition and group, $F(1, 33) = 7.89, p = 0.01$, also revealed a less accurate performance rotating the normal stimuli for the PreHD group ($M= 93.4$, $SE=1.5$) compared with Controls ($M= 98.7$, $SE=1.5$) but no difference between groups when rotating mirror stimuli. There was no significant main effect
of orientation, $F(1, 33) = 1.91, p = 0.18$ indicating that there was no difference in accuracy with increasing levels of rotation. There was also no significant interaction between orientation and group, $F(1, 33) = 0.34, p = 0.56$ or between condition and orientation, $F(1, 33) = 0.67, p = 0.42$. There was, however, a marginally significant interaction of a quadratic nature between condition, orientation and group, $F(1, 33) = 4.32, p = 0.05$, with post-hoc comparisons revealing the PreHD group (but not the control group) were significantly less accurate on the normal condition compared to the mirror condition only for rotations of 120 and 180 degrees ($p<0.05$), all other comparisons $p>0.05$.

**Tasks Sensitive to Anterior Brain Regions**

**Hand Mental Rotation**

*Figure 15* shows that the PreHD and Control groups show the expected curvilinear pattern of response time as reported in prior studies (e.g. Hamm, Johnson, & Corballis, 2004; Shepard & Metzler, 1971) and as was seen at T1 within this sample (Davison, 2009).

**Reaction Time:** Analyses of mean reaction times for the Hand Mental Rotation task revealed there was no significant main effect of group, $F(1, 33) = .001, p = 0.98$. The main effect of condition, $F(1, 33) = 4.21, p = 0.05$ was marginally significant, with longer reaction times for the left hand condition ($M=1488.83, SE=73.82$) compared with the right hand condition ($M=1436.87, SE=71.58$). There was a significant main effect of orientation both linear, $F(1, 33) = 252.48, p <.001$, and quadratic, $F(1, 33) = 134.95, p <.001$ with pairwise comparisons revealing reaction times increased as greater degree of mental rotation was required (all p-values <0.05). The analyses revealed no significant interactions between orientation and group, condition and orientation, or between condition, orientation and group (all p-values > 0.05).
**Figure 15.** Mean response times on Hand mental rotation task for the PreHD group and the Control group. Error bars indicate the standard error of the mean.

**Accuracy:** Figure 16 displays mean accuracy on Hand mental rotation task for the PreHD group and the Control group. Analyses for mean accuracy revealed there was no significant main effect of group, $F(1, 33) = 2.47, p = 0.13$, or condition, $F(1, 33) = 1.81, p = 0.19$ and no significant interaction between condition and group, $F(1, 33) = 0.61, p = 0.44$. There was a significant main effect of orientation, both linear, $F(1, 33) 23.65, p <.001$, and quadratic, $F(1, 33) = 11.24, p = .002$, with pairwise comparisons revealing less accuracy with increasing levels of rotation (all $p$-values $<0.05$). There were no significant interactions between orientation and group, $F(1, 33) = 1.00, p = 0.33$, or condition and orientation, $F(1, 33) = 0.48, p = 0.49$. There was, however, a significant interaction between condition, orientation and group, $F(1, 33) = 4.66, p = 0.04$, with pairwise comparisons revealing the PreHD group ($M=79.3, SE=3.7$) was significantly less accurate than the Control group ($M=96.1, SE=3.8$) ($p = <.001$) in the right hand condition only for rotations of 180 degrees, all other comparisons were not significant ($p>0.05$).
Figure 16: Mean accuracy on Hand mental rotation task for the PreHD group and the Control group. Error bars indicate the standard error of the mean.

Stockings of Cambridge

Repeated measures ANOVA’s were used to analyse the two accuracy measures (proportion of perfect solutions and number of excess moves to completion) and the four latency measures (initial thinking time, subsequent thinking time, motor initiation time and motor execution time) of the Stockings of Cambridge task. Problem difficulty level (1-4) and time (T1 and T2) were within-subject factors and group was a between-subject factor.

Perfect solutions and excess moves: Figure 17 displays the mean number of perfect solutions and excess moves for the PreHD and Control groups. There were no significant main effects of group for either the proportion of perfect solutions, $F(1, 33) = 0.16, p = 0.69$, or the number of excess moves, $F(1, 33) = 0.64, p = 0.43$. Similarly, the main effect of time was not significant for the proportion of perfect solutions, $F(1, 33) = 2.34, p = 0.14$, or the number of excess moves, $F(1, 33) = 0.61, p = 0.44$. There were also no significant
interactions between time and group for the proportion of perfect solutions, $F(1, 33) = 1.81$, $p = 0.19$, or the number of excess moves, $F(1, 33) = 2.2$, $p = 0.15$.

![Graph A](image1.png)

![Graph B](image2.png)

**Figure 17.** Displays (A) Proportion of perfect solutions and (B) Mean number of excess moves across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T2.
As expected, there was a significant main effect of problem difficulty for both the proportion of perfect solutions, \( F (2.42, 79.93) = 40.87, p <.001 \), and number of excess moves, \( F (1.76, 57.94) = 61.38 \) \( p <.001 \). The number of excess moves increased (see Figure 17), and the number of perfect solutions decreased (see Figure 17) for both groups with increasing problem difficulty. There were no other significant two- or three-way interactions for either the proportion of perfect solutions or number of excess moves (all \( p \)-values >0.05).

Overall results indicate that the PreHD and Control groups did not significantly differ in either measure of performance accuracy and the PreHD group did not differentially decline over time.

The SOC response time data were not normally distributed. To convert the data to a normal distribution, the data were transformed using a logarithm with base 10. The logarithm transformation was the same as used at T1 (Davison, 2009).

**Initial thinking time:** Analyses of initial thinking times for the Stockings of Cambridge task revealed no significant difference between the PreHD and Control groups, \( F (1, 31) = .005, p = 0.94 \). The main effect of time was marginally significant, \( F (1, 31) = 3.96, p = 0.06 \), with a significant interaction between time and group, \( F (1, 31) = 7.89, p = 0.01 \). Pairwise comparisons revealed the Control group had significantly faster initial thinking times at T2 \( (M= 6501.98, SE=884.12) \) than T1 \( (M= 9101.05, SE=1182.66) \) \( p <.001 \) but the PreHD group’s initial thinking times stayed similar across T1 and T2 \( (p = 0.56) \). No other comparisons were significant. As expected there was a main effect of difficulty level, \( F (2.01, 62.42) = 194.42, p <.001 \). Pairwise comparisons revealed that significant differences existed between all difficulty levels \( (p <.001) \) with initial thinking times increasing across levels of difficulty (see Figure 18). There were no significant interactions between difficulty and group, \( F (2.01, 62.42) = 1.36, p = 0.26 \), time and difficulty, \( F (2.38, 73.67) = 0.10 p = 0.93 \), or between time, difficulty and group, \( F (2.38, 73.67) = 0.10, p = 0.93 \).
**Figure 18.** Initial thinking time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2.

**Subsequent thinking time:** Analyses of subsequent thinking times revealed there was no significant main effect of group, $F(1, 31) = 0.38, p = 0.55$. There was a significant main effect of time, $F(1, 31) = 11.02, p = .002$, with faster subsequent thinking times at T2 ($M=578.30$, $SE=107.99$) than T1 ($M=792.50$, $SE=122.15$). There was, however, no significant interaction between time and group, $F(1, 31) = 0.35, p = 0.56$. As expected,
analysis showed a significant effect of difficulty, $F(2.44, 75.48) = 65.92$, $p < .001$, with pairwise comparisons revealing significant differences between all levels of difficulty (all $p$-values < .05) except between levels four and five ($p > .05$) (see Figure 19). There were no significant interactions between difficulty and group, $F(2.44, 75.48) = 0.60$, $p = 0.59$, time and difficulty, $F(2.45, 75.94) = 1.24$, $p = 0.30$, or between time, difficulty and group, $F(2.45, 75.94) = 0.90$, $p = 0.43$.

Figure 19. Subsequent thinking time (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2
Figure 20. Motor initiation time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2.
The motor control task in the SOC provided the measures of Motor Initiation and Motor Execution times.

**Motor initiation:** There were no significant main effects of group, $F(1, 31) = 2.25, p = 0.14$, or time, $F(1, 31) = 2.30, p = 0.14$, and no significant interaction between time and group, $F(1, 31) = 0.44, p = 0.51$. There was a main effect of difficulty level, $F(3, 93) = 17.84, p <.001$, with pair-wise comparisons revealing significantly slower initiation on level two problems ($M=1625, SE=68.85$) compared to difficulty levels three ($M=1429.51, SE=80.78$), four ($M=1396.70, SE=104.46$) and five ($M=1418.99, SE=133.55$) (all p-values <.05) (see *Figure 20*). No other comparisons were significant. There was no significant interaction between difficulty level and group, $F(2.51, 77.73) = 1.39, p = 0.25$, nor between time, difficulty and group, $F(2.52, 77.73) = 1.31, p = 0.28$.

**Motor execution:** Analyses revealed that motor execution times for the PreHD and Control groups were not significantly different, $F(1, 31) = 0.03, p = 0.86$. There was a significant main effect of time, $F(1, 31) = 9.22, p = 0.01$, with significantly longer motor execution times at T2 ($M=331.78, SE=20.93$) than T1 ($M=283.08, SE=14.73$). There was, however, no significant interaction between time and group, $F(1, 31) = 0.05, p = 0.83$. As with other SoC measures, there was a significant main effect of difficulty, $F(1.97, 61.05) = 230.25, p <.001$ with pair-wise comparisons revealing significant differences between all difficulty levels (all p-values <.001) except between level four and five (p>0.05) (see *Figure 21*). There were no significant interactions between difficulty and group, $F(1.97, 61.05) = 0.72, p = 0.49$, or time and difficulty, $F(2.35, 72.93) = 0.12, p = 0.92$. The interaction between time, difficulty and group was marginally significant, $F(2.35, 72.93) = 2.90, p = 0.05$ with pairwise comparisons revealing the PreHD group took significantly longer on difficulty levels two ($p = 0.01$) and three ($p = 0.05$) at T2 compared with T1 and the Control.
group took significantly longer on difficulty level three (p = 0.02) at T2 compared with T1. No other comparisons were significant.

Figure 21: Motor Execution time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T1 (A) and T2 (B).
A summary of the significant findings across the analyses of the six variables (two accuracy and four latency) in the Stockings of Cambridge are provided in Table 11.

Table 11

Overview of significant findings in the Stockings of Cambridge Analysis

<table>
<thead>
<tr>
<th></th>
<th>Main effect:</th>
<th>Main effect:</th>
<th>Main effect:</th>
<th>Time x Group</th>
<th>DIFF x Group</th>
<th>DIFF x Time</th>
<th>Time x Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockings of Cambridge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfect Solutions (Accuracy)</td>
<td>ns</td>
<td>ns</td>
<td>p &lt;0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Excess Moves (Accuracy)</td>
<td>ns</td>
<td>ns</td>
<td>p &lt;0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Initial Thinking (Latency)</td>
<td>ns</td>
<td>p = 0.06</td>
<td>p &lt;0.001</td>
<td>p = 0.01</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Subsequent Thinking (Latency)</td>
<td>ns</td>
<td>p &lt;0.001</td>
<td>p &lt;0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Motor Initiation (Latency)</td>
<td>ns</td>
<td>ns</td>
<td>p &lt;0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Motor Execution (Latency)</td>
<td>ns</td>
<td>p = 0.01</td>
<td>p &lt;0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>p = 0.05</td>
</tr>
</tbody>
</table>

Note: DIFF = Difficulty, ns = not significant

Mood Assessments

Table 12 provides the means and standard deviations of the HADS Anxiety and Depression and IDAS Inward Irritability and Outward Irritability scales for both groups at T1 and T2. One-way ANOVAs were conducted at T2 to provide an indication of the current mood of the PreHD and Control groups. The PreHD group had significantly higher levels of HADS Anxiety than the Control group, $F(1, 28.86) = 4.85, p = 0.04$. Additionally, the PreHD group significantly higher levels of IDAS Outward Irritability compared to controls, $F(1, 34) = 5.57, p = 0.02$. There were no significant differences between the PreHD and
Control groups on the HADS Depression scale, $F(1, 34) = 0.32, p = 0.56$, or the IDAS Inward Irritability scale, $F(1, 34) = 1.64, p = 0.21$.

**Table 12**

*Means and Standard Deviations of total scores for PreHD and Control groups on the HADS Anxiety and Depression and the IDAS Inward and Outward Irritability scales at T1 and T2.*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Group</th>
<th>PreHD ($n=18$)</th>
<th>Mean (SD)</th>
<th>Control ($n=17$)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS Anxiety</td>
<td>PreHD</td>
<td>6.61 (5.04)</td>
<td>6.78 (4.12)</td>
<td>Control</td>
<td>4.76 (3.68)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4.76 (3.68)</td>
<td>4.18 (2.77)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS Depression</td>
<td>PreHD</td>
<td>3.00 (1.50)</td>
<td>2.89 (2.70)</td>
<td>Control</td>
<td>2.82 (2.01)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2.82 (2.01)</td>
<td>3.41 (2.76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDAS Inward Irritability</td>
<td>PreHD</td>
<td>1.94 (1.59)</td>
<td>2.00 (1.97)</td>
<td>Control</td>
<td>1.06 (1.03)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1.06 (1.03)</td>
<td>1.29 (1.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDAS Outward Irritability</td>
<td>PreHD</td>
<td>3.33 (2.20)</td>
<td>3.67 (1.82)</td>
<td>Control</td>
<td>1.76 (1.44)</td>
</tr>
</tbody>
</table>

Chi Square analyses were conducted to examine whether PreHD participants were more likely than Controls to have abnormal mood scores (mild, moderate or severe ranges) for HADS; and Borderline or Morbid for IDAS). Small cell sizes meant the number of categories to be examined needed to be reduced in order to conduct valid Chi Square analyses. Thus mood scores were categorised as either falling into the ‘abnormal range’, which contained mood scores that fell into mild, moderate or severe ranges (HADS)/Borderline or Morbid (IDAS), or the ‘normal range’. Percentages of participants in each group that had abnormal scores mood scores are displayed in Table 13. Analyses revealed a significant difference between groups for abnormal anxiety, $X^2(1, 35) = 7.44, p = 0.01$, where the proportion of PreHD participants with anxiety scores in the ‘abnormal’ range was
significantly higher than Controls. There was no significant difference between groups in the frequency of abnormal depression, $X^2 (1, 35) = <.001, p = 0.95$, inward irritability, $X^2 (1, 35) = 2.00, p = 0.16$, or outward irritability, $X^2 (1, 35) = 1.91, p = 0.17$.

