Cortical thinning and neuropsychological changes in presymptomatic Huntington's Disease

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Abstract

Degeneration of the striatum and striatal-frontal circuits are generally thought to cause most of the neuropsychological symptoms experienced in Huntington's Disease (HD). Advances in cortical thickness mapping (an automated MRI method for precisely measuring the cortical thickness across the entire cortex) provide a new technique for examining changes in the brain in HD. Recent studies using this technology have reported provocative results. They found significant cortical thinning in participants with early HD (Rosas et al., 2002; Rosas et al., 2008) and even in presymptomatic HD (Rosas et al., 2005). Moreover, cortical thinning was most prominent in posterior regions of the brain, with relative preservation of the anterior frontal regions. The present study replicated Rosas et al.'s (2005) study but used a larger sample of presymptomatic HD participants (n = 19) and a control group matched for age, gender and education (n = 19). Presymptomatic HD participants were divided into two groups, PreHDclose and PreHDfar, based on their estimated proximity to clinical onset. The distribution of cortical thinning was assessed using an identical MRI method to previous cortical thinning studies with HD participants. Specific neuropsychological tests were used to assess cognitive and mood changes that may be associated with cortical thinning. It was hypothesised that cortical thinning would be more evident in posterior than frontal cortical regions. It was also hypothesised that presymptomatic HD participants would perform more poorly than controls on tests that are subserved primarily by specific posterior cortical regions, but not on tests that are subserved by anterior cortical regions. Lastly, it was predicted that poorer performance in the neuropsychological measures would be associated with greater thinning in cortical regions that are important during performance of these tasks.

Consistent with predictions, the presymptomatic HD group showed regionally-specific cortical thinning which was most prominent in the posterior cortices, particularly around the right parieto-temporal-occipital (PTO) junction. Thinning occurred in people up to 15 years before clinical onset, with little to no thinning before that. The presymptomatic HD group, and particularly the PreHDclose participants, performed significantly worse than controls in 2 of the 6 cognitive tests that are subserved primarily by posterior cortical regions (the Judgment of Line

Orientation test and modified Roadmap Test), but not in tests that are subserved primarily by frontal cortical regions. Correlational analyses showed a number of regionally-specific relationships between thinning and cognitive performance, although the distribution of these relationships did not generally support our region-of-interest predictions. The results contribute to a better characterisation of the cortical and neuropsychological changes that occur early in the development of HD, and provide tentative support for cortical thickness mapping as a valid and sensitive measure for assessing cortical changes in presymptomatic HD.

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List of Abbreviations

AD	Alzheimer's Disease
ANOVA	Analysis of Variance
BA	Brodmann Area
CVLT	Californian Verbal Learning Test
DLPFC	Dorsolateral prefrontal cortex
DRS	Dementia Rating Scale
fMRI	Functional Magnetic Resonance Imaging
HADS	Hospital Anxiety and Depression Scale
HD	Huntington's Disease
HVLT	Hopkins Verbal Learning Test
HVOT	Hooper Visual Organisation Test
ICV	Intracranial volume
IDAS	Irritability-Depression-Anxiety Scale
IGT	Iowa Gambling Test
JLOT	Judgement of Line Orientation Test
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
QNE	Quantified Neurological Examination
ROI	Region-of-interest
SDMT	Symbol Digit Modalities Test
SoC	Stockings of Cambridge task
TBI	Traumatic Brain Injury
TFC	Total Functional Capacity Scale
ToL	Tower of London task
UHDRS	Unified Huntington's Disease Rating Scale
VBM	Voxel-Based Morphometry
VLPFC	Ventrolateral prefrontal cortex

WCST	Wisconsin Card Sorting Test
WMS	Wechsler Memory Scale
YTO	Estimated Years To clinical Onset

Preface

This thesis investigated changes in the brain and neuropsychological performance in people presymptomatic for Huntington's disease. In specific terms, thinning of the cortex was assessed using magnetic resonance imaging (MRI), and neuropsychological performance was assessed using specific tests of cognitive performance and mood changes.

Chapter 1 provides a review of the literature relevant to this thesis. It begins with background information on Huntington's disease (HD), and proceeds to reviews of brain imaging studies in HD, neuropsychological studies in HD, and finally the relationship between brain measures and neuropsychological performance in HD. This chapter concludes with an overview of the present study. Chapter 2 describes the general methodology for the whole thesis. Chapters 3, 4 and 5 describe the methods and results of the three studies of this thesis, with each chapter concluding with a discussion of the findings. Chapter 3 focuses on the cortical thinning study, Chapter 4 on the neuropsychological study, and Chapter 5 on the correlational analyses between the cortical thinning and neuropsychological measures. Lastly, a general discussion of these findings is provided in Chapter 6.

Chapter One Literature Review

General Introduction

Huntington's Disease (HD) is a dominantly inherited neurodegenerative disease characterised by progressive motor, cognitive and affective impairment. HD symptoms generally develop around the age of 30 or 40, although subtle signs are often present earlier (Kosinski & Landwehrmeyer, 2005). Progression of HD is slow but steady, caused primarily by progressive degeneration in the striatum, and subsequent disruption of striatal-cortical circuits (Bates, Harper, & Jones, 2002). Both the symptoms and the rate of progression vary significantly between individuals, and different domains of motor, mood and cognitive functioning decline in an inconsistent fashion (Bates et al., 2002; Kosinski & Landwehrmeyer, 2005; Snowden, Craufurd, Griffiths, Thompson, & Neary, 2001). The involuntary choreiform movements are most conspicuous. However, the changes in cognition and mood are often considered at least as debilitating, both by the person with HD and their caregivers (Rosenblatt, 2007). Despite significant developments in HD research, there is currently no treatment to delay the onset, slow the progression, or cure the disease (Walker, 2007).

Following the identification of the HD gene in 1993 (Gusella et al., 1983; Huntington Study Group, 2009), HD research has grown exponentially. Studies have examined the neuropathological and clinical changes in HD, from presymptomatic stages, through early, moderate and advanced stages of the disease. International collaborations have led to large-scale longitudinal studies and recently, medical treatment trials (Huntington Study Group, 2009).

Structural neuroimaging, primarily magnetic resonance imaging (MRI), is increasingly being used to examine brain pathology in HD. Although it has been generally accepted that most of the clinical and neuropsychological difficulties experienced in HD are related to degeneration of the striatum and striatal-frontal circuits, a growing body of MRI studies have provided evidence of widespread changes in the cortex in HD (e.g. Douaud et al., 2006; Muhlau et al.,

2007; Rosas et al., 2008). However, it has not been determined how early cortical changes occur in people with HD, and whether these changes can be detected before clinical onset. The relationship between cortical degeneration and neuropsychological symptoms in HD is also uncertain. Findings of neuropsychological symptoms known to be subserved primarily by cortical regions of the brain could provide support for cortical pathology early in the disease process.

Background information on HD

Prevalence of HD

In populations of Western European descent, including New Zealand, HD has a stable prevalence of about 7-10 clinically diagnosed persons per 100,000 (Bates et al., 2002). Because HD is typically dormant until midlife, the actual disease gene frequency is 2-3 times higher (MacDonald, Gines, Gusella, & Wheeler, 2003). HD has a considerably reduced prevalence in Asia and Africa. In Japan for example, prevalence of HD is only 0.5 per 100,000 (Walker, 2007). There are also individual Huntington's Disease kindreds that have been so isolated, geographically and socially, that HD has multiplied from a single ancestor to become significantly more concentrated. Lake Maracaibo in Venezuela is the most renowned and researched example (Bates, 2002). Other isolated examples exist in Tasmania, South Wales, Scotland and Sweden (Bates et al., 2002; Pridmore, 1990). The juvenile-onset form of HD, arbitrarily defined as having an onset before 20 years of age, occurs in 1-10% of those affected (Walker, 2007).

Genetics of HD

Huntington's disease has an autosomal-dominant pattern of inheritance. Offspring of an affected parent have a 50:50 chance of inheriting HD and transmission is not possible via unaffected family members. Males and females equally transmit the disease, and are equally affected. In 1983 the HD gene, identified as IT15, was mapped to chromosome four by Gusella and colleagues (Gusella et al., 1983). It was not until 10 years later that an international collaborative research team found this gene to have a mutation in its first exon: a CAG trinucleotide repeat, which is expanded in people with HD (Huntington Disease

Collaborative Research Group, 1993). Normal CAG repeat lengths in this gene are lower than 27. CAG repeat lengths between 27 and 35 are rare and are not associated with clinical disease, but they show instability on replication and can expand into the disease range of 36 and above when transmitted through the paternal line (Imarisio et al., 2008). People with 36-39 repeats may have an incomplete penetrance (Langbehn, Brinkman, Falush, Paulsen, & Hayden, 2004) although these findings are based on predictions, and prospective studies are required to elucidate this finding. Most people with HD have a repeat length of 40-50, and expansions greater than 60 generally cause the juvenile form of HD (Nance & Myers, 2001). Predictive gene testing is widely available, although this option is often not pursued by people at risk of HD (Walker, 2007).

A large number of studies have illustrated a strong negative correlation between CAG repeat length and age of disease onset. CAG repeat length appears to account for approximately 60-70% of the variance in age of onset (Imarisio et al., 2008; Kosinski & Landwehrmeyer, 2005; Walker, 2007). There is considerable variation, however, in age of onset with a given CAG repeat number. Consequently, CAG repeat numbers have poor predictive power on age of onset for any given individual and are not recommended for individual predictions (Gusella & MacDonald, 2004). No consistent relationships have been found between CAG repeat length and rate of progression, or CAG repeat length and symptom subtype (Zappacosta et al., 1996).

The identification of the HD gene has provided an excellent model for studying disease progression. Changes in neuropathology and clinical symptomology can be assessed in presymptomatic HD gene-carriers, and examined over the course of the disease. Moreover, treatment trials can be administered — and ultimately it is hoped that treatment will be provided — before symptomatic onset of the disease.

Neuropathology of HD

The most striking and consistent changes in HD are prominent cell loss and atrophy in the caudate and putamen, jointly termed the striatum. Following an extensive histological study with human brains, Vonsattel et al. (1985) proposed that neuropathological changes in the

striatum in HD have a characteristic topographical distribution, beginning in medial and dorsal striatal regions, and progressing gradually into lateral and ventral striatal regions, until only a thin strip of striatal tissue remains. Atrophy within the striatum is selective: medium spiny neurons are most vulnerable and GABAergic efferent neurons that carry inhibitory output to the globus pallidus and substantia nigra are most affected (Kremer, 2002). Neuronal loss has also been identified in other regions of the brain, albeit to a lesser extent, including the globus pallidus, substantia nigra, hippocampus, thalamus, hypothalamus, cerebellum and brainstem (Vonsattel & DiFiglia, 1998; Walker, 2007).

There is also a growing awareness of cortical degeneration in HD. Post-mortem analysis of the brains of HD patients has shown considerable variation in cortical cell loss (15-50%) between HD participants, even with the same extent of striatal neuropathology (Thu, 2006). Pyramidal cells from cortical layers III, IV and VI are also known to degenerate (Gutekunst et al., 1999). Morphological changes in these cells also occur prior to pyramidal degeneration, for example a reduction in size and number of dendritic spines (Sapp et al., 1997), and an increase in glial density (Selemon, Rajkowska, & Goldman-Rakic, 2004). Neuronal loss is not uniformly distributed throughout the cerebral cortex (Selemon et al., 2004; Thu, 2008). However, because of the time-consuming nature of histological cell-counting, little is known about regional differences in cortical atrophy. Autopsy studies have shown the weight of the HD brains to be reduced by about 10-20%, which is primarily a result of atrophy in the cerebral cortex and subcortical grey matter (Halliday et al., 1998; Halligan, Fink, Marshall, & Vallar, 2003; Kosinski & Landwehrmeyer, 2005).

A seminal study in 1986 by Alexander, Delong and Strick (1986) presented evidence for five parallel, largely segregated circuits connecting the basal ganglia to distinct cortical regions. As regions of the basal ganglia are known to degenerate in HD, these circuits provided a platform for understanding the various clinical symptoms in HD (Andrews & Brooks, 1998). Each of these five cortico-striatal circuits receive input from several separate, but functionally related, cortical areas; they traverse distinct areas of the basal ganglia, and project back into restricted regions of the frontal cortex, including the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate cortices (see Figure 1). Motor function

is thought to be mediated by the motor and oculomotor circuits, cognitive function by the prefrontal circuits, and mood by the limbic (anterior cingulate) circuit (Afifi, 1994). The five circuits are alleged to process information in a parallel manner and remain both structurally and functionally segregated from one another, although an 'open interconnected model' of these circuits has been proposed by Joel (2001). It has been hypothesised that disruption of these circuits at the level of striatum may result in the motor, cognitive and mood changes evident in HD (Andrews & Brooks, 1998; Joel, 2001; Lawrence et al., 1998).

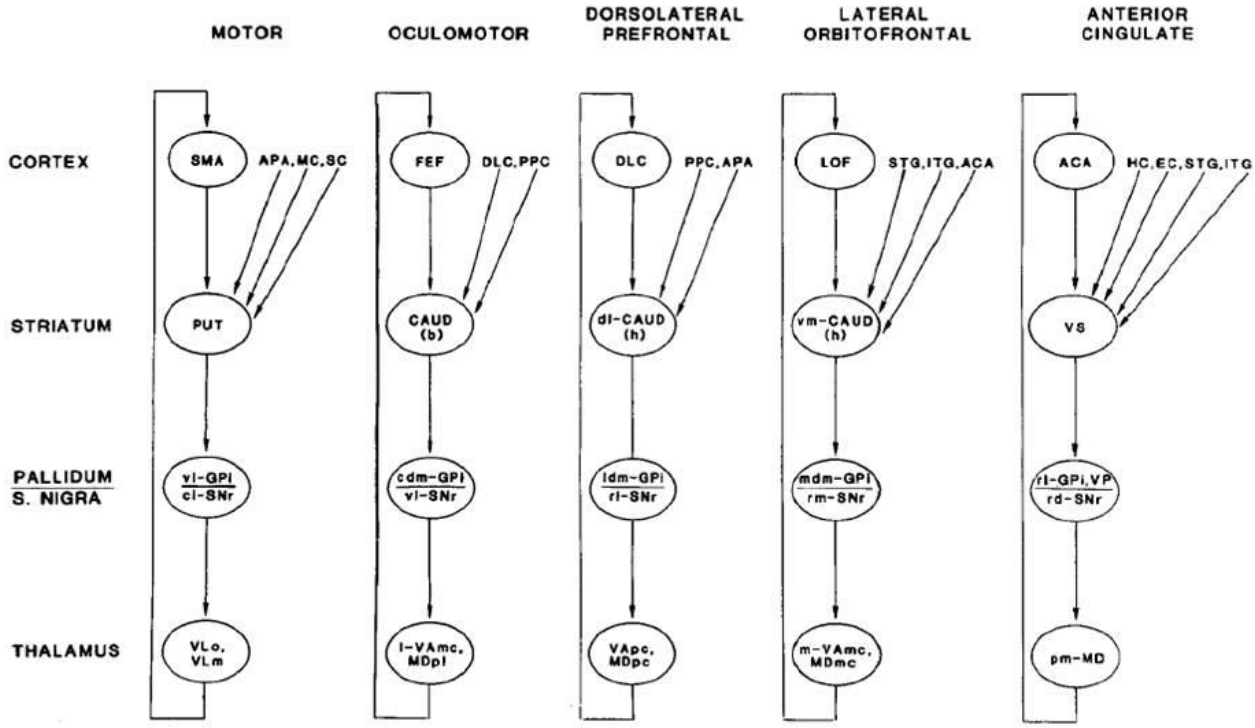

***Figure 1*: Basal-ganglia thalamo-cortical circuits from Alexander, Delong & Strick (1986). Each circuit comprises specific regions of the cerebral cortex, striatum, pallidum, substantia nigra and thalamus. Abreviations are as follows: ACA anterior cingulate area; APA: arcuate premotor area; CAUD: caudate (b) body (h) head; DLC: dorsolateral prefrontal cortex; EC: entorhinal cortex; FEF: frontal eye fields; GPi: internal segment of globus pallidus; HC: hippocampal cortex; ITG: inferior temporal gyrus; LOF: lateral orbitofrontal cortex; MC: motor cortex; MDpl: medialis dorsalis pars paralamellaris; MDmc: medialis dorsalis pars megnocellaris; MDpc: medialis dorsalis pars parvocellularis; PPC: posterior parietal cortex; PUT: putamen; SC: somatosensory cortex; SMA : supplementary motor cortex; Vapc: ventralis anterior pars parvocellularis; VLm: ventralis lateral pars medialis; VLo: ventralis lateralis pars oralis; VP: ventral pallidum; VS: ventral striatum; cl- caudolateral; cdm-: caudodorsomedial; dl-:dorsolateral; l-:lateral; ldm-:lateral dorsomedial; m-: medial; mdm-: medial dorsomedial; pm: posteromedial; rd-:rostrodorsal; rl-: rostrolateral; rm-: rostromedial; vm-: Ventromedial; vl-: ventrolateral.**

The mechanisms underlying HD neuropathology remain unknown. The normal IT15 gene encodes a protein named huntingtin, which is expressed not only in the brain but also in other tissues, such as muscle, liver and lymphocytes (Walker, 2007). The normal function of this protein, and the effects of the mutant gene, remain poorly understood (Kosinski & Landwehrmeyer, 2005). The CAG repeat found in the huntingtin gene is translated into a polyglutamine tract in the protein. The expansion of this tract results in abnormal conformation changes to the mutant form of the huntingtin protein. HD neuropathology may result from loss-of-function effects to the huntingtin protein (i.e., compromising the normal function of huntingtin), and/or from gain-of-function effects, whereby the expanded tract engages in aberrant molecular interactions that would not normally occur. Studies of HD mice and post-mortem HD brains have shown that fragments of the huntingtin protein form aggregates with themselves and with other proteins with which they interact. However, it is unclear whether this is a protective or adverse cell response. These aggregates are found all over the brain, and are more concentrated in cortical regions than in the striatum, perhaps suggesting that they are not a direct cause of neurodegeneration (Gutekunst et al., 1999). A number of neuropathological processes have been hypothesised to result directly or indirectly from the changes to the mutated huntingtin protein. These include glutamate-related excitotoxicity, the induction of an apoptotic signalling pathway, and mitochondrial dysfunction that causes deficits in energy metabolism (for review see Imarisio et al., 2008).

Diagnosis and prognosis of HD

The symptoms of HD may develop at any age, although clinical onset of the disease is typically between 35 and 45 years of age (Langbehn et al., 2004). The diagnosis may be delayed: the onset of HD is insidious, there is significant variability in symptoms between individuals, and early mood and cognitive symptoms are often not attributed to the disease (Folstein, 1989; Kosinski & Landwehrmeyer, 2005). According to the Huntington Study Group (Kieburtz et al., 1996), the presence of extrapyramidal motor abnormalities, otherwise unexplained, is the method for clinical diagnosis of HD in individuals carrying the HD gene. The Unified Huntington's Disease Rating Scale (UHDRS) Motor Assessment is most commonly used to quantify motor abnormalities and provide an HD diagnostic tool (Kieburtz et al., 1996). These diagnostic criteria are based purely on motor symptoms, and do not

include cognitive or mood measures. Cognitive and mood changes are often reported before the onset of motor symptoms, and thus the accuracy of the UHDRS motor scale for HD diagnoses is limited. In the present study, we used the standard method of diagnosis using UHDRS, but we acknowledge the possibility of early changes in mood or cognitive abilities.