Table 13  
*Percentage in abnormal range for PreHD and Control groups on the HADS Anxiety and Depression and IDAS Inward and Outward Irritability scales at T2.*

<table>
<thead>
<tr>
<th></th>
<th>PreHD ($n=18$)</th>
<th>Control ($n=17$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HADS Anxiety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in abnormal range</td>
<td>55.6%</td>
<td>11.8%</td>
</tr>
<tr>
<td><strong>HADS Depression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in abnormal range</td>
<td>11.1%</td>
<td>11.8%</td>
</tr>
<tr>
<td><strong>IDAS Inward Irritability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in abnormal range</td>
<td>11.1%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>IDAS Outward Irritability</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in abnormal range</td>
<td>22.2%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

Additional analyses were conducted to assess whether there was evidence of progression in severity of mood symptoms over time. Repeated measures analyses of the HADS anxiety scale revealed a trend towards a significant main effect of group, $F (1, 33) = 3.57, p = 0.07$ with the PreHD group tending to show higher anxiety scores overall. The main effect of time was not significant, $F (1, 33) = 0.10, p = 0.76$ nor was the interaction between time and group, $F (1, 33) = 0.32, p = 0.58$. Results point to higher levels of anxiety in the PreHD group compared to Controls (albeit not significant) across both time-points, but no significant changes in anxiety scores over the time between T1 and T2. HADS depression scale analyses revealed there were no significant main effects of group, $F (1, 33) = 0.07, p = 0.80$, or time, $F (1, 33) = 0.37, p = 0.55$, and no significant interaction between time and group, $F (1, 33) = 0.78, p = 0.38$.  

118
Repeated measures analyses of the IDAS Inward Irritability scale revealed a trend towards a main effect of group, $F (1, 33) = 3.64$, $p = 0.07$, with the PreHD group showing higher inward irritability scores overall. There was no significant main effect of time, $F (1, 33) = 0.26$, $p = 0.61$ and no significant interaction between time and group, $F (1, 33) = 0.10$, $p = 0.76$. Analysis of the Outward Irritability scale revealed a significant main effect of group, $F (1, 33) = 7.88$, $p = 0.01$ with the PreHD showing higher levels of outward irritability overall. There was no significant main effect of time, $F (1, 33) = 1.98$, $p = 0.17$ and no significant interaction between time and group, $F (1, 33) = 0.10$, $p = 0.75$.

**Proximity Group Results**

In order to investigate if the pre-symptomatic HD participants’ performance on the cognitive tasks were affected by estimated years to clinical onset, another set of analyses for all tasks were conducted, this time with the pre-symptomatic proximity groups (PreHDfar, PreHDclose) and Control group.

**UHDRS Cognitive Measures**

Table 14 provides the means and standard deviations of three UHDRS cognitive tasks (Verbal Fluency, Symbol Digit Modalities Test and the Stroop) for the PreHDclose, PreHDfar and Control groups. Analyses of Verbal Fluency scores for the proximity groups revealed a significant main effect of group, $F (2, 34) = 3.58$, $p = 0.04$. Post-hoc comparisons revealed a trend towards a better performance by the PreHDfar group compared to the PreHDclose ($p = 0.07$) and Control groups ($p = 0.07$), but no difference between the PreHDclose and Control group ($p>0.05$). Analysis of SDMT scores revealed a marginally significant main effect of group, $F (2, 34) = 3.43$, $p = 0.05$. No pairwise comparisons were significant although there was a trend towards worse performance by the PreHDclose group.
than the Control group ($p = 0.07$). Analyses of the Stroop trials revealed there was no
significant main effect of group for any of the three trials of Colour, $F(2, 34) = 0.25, p =
0.78$, Word, $F(2, 34) = 0.39, p = 0.68$, or Interference, $F(2, 34) = 1.91, p = 0.16$.

**Table 14**

**Mean scores and standard deviations for UHDRS cognitive tasks for PreHD, Close-to
Onset, Far-from Onset and Control groups at Timepoint-2 (T2).**

<table>
<thead>
<tr>
<th></th>
<th>PreHDClose ($n=9$) Mean (SD)</th>
<th>PreHDFar ($n=9$) Mean (SD)</th>
<th>Control ($n=17$) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Fluency</td>
<td>38.67 (12.07)</td>
<td>50.22 (8.48)</td>
<td>40.12 (10.24)</td>
</tr>
<tr>
<td>SDMT</td>
<td>45.78 (10.19)</td>
<td>56.44 (12.32)</td>
<td>55.59 (8.50)</td>
</tr>
<tr>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour</td>
<td>73.22 (10.23)</td>
<td>73.56 (17.94)</td>
<td>76.47 (11.06)</td>
</tr>
<tr>
<td>Word</td>
<td>92.44 (15.18)</td>
<td>93.89 (23.26)</td>
<td>98.59 (17.35)</td>
</tr>
<tr>
<td>Interference</td>
<td>37.67 (7.79)</td>
<td>47.33 (15.26)</td>
<td>43.53 (8.81)</td>
</tr>
</tbody>
</table>

**Psychomotor Speed Tasks**

Table 15 displays the means and standard deviations for the motor control and
reaction time tasks for the PreHDClose, PreHDFar and Control groups at T1 and T2. Analyses
of the Motor Screen task revealed there was no significant main effect of group, $F(2, 32) =
2.24, p = 0.12$. There was a significant main effect of time, $F(1, 32) = 9.76, p = 0.004$ with
faster response times at T2 ($M= 988.51$, $SE= 42.35$) than T1 ($M= 1150.32$, $SE= 53.73$). There
was, however, no significant interaction between time and group, $F(2, 32) = 1.62, p = 0.26$.
Analyses of reaction time scores revealed there was no significant main effect of group, $F(2,
30) = 1.32, p = 0.28$. There was a significant main effect of time, $F(1, 30) = 106.63, p < .001$,
with responses slower at T2 ($M= 708.28$, $SE =22.93$) than T1 ($M= 480.65$, $SE= 20.56$) but no
significant interaction between time and group, $F(2, 30) = 0.05, p = 0.95$. 

120
Table 15

Mean response times (ms) and standard deviations for Motor Screening and Reaction Time tasks for PreHD and Control groups at Timepoint-1 (T1) and Timepoint-2 (T2).

<table>
<thead>
<tr>
<th>Tasks Sensitive to Posterior Brain Regions</th>
</tr>
</thead>
</table>
| Table 16 displays the mean and standard deviations of accuracy scores (percentage) for the PreHDClose, PreHDFar and Control groups on four of the tasks administered that are sensitive to posterior parts of the brain. Analysis of the Collision Judgements task revealed no significant main effects of group, $F (2, 32) = 0.74, p = 0.49$, nor time, $F (1, 32) = 1.65, p = 0.21$ and no significant interaction between time and group, $F (2, 32) = 0.15, p = 0.86$. For the HVOT, there was no significant main effects of group, $F (2, 32) = 2.17, p = 0.13$ time, $F (1, 32) = 0.14, p = 0.71$ and no significant interaction between time and group, $F (2, 32) = 1.70, p = 0.20$.

Although the main effect of group was not significant for the JLOT, $F (2, 32) = 2.74, p = 0.08$, it did show a trend towards a significant effect. Based upon findings at T1 and subsequent predictions, planned comparisons were conducted, which revealed a trend towards a significant difference between the PreHDClose ($M = 82.96, SE = 3.64$) and Control groups ($M=93.08, SE= 2.65$) ($p = 0.09$). The main effect of time was not significant, $F (1, 32) = 3.33, p = 0.08$, but again showed a trend towards a significant effect with slightly lower accuracy at T2 ($M= 86.26, SE= 2.04$) than T1 ($M= 89.01, SE= 2.10$). There was, however, no significant interaction between time and group, $F (2, 32) = 0.78, p = 0.47$. |
Table 16
Mean and standard deviations of accuracy scores (percentage) for the PreHDclose, PreHDfar and Control groups on the Collision-Judgement test, HVOT, JLOT and Benton Facial Recognition at T1 and T2.

<table>
<thead>
<tr>
<th>Cognitive Task</th>
<th>PreHDclose (n=9)</th>
<th>PreHDfar (n=9)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collision: Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>81.36 (6.52)</td>
<td>83.09 (7.28)</td>
<td>84.05 (5.96)</td>
</tr>
<tr>
<td>T2</td>
<td>79.75 (6.47)</td>
<td>82.59 (5.93)</td>
<td>82.35 (5.19)</td>
</tr>
<tr>
<td>HVOT: Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>89.44 (8.54)</td>
<td>91.48 (8.56)</td>
<td>93.04 (4.65)</td>
</tr>
<tr>
<td>T2</td>
<td>89.82 (6.09)</td>
<td>86.67 (7.55)</td>
<td>93.14 (5.23)</td>
</tr>
<tr>
<td>JLOT: Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>82.96 (14.76)</td>
<td>89.26 (12.11)</td>
<td>94.80 (10.06)</td>
</tr>
<tr>
<td>T2</td>
<td>82.96 (11.60)</td>
<td>84.44 (13.64)</td>
<td>91.37 (10.28)</td>
</tr>
<tr>
<td>Facial Recognition: Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>90.12 (7.86)</td>
<td>86.42 (4.54)</td>
<td>88.23 (7.20)</td>
</tr>
<tr>
<td>T2</td>
<td>85.19 (8.07)</td>
<td>82.72 (7.86)</td>
<td>90.20 (7.04)</td>
</tr>
</tbody>
</table>

Analyses of the Benton Facial Recognition task (Short Form) revealed there were no significant main effects of group, $F (2, 32) = 1.69, p = 0.20$, or time, $F (1, 32) = 2.85, p = 0.10$. Importantly, however, the interaction between time and group, $F (2, 32) = 3.15, p = 0.06$ approached significance, with planned comparisons indicating the PreHDclose group performed worse at T2 compared with T1 ($p = 0.06$) but the PreHDfar and Control groups did not. No other comparisons were significant. The converted long form scores were also analysed, revealing essentially identical results to the Short form analyses.

Roadmap Test

Figure 22, Table 17 and Table 18 display the accuracy scores and response times respectively for the PreHDclose, PreHDfar and Control groups on the Roadmap test at both time-points. Analysis of the accuracy scores for the Roadmap test revealed that the main effects of group, $F (2, 32) = 2.46, p = 0.10$, and time, $F (1, 32) = 0.41, p = 0.53$ and the interaction between time and group, $F (2, 32) = 2.16, p = 0.14$, were all not significant. As
expected, there was a significant main effect of turn-type, $F(1.17, 37.30) = 20.52, p < .001$, with lower accuracy for turns with increasing rotation (all $p$-values < 0.05). There was no significant interaction between turn-type and group, $F(3.33, 37.30) = 1.61, p = 0.21$ but the interaction between time and turn-type, $F(1.54, 49.22) = 2.67, p = 0.09$ showed a trend towards a significant effect. This is further clarified by a significant interaction between time, turn-type and group, $F(3.08, 49.22) = 5.61, p = 0.03$, as can be seen in Figure 22. Pairwise comparisons revealed the PreHDclose group performed significantly less accurately on HR turns than the PreHDfar ($p = 0.02$) and Control groups ($p = 0.04$) at T2 but not at T1, and also performed significantly less accurately on FR turns than the Control group ($p = 0.04$) at T2 but not at T1.

Combining the rotation turns produced similar results. There was no significant main effect of group, $F(2, 32) = 2.50, p = 0.10$, no significant main effect of time, $F(1, 32) = 0.28, p = 0.60$ and no significant interaction between time and group, $F(2, 32) = 1.76, p = 0.19$. Again, there was the expected significant main effect of turn-type, $F(1, 32) = 16.25, p <.001$, but no significant interaction between turn-type and group, $F(2, 32) = 1.78, p = 0.18$, or between time and turn-type, $F(1, 32) = 0.07, p = 0.80$. The interaction between time, turn-type and group, however, did approach significance, $F(1, 33) 3.47, p = 0.07$, reflecting lower accuracy of the PreHDclose group on turns requiring rotation (HR+FR) at T2, than the Control group and PreHDfar groups.
Figure 22. (A) displays accuracy for PreHDbclose, PreHDfar and Control groups on Roadmap test at T1; (B) displays accuracy for PreHDbclose, PreHDfar and Control groups on Roadmap test at T2.
Table 17

Accuracy scores (NR and HR+FR [combined half and full rotation]) for the PreHDclose, PreHDfar and Control groups on the Roadmap Test at time-point-1 (T1) and time-point-2 (T2)

<table>
<thead>
<tr>
<th>Accuracy Scores</th>
<th>T1 Mean (SD)</th>
<th>T2 Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rotation [NR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreHDclose (n=9)</td>
<td>95.10 (7.51)</td>
<td>93.11 (13.32)</td>
</tr>
<tr>
<td>PreHDfar (n=9)</td>
<td>95.78 (5.47)</td>
<td>98.00 (3.00)</td>
</tr>
<tr>
<td>Control (n=17)</td>
<td>99.03 (2.91)</td>
<td>97.18 (7.37)</td>
</tr>
<tr>
<td>Half and Full Rotation [HR+FR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreHDclose</td>
<td>84.97 (18.33)</td>
<td>78.56 (19.38)</td>
</tr>
<tr>
<td>PreHDfar</td>
<td>91.61 (13.51)</td>
<td>94.44 (9.36)</td>
</tr>
<tr>
<td>Control</td>
<td>91.95 (12.10)</td>
<td>92.88 (10.76)</td>
</tr>
</tbody>
</table>

Table 18

Response times for the PreHDclose, PreHDfar and Control groups on the Roadmap Test at time-point-1 (T1) and time-point-2 (T2)

<table>
<thead>
<tr>
<th>Reaction Time (ms)</th>
<th>T1 Mean (SD)</th>
<th>T2 Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Rotation [NR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreHDclose (n=9)</td>
<td>1695.09 (929.71)</td>
<td>1986.50 (582.38)</td>
</tr>
<tr>
<td>PreHDfar (n=9)</td>
<td>1917.57 (1108.13)</td>
<td>2070.71 (829.93)</td>
</tr>
<tr>
<td>Control (n=16)</td>
<td>1442.23 (731.10)</td>
<td>1792.72 (542.48)</td>
</tr>
<tr>
<td>Half Rotation [HR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreHDclose</td>
<td>2273.10 (1203.96)</td>
<td>2508.23 (1141.62)</td>
</tr>
<tr>
<td>PreHDfar</td>
<td>2461.67 (1195.99)</td>
<td>2453.81 (1146.87)</td>
</tr>
<tr>
<td>Control</td>
<td>1746.38 (775.57)</td>
<td>2074.46 (734.72)</td>
</tr>
<tr>
<td>Full Rotation [FR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreHDclose</td>
<td>3240.22 (2167.73)</td>
<td>2835.94 (1558.55)</td>
</tr>
<tr>
<td>PreHDfar</td>
<td>3441.78 (2250.02)</td>
<td>2922.46 (1594.47)</td>
</tr>
<tr>
<td>Control</td>
<td>2560.00 (1288.15)</td>
<td>2420.65 (995.17)</td>
</tr>
<tr>
<td>Half and Full Rotation [HR+FR]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PreHDclose</td>
<td>2756.66 (1664.92)</td>
<td>2672.09 (1286.14)</td>
</tr>
<tr>
<td>PreHDfar</td>
<td>2951.73 (1685.77)</td>
<td>2688.14 (1328.81)</td>
</tr>
<tr>
<td>Control</td>
<td>2153.19 (1017.62)</td>
<td>2247.56 (860.21)</td>
</tr>
</tbody>
</table>
Analysis for the reaction times on the Roadmap test revealed that there was no significant main effect of group, $F(2, 31) = 0.96, p = 0.39$, no significant main effect of time, $F(1, 31) = 0.07, p = 0.80$ and no significant interaction between time and group, $F(2, 31) = 0.57, p = 0.57$. As expected, there was a significant main effect of turn-type, $F(2, 62) = 33.46, p < .001$, where all groups were progressively slower on turns with increasing rotation (all p-values < 0.05). There was also a significant interaction between time and turn-type, $F(1.88, 58.40) = 18.95, p < .001$, demonstrating significantly slower reaction times on NR turns at T2 compared with T1 (p = 0.02) and marginally faster reaction times on FR turns at T2 compared with T1 (p = 0.05). There was no significant interaction between turn-type and group, $F(4, 62) = 0.42, p = 0.80$ or between time and turn-type and group, $F(3.77, 58.40) = 0.27, p = 0.89$.