Huntington's disease progresses slowly, with increasing neural degeneration resulting in more severe motor, cognitive and mood symptoms. Earlier onset in HD is associated with more severe symptoms and quicker disease progression, with the juvenile form of HD being particularly severe with rapid progression (Nance & Myers, 2001). The rate of decline is variable, however, and different domains of motor, cognitive and psychiatric functioning do not decline in a uniform fashion (Kosinski & Landwehrmeyer, 2005; Snowden, Craufurd, Griffiths, Thompson, & Neary, 2001). Montoya, Price, Menear, and Lepage (2006) noted that HD individuals have a 'diversity of clinical presentations, rates of progression, and responses to therapy, suggesting existence of different subgroups and possible variations in underlying pathological processes'. Most people with HD die 15-20 years after clinical onset (Mendez, 1994), usually as a result of pneumonia (secondary to dysphagia), cardiovascular disease, cachexia, complications arising from falls and inanition, or suicide (Kosinski & Landwehrmeyer, 2005; Sorensen & Fenger, 1992).

The Total Functional Capacity Scale (TFC) of the UHDRS is the most commonly used measure of disease progression. It has been found to be a more reliable, relevant and reproducible indicator of disease progression than the severity of the motor disorder (Kosinski & Landwehrmeyer, 2005). The TFC is relatively sensitive to deterioration in early and mid-disease stages with an average decline of about 0.6-0.7 per year (Marder et al., 2000). It has limited value, however, for assessing disease progression in presymptomatic or late-stage HD, which yield ceiling and floor effects respectively (Marder et al., 2000).

Structural neuroimaging in HD

Before neuroimaging techniques were developed, the measurement of brain volume required histological examination. This exercise takes considerable time and effort, and severely limits

the extent of the brain that can be examined and the number of participants that can be sampled. Neuroimaging, on the other hand, can be used to examine specific regions of the brain, or the brain in its entirety, within a much shorter period. Structural neuroimaging has been increasingly used as a tool for detecting, monitoring and characterising the disease process in HD. Despite its advantages, neuroimaging studies with HD vary considerably in methodology, and perhaps as a result, findings are often inconsistent. Many studies have grouped together participants in all stages of the disease, with little attempt to distinguish early or late neuropathological profiles. Other studies have addressed this by stratifying participants according to the length of illness (e.g. years since diagnosis), progression of the disease (e.g. TFC stages of the disease, severity of motor symptoms), or in the case of presymptomatic individuals, estimated proximity to disease onset.

Subcortical changes in HD

Changes in the striatum and basal ganglia have been central to pathological models of HD. Consequently, these regions have been the primary focus of early imaging studies in HD. Not surprisingly, MRI studies with HD individuals have consistently reported significant atrophy in the striatum. In the early stages of the disease, assessed as Stage I or II in the TFC, the caudate and putamen already show significant atrophy (Aylward et al., 2000; Aylward et al., 2003; Douaud et al., 2006; Kassubek, Juengling et al., 2004; Peinemann et al., 2005; Rosas & Goldstein, 2004; Rosas et al., 2001; Rosas et al., 2003). Douaud et al. (2006) reported the head and body of the caudate to be reduced in volume by more than half (52-53% and 54-60% respectively) compared with controls. Rosas et al. (2001) found an average volume loss in the caudate of 41%, and Rosas et al. (2003) reported a smaller, but still considerable 23% volume loss in the caudate. Atrophy in the putamen shows a similar level of atrophy in early HD, with different studies consistently reporting 48-53% volume loss (Douaud et al., 2006; Rosas et al., 2001; Rosas et al., 2003). Longitudinal studies have shown the striatum to degenerate at an average of about 4-10% volume loss per year, although this rate of atrophy varies considerably between individuals (Aylward et al., 2000; Aylward et al., 1997; Aylward et al., 2003). The caudate shows the most significant loss over time (Aylward et al., 1997), and HD participants with higher levels of motor symptoms show greatest caudate atrophy

(Aylward et al., 2000). These studies demonstrate a gradual, albeit significant loss of caudate and putamen volume in participants with symptomatic HD.

The genetic marker for HD provides an opportunity to assess brain changes in individuals who are gene-positive but have not developed clinical symptoms of the disease. MRI studies have consistently reported striatal volume loss in presymptomatic HD participants (Aylward et al., 1996; Aylward et al., 2000; Aylward et al., 2004; Campodonico et al., 1998; Kipps et al., 2005; Paulsen, Magnotta et al., 2006; Thieben et al., 2002). Paulsen et al. (2006) found the caudate and putamen to be significantly smaller than controls, with volume losses of 13% and 29% respectively. To assess onset and progression of striatal changes, Paulsen and colleagues divided their presymptomatic group into two groups based on their estimated proximity to symptom onset. The close to onset group had significant atrophy in both the caudate and the putamen, whereas the far from onset group only showed atrophy, and to a lesser degree, in the putamen. In a similar study, Harris et al. (1999) compared the striatal atrophy between a close to onset group (estimated years to onset (YTO) < 6 years) and a far to onset group (YTO > 6 years). Whilst the far to onset group showed no differences from controls, both the caudate and putamen volumes were significantly smaller in the close to onset group.

Other studies have found caudate and putamen atrophy to be apparent as early as 11 and 9 years before onset respectively, with striatal volumes 'nearly identical' before this (Aylward et al., 1996; Aylward et al., 2004). Aylward et al. (2000) investigated the change of caudate volume loss in presymptomatic participants (YTO < 12). Over a period of 36 months the presymptomatic group showed a gradual, but significant loss of caudate volume at an average of 2.43% per year. Perhaps surprisingly, this rate of caudate atrophy was not significantly lower than the mild and moderately affected symptomatic HD groups in this study. This indicates that the rate of caudate change is constant, resulting in a linear decrease in volume, that begins before clinical onset.

Striatal atrophy in HD may not be symmetrical. A number of studies have reported greater volume loss in the left striatum than the right in both presymptomatic HD (Kipps et al., 2005;

Thieben et al., 2002) and early HD (Muhlau et al., 2007; Rosas et al., 2001; Ruocco, Lopes-Cendes, Li, Santos-Silva, & Cendes, 2006). However, others have refuted this finding, and reported atrophy in the striatum to be symmetrical or 'almost symmetrical' (Kassubek, Juengling et al., 2004; Peinemann et al., 2005). The only MRI study that has statistically compared left and right striatal volumes found a significant leftward bias in both the caudate and the putamen; this bias was more apparent in those with greater motor impairment (Muhlau et al., 2007). Muhlau and colleagues posited that leftward–biased striatal loss is caused by increased cumulative lifetime neuronal activity in the left (dominant) compared with the right striatum. The increased activity in this hemisphere may increase pathological processes, such as mitochondrial dysfunction and glutaminergic excitotoxicity, which have been shown to be correlated with neuronal activity.

In a histopathological study, Vonsattel and colleagues (1985) proposed that neuropathological changes in the striatum in HD have a characteristic topographical distribution, starting in medial and dorsal regions, and progressing gradually to lateral and ventral striatal regions. Advanced structural neuroimaging techniques have allowed for the segmentation of the striatum into different sub-regions. In contrast with Vonsattel et al., a recent presymptomatic MRI study reported striatal atrophy to be most concentrated in ventral regions (Thieben et al., 2002). However, a two year follow-up of this study (Kipps et al., 2005) found striatal volume loss more prevalent in both medial and lateral dorsal regions. Moreover, two recent MRI studies with symptomatic HD participants have reported significantly decreased density of grey matter in the dorsal striatum, with relatively sparing of ventral regions (Douaud et al., 2006; Kassubek, Juengling et al., 2004). These findings support a topographical progression from dorsal to ventral regions of the striatum in HD, although this pattern may vary between individuals with HD, and may be less evident before the onset of the disease.

A number of subcortical regions other than the striatum are also affected in HD, although there is greater controversy as to the magnitude and timing of these changes. Douaud et al. (2006) reported globus pallidus (GP) atrophy in participants with early HD to be as marked as striatal areas, with an average of 55-58% volume loss. Rosas et al. (2003) reported a 31% volume loss in the GP. In presymptomatic HD, the external GP was shown to be significantly

smaller than controls, whereas the internal GP was relatively spared (Kipps et al., 2005). Aylward et al. (1996) found GP atrophy in gene-mutation carriers with approximately three years to clinical onset, but not in those further from onset. In contrast, other studies have found no differences in GP volume in presymptomatic participants (Campodonico et al., 1998; Harris et al., 1999). MRI studies have illustrated moderate thalamic atrophy in early HD (Douaud et al., 2006; Fennema-Notestine et al., 2004; Kassubek, Juengling, Ecker, & Landwehrmeyer, 2005) and a 4-6% reduction in thalamic volume in presymptomatic HD (Harris et al., 1999; Paulsen, Magnotta et al., 2006). In contrast, Rosas et al. (2003) found participants diagnosed with HD to have significant volume loss in the nucleus accumbens, brainstem, GP, hippocampus and amygdala, but found no degeneration in the thalamus.

In summary, MRI techniques have played an important role in characterising the progressive structural changes within subcortical regions of the brain, both in symptomatic and presymptomatic HD. Striatal areas are affected most, and show a gradual loss of volume beginning about 6-12 years before clinical onset, with no apparent changes before this. Some studies support a leftward bias, and dorsal to ventral progression of volume loss in HD, although variability in these studies may be indicative of the heterogeneity inherent in HD pathology.