When rotation turns were combined, the analysis of reaction time revealed very similar results. There were no significant main effects of group, $F(2, 31) = 0.95, p = 0.40$, or time, $F(1, 31) = 0.60, p = 0.44$ and no significant interaction between time and group, $F(2, 31) = 0.52, p = 0.60$. The main effect of turn-type was significant, $F(1, 31) = 45.51, p < .001$, with slower reactions times for turns requiring rotation (NR+FR) (p <.001). Once again the significant interaction between time and turn-type was significant, $F(1, 31) = 14.23, p < .001$, with slower reaction times on NR turns at T2 than at T1 (p = 0.02). There were no significant interactions between turn-type and group, $F(2, 31) = 0.76, p = 0.48$ or between time, turn-type and group, $F(2, 31) = 0.32, p = 0.73$.

**Mental Rotation Tasks (Letter and Hand)**

Three-way ANOVAs were again used to analyse the mean response time and mean accuracy measures, with Orientation (6 angles of rotation about 360°), and condition (mirror and normal) within subjects factors, and Group (PreHDclose, PreHDFar and Control) the between subjects factor.
Letter Mental Rotation

Figure 23 shows that the response time performance of all three groups on the letter mental rotation task exhibits the curvilinear pattern of response times across the degrees of rotation.

![Graph showing response times](image)

Figure 23. Mean response times for the PreHDclose, PreHDfar and Control groups on the Letter F mental rotation task. Error bars indicate the standard error of the mean.

**Response time**: Analyses of mean response time for the Proximity Groups revealed there was no significant main effect of group, $F (2, 32) = 0.24, p = 0.79$. There was a significant main effect of condition, $F (1, 32) = 26.84, p <.001$, with all groups taking longer to respond on the mirror condition ($M=1194.40\text{ms}$, $SE= 71.63\text{ms}$) than the normal condition ($M= 1041.12\text{ms}$, $SE= 60.32\text{ms}$). The main effect of orientation was significant, both linear, $F (1, 32) = 77.74, p <.001$, and quadratic, $F (1, 32) = 19.81, p <.001$ indicating that reaction times increased as a greater degree of mental rotation was required. Analysis also revealed a significant interaction between condition and orientation of a quadratic nature, $F (1, 32) = 5.85, p = 0.02$, with post-hoc comparisons indicating significantly slower reaction times for
the mirror condition only on rotations of 0 degrees, 60 degrees, 240 degrees, and 300 degrees (all p-values <0.05). There were no significant interactions between condition and group, $F(2, 32) = 0.62, p = 0.55$, orientation and group, $F(2, 32) = 0.57, p = 0.57$, or between condition, orientation and group, $F(1, 33) = 1.59, p = 0.96$.

**Accuracy:** Analysis for mean accuracy revealed there was no significant main effect of group, $F(2, 32) = 2.29 p = 0.12$ (see *Figure 24*). There was a significant main effect of condition, $F(1, 32) = 14.83, p <.001$; interestingly with lower accuracy rotating the normal stimuli ($M=95.2, SE=1.1$) compared with mirror stimuli ($M= 98.5, SE= 0.4$). This is further explained by the significant interaction between condition and group, $F(2, 32) = 3.86, p = 0.03$; the PreHDclose and PreHDfar groups performed less accurately when rotating normal stimuli (PreHDclose: $M=93.6, SE=2.0$; PreHDfar: $M=93.2, SE=2.0$) than rotating mirror stimuli (PreHDclose: $M=98.7, SE=0.8$; PreHDfar: $M=97.8, SE=0.8$). There was no significant main effect of orientation, $F(1, 32) = 2.35, p = 0.14$, and no significant interaction between orientation and group, $F(2, 32) = 1.22, p = 0.31$ or condition and orientation, $F(1, 32) = 1.28, p = 0.27$. There was, however, a significant interaction of a quadratic nature between condition, orientation and group, $F(2, 32) = 3.68, p = 0.04$. Pairwise comparisons revealed the PreHDclose group was significantly less accurate in the normal condition only on rotations of 180 degrees ($M=83.6, SE=4.8$) than the Control group ($M=98.8, SE=3.5$) ($p = 0.04$).
Figure 24: Mean accuracy for the PreHDclose, PreHDFar and Control groups on the Letter F mental rotation task. Error bars indicate the standard error of the mean.

Tasks Sensitive to Anterior Brain Regions

Hand Mental Rotation

Figure 25 shows that both PreHD groups and Control group show the expected curvilinear pattern of response time as indicated in prior studies and as was seen at T1 (Davison, 2009). Although the reaction times of the PreHDclose group were slowest, there was no significant main effect of group, $F(2, 31) = 0.85, p = 0.43$. There was a significant main effect of condition, $F(1, 31) = 5.10, p = 0.03$, with longer reaction times when rotating left hands ($M=1486.84ms$, $SE=76.39ms$) than when rotating right hands ($M=1427.36ms$, $SE=75.44ms$). There was a significant main effect of orientation both linear, $F(1, 31) = 226.59, p <.001$, and quadratic, $F(1, 31) = 124.96, p <.001$; reaction times increased as a greater degree of mental rotation was required (all p-values <.001). There were no other significant two-way or three-way interactions (all p-values >0.2).
Figure 25. Mean response times for PreHDclose, PreHDFar and Control groups on the Hand mental rotation task. Error bars indicate the standard error of the mean.

Figure 26 displays the mean accuracy for PreHDclose, PreHDFar and Control groups. Analyses of mean accuracy scores on the Hand rotation task revealed no significant main effects of group, $F(2, 32) = 1.92, p = 0.16$, or condition, $F(1, 32) = 1.07, p = 0.31$ nor a significant interaction between condition and group, $F(2, 32) = 0.65, p = 0.53$. There was a significant main effect of orientation, both linear, $F(1, 32) = 24.48, p <.001$, and quadratic, $F(1, 32) = 13.28, p = <.001$, with significantly less accuracy on orientations of 180° compared than all other orientations (all p-values <.05). There were no other significant two-way or three-way interactions (all p-values >0.1).
Figure 26. Mean accuracy for PreHDclose, PreHDfar and Control groups on the Hand mental rotation task. Error bars indicate the standard error of the mean.

Stockings of Cambridge

Repeated measures ANOVA’s were used to analyse the two accuracy measures (proportion of perfect solutions and number of excess moves to completion) and the four latency measures (initial thinking time, subsequent thinking time, motor initiation time and motor execution time) of the Stockings of Cambridge task.

Perfect solutions: Figure 27 displays the mean number of perfect solutions across the difficulty levels for PreHDclose, PreHDfar and Control groups. There were no significant main effects of group, $F(2, 32) = 0.46, p = 0.63$, or time, $F(1, 32) = 1.04, p = 0.32$ nor a significant interaction between time and group, $F(2, 32) = 0.96, p = 0.40$. As expected, there was a significant main effect of problem difficulty, $F(2.33, 74.59) = 43.70, p <.001$, with the number of perfect solutions decreasing for all groups with increasing problem difficulty (all p-values <.05), except between levels four and five where the difference was not significant.

There was also a significant interaction between difficulty and group, $F(4.66, 75.59) = 3.06,$
p = 0.02. Post-hoc comparisons revealed the PreHDclose group ($M = .53, SE = .07$) had a significantly lower number of perfect solutions on difficulty level four than the PreHDfar group ($M = .78, SE = .07$) ($p = 0.03$) and the Control group ($M = .74, SE = .05$) ($p = 0.04$). There were no significant interactions between time and problem difficulty, $F (2.36, 75.50) = 1.08, p = 0.35$, or time, difficulty and group, $F (4.72, 75.50) = 1.11, p = 0.36$.

**Figure 27.** Proportion of perfect solutions across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T2.

**Excess moves:** A similar pattern of results was found with analysis of the excess moves on the Stockings of Cambridge task (see Figure 28). The effects of group, $F (2, 32) = 1.11, p = 0.34$, time, $F (1, 32) = 0.08, p = 0.79$ and the interaction between time and group, $F (2, 32) = 1.46, p = 0.25$ were all not significant. There was the expected significant main effect of problem difficulty, $F (1.61, 51.35) = 37.52, p <.001$. Pairwise comparisons revealed that although the number of excess moves increased with increasing problem difficulty, it was only significant when level two was compared with levels four and five, and when level three was compared with levels four and five (all p-values <.001) (see Figure 28). There were
no significant interactions between problem difficulty and group, $F (3.21, 51.35) = 5.66, p = 0.19$; time and problem difficulty, $F (1.63, 52.07) = 1.34, p = 0.27$, or time, difficulty level and group, $F (3.25, 52.07) = 0.77, p = 0.52$.

![Figure 28. Mean number of excess moves across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T2.](image)

**Initial thinking time:** Analyses of the transformed initial thinking times revealed the main effects of group, $F (2, 30) = 0.19, p = 0.83$, and time, $F (1, 30) = 0.94, p = 0.34$ were not significant. There was, however, a significant interaction between time and group, $F (2, 30) = 3.97, p = 0.03$ (see Figure 29). Post-hoc comparisons revealed the Control group had significantly ($p <.001$) shorter initial thinking times at T2 ($M=6501.98, SE=895.20$) compared with T1 ($M=9101.05, SE=1201.71$) but the PreHDClose and PreHDfar groups did not. As expected there was a main effect of difficulty, $F (1.85, 55.52) = 179.84, p <.001$. Pairwise comparisons revealed significant differences existed between all difficulty levels (all $p$-values $<.001$) with initial thinking times for all groups increasing with progressing difficulty. There were no significant interactions between difficulty level and group, $F (3.70, 55.52) = 1.79, p$
= 0.15, time and difficulty, $F(2.32, 69.63) = 0.05$ p = 0.97, or time, difficulty and group, $F(4.64, 69.63) = 0.42$, p = 0.82.

Figure 29. Initial thinking time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at T1 (A) and T2 (B)
**Subsequent thinking time:** Analyses of subsequent thinking times revealed there was no significant main effect of group, $F(2, 30) = 1.37, p = 0.27$. There was a significant main effect of time, $F(1, 30) = 8.67, p = 0.01$, with overall faster subsequent thinking times at T2 ($M = 648.87, SE = 111.04$) than T1 ($M = 798.06, SE = 128.07$). There was, however, no significant interaction between time and group, $F(1, 31) = 0.35, p = 0.56$. As expected, there was a significant effect of difficulty, $F(3, 90) = 65.11, p < 0.001$: subsequent thinking times significantly increased (all $p$-values $< 0.05$) with increasing problem difficulty levels except between level four and five (see Figure 30). There were no significant interactions between difficulty and group, $F(6, 90) = 1.99, p = 0.08$, time and difficulty, $F(2.43, 73.74) = 1.17, p = 0.32$, or time, difficulty and group, $F(4.85, 72.74) = 0.70, p = 0.62$.

**Motor initiation:** Analyses of motor initiation times (see Figure 31) for the proximity groups revealed there were no significant main effects of group, $F(2, 30) = 1.10, p = 0.35$, or time, $F(1, 30) = 2.83, p = 0.10$, nor a significant interaction between time and group, $F(2, 30) = 0.44, p = 0.65$. There was a main effect of difficulty level, $F(3, 90) = 15.83, p < 0.001$, with pair-wise comparisons revealing motor initiation times at level two ($M = 1657.08, SE = 73.14$) were significantly longer than all other problem difficulty levels (all $p$-values $< 0.05$). There were no significant interactions between difficulty level and group, $F(6, 90) = 1.10, p = 0.37$, time and difficulty, $F(2.48, 74.45) = 1.99, p = 0.13$ or time, difficulty and group, $F(2.48, 74.45) = 1.58, p = 0.18$. 

135
Figure 30. Subsequent thinking time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2.
Figure 31. Motor initiation time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2.

**Motor execution:** Analyses revealed that motor execution times (see Figure 32) between groups were not significantly different, $F(2, 30) = 0.02, p = 0.98$. There was a significant main effect of time, $F(1, 30) = 9.00, p = 0.01$, with significantly longer motor execution times at T2 ($M=333.98, SE=22.22$) than T1 ($M=285.78, SE=15.40$). As with other Stockings of Cambridge measures, there was a significant main effect of difficulty, $F(1.95, 58.41) = 206.42, p < .001$. Pairwise comparisons revealed significantly shorter motor
execution times on level two and level three compared with all other difficulty levels (all p-values < .001). There were no significant interactions between time and group, $F (2, 30) = 1.92, p = 0.17$; difficulty and group, $F (3.89, 58.41) = 0.57, p = 0.68$; time and difficulty, $F (2.34, 70.33) = 0.35, p = 0.79$ or time, difficulty and group, $F (4.69, 70.33) = 1.48, p = 0.21$.

**Figure 32.** Motor Execution time in milliseconds (ms) across four levels of problem difficulty on Stockings of Cambridge task for PreHD and Control groups at (A) T1 and (B) T2.
An overview of the significant findings for the proximity group analyses across the six variables in the Stockings of Cambridge are provided in Table 19.

Table 19

Overview of significant findings in the Stockings of Cambridge Analysis for proximity groups

<table>
<thead>
<tr>
<th>Stockings of Cambridge</th>
<th>Main effect: Group</th>
<th>Main effect: Time</th>
<th>Main Effect: DIFF</th>
<th>Time x Group</th>
<th>DIFF x Group</th>
<th>DIFF x Time</th>
<th>Time x DIFF x Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfect Solutions (Accuracy)</td>
<td>ns</td>
<td>ns</td>
<td>p &lt; 0.001</td>
<td>ns</td>
<td>p = 0.02</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Excess Moves (Accuracy)</td>
<td>ns</td>
<td>ns</td>
<td>p &lt; 0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Initial Thinking (Latency)</td>
<td>ns</td>
<td>ns</td>
<td>p &lt; 0.001</td>
<td>p = 0.03</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Subsequent Thinking (Latency)</td>
<td>ns</td>
<td>p = 0.01</td>
<td>p &lt; 0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Motor Initiation (Latency)</td>
<td>ns</td>
<td>ns</td>
<td>p &lt; 0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Motor Execution (Latency)</td>
<td>ns</td>
<td>p = 0.01</td>
<td>p &lt; 0.001</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

Note: DIFF = Difficulty, ns = not significant

Mood Assessments

Table 20 provides the means and standard deviations of the HADS Anxiety and Depression and IDAS Inward Irritability and Outward Irritability results for PreHDclose, PreHDfar and Control groups at T2. One-way ANOVAs, conducted to examine current mood of the proximity groups, revealed a significant effect of group on the HADS Anxiety scale, $F(2, 34) = 5.24$, $p = 0.01$. Post-hoc comparisons revealed the PreHDclose group had significantly higher scores than the Control group ($p = 0.01$), and a trend towards higher scores than the PreHDfar group ($p = 0.09$). There was a trend towards a significant effect of group for the IDAS Outward Irritability scale, $F(2, 34) = 2.70$, $p = 0.08$. Planned post-hoc comparisons revealed this was due to the PreHDclose group showing a trend towards higher
outward irritability scores than Controls (p= 0.08). There were no significant effects of group on the Depression scale, $F(2, 34) = 0.39$, $p = 0.68$, or the Inward Irritability scale, $F(2, 14.71) = 0.88$, $p = 0.44$.

Table 20

Means and Standard Deviations of total scores for PreHD and Control groups on the HADS Anxiety and Depression and the IDAS Inward and Outward Irritability scales at T1 and T2.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Group</th>
<th>T1 Mean (SD)</th>
<th>T2 Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PreHD (n=18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control (n=17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>PreHDclose</td>
<td>7.22 (4.84)</td>
<td>8.56 (3.78)</td>
</tr>
<tr>
<td></td>
<td>PreHDfar</td>
<td>6.00 (5.45)</td>
<td>5.00 (3.84)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>4.76 (3.68)</td>
<td>4.18 (2.77)</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>PreHDclose</td>
<td>3.22 (1.30)</td>
<td>3.33 (2.83)</td>
</tr>
<tr>
<td></td>
<td>PreHDfar</td>
<td>2.78 (1.72)</td>
<td>2.44 (2.65)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2.82 (2.01)</td>
<td>3.41 (2.76)</td>
</tr>
<tr>
<td>IDAS Inward</td>
<td>PreHDclose</td>
<td>1.78 (1.56)</td>
<td>2.44 (2.46)</td>
</tr>
<tr>
<td>Irritability</td>
<td>PreHDfar</td>
<td>2.11 (1.69)</td>
<td>1.56 (1.33)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1.06 (1.03)</td>
<td>1.29 (1.16)</td>
</tr>
<tr>
<td>IDAS Outward</td>
<td>PreHDclose</td>
<td>3.44 (2.04)</td>
<td>3.67 (2.12)</td>
</tr>
<tr>
<td>Irritability</td>
<td>PreHDfar</td>
<td>3.22 (2.11)</td>
<td>3.67 (1.58)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>1.76 (1.44)</td>
<td>2.29 (1.61)</td>
</tr>
</tbody>
</table>

Chi Square analyses, examining those falling into the ‘abnormal range’ or the ‘normal range’ across the mood scales (see Table 21) revealed a significant difference between groups for abnormal anxiety, $X^2 (2, 35) = 11.39$, $p < 0.001$, where the proportion of PreHDclose and PreHDfar participants with anxiety scores in the ‘abnormal’ range was higher than the Control group. Additionally, there was a marginally significant difference between groups for frequency of abnormal inward irritability scores, $X^2 (2, 35) = 6.13$, $p = 0.05$, where the proportion of PreHDclose participants with abnormal inward irritability scores was significantly higher than the PreHDfar and Control groups. There was no significant
difference between the groups in the frequency of abnormal depression, \( X^2(2, 35) = .001, p = 0.99 \), or outward irritability, \( X^2(2, 35) = 1.91, p = 0.39 \).

Table 21

*Percentage in abnormal range for PreHD and Control groups on the HADS Anxiety and Depression and IDAS Inward and Outward Irritability scales at T2.*

<table>
<thead>
<tr>
<th></th>
<th>PreHDclose (n=9)</th>
<th>PreHDFar (n=9)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS Anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in abnormal range</td>
<td>77.8%</td>
<td>33.3%</td>
<td>11.8%</td>
</tr>
<tr>
<td>HADS Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in abnormal range</td>
<td>11.1%</td>
<td>11.1%</td>
<td>11.8%</td>
</tr>
<tr>
<td>IDAS Inward Irritability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in abnormal range</td>
<td>22.2%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>IDAS Outward Irritability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% in abnormal range</td>
<td>22.2%</td>
<td>22.2%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

Repeated measures analyses of the HADS anxiety scale revealed a trend towards a significant main effect of group, \( F(2, 32) = 2.94, p = 0.07 \). Planned post-hoc comparisons revealed the PreHDclose group (\( M=7.89, SE=1.14 \)) had marginally higher anxiety scores than the Control group (\( M=4.47, SE=0.83 \)) (\( p=0.06 \)). The main effect of time was not significant, \( F(1, 32) = 0.02, p = 0.90 \), nor was the interaction between time and group, \( F(2, 32) = 0.96, p = 0.39 \). For the Depression scale, there were no significant main effects of group, \( F(2, 32) = 0.29, p = 0.75 \), or time, \( F(1, 32) = 0.09, p = 0.77 \), and no significant interaction between time and group, \( F(2, 32) = 0.46, p = 0.63 \).

Repeated measures analyses of the IDAS Inward Irritability scale revealed no significant main effects of group, \( F(2, 32) = 1.89, p = 0.17 \), or time, \( F(1, 32) = 0.16, p = 0.70 \) and no significant interaction between time and group, \( F(2, 32) = 1.28, p = 0.29 \). There was a significant main effect of group, \( F(2, 32) = 3.83, p = 0.03 \) for Outward Irritability scores. Post-hoc comparisons revealed this reflected a trend (\( p = 0.08 \)) towards higher
outward irritability scores in the PreHDclose group ($M=3.56$, $SE=0.52$) than the Control group ($M=2.03$, $SE=0.38$). There was, however, no significant main effect of time, $F (1, 32) = 1.51$, $p = 0.23$ and no significant interaction between time and group, $F (2, 32) = 0.08$, $p = 0.92$. 
Chapter 4: Discussion

The purpose of this study was to re-examine the neuropsychological performance of a sample of individuals pre-symptomatic for HD, who had been initially assessed three years earlier. At the initial assessment this PreHD sample underwent MRI scanning which revealed evidence of significant cortical thinning (Davison, 2009). The thinning was not uniform, however, but was significant in posterior cortical regions, with unremarkable cortex in anterior regions. Tasks that are sensitive to the integrity of posterior cortical regions were selected during the initial study to see if this regional cortical thinning was affecting cognitive functions associated with these regions. Tasks reliant on anterior cortical regions were also administered in order to provide a comparison. The initial study found that the PreHD sample performed more poorly than Controls on two of the tasks sensitive to the integrity of posterior cortical regions (JLOT, Roadmap test) and showed a trend towards poorer performance on a third task (HVOT), while showing an unremarkable performance on tasks sensitive to anterior cortical regions.

The supposition is that these posterior cortical changes are caused by the HD gene, and therefore reflect some form of underlying pathology, and are likely to have functional consequences. The study reported in this thesis sought, through a longitudinal investigation, to examine if the cognitive test findings seen at the baseline assessment were detecting genuine differences between PreHD and Control participants at the initial assessment; and were thus potentially detecting functional consequences of the cortical thinning reported in our sample. If this is the case, then we should be able to replicate the pattern of test performance seen three years ago, and decline in performance would also likely emerge as the group of PreHD participants’ progress towards clinical onset. At this second assessment point, we predicted the PreHD group would perform more poorly on the JLOT, Roadmap test
and HVOT, significantly differentiating them from matched Controls; and the PreHD group would potentially show poorer performance than Controls on the other cognitive tasks sensitive to posterior cortical regions. We predicted we would see evidence of decline on the posterior tasks over the three year period as the PreHD sample neared clinical onset, based on the logic that those closer to clinical onset would have increasing neuropathology and thus show greater decline. Additionally, we expected that the PreHD group would again show an unremarkable performance compared to Controls on tasks sensitive to anterior brain regions.

Consistent with these predictions, the PreHD group performed worse than the matched Control group on three of the six tasks sensitive to posterior cortical function (JLOT, Roadmap test and Benton Facial Recognition) and showed a trend towards poorer performance on the HVOT. There was also evidence of deterioration in the performance of PreHD group over the three-year period on the Roadmap test and the Benton Facial Recognition task. As expected, PreHD participants generally did not perform more poorly than the Control group on measures sensitive to anterior functions.

**Significant Findings from “Posterior Cortical” Tasks**

Performance of the PreHD group on the JLOT was worse overall than that of the Control group, and was marginally more pronounced in the PreHDClose group. This was consistent with findings three years ago. The persistent, and therefore reliable, between-group difference indicates the performance of this PreHD group is genuinely poorer than matched Controls on the JLOT. Poorer performance of our PreHD group on the JLOT suggests subtle visuospatial perceptual deficits, as this is a basic task of perceiving and matching lines at different angles. Brain regions shown to be important in JLOT performance from fMRI studies are occiptio-temporal regions and the right parietal lobe, with particular emphasis in the superior parietal lobe (Ng et al., 2000). The right parietal-temporal occipital junction, as well as portions of the inferior parietal cortex, were some of the regions shown as thinned at
the initial assessment. Thus the general location of regions identified as thinned in this pre-
symptomatic HD group are in-line with crucial brain regions implicated in performance of
this task. Other studies using this task have not detected significant differences in their pre-
symptomatic HD samples (Blackmore et al., 1995; Gomez-Anson et al., 2009; Soliveri et al.,
2002). In two studies, however, the controls were not matched for education (Gomez-Anson
et al., 2009; Soliveri et al., 2002) and the other had a smaller sample of 13 pre-symptomatic
and 17 controls (Blackmore et al., 1995), which, while marginally smaller in numbers to our
study, could have resulted in insufficient power to detect differences.

As symptomatic HD participants are known to show impairments in this test
(Lineweaver et al., 2005; Soliveri et al., 2002), we predicted the performance of our PreHD
group would decline over time. Although the PreHD group performed more poorly at the
second time-point, they did not decline differentially relative to the Control group, whose
performance was also poorer at the second time-point. This decline of both groups may
indicate that this task could be sensitive to aging.

The Roadmap test assesses egocentric mental rotation and left-right discrimination.
As seen at the first assessment, the performance of the PreHD group at the second assessment
was comparable to that of the Control group in terms of accuracy and speed. At first glance,
these findings appear to support others who failed to find significant differences between pre-
symptomatic HD and control groups (e.g. Brandt et al., 2002; Bylsma et al., 1992;
Campodonica et al., 1996) suggesting that the Roadmap test measures functions that do not
decline until later in the disease process. Brandt et al. (2002), however, found that when they
split their pre-symptomatic sample into proximity groups, the close-to-onset group (less than
8.11 years) were impaired on the Roadmap test, and this effect remained after controlling for
motor signs and age. Similarly, when Snowden et al. (2002) looked at proximity groups, they
found a trend towards their close-to-onset group (less than 5 years) performing worse than
their far-from-onset group (greater than 10 years). Our data also revealed a novel finding once the PreHD sample were split into proximity groups: The PreHDClose group performed less accurately on the second testing occasion than on the initial testing, but only on turns requiring rotations (either half or full rotations) compared with the PreHDFar and Control groups. This suggests that the decline in performance was due to demands for egocentric mental rotation. As they had no difficulty on turns requiring no rotation, this finding is unlikely to reflect difficulty with left-right discrimination. This suggests that difficulties in egocentric mental rotation may begin to emerge as individuals come within 12 years of estimated clinical onset. Regions of cortical thinning seen in our sample at the initial assessment are in-line with two regions implicated in task performance for tests of egocentric mental rotation, namely the parieto-occipito-temporal junction and the inferior parietal lobes (Creem-Regehr, Neil, & Yeh, 2007; Zacks, Vettel, & Michelon, 2003). It is possible, therefore, that performance on the Roadmap seen for this sample is a consequence of the cortical thinning in our sample.

The Roadmap test has failed to show decline in pre-symptomatic HD in other studies (Campodonica et al., 1996; Brandt et al., 2008). The modified version of the Roadmap test used in this study may be more sensitive in its ability to detect changes because the test is administered twice (normal and inverted versions); offering higher numbers of half, full and no rotation turns, providing greater power to the task. Additionally, some studies have not examined accuracy separately for the different types of turns (half, full, etc.); rather have measured general accuracy which may be less sensitive (Bylsma et al., 1992; Campodonica et al., 1996). Like this study, significant findings have only been found in previous studies once participants were split into proximity groups (Brandt et al., 2002; Snowden et al., 2002).

Deficits in performance on the Roadmap test (Bylsma et al., 1992; Lineweaver et al., 1999; Snowden et al., 2001) and a similar street map test (Mohr et al., 1991; Mohr et al.,
1997) have been reported in symptomatic HD, and Snowden et al. (2001) suggests that the Roadmap test is robust enough to detect accuracy deficits even when controlling for motor slowing. Thus, given deficits are prevalent in symptomatic HD on this measure, our findings suggest that decline in egocentric mental rotation ability begins in the pre-symptomatic stages of HD.

The Benton Facial Recognition Test assesses visual perception of unfamiliar faces. Three years ago the PreHD group performed comparably to the Control group, but on this occasion the PreHD group’s performance declined, while the Control group’s level of performance was unchanged. When the performances of the proximity groups were analysed, this revealed the decline in performance was only seen in the PreHDclose group. The perception of unfamiliar faces has been previously reported as undisturbed in pre-symptomatic HD (Aviezer et al., 2009; Diamond et al., 1992; Sprengelmeyer et al., 2006), and even showed no decline over a 6-month and 12-month period (Sprenglemeyer et al., 2006). These studies, however, either did not have age, gender or education-matched controls; or no information was provided regarding the proximity to clinical onset of these prodromal groups. Thus, participants in these studies may have been further from estimated clinical onset, at a point where impairments in face perception are not yet manifest. Failure to show decline over 6 and 12 months in Sprenglemeyer et al.’s study may be due to these reasons, and additionally may be related to the short follow-up time, in which pathological changes may be minimal and where there is a risk of practice effects. Stout et al. (2011), however, found effects on this task once they stratified their pre-symptomatic participants into proximity groups. They found that their near- (less than 9 years to onset) and mid-to-onset groups (9-15 years to onset) showed deficits on this task, but their far-from-onset group (greater than 15 years to onset) did not. Our findings of deficits on the Benton Facial
Recognition task, particularly in our close to onset group, are consistent with the findings reported by Stout et al. (2011).