Cortical changes in HD

The last decade of neuroimaging studies has shown that cortical changes not only occur in late-stage HD (as has been revealed by post-mortem histological studies), but that the cortex is affected throughout the disease process. Conventional MRI studies have used manual segmentation methods which are generally restricted to providing a general measure of total brain volume or selected region-of-interest measures. More recent neuroimaging studies have used automated segmentation methods, which can provide efficient structural measures across the entire brain.

It is well-known that cortical atrophy is widespread in late-stages of the disease. An MRI study with deceased HD participants, Halliday et al. (1998) found all seven HD brains to exhibit significant cortical atrophy, with average reductions in the volume of grey matter of

23%. Rather than being localised to frontal areas involved in the basal ganglia-cortical circuits, the cortical atrophy was widespread and relatively uniform across the cortex. In vivo MRI studies also report cortical atrophy in HD. A significant reduction in total grey matter has been reported in studies with HD participants at all stages of the disease[1] (Aylward et al., 1998; Fennema-Notestine et al., 2004; Ruocco et al., 2006), as well as those in the early stage of the disease (Ge et al., 2002; Kassubek, Landwehrmeyer et al., 2004; Paulsen, Magnotta et al., 2006; Rosas et al., 2003). However, total grey matter is a particularly general measure of cortical atrophy, and accordingly has little sensitivity or validity to regional cortical changes. Thus, although some studies report no reduction in total cortical volume in early HD (Aylward et al., 1998; Beglinger et al., 2005) and presymptomatic HD (Rosas et al., 2005) participants, this may obscure significant regional changes within the cortex.

To investigate the cortical changes within specific areas of the brain, MRI studies have traditionally used region-of-interest (ROI) techniques. ROI analysis involves computing overall volume for one or more regions of the brain selected prior to analysis, usually based on prior knowledge or theory of pathology (Apostolova & Thompson, 2007). The ROIs used to study cortical changes in HD participants have varied significantly between studies. Using only the frontal lobe as an ROI, Aylward et al. (1998) found a mildly symptomatic HD group was 'essentially identical to those of control subjects', whilst a moderately symptomatic HD group showed significant reductions (17%) in their frontal lobe volume. Jernigan and colleagues Jernigan, Salmon, Butters and Hesselink, (1991) used four 'anterior' and four 'posterior' cortical regions of the brain, which were further defined as either 'inferior' or 'superior' regions. People with HD had significant volume reductions in the inferior anterior and posterior regions, but not in the superior cortical regions of the brain. In a study with 'very mild to moderate' HD participants using 10 ROIs, Fennema-Notestine et al. (2004) found grey matter reductions in the frontal, temporal, mesial temporal and cerebellar cortices, as well as the insula and cingulate cortex. In contrast, a presymptomatic HD study (Paulsen, Magnotta et al., 2006) found the cerebral cortex was significantly *increased* in volume, with

[1] Intracranial volume (ICV) is defined by the summation of total grey matter (GM), total white matter (WM), and cerebrospinal fluid (CSF; Ge, Grossman et al., 2002).

no difference between the four cortical lobes. The authors theorised that increased brain volume in HD could reflect aberrant brain development in people with HD.

Conventional MRI studies have a number of limitations. They require manual segmentation method, which not only rely on a rater's skill and bias, but are labour-intensive, requiring several days of effort by a trained anatomist (Fischl & Dale, 2000). Because it is impractical to obtain accurate volume measures for the entire cortex, these studies tend to use smaller sample sizes and provide limited information on regional differences of neural atrophy (Ashburner & Friston, 2000). Although ROI analysis can provide a useful and simple measure of volume loss in predetermined areas, its focus on a restricted number of areas means that it does not adequately capture the complex profile of disease progression in HD. In addition, ROI analysis leads to a bias towards unambiguous structures of the brain, such as the hippocampus or the ventricles, or towards non-specific areas of the brain, such as 'the frontal lobe'.

The recent advent of automated MRI methods has enabled a faster, more objective and reproducible approach for studying brain changes. A small number of studies have used automated MRI methods — in particular, voxel-based morphometry (VBM) and cortical thickness mapping — to study the neuropathology of HD. VBM is an automated, whole-brain technique that can provide a comprehensive assessment of morphometric changes in both subcortical and cortical regions. Unlike ROI analysis, VBM can provide an unbiased measure of highly localised regions without the need to define anatomical borders a priori (Ashburner & Friston, 2000). VBM detects differences in the concentration of grey matter on a regional scale after discounting large scale differences in gross anatomy and position. This usually involves a number of automated pre-processing steps that include: extraction of the entire brain into a three dimensional brain MRI image; segmentation into grey matter; white matter and CSF compartments; spatial normalisation of each individual's grey matter image to the same stereotactic space (using a common brain template), modulation for volume changes caused by spatial normalisation; smoothing with a Gaussian kernel filter; and finally, statistical analysis to localise, and make inferences about group differences (Apostolova &

Thompson, 2007; Ashburner & Friston, 2000). The between-group differences in the density of grey matter are presented on a spatial brain map.

VBM studies have illustrated significant cortical changes in HD, although the distribution of these changes varies between studies. These differences are emphasised in studies of early HD. Muhlau et al. (2007) reported significant loss of grey matter density within the frontal, parietal, temporal and occipital cortices of participants in the early and presymptomatic stages of HD, whereas Peineman et al. (2005) reported cortical reductions only in a single cluster in the left anterior cingulate cortex. Two other studies of early HD participants had more consistent findings. Douaud et al. (2006) found grey matter loss centred predominantly around the central and precentral sulcus in both hemispheres, with significant reductions also apparent in the left insula and premotor cortices. Similarly, Kassubek, Juengling et al. (2004) reported reductions in the right precentral gyrus and paracentral lobule, and the bilateral insula. In a recent VBM study comparing brain volumes between symptomatic and presymptomatic HD participants, with no control participants, the symptomatic HD group had reduced grey matter in a number of regions within the parietal, occipital and cerebellar cortices, but surprisingly, no significant differences within the frontal or temporal lobes (Beste et al., 2008).

Only one VBM study to date has compared HD participants in the presymptomatic stage of the disease with control participants. Thieben et al. (2002) compared 18 presymptomatic participants with 16 controls. In addition to atrophy in the left striatum, the presymptomatic HD group had volume loss within two cortical areas: the bilateral insula and the posterior intraparietal sulcus, the latter of which reached corrected significance only in the right hemisphere. The same participants were tested again with identical MRI methodology 22 months later (Kipps et al., 2005). Despite significant volume reductions in a number of basal-ganglia structures over this period, the presymptomatic group showed no changes in cortical grey matter compared with gene-negative controls. These findings suggest that people with presymptomatic HD may present with cortical changes before the onset of motor symptoms, and that these cortical structures may degenerate at a different rate from that of subcortical structures. The authors also raise the possibility that rapid cortical atrophy does occur in

presymptomatic HD, but is more widespread and more variable in location in comparison with the relatively concentrated striatal loss, and therefore harder to detect with a volumetric approach.

These studies clearly indicate that regional cortical atrophy occurs in early and even presymptomatic HD, and can be monitored over relatively short periods of time. In addition, although the findings of VBM studies are difficult to reconcile, cortical changes appear to occur in regions of the cortex outside of the frontal cortex, including parietal, temporal and occipital cortices, perhaps even in presymptomatic HD.

Voxel-based MRI methods have a number of limitations. Firstly, the nature of gray and white matter changes identified with VBM is still poorly understood. In particular, the measure of 'grey matter density' does not directly correspond to a particular morphometric property of cerebral tissues (i.e., volume, thickness, surface area) (Mechelli, Price, Friston, & Ashburner, 2005). Secondly, the transformation of individual MRI data into stereotactic space is insensitive to the range of normal individual variance in cortical morphologic features, such as gyral and sulcal patterns (Dickerson et al., 2008). These transformations can results can result in significant measurement errors. Thirdly, the highly folded nature of the cortex is problematic for VBM methods (Fischl & Dale, 2000). This means, for example, that differences in the volume of grey matter may result from more folding or from thicker grey matter. Volume measurements derived from these methods may suffice to detect gross changes in the cortex, but they do not provide the submillimetre precision necessary to characterise the location and progression of subtle cortical atrophy that may occur in early stages of HD.

Cortical thickness mapping, commonly termed *cortical thinning*, is an automated MRI technique used to measure thickness of grey matter across the cerebral cortex (Fischl & Dale, 2000). Measuring the thickness of the cortical ribbon requires particularly accurate MRI techniques because the cortical ribbon has an average thickness of only 2.5mm (ranging from 1 – 4.5mm). Although histological studies are able to provide accurate measures of the cortical ribbon, brains are analysed post-mortem and as a result are predominantly from

people with advanced stage HD. In addition, these studies are limited by the labour-intensiveness of the measurement techniques, and a small sample size because of the difficulties in collecting postmortem brains (Venkatasubramanian, Jayakumar, Gangadhar, & Keshavan, 2008).

In contrast, cortical thinning provides an efficient and precise measure of differences in thickness across the entire cortex. Difficulties with the highly folded nature of the cortex (discussed above) are surpassed in cortical thinning with an automated surface reconstruction method that maps measures of thickness onto an 'inflated' reconstruction of the brain. This procedure allows for visualization of data across both the gyri and sulci of the entire cortical surface without interference from cortical folding (Fischl, Sereno, & Dale, 1999). In addition, a high-resolution surface-based averaging technique is used to precisely align each participant's cortex to a common surface template by aligning cortical folding patterns. This procedure reduces registration errors considerably, and makes it easier to detect subtle differences in grey matter when comparing data across individuals and groups (Fischl et al., 2008). By generating highly accurate models of both the grey/white and pial surfaces, cortical thinning techniques have shown the capacity to calculate the thickness of the grey matter at any point of the cortex with submillimetre accuracy. Similarly to VBM studies, the between-group differences in cortical thickness are presented on a spatial map. Cortical thickness techniques have been shown to be reliable (Han et al., 2006), and have been validated against manual tracings made on post-mortem tissue (Rosas et al., 2002) and in vivo MRI scans (Salat et al., 2004).

Cortical thickness mapping has recently been employed with HD participants. In a study of 11 participants at different stages of HD progression, Rosas et al. (2002) found regionally specific cortical thinning, which was heterogeneous, even within gyral regions. This thinning occurred early in the disease, and differed among participants at different stages of the disease. Surprisingly, in the participants with early-stage HD, thinning was most prominent over posterior cortical regions of the brain, including the supramarginal and angular gyri and the middle temporal and occipital gyri. With disease progression, cortical thinning progressed to include anterior cortical regions, with more prominent thinning in the left hemisphere (see

Figure 2). When all 11 HD participants in different clinical stages of HD were compared with control participants, the most prominent areas of thinning included the pre- and post-central regions (Brodmann Area [BA] 1, 2, 3 and 4), inferior temporal regions (BA37) and the dorsal occipital cortex (BA17, 18 and 19). The greatest differences were in the order of 1mm, which corresponded to greater than 30% loss of thickness.

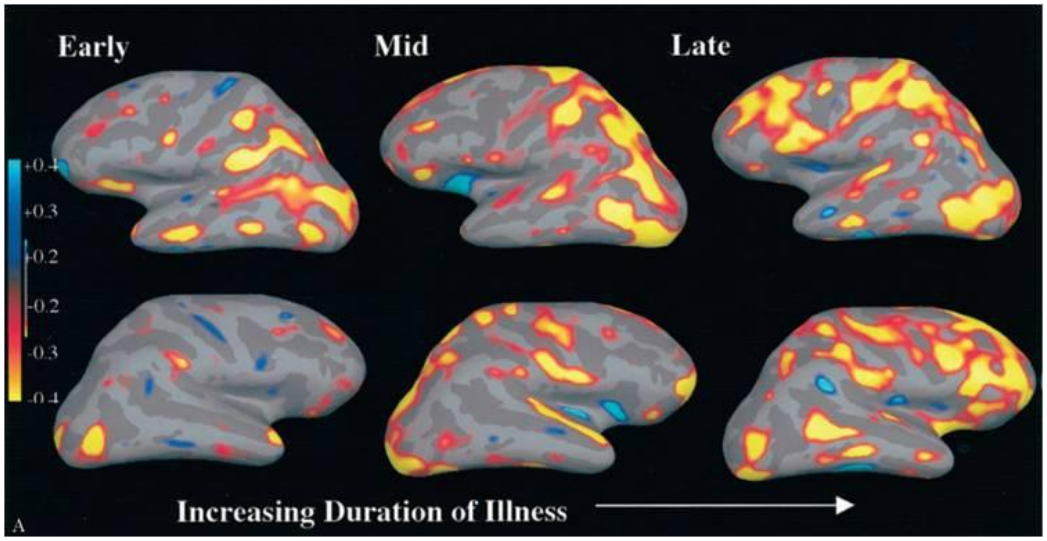

***Figure 2*: Mean cortical thickness maps from Rosas et al. (2002). The surface reconstruction demonstrates mean thickness differences of three different subjects with Huntington's disease (HD) in differing stages of disease. Darker grey areas correspond to sulci; lighter grey areas correspond to gyri. Red to yellow indicates lesser to greater thinning. Left hemispheres are shown on the top, right hemispheres on the bottom. These maps demonstrate cortical thinning predominantly in the posterior cortical regions early in disease, with thinning becoming more generalised and progressing to anterior regions as the disease progresses.**

Rosas et al.'s (2002) study was recently replicated by the same research group (Rosas et al., 2008) with a larger sample size: 33 individuals with HD, ranging from Stage I-IV in the TFC, and 22 age- and sex-matched controls. The distribution and magnitude of the cortical thinning in the HD group were found to be comparable to their previous study, with increased thinning in most posterior regions of the brain (see Figure 3). They found 22 early HD participants (Stage I and II of the TFC) to have significant thinning in the pre- and post-central regions (BA1, 2, 3 and 4), the superior parietal cortex (BA5), precuneus (BA7), occipital cortex (BA17, 18 and 19), portions of the superior temporal cortex (BA41 and 42), and posterior regions of the superior and middle frontal cortex. Interestingly, the anterior cingulate was thicker in the HD group throughout all stages of the disease. Like the previous study of Rosas

et al. (2002), the cortical thinning in early HD was heterogeneous even within gyri, and differed in magnitude from less than 5% (e.g. posterior frontal regions) to more than 20% (e.g. primary visual cortex). Cortical thinning increased with disease progression: Stage II showed greater thinning than Stage I, and by Stage III, most of the cortex was thinned, with the relative preservation of the most anterior frontal and inferior temporal regions. In some of the most severely thinned regions, thinning exceeded 30%.

Thinning of the cortical ribbon illustrated in the above studies is likely to be a result of loss of neuronal cells, glial cells or other cellular components (Rosas et al, 2008). Thinning may also reflect morphological changes to cerebral tissue, for example altered size and number of dendrites which occur in cortical pyramidal cells in HD (DiFiglia et al., 1997; Ferrante, Kowall, & Richardson, 1991).

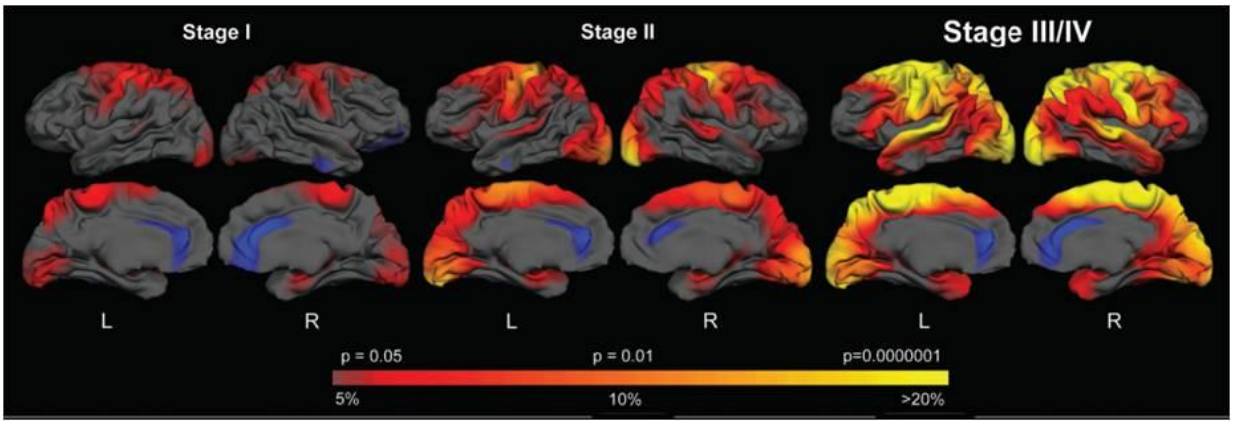

***Figure 3*: Mean cortical thickness maps from Rosas et al. (2008). The colour scale at the bottom represents the significance of the thickness difference, with red to yellow indicating regions of more significant thinning in HD compared to matched controls, The magnitude of the thickness change is displayed as well, transitioning from red (5% loss) to yellow (>20% loss).**

In addition to the two symptomatic HD studies above, Rosas and colleagues have recently published a cortical thinning study with individuals in the presymptomatic stage of HD (Rosas et al., 2005). Fifteen gene-positive participants without motor symptoms were compared to 27 age- and sex-matched control participants. Despite no overall difference in whole brain volumes, cortical thinning was evident in a number of regions across the cortex (see Figure 4). Significant thinning was present bilaterally within superior parietal regions (approximating BA7), occipital regions (approximating BA17, 18 and 19), superior, middle

and inferior temporal regions, precentral gyri, middle and superior frontal regions (approximating BA4, 6 and 8), and left precuneus (approximating BA7). No cortical thickening was reported. Volume measures of the caudate and putamen were introduced as covariates, both separately and jointly, to investigate their potential contribution to cortical degeneration. Introducing these areas into statistical analysis resulted in the reduction of apparent thinning over posterior frontal and superior temporal regions respectively. Importantly, controlling for striatal volumes had no effect on some areas of cortical thinning, implying that cortical degeneration may involve neuropathological processes that are independent of the subcortical degeneration processes. The findings of Rosas and colleagues are highly significant. They suggest that early changes in the cortex may occur in posterior cortical regions and may precede frontal cortical changes. Moreover, these changes may be evident even before clinical onset.