Deficits on the Benton Facial Recognition test have been reported in symptomatic HD groups (Henley et al., 2008; Jacobs et al., 1995). Poorer performance on this task in this study suggests that a deficit of visual perception of unfamiliar faces possibly begins in the pre-symptomatic stages of HD. Occipito-temporal regions, mainly in the right hemisphere, are shown to be important in being able to perceive faces, as well as inferior occipital and superior temporal regions which are shown to be activated in this task (see Appendix A). While not all these regions showed significant thinning in this sample three years ago, there was significant thinning in occipito-temporal regions, and pathology may have progressed in key regions for this task, resulting in the deficits seen at this assessment.

Visual scanning difficulties may have also contributed to poorer performance on this task, where participants may have tended to focus on one particular feature of the face in order to make their response choice from the multi-choice options. This observation was made in a pre-symptomatic group when identifying facial expressions of emotion (Henley et al., 2008). While identifying emotional expressions recruits different circuitry than in unfamiliar face perception, this behavioural tendency may also be present in more basic face perception, particularly when participants are required to select faces of different angles and shadows of the stimulus face. This portion of the task is hardest and was where the PreHD participants experienced difficulty.

The HVOT assesses both visuo-spatial integration and object recognition. Our results showed a trend towards the PreHD group performing worse than Controls, which was also seen at the baseline assessment. The persistence of this effect over time suggests that our PreHD is subtly worse than our Control group on this task, despite the near ceiling effects seen at both assessment time-points. Not many studies have examined performance of pre-
symptomatic HD individuals on this task, although Gomez-Tortoza et al. (1996) found no
deficits in their pre-symptomatic group compared to controls, again reporting a ceiling effect
in the scores. Their early symptomatic HD group did, however, show deficits on this task.
From observation, the HVOT lacks adequate progression in difficulty, making the overall
task fairly easy to complete. In this study both PreHD and Control participants identified
most of the objects with little effort, but it was clear that some PreHD participants struggled
on some items in the task. Many brain injured persons perform well on the HVOT according
to Wetzel and Murphy (1991), which may be an indication that the task lacks sensitivity.
Subtle lowering of performance seen on this task may reflect mild problems with perceptual
integration or alternatively may be due to disruption of other aspects of basic visual
perception that are required for this task. Bilateral activation of the superior and lateral
occipital lobes and the posterior superior parietal lobe is seen in fMRI studies using this task
(Moritz, Johnson, McMillan, Haughton, & Meyerand, 2004). One of these regions (lateral
occipital lobe) was shown to have significant cortical thinning in our sample three years ago.
Moritz et al. (2004) report that the lateral occipital lobe subserves object identification in this
task. It remains possible, therefore, that the performance of the PreHD group is reflecting
subtle perceptual deficits, such as object identification, resulting from thinning in the lateral
occipital lobe.

We also see that the PreHD group showed a less accurate performance on the Letter
Mental Rotation task. While this lends support to our predictions, it seems that there was a
tendency for the PreHD group to have difficulty on trials that required rotations of 180
degrees and 120 degrees only. It may be that participants had a tendency to ‘flip’ the letter F
in these orientations to achieve their answer, leading to poorer accuracy overall. The mental
rotation function, however, shown for the PreHD group is normal, and not different from the
Control group, suggesting that there is no evidence to indicate a significant issue in this task.
Overall, the findings on tasks that involve posterior regions of cortex indicate that reliable differences are being detected between our PreHD sample and Controls, with two of these tasks showing evidence of decline in function. Given the regions that showed cortical thinning in the PreHD sample at the first assessment, and their relation to the areas crucial for performance of the task where the pre-symptomatic participants exhibited poorer performance, it is likely that differences detected in both the initial and current assessments reflect functional consequences of this thinning. When the analysis of MRI scans for this sample (PreHD and Control) conducted at this second time-point are completed, it will provide information as to whether and how cortical thinning has progressed, and will shed further light onto whether it is likely that cortical changes are contributing to the cognitive changes being witnessed. For all the tasks discussed above, replication of these findings in larger samples with matched controls and longitudinal design needs to occur in order to ensure that the findings seen are not specific to this sample. If these findings are shown to be robust, then these tasks may be significant contenders for successful cognitive biomarkers.

**Lack of Decline on “Posterior Cortical” Tasks**

Although we found sustained differences in cognitive tasks across time, no decline in performance was observed for two these tasks (JLOT, HVOT) on which the PreHD group performed more poorly, or showed a trend towards poorer performance, than Controls at the first assessment. The possible reasons for this are numerous. As argued by Tabrizi et al. (2012), plasticity of the brain may make decline in function harder to detect, as neural compensation may keep the level of cognitive function steady, even using different networks to achieve this. Alternatively, it may be that the pathology underlying the cortical thinning has not progressed significantly in regions recruited during performance of these tasks, but has remained relatively constant since the baseline assessment. Whether or not this is the case may be clearer once it is possible to examine the MRI data collected for this group at the
second time-point. Additionally, it could be that these two tasks are insufficiently sensitive to detect insidious decline, as changes in function are more subtle in pre-symptomatic HD as the pathological processes are at their beginnings.

Findings from “Anterior Cortical” Tasks

Our predictions were generally correct with regards to the PreHD group’s performance on tasks sensitive to dysfunction in anterior cortical regions. Overall, our PreHD participants did not show significant differences compared to Controls on tasks sensitive to anterior brain regions, and this was also apparent for analyses of the proximity groups. There was, however, some indication that those close-to-onset experienced mild difficulty on some components of the SoC. The PreHD close group performed worse on problems at difficulty level four for perfect solutions and approached significance for the same difficulty level for subsequent thinking. It is speculated that either one problem within that difficulty level was particularly challenging, or there was a jump in difficulty from the level prior that caused this effect. This is because this difference can be witnessed graphically at both the first and second assessment for these measures and this effect was not witnessed to the same extent on the harder difficulty level five. The pattern of effects observed may of course reflect the subtle beginnings of frontostriatal-disruption for those nearing clinical onset of HD. Overall, however, across the SoC and Hand Mental Rotation task, results do not point to any major differences in task performance between PreHD and Control groups. Had the data not been lost from the Iowa Gambling task, there would have been broader testing of anterior cortical functions. It must be acknowledged that tasks of anterior cortical function are less well represented in this study, limiting conclusions. Nonetheless, the consistency of our findings does suggest that functions tested by the tasks selected to recruit anterior brain regions are not significantly affected in pre-symptomatic HD.
**Motor Speed and Psychomotor Performance**

Results from the psychomotor speed tasks showed that the PreHD participants were marginally slower compared to Controls on the Motor Control task, however, both groups were significantly faster at this second assessment than they were three years ago. This is likely to reflect a practice effect, as participants may have been more familiar with the testing process/using the touch screen and may have felt more confident in the completing this task (as it was the first task in the testing procedure at both time-points). The PreHD and Control groups did not perform differently on the Reaction Time task, however, both groups were slower at the second assessment than they were at the first assessment. Rather than indicating slowing of reaction times in both groups, this difference is likely to reflect an administration difference; where participants at the first assessment were told to hover their finger near the screen to respond but this was not stated explicitly at the second assessment.

Previous findings are mixed: Some report slowing (Giordani et al., 1995; Kirkwood et al., 2000; Talbrizi et al., 2010), and others no slowing on motor speed tasks in pre-symptomatic HD participants compared to controls over time (Brandt et al., 2008). Decline in motor speed appears not to be detectible over short time frames such as 12 months (Tabrizi et al., 2011), but is detectible over longer periods (e.g. 10 years) and is most apparent in those close to clinical onset (Maroof et al., 2011; Solomon et al., 2008). Our findings suggest that the motor speed of our PreHD group was not significantly different from the Controls. Brandt et al. (2002) also found that while their pre-symptomatic HD group showed subtle motor symptoms (as assessed by QNE) these signs did not distinguish their motor speed from controls. Additionally, even when controlling for motor symptoms, they still showed selective cognitive impairments. While we did not control for motor symptoms in our analyses, it suggests that the poorer cognitive performance and decline in performance of the PreHD group witnessed in this study is not necessarily associated with motor symptoms or
motor speed ability, particularly given the main findings were on tasks that did not test speed of response or psychomotor speed.

**Findings from UHDRS Cognitive Tasks**

Three cognitive tasks from the UHDRS were added in order to enhance comparability of our sample and those in other HD studies. We found that the PreHD group did not perform differently than Controls on any of the three UHDRS cognitive tasks (Verbal Fluency, SDMT and Stroop). This is broadly consistent with findings of other studies involving pre-symptomatic HD samples (Brandt et al., 2002; Gomez-Anson et al., 2007; Talbrizi et al., 2010; Witjes-Ane et al., 2007). There have, however, been findings contradictory to ours, most notably poorer performance on Word and Colour trials of the Stroop, which we did not see (Paulsen, Zhao, et al., 2001). The Stroop Word and Colour trials are more basic assessments of psychomotor ability, and suggest that our group are generally not showing difficulties with basic psychomotor function. A trend, however, in our data became apparent when we examined the proximity groups, such that the PreHDclose group exhibited lower scores, albeit not significantly lower, on the SDMT. Deficits on the SDMT for pre-symptomatic HD have been found, especially in those groups close to disease onset (Brandt et al., 2002; Hahn-Barma et al., 1998; Maroof et al., 2011; Paulsen, Zhao et al., 2001). The SDMT task also examines psychomotor speed, however, its level of complexity is greater than the Stroop Colour and Word trials. It could be that the close-to-onset group had a subtle level of psychomotor slowing or processing speed deficits that were picked up by this task.

Lastly, the tasks of Verbal Fluency and Stroop interference trial both tap into executive functions. The pre-symptomatic group did not show poorer performance on these tasks, and in the case of Verbal fluency, the PreHDFar group showed a trend towards better performance than Controls. Thus, even though we acknowledge the dearth of tasks sensitive
to anterior cortical function, these findings support that our group are not showing difficulties on tasks that are dependent on functions associated with anterior cortical regions.

**Findings from Mood Assessments**

Our examination of current mood revealed this sample of individuals pre-symptomatic for HD had higher levels of anxiety than Controls, largely due to elevated levels of anxiety in the PreHDclose group, although there was a trend for the PreHDFar group to exhibit this also. Furthermore, 77.8% of the PreHDclose group exhibited abnormal anxiety scores, while only 33.3% and 11.8% of PreHDFar and Controls exhibited abnormal scores respectively. Higher levels of outward irritability were also present in the PreHD group, and again, it was the PreHDclose group who accounted for much of this. In contrast there were no differences between the PreHD and Control groups on measures of depression and inward irritability. It is important to note that those who had abnormal mood scores generally fell in the mild (HADS) or borderline (IDAS) category, with a few participants falling into the moderate category. Thus while these findings indicate that significant mood changes of irritability and anxiety are present in the pre-symptomatic stages of HD, particularly in those close to motor onset, it is unlikely that the elevation of mood was enough to result in significant adverse impacts on neuropsychological task performance.

The study of anxiety symptoms seems to receive little attention compared to other affective disorders in pre-symptomatic HD (Anderson, 2011), and thus anxiety is not always reported as a significant psychiatric symptom in HD (Novak & Tabrizi, 2011; Thompson et al., 2012). Nonetheless, anxiety is still a psychiatric disturbance reported in both pre-symptomatic HD and symptomatic HD (Duff et al., 2007; Kirkwood et al., 2002a; Paulsen, Ready et al., 2001). Greater anxiety in those individuals close to clinical onset may be a response to experiencing more signs associated with the onset of HD, but may also be a consequence of pathology (Julien et al., 2007). The presence of this symptom deserves
further attention in future studies, as mood changes are proposed to be some of the earliest outward manifestations of neural pathology in HD (Duff et al., 2007) and further investigation is important to understand when anxiety presents in the pre-symptomatic stages.

The presence of outward irritability in our pre-symptomatic HD sample is consistent with a number of other findings (Kirkwood et al., 2002a; Mendez, 1994; Kloppel et al., 2010), including those that suggest irritability is greater in those closer to clinical onset (less than 10 years) (Julien et al., 2007). Irritability may be due to frustration at subtle cognitive and motor changes that may be experienced more by those nearing onset of the disease (Marshall, 2004). Outward irritability may also, however, be a manifestation of depression in Huntington’s Disease (Rosenblatt et al., 2007) or could be an expression of pent-up anxiety. Additionally, signs of irritability may also reflect personality change reported in HD (Marshall, 2004; Naarding et al., 2001; Paulsen, Ready et al., 2001), which is proposed to result from frontal dysfunction, presenting in a cluster of symptoms of aggression, irritability and apathy (Rosenblatt et al., 2007). Julien et al. (2007) note that irritability symptoms may appear up to 10 years before clinical onset, and suggest that it could be the earliest detectible mood alteration in prodromal HD. In support of this, irritability was the only mood alteration able to be detected in this PreHD sample three years earlier (Davison, 2009).

Depression is a common symptom in HD (Epping & Paulsen, 2011), reported in both symptomatic HD (De Marchi & Mennella, 2000; Naarding et al., 2001; Paulsen et al., 2005) and pre-symptomatic HD (Duff et al., 2007; M. Smith et al., 2012). Depression was previously suspected to be the first detectible change in prodromal HD (Duff et al., 2007; Unschuld et al., 2012), however, recent evidence suggests that depression may be highly prevalent when individuals are very close to disease onset and then again at Stage 2 of HD (Epping & Paulsen, 2011; Julien et al., 2007). The PreHD sample in this study had no significant elevation of depressive symptoms relative to Controls, even when the PreHDClose
group were examined. Other studies have also failed to find depression in pre-symptomatic HD samples (Campdonico et al., 1996; Tabrizi et al., 2009); and in a recent evaluation of neuropsychiatric symptoms, depression was the least prevalent symptom among symptomatic HD (Thompson et al., 2012).

Our longitudinal data show that none of the mood measures progressed in severity over the past 3 years. Anxiety levels were not significantly higher in the PreHD group than Controls three years ago, although, they were at the current assessment. It seems, however, that this change was not large enough to create a significant increase in anxiety levels of the PreHD group compared to Controls over this time, likely because there was a non-significant elevation of anxiety at the first assessment.

The findings of elevated outward irritability were consistent across time and add to the evidence that the presence of this symptom may be one of the earliest indicators of change related to pathology in pre-symptomatic HD (Julien et al., 2007; Kloppel et al., 2010). Kirkwood et al. (2002a), however, additionally found an increase in irritability over a four year period in their pre-symptomatic group, which our study was unable to show. Duff et al. (2007) note that more longitudinal studies of mood changes in pre-symptomatic HD are needed. If mood changes may be the first signs indicative of pathological change in the pre-symptomatic HD brain (Julien et al., 2007; Unschuld et al., 2012), then detailed measurement of these changes needs to occur.