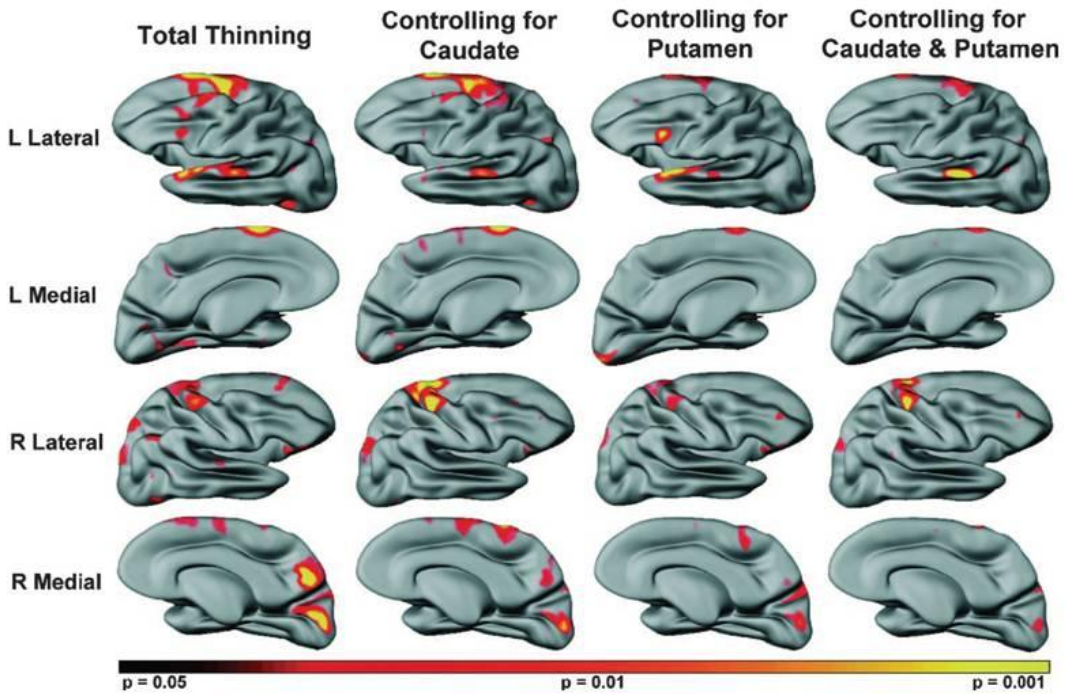

***Figure 4*: Mean cortical thickness maps from Rosas et al. (2005). Significant cortical thinning was present in the presymptomatic HD group as compared to controls. When adjusting for caudate volumes, the intergroup variance in thinning was less prominent over portions of the superior temporal gyrus; when adjusting for putamen volumes, variance was less prominent over posterior frontal regions. Some areas of thinning appeared to be independent of caudate or putamen volumes. Red to yellow indicates lesser to greater thinning (p = 0.05 to p = 0.001).**

In summary, MRI studies clearly indicate regionally-specific changes in the cortex in early and even presymptomatic HD. Although the distribution of these changes differs between studies, cortical changes in HD are evident outside of the frontal cortex, including parietal, temporal and occipital cortices. Only a small number of studies have investigated cortical changes in presymptomatic HD. Surprisingly, these studies have reported changes in posterior regions of the cortex, which may occur even earlier than anterior changes.

Neuropsychological changes in HD

Neuropsychological impairments impact significantly on the daily lives of people with HD, and contribute prominently to loss of independence (Kosinski & Landwehrmeyer, 2005). They may occur earlier than motor symptoms, but are often not attributed to the disease until the person has been diagnosed with HD (Kosinski & Landwehrmeyer, 2005). Different cognitive domains tend to be affected at different stages of the disease and they do not decline in a uniform fashion; some show acute onset, whilst others are more insidious (Snowden et al., 2001). Moreover, cognitive impairments can vary considerably between different individuals with HD. In addition to the variability of cognitive impairments inherent in the disease, neuropsychological studies have varied significantly in their methodology. Like neuroimaging studies, some cognitive studies have combined together participants in all stages of the disease, with little attempt to distinguish early or late neuropsychological profiles, whilst others have stratified participants according to the progression of the disease. The section below is divided into neuropsychological domains, and within each of these subsections, the nature, magnitude and progression of impairments are reviewed.

Psychomotor abilities

Psychomotor performance is significantly impaired in HD, and is indicative of a general slowing of processing speed (bradyphrenia) and execution (bradyarthria or bradykinesia). Cognitive tests requiring psychomotor abilities, including Stroop word reading and colour naming, Trails A of the Trail-making Test (TMT), Symbol Digit Modalities Tests (SDMT) and Digit Symbol (DS), show the earliest and most significant changes in HD, and are most sensitive to disease progression (Brandt, Shpritz, Codori, Margolis, & Rosenblatt, 2002; Ho,

Sahakian et al., 2003; Lemiere, Decruyenaere, Evers-Kiebooms, Vandenbussche, & Dom, 2002, 2004; Snowden et al., 2001). The SDMT and the DS are often the only cognitive tests showing significant differences in presymptomatic HD compared with controls (Kirkwood et al., 1999; Lemiere et al., 2002, 2004). Moreover, these two tasks are highly sensitive to change in both symptomatic and presymptomatic HD (Kirkwood et al., 2000; Kirkwood et al., 1999; Lemiere et al., 2002, 2004; Witjes-Ane et al., 2007). Presymptomatic individuals do not seem to be impaired in the Stroop (Brandt et al., 2002; Campodonico et al., 1998; Campodonico, Codori, & Brandt, 1996; Hahn-Barma et al., 1998; Lemiere et al., 2002, 2004; Witjes-Ane et al., 2003) or the Trail Making Test (Brandt et al., 2002; Hahn-Barma et al., 1998; Lemiere et al., 2002). Psychomotor slowing may affect performance on other cognitive tests, particularly if they are timed.

Curiously, people with HD tend to perform more poorly on tests that are cognitively undemanding rather than on tests that are cognitively demanding. For example, in the Stroop, HD individuals have been found to perform worse on the colour reading and colour word reading conditions than on the interference condition; this pattern is seen in both cross-sectional studies (Snowden et al., 2001; Ward et al., 2006; Zakzanis, 1998) and longitudinal studies (Bachoud-Levi et al., 2001; Ward et al., 2006). Similarly, HD participants were more impaired naming months in forward rather than reverse order; more impaired in time taken to deal cards in the WCST, but not in time taken to complete the task (Snowden et al., 2001), and performed similarly on Trails A and B of the TMT (Ho, Manly et al., 2003; Zakzanis, 1998). Based on these findings, it has been suggested that striatal dysfunction causes people with HD to have difficulty with executing automatic response programs: a deficit that would have a disproportionate effect on undemanding tasks compared with cognitively demanding tasks that demand effort rather than automatic control (Snowden et al., 2001).

Attention

Impaired attention is among the most prominent of cognitive deficits in HD, showing early and progressively severe impairment (Brandt & Bylsma, 1993). Concentration and mental tracking are impaired at every stage of the disease (Folstein, 1989), and attentional span, usually assessed by immediate digit recall, reduces as the disease progresses (Brown &

Marsden, 1988). HD participants show impaired performance on the Brief Test of Attention, a test of auditory divided attention (Brandt, Leroi, O'Hearn, Rosenblatt, & Margolis, 2004; Ward et al., 2006), although no differences are apparent on this test in presymptomatic HD (Brandt et al., 2002). Sprengelmeyer and colleagues (Sprengelmeyer, Lange, & Homberg, 1995) used specific tests of attention to separate out different deficits in 20 mild-to-moderate stage HD participants. In particular, HD participants had greater error rates in tests of focused and divided attention, and were severely impaired in their ability to simultaneously attend to different inputs compared with age- and education-matched controls.

Executive functioning

Executive function refers to a multidimensional construct of cognitive functions of a higher order that enable a person to engage successfully in independent, purposeful, self-serving behaviour (Lezak, 1995). People with HD often exhibit executive dysfunction. This includes deficits in working memory, planning and cognitive flexibility, diminished self-generated activity, and impaired behavioural regulation. These functions are caused primarily by degeneration of striatal-frontal circuits.

Cognitive flexibility / attentional set shifting

A meta-analysis of 36 studies designed to evaluate the magnitude, sensitivity and consistency of neuropsychological tests in HD (Zakzanis, 1998) found 'cognitive flexibility and abstraction' to be significantly impaired in symptomatic HD. The Wisconsin Card Sorting Test (WCST) is a classical test of cognitive flexibility, and more specifically attentional set-shifting. It is associated with a number of striatal-frontal brain regions, including the head of the caudate nucleus (Ashby & Spiering, 2004). HD participants have little or no difficulty forming or maintaining set in this task, but they often have deficits in shifting cognitive set (Georgiou, Bradshaw, Phillips, & Chiu, 1996; Lawrence et al., 1996; Sprengelmeyer et al., 1995) and show significant perseverative behaviour, whereby they persist with, and have difficulty inhibiting a response set that is no longer appropriate to the task.

Although attentional set shifting is often impaired in HD, the WCST does not seem to be an adequate marker of disease progression Despite widespread cognitive impairments, the

WCST shows no decline over three to six years in early to mid stage HD (Snowden et al., 2001; Ward et al., 2006), or even shows an improvement over time in performance attributed to practice effects (Bachoud-Levi et al., 2001; Ho, Sahakian et al., 2003). Moreover, WSCT measures show no differences between individuals with presymptomatic HD and controls (Brandt et al., 2002; Campodonico et al., 1996; de Boo et al., 1999; de Boo et al., 1997; Witjes-Ane et al., 2003).

Computerised analogues of this task, however, may provide more sensitive measures of HD pathology. One such task divides attentional set-shifting into various subcomponents, including a simple reversal stage (where the previously non-rewarded stimulus becomes rewarded and vice versa) and an extra-dimensional shift stage. In this ED shift the previously relevant dimension becomes irrelevant for reward and another previously irrelevant dimension becomes relevant (for detailed description see Roberts, Robbins, & Everitt, 1988). In this task, participants with early ('mildly symptomatic') HD have little or no difficulty on the reversal stage, but often have deficits in the ED shift stage task (Lange, Sahakian, Quinn, Marsden, & Robbins, 1995; Lawrence et al., 1996). Moreover, in one double-blind study even participants presymptomatic for HD made more errors on the ED shift stage compared with age- and IQ-matched gene-negative controls (Lawrence et al., 1998). The set-shifting impairment in HD worsens over the course of the disease, and people with late-stage HD are often not able to shift cognitive set even within the easiest (reversal) stages of the task (Lange et al., 1995).

Lawrence and colleagues (1996) proposed that the progressive emergence of frontal-lobe deficits in HD is related to progressive pathology in the striatum. The dorsal striatum is a component of the dorsolateral prefrontal cortico-striatal circuit, whereas the ventral striatum is associated with the orbitofrontal circuitry. As extra-dimensional shifting and reversal learning have been associated with these two circuits respectively (Dias, Robbins, & Roberts, 1997; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000), the progression of these cognitive impairments may be a result of dorsal to ventral striatal degeneration apparent in HD. Impairments in set-shifting may manifest clinically in HD as inflexibility, and difficulty in multitasking and adapting to change (Kosinski & Landwehrmeyer, 2005).

Planning and decision making

The most widely used task of planning is the Tower of London task, based on the Tower of Hanoi, which assesses the ability to plan an increasing complexity of sequential moves. In a meta-analysis of neuropsychological tests in HD, Zakzanis (1998) concluded that planning was often impaired in HD, with the ToL task discriminating 79% of HD participants from controls (d=1.90). Two computerised versions of this task have been created that control for the psychomotor component of the task. The one-touch Tower of London (Owen, Sahakian, Semple, Polkey, & Robbins, 1995) requires a multi-choice decision about the number of moves a trial requires, and the modified Tower of London (Owen, Downes, Sahakian, Polkey, & Robbins, 1990) has a yoked motor control task which is subtracted from the planning task, providing a purer measure of planning time. Watkins et al. (2000) found that people with early HD produce fewer correct solutions in the one-touch ToL, particularly in trials that required greater demands of planning. People with early to moderate stage HD show impairments on the most sensitive of measures of the ToL (proportion of perfect solutions) but not in the number of excess moves (Lange et al., 1995; Lawrence et al., 1996). They also take longer to plan their moves, even when their scores are controlled for motor response times (Lawrence et al., 1996). Planning impairments become more pronounced in people with advanced HD, who struggle even with the relatively routine and simple 2-3 move solutions (Lawrence et al., 1998). In contrast, people with presymptomatic HD may not have any planning deficits; one double-blind study found that 22 presymptomatic HD participants performed as well as controls on measures of accuracy and latency in the one-touch ToL (Lawrence et al., 1998).

The Tower of London tasks are particularly sensitive to frontal lobe lesions and strongly associated with DLPFC activity in functional neuroimaging studies (Shallice & Burgess, 1989; van den Heuvel et al., 2003). The planning deficits apparent on these tasks in HD may result from degeneration in the 'spatial' cortico-striatal circuit which links the head of the caudate and the DLPFC (Lawrence et al., 1998).

In contrast to the ToL which is sensitive to DLPFC lesions, decision-making tasks (like the Cambridge Gamble task and the Iowa Gambling task) appear to be differentially sensitive to

ventral prefrontal lesions. Watkins and colleagues (2000) found no difference in performance on the Cambridge Gamble task between early HD participants and controls. They proposed a double dissociation between the tests of planning (for instance the ToL) which are subserved primarily by DLPFC circuitry, and tests of decision-making which are subserved by orbitofrontal PFC circuits. Conversely, Stout, Rodawalk, and Siemers (2001) found that a similar aged symptomatic group of HD participants performed worse on the Iowa Gambling test than both matched controls and individuals with Parkinson's disease. These tests have not been used with participants presymptomatic for HD or in the advanced-stages of HD.

Working Memory

Two common measures of working memory, Digit Span and Spatial Span, are consistently impaired in early-stage HD participants when compared to presymptomatic HD participants (Snowden, Craufurd, Thompson, & Neary, 2002) and control participants (Lawrence et al., 1998). In contrast, people with presymptomatic HD have no difficulties in performing either the span forwards or span backwards subtests (Hahn-Barma et al., 1998; Lemiere et al., 2002; Kirkwood et al., 2000; Snowden et al., 2002; Witjes-Ane et al., 2003). Similar findings are reported with a computerised spatial working memory task (Owen et al., 1990), which involves both the mnemonic and manipulation components of working memory. People with presymptomatic HD perform normally (Lawrence et al., 1998), whilst people with early- and moderate-stage HD perform poorly (Lange et al., 1995; Lawrence et al., 1996). Impairments in working memory become increasingly more profound over the course of the disease, although the rate of progression may be more subtle compared with other cognitive functions (Ho, Sahakian et al., 2003; Lemiere et al., 2004). The working memory deficits apparent in HD may result from degeneration in the spatial cortico-striatal loop (Lawrence et al., 1998). This loop involves projections from the dorsal lateral prefrontal cortex (DLPFC) and the posterior parietal cortex to the head of the caudate and back into the DLPFC.

Verbal fluency

Verbal fluency, the ability to quickly generate words, is often used as a test of frontal lobe functioning. Loss of verbal fluency often occurs in early HD (Henry, Crawford, & Phillips, 2005; Zakzanis, 1998) and worsens with disease progression (Snowden et al., 2001).

Individuals with presymptomatic HD have little to no difficulty in either phonemic or semantic tests of verbal fluency (Blackmore, Simpson, & Crawford, 1995; Henry et al., 2005), and these tests are not sensitive to presymptomatic cognitive changes over time (1 - 2.5 years) (Lemiere et al., 2002, 2004). Although the loss of fluency is similar or even greater than that of Alzheimer's Disease (Henry, Crawford, & Phillips, 2004), it is significantly lower than the effects observed with focal frontal lobe lesions (Henry & Crawford, 2004). In a recent meta-analysis of 30 verbal fluency studies, Henry et al. (2005) found HD participants to be disproportionately worse in semantic fluency compared with phonemic fluency; this implies that verbal fluency deficits may be a result of impaired semantic memory and temporal lobe dysfunction. However, when they assessed only the studies that used the same participant sample for both semantic and phonemic fluency tests, they found HD participants to be equally impaired on both tasks. This suggest that HD verbal fluency impairments are likely to be a result of executive dysfunction (i.e., difficulty generating strategies to generate words) and/or generalised cognitive slowing.

Insight/awareness of deficits

Until recently, the degree of insight that people with HD have into their symptoms has received little attention in HD research. Recent studies have shown HD participants to under-report the severity of their symptoms, although this appears to vary significantly between individuals. Ho and colleagues (Ho, Robbins, & Barker, 2006) used the Dysexecutive Questionnaire (DEX) of the Behavioural Assessment of the Dysexecutive Syndrome (BADS) battery to assess level of insight in 75 symptomatic HD participants (mean TFC = 11.89, SD = 0.76). HD participants consistently underestimated the extent of their own dysexecutive behaviours by an average of 26%. Although this figure is lower than in people with traumatic brain injuries, it is twice as high as that found in elderly rehabilitation patients with no neurodegenerative disease. Hoth and collegues (2007) reported similar findings in a study with 66 HD participants who were at a slightly later stage of the disease (mean TFC = 8.6, SD = 3.1). Whilst the HD participants were able to accurately rate their carer's functioning, they consistently overestimated their own behavioural and emotional control and their ability in activities of daily living on the patient competency rating scale. However, there was considerable variability, with some participants acutely aware of their level of functioning.

Memory

Memory impairments are prevalent in people with HD and can significantly affect their ability to work, manage a household or care for themselves (Caine, Hunt, Weingartner, & Ebert, 1978). A large number of studies have provided quantitative and qualitative descriptions of memory in HD, comparing memory performance in HD in both control participants and other neurological disorders. The most common memory tests used in HD studies are tests of verbal learning and memory, including the California Verbal Learning Test (CVLT) and the Rey Auditory Verbal Learning Test (RAVLT). Tests of immediate and delayed verbal and non-verbal memory are also used, including the Logical Memory, Visual Reproduction and Paired Associates subtests of the Wechsler Memory Scale (WMS).

Memory impairments in HD are generally assumed to be secondary to executive dysfunction, which affects the efficiency of which information can be encoded and retrieved. In a meta-analysis of episodic memory using 49 studies (544 symptomatic and 244 presymptomatic participants), Montoya, Pelletier et al (2006) found memory performance in symptomatic HD (including free recall, cued recall and recognition tasks) to be 'profoundly' impaired, with large effects sizes. Moreover, these deficits were present even when the symptomatic participants were divided into 'mild dementia' and 'moderate to severe dementia' groups based on their MMSE and Dementia Rating Scale scores.

In general, studies comparing memory performance between presymptomatic HD participants and control participants have not found significant differences (Lawrence et al., 1998 [pattern and spatial recognition]; de Boo et al., 1999 [WMS and CAVLT]; Brandt et al., 2002 [HVLT]; Soliveri et al., 2002 [Short Tale Test]). Longitudinal studies involving people with presymptomatic HD have had inconsistent results. Some studies have reported no change in memory performance over time in people with presymptomatic HD (Lemiere et al., 2002, 2004). Others, perhaps surprisingly, have found tests of memory performance to be particularly sensitive to change in presymptomatic HD (Campodonico et al., 1996; Wahlin, Lundin, & Dear, 2007), particularly in participants who are closer-to-onset (Wahlin et al., 2007). Although memory deficits are mild or absent in presymptomatic HD, memory functioning declines significantly around the time of clinical onset of HD (Bamford, Caine,

Kido, Cox, & Shoulson, 1995; Lawrence et al., 1996; Snowden et al., 2002); and shows a mild to moderate decline over time (2-6 years) (Bamford et al., 1995; Ward et al., 2006; Bachoud-Levi et al., 2001; Ho, Sahakian, et al., 2003).