**Summary of Findings**

In summary, our PreHD sample performed more poorly than Controls on three tasks sensitive to posterior cortical regions (JLOT, Roadmap test & Benton Facial Recognition), and showed a trend towards poorer performance on a fourth task (HVOT). Additionally, performance on two of these tasks (Benton Facial Recognition & Roadmap test) significantly declined over the three-year interval between assessments. Overall, these findings indicate
that our selected tasks reliably detected poorer performance of the PreHD group compared to Controls, as group differences were detected at two time-points, three years apart. These findings suggest that the cortical thinning witnessed for this group three years ago is affecting related cognitive functions in our sample. It is possible that the decline in performance evident on two of these tasks may be related to progression of cortical thinning in our sample over the last three years but analyses of the MRI scans of this sample need to be completed to test this prediction. As expected, our tasks selected to recruit anterior regions of cortex generally did not differentiate our PreHD sample from Controls. The consistency of findings from tasks selected to recruit posterior regions and anterior regions from the first assessment, then again three years later, supports the claim that posterior cortical changes are likely to occur prior to anterior cortical changes in pre-symptomatic HD (Rosas et al., 2005).

Anxiety and outward irritability were elevated in our PreHD group, and more so in those close-to-onset. While these mood states did not increase over time, the findings indicate that mood changes occur relatively early in pre-symptomatic HD and lend support to the view that irritability may be the first detectible mood change, and indicate that anxiety is another mood change to be given more attention in future investigations.

Both our cognitive and mood findings suggest potential biomarkers worthy of further investigation. Relevant considerations regarding this study, the implications of findings and future directions are discussed below.

Inclusion of Participants who ‘Converted’ to Symptomatic

The two participants who became symptomatic during the three year interval were included in all analyses. This was done because the aim of the study was to evaluate performance of a pre-symptomatic sample over time, tracking changes that occur as these individuals approach symptomatic onset of the disease. Previous longitudinal studies of pre-symptomatic HD participants also include those individuals who converted to symptomatic
status during the course of the study (Paulsen et al., 2001; Solomon et al., 2008; Talbrizi et al., 2011; Talbrizi et al., 2012). Our results indicate that the PreHDclose group were often large contributors to effects seen, as proximity group analyses primarily revealed differences involving the PreHDclose group. Thus, a critique could be that given the small sample size, the inclusion of symptomatic participants was the cause of these effects. Examination of the data, however, revealed that the test scores of the symptomatic participants did not fall outside of the range of other members of the PreHDclose group. Additionally, the scores of the symptomatic participants were not the lowest for tasks where the PreHDclose group performed significantly poorer.

In general our findings show that the most pronounced decline in task performance was mostly witnessed with the PreHDclose group. Those close to disease onset show greater levels of brain changes compared to those further from disease onset, and consequently changes in cognitive domains also become more apparent and striking the closer participants are to disease onset (Campodonico et al., 1996; Farrow et al., 2006; Maroof et al., 2011; Paulsen et al., 2001; Paulsen et al., 2008; Solomon et al., 2008). It may seem contradictory then that our two symptomatic participants were not the worst performers in our sample, but variation in disease presentation and individual differences are likely to account for this. Our general finding of poorer performance in our PreHDclose group is consistent with current research. The contribution of our findings, however, is not that we detected change in those close-to-onset, but rather that we showed evidence of sustained differences and decline on visuo-spatial functions, a relatively under-researched area of cognition not at the forefront of investigations for potential cognitive biomarkers in HD (Papp et al., 2011; Stout et al., 2011).
Reflection on Findings

Our findings are novel in a number of ways. Notably, our PreHD group performed more poorly than Controls on four of the six tasks selected to recruit posterior brain regions used in this study. This is impressive given many other studies of pre-symptomatic HD individuals find it very difficult to detect any differences even when using large batteries of tests (Papp et al., 2011). In a recent review of cognitive studies in pre-symptomatic HD, Papp et al. (2011) noted that only 9 of the 15 studies which compared pre-symptomatic carriers and non-carrier controls found significant differences in cognitive task performance. Previously the most reliable findings have involved psychomotor and/or attention/working memory tasks (Stout et al., 2012; Paulsen & Long, 2012; Papp et al., 2011). That our selected tasks detected performance differences between our PreHD sample and Controls reliably over time is a relatively unique occurrence in pre-symptomatic HD research (Papp et al., 2011; Stout et al., 2012). Performance on two of these tasks also deteriorated over the 3-year interval between the first and second testing occasions. Other longitudinal studies using different cognitive measures have struggled to detect deterioration, even with large participant numbers and cognitive tests that have been specifically selected for differentiating pre-symptomatic and control participants in cross-sectional studies (Tabrizi et al., 2011; Tabrizi et al., 2012). What is also striking about our findings is that we have shown consistent effects on visuo-spatial tasks, a cognitive domain in which pre-symptomatic HD participants do not regularly perform more poorly on than controls (Anderson, 2011; Papp et al., 2011; Wier et al., 2011).

Although some other studies have failed to find the same effects on tasks that our PreHD sample performed poorly on, there were generally methodological differences between those studies and this study. For example, sample sizes were sometimes smaller, and perhaps more importantly proximity to onset was often not calculated and control groups were not always matched for age and/or education.
Treating a pre-symptomatic group as homogenous limits findings for a number of reasons. Firstly, while all pre-symptomatic individuals are broadly classed as in the same stage of the disease, the reality is that many are at different stages of progression in relation to clinical onset. Cognitive and neurological changes have been shown to develop any time from 15 years prior to clinical onset onwards (Paulsen, 2010), and have an insidious progression, with more rapid decline typically occurring around 5 years before clinical onset of motor symptoms (Brandt et al., 2008; Solomon et al., 2008). Clumping all pre-symptomatic participants into one group, therefore, does not reflect this general pattern of disease progression that occurs prior to motor onset. Detecting change in a pre-symptomatic group then becomes less likely as those further from onset can mask effects that may be present in individuals close to disease onset.

A small number of different formulas are used to calculate estimated time to motor diagnosis (Papp et al., 2011), thus differences in the outcome of calculations affect the comparability of findings. Nevertheless, using a formula to define proximity groups still gives more definition to the group than clumping all pre-symptomatic participants into one. A formula developed by Langbehn et al. (2004) derived from a sample of 2913 individuals seems to be used in most recent studies. This is promising as consistent use of a validated formula would increase comparability across studies (Paulsen, 2010). The other side of the argument, however, is that no calculation is completely accurate (Langbehn et al., 2004). Within the most widely used formula currently (Langbehn et al., 2004) large variation is still seen, thus there is still the potential to wrongly predict an individual’s estimated time to motor onset. Many disease modifiers also contribute to clinical onset of the disease, thus a formula that is based on age and CAG repeat length does not fully account for other significant factors that may contribute to age of clinical onset.
One could also argue that classifying onset based on motor diagnosis is not taking into account cognitive and psychiatric disturbance that may develop prior to motor symptoms in HD. Disease variability in HD makes this more complicated, as cognitive, motor and psychiatric symptoms can vary as to when they appear in each individual, the intensity they present, as well as the rate of progression even when CAG repeat length and age are similar. The extensive and complicated neuropathology in HD makes the exact reasons for these differences hard to identify; it is known, however, that variability occurs even at neurochemical levels, affecting resultant presenting symptoms (Tippett et al., 2007). Such variability in disease presentation makes hard work of establishing a thorough formula to predict estimated time to clinical onset. Regardless, the capacity to calculate an estimated time to onset as a research tool, even if not 100% precise and based on motor onset only, has led to greater precision in research. The use of these formulas with prospective data will allow greater refinement of the formula, and indeed recent publications indicate the beginnings of this refinement (Langbehn et al., 2010).

Currently, it seems that most studies split their groups on median age to clinical onset (Papp et al., 2011), as is done in this study. A suggested better way of splitting groups, is to have pre-determined separations that researchers follow i.e. splitting groups every 5 years to clinical onset (e.g. 5 years, 10 years, 15 years) (Papp et al., 2011). This would make investigations more consistent, and enable better defined characterisation of deficits within specific estimated time to diagnosis windows. The difficulty with this, however, is for smaller studies to be able to gain enough power by splitting into such groups. The movement towards large-scale studies, however, means that for studies of significant size, this is not an issue.

The characterisation of control groups also needs to be mentioned. Our study included age, gender and education matched controls for a number of reasons. Firstly, when testing cognition, there are obvious differences in potential cognitive ability of a university educated
individual versus someone who completed high school. While tasks chosen in this study are not tests of scholarly ability, education and age do still significantly affect performance. Other factors that affect cognitive outcomes are ‘cognitive reserve’ and ‘neural compensation’, which are both affected by education and age. Cognitive reserve is the idea that an individual has neural networks robust enough to maintain previous levels of functioning in the face of neural deterioration, while neural compensation is recruiting new networks to carry out the functions of a disrupted non-functioning network. Failure to show cognitive decline when pathology is progressing may be due to some of these factors (Tabrizi et al., 2012). Thus, if cognitive changes due to pathology are to be accurately detected, having age, gender and education matched controls helps to control for some of this variability, and will hopefully allow real differences to detected more easily. If we are to establish cognitive bio-markers, then matched controls will need to become a priority in order to take into account these aspects.

What our Findings say about Cortical Thinning in Pre-symptomatic HD

Cortical thinning findings of Rosas et al. (2005), Nopoulos et al. (2010) and Tabrizi et al. (2009) all show regionally selective thinning in posterior regions of cortex, while anterior cortical regions seem to be relatively undisturbed in pre-symptomatic HD. Significant controversy, however, exists around these findings. The reason for this is the foundation of knowledge regarding the central pathology of HD, which asserts that the primary degeneration is striatal, which then disrupts cortico-subcortical-cortical circuits, giving rise to the many symptoms seen in HD. The MRI findings that show thinning occurs in the posterior cortex before anterior cortical changes are not consistent with this. These findings potentially indicate that there may be other pathological processes that occur semi-independently of striatal changes; and that these changes occur before clinical onset. Indeed, Rosas et al. (2005) showed that when controlling for caudate and putamen volumes, posterior cortical
thinning in their pre-symptomatic HD group still remained significant, suggesting that regional cortical thinning is somewhat independent of striatal pathology (Paulsen, 2010).

Our pre-symptomatic HD sample showed sustained poorer performance on tasks that depend upon posterior cortical regions and decline on two of these tasks at the second assessment. In addition to this, there was a general lack of findings on tasks selected to recruit anterior brain regions. From the baseline assessment, we know this sample exhibited cortical thinning in posterior cortical regions, and that some of these regions shown to be thinning are implicated in performance of the tasks we found differences in. Overall, we can thus infer that there are detectible functional consequences of the posterior cortical pathology occurring in the pre-symptomatic HD. It may be that the performances seen by our PreHD sample are evidence of some of the first cognitive symptoms associated with early cortical changes to be detected. Our findings support the idea that the disease process in pre-symptomatic HD is not as linear as the striatal pathology model implies, but rather suggests there may be independent streams of pathology co-occurring.

It must be noted, however, that there were only two anterior tasks (Hand Mental Rotation and SoC) in our test battery, thus in order to fairly make the claim about a lack of finding in anterior tasks would require an equal number of tasks selected in similar precision to be compared. Another critique that could fairly be made is that our sample size is small, which means that our findings could be idiosyncratic to our sample. Other current longitudinal studies (Tabrizi et al., 2012; Paulsen et al., 2009) have very large sample sizes, thus the clinical variability evident in HD is better represented in those samples, as one could argue that our sample could by chance, happen to have a propensity towards cognitive dysfunction. Conversely, the reliability of our findings on tasks specifically selected for sensitivity to regional neural changes increases the likelihood that these findings are not Type I errors in this small sample.
Although the notion of a semi-independent stream of pathology is gaining momentum in current HD research (Paulsen, 2010; Nopoulos et al., 2010), the discovery that these cortical changes have functional consequences is striking. The salience of these findings is due to the controversy surrounding cortical thinning findings; and additionally, changes in cognitive functions that rely on these posterior regions are not traditionally reported to be detectible in the pre-symptomatic stages of HD (Papp et al., 2011). While posterior cortical pathology does not nullify the significance of striatal pathology, it does highlight the need to start considering the cortex as a significant factor in the early stages of HD pathology.

Very little research has been dedicated to investigate these selective cortical changes in pre-symptomatic HD, with the most thorough investigation so far by Nopolous et al. (2011) with a sample of over 400 pre-symptomatic individuals. Nopoulos et al.’s (2011) study confirms the significance of posterior cortical pathology, in very similar regions to those seen in previous studies (Davison, 2009; Rosas et al., 2005; Tabrizi et al., 2009). Further investigation, however, needs to be carried out in order to investigate the processes occurring at neural network and cellular levels. Maybe if this area of pathology becomes a focus, more can be understood as to how it contributes to, and is affected by, the other pathological processes occurring simultaneously. This may be a game changer in how we understand the disease, and how we move forward in studying the pathology of HD. Measures such as DTI, may be important in further investigation, by using ‘seed points’ to track white matter integrity from the posterior cortical regions showing the earliest changes (Rosas et al., 2006). What mechanisms underlie the selective posterior cortical pathology are also unknown. Is it that there are networks associated with posterior cortical regions deteriorating first that give rise to this pathology or are the origins of this in the cortex itself? More needs to be understood at micro levels about the pathology occurring, in order to
further comprehend this process but also to shed light on what preventative therapies may then be effective at targeting these changes.

**Could Striatal Pathology be Responsible for our Findings?**

Most tasks that differentiated the PreHD group from Controls at this second assessment were basic perceptual tasks, in which posterior cortical regions are crucial in completion of the task. It could be argued, however, that our pattern of results on some tasks, such as the Roadmap test, may in fact be due to striatal pathology. While many imaging studies have determined that mental rotation ability, and egocentric mental rotation ability are primarily served by the parietal lobes (Harris, Harris, & Caine, 2002), there is also evidence showing the basal ganglia is implicated in mental rotation processes (Jordan, Schadow, Wuestenberg, Heinze, & Jancke, 2004). Tasks that have tended to show this relationship, however, involve mental rotation of hands or body parts, which is argued to involve motor cortices (Harris et al., 2002). Thus if pathology in the basal ganglia was the main contributor to the effects seen in the Roadmap test, then it is likely that we would have also have witnessed deterioration on the Hand Mental Rotation task (Harris et al., 2002). Jordon et al. (2004) explored differential activation between allocentric and egocentric strategy when navigating through a 3D maze. They found that it was allocentric strategy (using landmarks other than ones-self as a reference point) that preferentially activated sub-cortical regions while egocentric mental rotation only activated parietal and occipital areas. Similarly, Campodonico et al. (1998) found no relationships between striatal structures and the Roadmap test. As the connections between the basal ganglia and cortex are so complex, it is hard to rule out the possibility that striatal pathology may contribute to the effects seen. The alternative evidence, however, suggests that posterior cortical changes are present and therefore are more likely to be the larger contributing factor. One way to determine if striatal pathology is affecting performance on our tasks, might be to incorporate the results of
structural MRI into the analyses. Alternatively fMRI studies with pre-symptomatic HD might provide some insight into this issue.

**Future Directions and Conclusions**

Paulsen (2010) describes the need to minimise redundant cognitive findings, that is, not publishing another study that shows impairment for another cognitive test in pre-symptomatic HD. New findings need to assess whether the cognitive measures being studied improve upon the current measures shown to be differentiating pre-symptomatic HD carriers and non-carriers (Paulsen & Long, 2012; Stout et al., 2012). Additionally, aspects such as whether findings are consistent across time, reliability of the measure and cost of implementing such a measure, are all important factors to consider. Paulsen (2010) also highlights that new findings need to contribute new knowledge about the disease process in HD. From this perspective, I believe our findings fit these criteria. We have shown that our findings hold their effects across time, signifying the potential of such tasks being able to reliably detect functional consequences of posterior cortical changes in pre-symptomatic HD. The tasks used are easy to implement, are not time consuming and fit criteria of feasibility for clinical trials, in terms of portability and size. Our findings also contribute new information regarding the occurrence of cognitive deficits in visuo-spatial domains. This seems to be an area that lacks enough findings and consistency, particularly in pre-symptomatic HD (Papp et al., 2011). Our findings are also the first to support the current imaging data that indicates significant posterior cortical thinning in pre-symptomatic HD, lending support to the suggestion that these cortical changes are potentially a semi-independent pathological process (Paulsen, 2010).

While the findings of this study are not sufficient to identify a definite clinical marker, they certainly suggest new in-roads for investigation into cognitive measures that may be sensitive to very early pathology in pre-symptomatic HD. If, from further investigation, these
tasks are shown to reliably detect such pathology and track decline, then these could serve as
effective clinical biomarkers. This study highlights an important difference in task
recruitment, that instead of choosing tasks by category (e.g. psychomotor, attention), it may
be more productive to choose tasks based upon evidence of their sensitivity or dependence
upon key neural regions (from fMRI and lesion studies). While no task can be selected for
pure activation of a certain region, there are tasks that are more highly depended on functions
that are subserved by particular brain regions. If we are trying to have indicators of
pathology, then we need to be able to test cognitive domains that are aligned with regions
showing early change.

The original intentions of this study were to be able to correlate the cognitive findings
with cortical thinning data from the MRI scans that this sample underwent. Unfortunately,
due to problems experienced by our international collaborators, this was unable to occur in
time for the publication of this thesis. When these results become available, it will be possible
to see if any significant relationships can be established between areas of cortical thinning
and cognitive test performance. While significant relationships between areas of thinning and
task performance were not evident three years ago, it is possible that progression in the 3-year
interval between investigations will result in the emergence of clearer patterns.

A future step would be to pursue fMRI studies for these tasks. As many of the tasks
are visuo-spatial, it makes them prime candidates to use within the MRI scanner. Examining
these tasks with fMRI would enable greater detail of functional relationships to be
characterised, rather than determining the relationship through correlation as fMRI is reported
to be more sensitive to the earliest changes in HD, before structural changes are present (Wier
et al., 2011).

All biomarkers considered thus far, whether imaging, biological samples or clinical
measures have all shown their limitations in one way or another (Wier et al., 2011). Thus a
single measure alone is likely to be insufficient to fulfil all the required roles of a biomarker. Rather, the use of a combination of biomarkers may be needed in order to maximise the sensitivity to detect clinically significant changes that are indicative of the evolution of the HD disease process (Sturrock & Leavitt, 2011). The end goal is to be able to monitor disease state, and track disease evolution, in a way that can effectively assess the therapeutic response of a trailed intervention. Both imaging and biological measures are being studied in large cohorts around the world, but there is still a great need for the refinement of cognitive markers being trialled (Sturrock & Leavitt, 2010; Papp et al., 2011). It is hoped that our findings will shed some new light on the search for cognitive biomarkers within the HD field, an avenue of research that is expected to exponentially grow in the near future (Stout et al., 2011). The field of HD research is at an exciting stage, where the knowledge gained thus far has heightened agreement for future directions and is propelling research forward into new domains. It is with great anticipation that both HD researchers and the general HD community await the outcomes of both large-scale longitudinal studies and large-scale therapeutic trials, and with the hope that these will move us even closer to effective interventions for those who suffer with HD.
List of Appendices

Appendix A: Rationale for cognitive tests used in this study

Appendix B: Cortical Thinning Methods

Appendix C: Structured interview

Appendix D: Study consent form

Appendix E: MRI safety and consent form
Appendix A: Rationale for cognitive tests used in this study

This appendix describes the rationale for selecting each cognitive test in this study. It is taken un-edited from the thesis published by John Davison (Davison, 2009). It is included to detail the rational for inclusion of the neuropsychological tasks at T1.

Decisions about tasks were based mainly on findings from neuropsychological lesion studies and functional neuroimaging studies with healthy individuals. Lesion studies can be used to demonstrate the effects of regional brain damage on specific neuropsychological functions and performance on specific tasks. Functional imaging techniques indicate regions of the brain that are activated whilst participants are performing cognitive tasks. Although performance on cognitive tasks inevitably activates a circuit of brain regions, neuroimaging studies employ a number of methods to help specify which brain regions of the circuits are most critical for the task. The brain activation during an experimental task is usually subtracted from a similar task that controls for cognitive, perceptual or motor functions not of interest but which may also be activated during the task (such as general attention to visual stimuli, processing of colour, pressing a keypad etc). Additionally, regional brain activity can be correlated with the level of task difficulty; areas that are crucial to the cognitive function being measured are hypothesised to become increasingly active as the task demands increase, whereas areas that play a secondary role in the task do not show relative increases in activation (Carpenter, Just, Keller, Eddy, & Thulborn, 1999).

Benton Judgement of Line Orientation Test (Benton et al., 1978)

The JLOT test was used as a measure dependent on the superior parietal cortex, as well as the precuneus and occipitotemporal regions. When JLOT performance was compared between people with either left or right parietal, temporal or frontal lesions (Warrington & Rabin, 1970), the right parietal lesion group showed the greatest number of errors. Ng et al. (2000) reported more than 90% (10 of 11) of a right parietal lesion group and 50% (3 of 6) in a left parietal group to fall in the impaired range on this test. Numerous neuroimaging studies based on this task have shown superior parietal and occipitotemporal regions to play a crucial role in this task (Dupont et al., 1998; Faillenot, Sunaert, Van Hecke, & Orban, 2001; Hannay et al., 1987; Herrmann, Ehlis, Wagener, Jacob, & Fallgatter, 2005; Ng et al., 2001; Ng et al., 2000; Orban, Dupont, Vogels, Bormans, & Mortelmans, 1997; Vandenberghhe et al., 1996)
with only occasional reports of prefrontal cortex activation (Vandenberghe et al., 1996). In an fMRI study, Ng et al. (2000) compared activation patterns in JLOT with a similar control task requiring no orientation judgments. They found robust and significant activation in the bilateral superior parietal lobe, the precuneus and the extrastriate regions (BA 18).

**Hooper Visual Organisation Test (Hooper, 1983)**

The Hooper test was selected as a reliable measure of bilateral occipital and superior parietal regions. One lesion study has compared performance on the HVOT between a right parietal lesion group and a ‘non-parietal lesion’ group (Fitz, Conrad, Hom, Sarff, & Majovski, 1992). They found the HVOT scores, when adjusted for age and education, to be significantly lower in the right parietal group. An fMRI study of the HVOT (Moritz et al., 2004) found reported the most robust activation to be centered in bilateral superior occipital and posterior superior parietal lobes. Significant activation was also evident in bilateral regions of lateral occipital lobe and the fusiform gyri. A left frontal lobe cluster (proximal to Broca’s area) was assumed to reflect the covert naming response required for the fMRI paradigm. Parietal lobe activity showed a right lateralization effect in the parietal cortex, although lesion studies (Boyd, 1981; P. L. Wang, 1977) have found no significant difference between lateralization of injury and HVOT performance score.

**Collision Judgments Task (Assmus et al., 2003)**

The Collision Judgments task was selected to assess functioning related to the left inferior parietal lobe, and particularly the left supramarginal gyrus. In an fMRI study, Assmus et al. (2003) compared neural activity during the Collision Judgment task with a control task that used the same visual presentation, but required simple size judgments of the moving balls, rather than collision judgments. The collision judgments, relative to the control task, were associated with significant neural activation in the supramarginal gyrus only. Moreover, when the Collision Judgments task was divided into varying levels of difficulty in an event related fMRI study, the fMRI signal in the left IPL showed a linear increase with task demands (Assmus, Marshall, Noth, Zilles, & Fink, 2005). Eye-movement recordings have shown that participants maintain central fixation even when allowed to move their eyes (Assmus et al., 2003) and thus the task is unlikely to be confounded by any impairment in saccadic eye movements.

**Facial Recognition Test (Benton et al., 1973)**

Studies investigating the neuroanatomical correlates of facial perception and recognition have consistently shown the occipitotemporal visual extrastriate cortex to play a critical role in these functions. Brain lesions in the fusiform gyrus (termed the ‘fusiform face
area’) (Kanwisher, McDermott, & Chun, 1997), and adjacent occipitotemporal regions are often associated with an inability to recognise faces, termed prosopagnosia (A. R. Damasio, Tranel, & Damasio, 1990; Sergent & Signoret, 1992; Sorger, Goebel, Schiltz, & Rossion, 2007). Numerous functional imaging studies have used modified versions of the Facial Recognition Test, in which participants are required to match an unfamiliar face to one of two exemplars (Clark et al., 1996; Haxby, 1999; Haxby, Hoffman, & Gobbini, 2000; Haxby et al., 1994; McCarthy, Puce, Gore, & Allison, 1997). This task has consistently been found to evoke significant activity in the lateral fusiform gyrus, the inferior occipital gyri, and the superior temporal sulcus. The majority of studies report bilateral or predominantly right hemisphere neural activity in these areas (Haxby et al., 2000).

**Roadmap Test of direction sense (Money et al., 1965)**

Vingerhoets et al. (1996) found patients with predominantly parietal brain lesions performed significantly worse on the Roadmap Test than patients with predominantly frontal lesions. When the turn types were divided into those requiring, and not requiring, egocentric mental rotation, the parietal group was shown to perform significantly worse only in the mental rotation turns. No significant differences were found between those with left and right parietal lesions. Although there are no functional imaging studies to date for the Roadmap Test, tasks involving egocentric mental rotation have consistently shown activation to bilateral inferior and superior parietal lobes (Creem-Regehr et al., 2007; Creem & Proffitt, 2001; Zacks et al., 2003), with some studies indicating a specialized role of the parieto-temporal-occipital (PTO) junction (Auer et al., 2008; Blanke et al., 2005; Zacks, Rypma, Gabrieli, Tversky, & Glover, 1999; Zacks et al., 2003).

**Letter Mental Rotation Task (Cooper & Shepherd, 1973)**

Studies of the neural substrates of mental rotation tasks, including lesions studies (Ditunno & Mann, 1990; Farah & Hammond, 1988; Ratcliff, 1979) and functional neuroimaging studies (Alivisatos & Petrides, 1997; Cohen et al., 1996; Harris et al., 2000; Jordan, Heinze, Lutz, Kanowski, & Jancke, 2001; Podzhebenko, Egan, & Watson, 2002), have consistently demonstrated the crucial role of the parietal cortex in mental rotation of 2D and 3D objects. Although the motor and precentral frontal cortex are also often activated in mental rotation tasks, these activations appear to reflect incidental features of the tasks (e.g. executing motor responses) or reflect the degree to which the task affords the use of a motor simulation strategy to solve the task (Windischberger, Lamm, Bauer, & Moser, 2003; Zacks, 2008). Using the alphanumeric mental rotation task, one PET study (Harris et al., 2000) found only the intraparietal sulcus of the right posterior parietal lobe to be significantly
correlated with mental rotation task demands. Similarly, other studies have shown the inferior parietal lobe to be activated during this task, both bilaterally (Jordan et al., 2001) and predominantly in the left hemisphere (Alivasatos & Petrides, 1997). In an fMRI task similar to alphanumeric mental rotation, in which participants mentally rotated an L shape, Ng et al. (2000) found that response time was most strongly associated with bilateral (although predominantly right) superior parietal cortex. Moreover, in their rTMS study, Harris et al. (2003) found that disrupting neural activity in the right, but not left, superior parietal lobe interfered with the speed at which participants could mentally rotate alphanumeric characters. The alphanumeric mental rotation task was selected as a reliable measure of inferior and superior parietal lobe functioning.

It has been well-documented that the response times in mental rotation tasks increase in a direct linear relationship to the degree of angular displacement of the object being rotated (Shepard & Metzler, 1971). The more the object needs to be mentally rotated, the more difficult and timely the task is. In mental rotation tasks requiring a mirror-normal judgment, the increase in latency is not purely linear, but rather curvilinear upwards (Cooper & Shepard, 1973; Hamm, Johnson, & Corballis, 2004). Differences in the slope of linear and curvilinear function can be used to compare the relative mental rotation abilities across different groups.

**Hand Mental Rotation task (Ganis et al., 2003)**

While the mental rotation of objects requires visuospatial functions mediated mostly by the parietal lobes, the mental rotation of hands also engages frontal motor processes (Amick, Schendan, Ganis, & Cronin-Golomb, 2006; Creem-Regehr et al., 2007; Kosslyn, Digirolamo, Thompson, & Alpert, 1998). Kosslyn et al. illustrated the different cortical pathways in these two different processes while participants mentally rotated either hands or 3D objects. Mental rotation of objects activated the bilateral parietal and extrastriate cortex, whilst rotation of hands engendered activation in similar posterior regions, as well as the precentral gyrus (M1), and frontal areas BA6 and BA9. The strongest activations in the hand task were in the left precentral gyrus and BA6. The Transcranial Magnetic Stimulation technique (TMS) has also been used to illustrate the crucial role of the frontal lobe, particularly the primary motor hand area (M1) in the mental rotation of hands. Temporary stimulation of the left M1, participants resulted in slower (verbal) response speeds in a hand mental rotation task, but not in a letter mental rotation task (Tomasino, Borroni, Isaja, & Rumiati, 2005). Another TMS study found that stimulating the left M1 significantly slowed participants’ response speeds when mentally rotating hands, but not feet (Ganis et al., 2000).
Ample evidence from lesion and neuroimaging studies suggests that specific areas of the prefrontal lobe are involved in higher executive function of planning. Shallice and Burgess (1989) found participants with left frontal lesions to perform significantly worse on the Tower of London task than those with posterior lesions, who showed no differences from controls. The neural specificity of this task is also apparent from lesion studies showing people with temporal lobe excisions and amygdalohippocampectomy to perform similar to, or better than, the control group (Owen et al., 1995). Most neuroimaging studies illustrate a frontal-parietal network activated during this task, with some tasks showing activation in subcortical areas (van den Heuvel et al., 2003). However, studies correlating regional brain activity with increasingly levels of difficulty in the ToL have consistently reported the prefrontal lobe, and particularly the DLPFC, as the crucial region mediating performance on this task. One PET study found relative regional cerebral blood flow (rCBF) activity in the DLPFC to covary with task difficulty, while activity in parietal and occipital cortices were shown to be independent of task difficulty (Dagher, Owen, Boecker, & Brooks, 1999). Another study using event related fMRI study found the rostro-lateral prefrontal cortex (BA 10) the only brain region to show a BOLD signal increase over the four planning levels, compared with the control conditions (Wagner, Koch, Reichenbach, Sauer, & Schlosser, 2006). Numerous PET, fMRI and SPECT studies have supported the role of prefrontal (and particularly DLPFC) involvement in the ToL and SoC tasks (Lazeron et al., 2000; Morris, Ahmed, Syed, & Toone, 1993; Owen et al., 1996; Rasmussen et al., 2006; Schall et al., 2003; Unterrainer et al., 2005; van den Heuvel et al., 2003). These findings indicate that, within a wider network involving posterior and subcortical regions of the brain, the DLPFC plays a critical role in the ToL planning task. In a review of the lesion and neuroimaging literature using the ToL, Unterrainer and Owen (2006) conclude that within the dorsolateral frontal region, neither the left nor the right hemisphere plays a dominant role in the ToL task.
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<thead>
<tr>
<th>Cognitive Tasks</th>
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<tbody>
<tr>
<td><strong>Posterior tests</strong></td>
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<tr>
<td>JLOT</td>
<td>Superior parietal; precuneus; occipital temporal; extrastriate gyri</td>
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<td>HVOT</td>
<td>Superior occipital; posterior superior parietal; fusiform gyrus</td>
</tr>
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<td>Collision Judgement</td>
<td>Left supramarginal gyrus</td>
</tr>
<tr>
<td>Benton Facial Recognition</td>
<td>Inferior and superior temporal; inferior occipital</td>
</tr>
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<td>Roadmap test</td>
<td>Inferior and superior parietal cortex</td>
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<tr>
<td>Letter Mental rotation</td>
<td>Inferior and superior parietal cortex</td>
</tr>
<tr>
<td><strong>Frontal tests</strong></td>
<td></td>
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<tr>
<td>Iowa Gambling task</td>
<td>Ventromedial prefrontal cortex (VMPFC)</td>
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<td>Stockings of Cambridge</td>
<td>Dorsal-lateral prefrontal cortex (DLPFC)</td>
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<tr>
<td>Hand Mental Rotation</td>
<td>Precentral, premotor, caudal middle and superior frontal (in addition to</td>
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<td>inferior and superior parietal cortex)</td>
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Appendix B: Cortical Thinning Methods

PreHD and Control samples both underwent MRI scanning at T1, approximately three years prior to the current assessment to measure whether any cortical thinning was evident, and to determine the pattern of distribution of this thinning. Analyses of MRI data was conducted by collaborators H. Diana Rosas (H.D.R) and colleagues in Boston, using identical automated MRI segmentation techniques to their previous studies (Rosas et al., 2005; Rosas et al., 2008).

The details of the methods used for the acquisition of MRI data, and the cortical thinning technique used to analyse the scans are detailed below.

Scan Acquisition

All scans were conducted on a Siemens Magnetom Avanto 1.5 Telsa scanner at the Centre for Advanced MRI (CAMRI) at the University of Auckland. All participants were required to adhere to the safety regulations of CAMRI (see Appendix H). MRI sequences for scan acquisition were provided by our research collaborators (H.D.R) from the Athinoula A. Martinos Centre for Biomedical Imaging, Boston, Massachusetts, USA. Two whole-brain high resolution T1-weighted MPRAGE scans were obtained for each participant. Image acquisition included echo time (TE) = 3.31ms, repetition time (TR) = 2730 ms, flip angle = 7 deg, field of view = 256mm, matrix = 256 x 192, 1.33mm sagittally acquired slices, number of excitations = 1.

Automated Surface Reconstruction and Estimation of Cortical Thickness

Cortical surface reconstruction was conducted by our collaborators using a fully automated processing pipeline (Han et al., 2006) from the Freesurfer toolkit which is now freely available through the website http://www.surfer.nmr.mgh.harvard.edu/. Two T1
weighted MPRAGE acquisitions for each participant were motion corrected then averaged to create a single image volume with high signal-to-noise ratio (Dale et al., 1999; Salat et al., 2004). Pre-processing steps to increase differentiation between gray and white matter boundaries included spatial normalisation, intensity normalisation and skull stripping (Dale et al., 1999; Dickerson et al., 2008). A surface based automatic topology correction was also performed which allows defects in the topology of the cortical surface to be removed or filled (Fischl et al., 2001). The gray/white boundary was used as the starting point for algorithms to deform the surface outward in order to locate the pial surface with sub-millimetre accuracy (Fischl & Dale, 2000; Kuperberg et al., 2003). Cortical thickness estimates were then obtained by calculating (i) the shortest distance between the gray/white boundary to the pial surface, and (ii) the shortest distance from the pial surface to the gray/white boundary. The cortical thickness at each point was set to the average of the two values obtained and this was completed for each of 160,000 points on each hemisphere (Fischl & Dale., 2000).

Once this process was complete thickness measurements were mapped onto the inflated surface of each brain reconstruction, which allowed visualisation of the data across the entire cortical surface without disturbance from cortical folding (Fischl et al., 1999). The cortical map for each subject was smoothed using a circulatory symmetric Gaussian kernel of a given standard deviation in order to remove any noise-induced variation (Fischl & Dale., 2000; Salat et al., 2004). The image was then further inflated into a sphere in a manner that minimizes geometric distortion. This image was then aligned with an average spherical cortical map which indexes all points on an individual subjects cortical map to a co-ordinate system (Fischl, Sereno, Tootell, et al., 1999). The end product provides accurate alignment of homologous cortical locations among participants using each individual’s anatomy (Salat et al., 2004). A mean measure of cortical thickness at each point on the reconstructed cortical surface for the group studied is produced and allows between group comparisons (Salat et al.,
Statistical comparisons of the data are then computed using a general linear model for cortical thickness at each vertex. The results are mapped onto the reconstructed cortical surface so differences in cortical thickness between the groups are able to be visualized on a cortical thickness map (Salat et al., 2004).

Follow-up study MRI scans

While cross-sectional data exists for cortical thinning, longitudinal data lacks (Wier et al., 2011). The present study sought to investigate the progression of cortical thinning in a pre-symptomatic HD sample through a longitudinal investigation using identical methodology to that used at T1 and in the study by Rosas et al. (2005).

MRI scans were collected for all 36 participants in this study (see Chapter 2 for participant details). The scan acquisition methods used are identical to those described in the procedure used three years ago. The MRI scan data for our sample has been sent electronically to our collaborators (H.D.R) at the Athinoula A. Martinos Centre for Biomedical Imaging in Boston. Automated surface reconstruction and cortical thickness estimates will be gained with the exact same methodology outlined above, but will also include a longitudinal comparison of our current PreHD and Control group to the MRI data obtained three years ago for the same groups. Analyses of the MRI data were unable to occur in time for the publication of this thesis. We are currently awaiting the results of these analyses.
Appendix C: Structured interview

Participant Number: __________

1. Are you: Male □ Female □

2. What is your date of birth? ________________

3. With which ethnic group do you identify?
__________________________________________

4. Are you left-handed or right-handed? ________________

5. At what age did you receive your diagnosis of Huntington’s disease (if applicable)?
____________________

6. Have you had any symptoms you think may be indicative of HD? What were these symptoms, and when did they start?
_______________________________________________

7. Have you had any neurological complications other than Huntington’s disease (such as stroke or head injury)?
_______________________________________________

8. Have you ever been diagnosed with a psychiatric disorder/problem?

9. How many years of academic study have you done? _____

   What is the highest educational qualification you have received? And what were these qualifications?
   None / Secondary School / Polytechnic or similar / University
   __________________________________________________________________________

10. What is your current occupation?

    __________________________________________________________________________

11. What employment have you had in the past?

    __________________________________________________________________________

12. Are you currently taking any prescribed medication or receiving any of the following treatments?
    Risperidone / Haloperidol
Antidepressant / Anxiolytics / Anti-psychotics / Radiotherapy treatment / Chemotherapy / Naturopathic medicines/therapy
Other: ________________________________________________

13. How long have you been taking this/these medication/treatments?
   ______________________________________________________
   ______________________________________________________

14. How often do you drink alcohol?
   Less than one standard drink per day
   1-2 standard drink per day
   3-4 standard drinks per day
   More than 4 standard drinks per day
   Over the last year?
   In the past?

15. Do you use any drugs? If so, which drugs and how often?
   ______________________________________________________
   ______________________________________________________
   Over the last year?
   In the past?

16. Do you smoke cigarettes? If so how many do you smoke per day? ______

17. Have you had any significant health problems?
   ______________________________________________________
   ______________________________________________________

18. Do you know the number of CAG repeats in your HD gene? ______
Appendix D: Study consent form

CONSENT FORM
PARTICIPANTS WITH THE HD GENE

Title of Project: Early brain changes and level of functioning in pre-symptomatic Huntington’s disease – A follow up study

Principal Researcher: Sasha Bruneau-Herman

Name of Participant: ____________________________ Age: ______ years
Participant Number: ______

<table>
<thead>
<tr>
<th>Language</th>
<th>Statement</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>English</td>
<td>I wish to have an interpreter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maori</td>
<td>E hiahia ana ahau ki tetahi tangata hei korero Maori ki ahau</td>
<td>Ae</td>
<td>Kao</td>
</tr>
<tr>
<td>Samoan</td>
<td>Oute mana’o e iai se fa’amatata upu</td>
<td>Ioe</td>
<td>Leai</td>
</tr>
<tr>
<td>Tongan</td>
<td>‘Oku fiema’u ha fakatonulea</td>
<td>Io</td>
<td>Ikai</td>
</tr>
<tr>
<td>Cook Island</td>
<td>Ka inangaro au i tetai tangata uri reo</td>
<td>Ae</td>
<td>Kare</td>
</tr>
<tr>
<td>Niuean</td>
<td>Fia manako au ke fakaaoa e tagata fakahokohoko vagahau</td>
<td>E</td>
<td>Nakai</td>
</tr>
</tbody>
</table>

I …………………………………………………. have read and understand the participant information sheet dated 20/09/09. I have had the opportunity to discuss this study and am satisfied with the answers I have been given. I have had the opportunity to discuss the study with whanau, family or friends.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and this will not have any adverse consequences for me. I have had time to consider whether to take part. I know who to contact if I have any concerns or questions about the study.

I understand that my participation in this study is confidential and that no material which could identify me will be used in any reports on this study. This consent form and data from the project will be stored for ten years from the completion of this project.

I understand that the information collected in this study may be used in future research however ethical approval will be sought prior to the use of this data in further studies.

This study has been approved by the Northern Y Regional Ethics Committee NTY-09-09-085

I agree to provide the researchers with the CAG length of my HD gene YES/NO
I agree to my MRI data being sent to the USA for analysis YES/NO
I wish to receive a copy of the results YES/NO
I wish to receive a copy of my own images on CDROM YES/NO

Signed……………………………... Name………………………………. Date…………………….

Project explained by: Sasha Bruneau-Herman Project role: Primary Investigator
Signature…………………………….. Date…………………….
Appendix E: MRI safety and consent form

MRI SAFETY AND CONSENT FORM

Name ________________________________________________

Date of Birth _____/____/____  NHI _________________

Weight ________________ kg  Height ________________ cm

Magnetic Resonance Imaging involves the use of an extremely powerful magnet. For your safety please answer the following questions:

Have you had a previous MRI scan?  □ yes  □ no
Do you have or have you ever had a cardiac pacemaker?  □ yes  □ no
Do you have a brain aneurysm clip?  □ yes  □ no
Have you ever had an injury to the eye with a metallic object or fragment?  □ yes  □ no
Have you had any previous surgery?  □ yes  □ no

Please list _______________________________________

Do you have any allergies to medications?  □ yes  □ no

Please list _______________________________________

Do you have any of the following:
Anaemia, blood disorders, kidney disease or seizures?  □ yes  □ no

CONTRAST

Some scans may require the use of contrast to add additional information to the results. This is a clear fluid that is administered via a vein in the arm. Although it is very safe and rarely produces an allergic reaction, the occurrence of an allergic reaction cannot be completely excluded.

Do you consent to the use of contrast?  □ yes  □ no  Signature ____________________________

Research participants only - If you are part of a research study requiring the use of contrast this will have been discussed in detail in the patient information sheet. If this has not been mentioned, you do not need to answer this question.

FEMALE PATIENTS

Is there any chance that you could be pregnant?  □ yes  □ no
Are you currently breastfeeding?  □ yes  □ no

PLEASE ANSWER THE QUESTIONS ON THE BACK OF THIS SHEET
DO YOU HAVE ANY OF THE FOLLOWING?

- Implanted cardiac defibrillator
- Implanted electronic or magnetic device
- Metallic stent, filter or coil
- Cochlear implant or other ear implant
- Heart valve prosthesis
- Any type of prosthesis (eye, limb etc.)
- Joint replacement
- Screws, plates or wires in bones or joints
- Shunt (spinal, intraventricular, or heart)
- Vascular or drug access port or catheter
- Radiation seeds or implants
- Medication patches (Nicotine or hormone)
- Tattoo or permanent makeup
- Dentures or partial plate
- Hearing aid
- Shrapnel, bullets or other metal

BEFORE ENTERING THE MR SCAN ROOM

You must remove all metallic objects, including jewellery, watches, keys, coins, credit cards, pens, cell phones, hearing aids, clothing with metallic zips and fasteners, metallic threads, or glitter finishes. You may be asked to change into a gown.

Owing to the loud noises emitted by the MR system, you will be given headphones or ear plugs to protect your hearing.

If you answer YES or are uncertain regarding any of the above, please contact us on (09) 303 5966 prior to your appointment.

USE OF YOUR IMAGES

As a University it may be useful to use your images (without your name or other identifying details) for all or some of the following purposes -
- education and training by Centre for Advanced MRI staff
- scientific publications, reports and presentations
- University teaching
- publicity material for the Centre for Advanced MRI
- the Centre for Advanced MRI website and websites of organisations we collaborate with (e.g. Siemens the manufacturer of the machine)
- publicity materials for non-profit organisations
- television documentaries or other public interest media
- databases that may be published on the internet

I give consent for my images to be used for the above purposes provided that all details that could allow me to be identified have been removed  

- yes  
- no

I confirm that the above information is correct to the best of my knowledge.

Signature ____________________________ Date____/____/____

Screening form checked by ____________________________________________
List of References


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201


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