Poor memory performance in HD appears to result largely from a person's inability to initiate and carry out the systematic retrieval of stored information (Montoya, Pelletier et al., 2006). Support for impaired retrieval processing in HD comes from studies that have compared performance in free recall and recognition tasks. A number of these studies have found people with HD to have significant difficulties recalling previously learnt information, but their performance improved significantly when tested with a recognition format (Brandt et al., 2004; Butters, Wolfe, Granholm, & Martone, 1986; Lundervold, Reinvang, & Lundervold, 1994). Indeed, this notion of retrieval-based deficits in HD has been used to differentiate HD from other disorders and to differentiate subcortical from cortical dementias in which performance is often not improved with recognition prompts (Paulsen et al., 1995). While the simplicity of this distinction has been appealing, other studies have suggested that recognition memory is also impaired in HD (Beatty & Butters, 1986; Hamilton, Murphy, & Paulsen, 1999). Montoya et al. found no difference between effect sizes in recall tasks and recognition tasks in symptomatic HD participants. There is some evidence, however, that recognition may be less impaired than recall earlier in the disease process: Montoya et al. found the effect size for recognition to be significantly lower than recall in participants with mild dementia (as assessed by the MMSE or DRS), whereas both processes were impaired in participants with moderate to severe dementia. Moreover, the presymptomatic group were impaired in free recall, but not in recognition.

Studies have presented contradictory evidence for encoding impairments in HD, with some studies reporting poor encoding (Wilson et al., 1987) and others reporting no differences from controls (Beatty & Butters, 1986; Granholm & Butters, 1988). The ability to retain information over time (both within the verbal and non-verbal domains) remains relatively intact in people with HD, with no worsening of performance in tests of delayed recall compared with tests of immediate recall when compared with controls (Lundervold et al., 1994; Montoya, Pelletier, et al., 2006).

People with HD are impaired in both verbal and non-verbal tests of memory (Lang, Majer, Balan, & Reischies, 2000; Lange et al., 1995). In their meta-analysis, Montoya et al. (2006) found no significant difference between verbal and non-verbal memory performance. Some differential impairments, however, have been reported between different non-verbal stimuli in memory tasks. For example, Brandt and colleagues (Brandt, Shpritz, Munro, Marsh, & Rosenblatt, 2005) found HD participants to be preferentially impaired in delayed recall of spatial locations compared with delayed recall of object identity. Lawrence et al. (1996) reported that participants with early-stage HD showed differential impairments in pattern recognition compared with spatial recognition, although both were significantly impaired. In the light of recent findings of cortical atrophy in early HD, these differential impairments in visual memory may result from selective damage to cortical areas, for example the dorsal and ventral visual streams (Lawrence et al., 1998).

Although there is significant variability between studies, HD memory impairments are generally assumed to be secondary to executive dysfunction. Thus, memory impairments in HD are assumed to be caused primarily by striatal-frontal degeneration, rather than a classic amnesia resulting from temporal lobe dysfunction (as is the case in Alzheimer's Disease).

Visuospatial abilities

Tests of visuospatial functioning have often been excluded from large-scale studies, because of the preferential focus on functions associated with striatal-frontal circuits (Hahn-Barma et al., 1998; Paulsen, Magnotta et al., 2006). Most studies that do assess visuospatial functioning in HD have combined together participants in all stages of the disease, rather than distinguishing between early or late neuropsychological profiles. Consequently, it is unclear how early in the disease process visuospatial abilities are affected, and how quickly they deteriorate. Nonetheless, a number of studies have illustrated a wide range of significant impairments in tests of visuospatial functioning in HD.

A meta-analysis of standard neuropsychological tests before 1998 found HD participants to be significantly more impaired on the visuospatial composite (consisting of WAIS

Performance IQ subtests and the Rey Copy) compared with the verbal composite (Zakzanis, 1998). However, the two tests with the greatest effect sizes, digit symbol coding and block design, are timed psychomotor tasks, and thus confounded by cognitive slowing and motor deficits. The copy condition of the Rey Complex Figure showed a moderate effect, although this task can also be confounded by executive dysfunction and motor impairments. The WAIS-R Performance IQ subtests (Picture Completion, Picture Arrangement and Object Assembly), although not pure tests of visuospatial functioning, all showed smaller effect sizes that discriminated fewer than 65% of HD participants from control participants.

In the last decade, however, a number of studies have shown participants with HD to be significantly impaired in a range of specific visuospatial functions. People with symptomatic HD perform more poorly than controls in a number of tests of visual perception, including the Judgement of Line Orientation Test (Lineweaver, Salmon, Eberson-Shumate, & Corey-Bloom, 1999; Soliveri et al., 2002), the Figure Matching test (Lineweaver, Salmon, Bondi, & Corey-Bloom, 2005; O'Donnell et al., 2003) motion discrimination (O'Donnell et al., 2003), facial recognition (Jacobs, Shuren, & Heilman, 1995; Sprengelmeyer et al., 1996) and the Cancellation Test (Arango-Lasprilla et al., 2006; Ho et al., 2004). Many of these tasks, however, have only been used within a single study, and replication is required to confirm visual-perceptual impairments in HD.

HD studies have shown contradictory results in the Visual Object and Space Perception battery (VOSP), a basic screening battery for visuoperceptual and visuospatial functioning. Lemiere et al. (2002) found 21 HD participants performed significantly worse than presymptomatic HD participants on all nine VOSP subtests, although the presymptomatic participants were an average of 10 years younger than the symptomatic participants. In contrast, Lawrence and colleagues (Lawrence, Watkins, Sahakian, Hodges, & Robbins, 2000) found a similar sized and aged sample of HD participants were impaired on only one of the VOSP subtests, Object Decision. Ho and colleagues (Ho, Sahakian et al., 2003) found that the VOSP was not a good indicator of change in HD, with none of the nine subtasks showing a significant difference over a 2-4 year interval.

People with HD appear to have difficulties in tests requiring visuo-constructive and visuo-motor integration. HD participants perform more poorly than controls in the Clock Drawing test (Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992) and the Block Design subtest of the WAIS (Backman, Robins-Wahlin, Lundin, Ginovart, & Farde, 1997; Foroud et al., 1995; Ho, Sahakian et al., 2003; Uc et al., 2006). Most studies have found HD participants perform more poorly on the Rey Copy (Arango-Lasprilla et al., 2006; Backman et al., 1997; Jacobs et al., 1995; Uc et al., 2006), although some have reported equally accurate copy performance (Brouwers, Cox, Martin, Chase, & Fedio, 1984; Jason et al., 1988). Brandt et al. (2004) reported a group of 21 HD participants had 'substantial spatial deficits' illustrated by performance in Developmental Test of Visuo-motor Integration, which requires participants to copy drawings of geometric shapes. Although these findings suggest significant visuo-constructive impairments in symptomatic HD, all of these tests involve motor responses, and thus may be confounded to some extent by motor impairments.

A number of studies have found HD participants to show poorer performance in tests of mental rotation. Lineweaver et al. (1999) found 18 symptomatic HD participants showed significant impairments in tests of egocentric mental rotation (i.e., mentally rotating a representation of oneself). The Money's Roadmap Test requires participants to mentally orientate themselves through a visual roadmap by judging the direction of each turn on a specified route. HD participants were impaired in the Roadmap turns that required them to mentally rotate themselves by 180º, but not in the turns requiring a smaller degree of personal rotation (0º and 90º). These latter participants also had significant difficulties in the stick construction task when they were required to copy patterns opposite them, but not when copying patterns alongside them. They were also impaired in a right-left orientation test when they were identifying the laterality of body parts on an examiner facing them, but not when referring to their own body parts. Bylsma and colleagues (Bylsma, Brandt, & Strauss, 1992) also found HD participants performed poorly on two tests of egocentric mental rotation, with slower performance on the Roadmap Test, and lower accuracy on the turn but not the no-turn condition of the Route Walking task. In a large-scale 12-month longitudinal study, Snowden et al. (2001) found 87 HD participants showed mild deterioration ($p = 0.05$) in the Roadmap Test accuracy score compared with controls, while not performing the task more slowly.

These results suggest that HD participants have specific impairments in mental rotation abilities that are not simply a secondary effect of bradyphrenia or bradykinesia. In a test of extrapersonal mental rotation involving mental rotation of stick figures, Lineweaver et al. (2005) found HD participants performed more slowly and less accurately than age-matched controls. Moreover, the HD participants' speed of mental rotation (although not accuracy) decreased abnormally with increasing angle of orientation. These studies suggest that people with symptomatic HD may show impairments in both egocentric and extrapersonal mental rotation.

Visuospatial functioning has also been assessed in participants who are presymptomatic for HD. In contrast to symptomatic HD studies, most presymptomatic studies have found no significant impairments of visuospatial functioning in presymptomatic individuals. Most studies have found no difference in the WAIS Performance IQ subtests, including Block Design, Picture Arrangement and Object Assembly (Blackmore et al., 1995; Brandt et al., 2002; Campodonica et al., 1996; de Boo et al., 1997; Diamond et al., 1992; Foroud et al., 1995; Kirkwood et al., 1999). Conversely, one large-scale study (Kirkwood et al., 2000) found that 171 asymptomatic HD gene carriers were significantly impaired on Picture Arrangement compared with 414 controls. However, this test is not specific to visuospatial functioning, and other factors, including executive dysfunction, could contribute to these findings.

People with presymptomatic HD have not performed significantly worse than controls in a number of visuo-perceptual and visuo-spatial tests. These include cancellation and line bisections tests (Gomez-Tortosa, del Barrio, Barroso, & Ruiz, 1996); tests of motion discrimination (O'Donnell et al., 2003); the Judgement of Line Orientation test (Blackmore et al., 1995; Soliveri et al., 2002); facial recognition (Diamond et al., 1992); and the Hooper Visual Organisational Test (Gomez-Tortosa et al., 1996). Presymptomatic participants do not differ significantly from controls on the Rey Complex Figure Copy (Wahlin et al., 2007), even when the inaccuracy of lines was overlooked to control for motor deficits (Gomez-Tortosa et al., 1996). In contrast to symptomatic HD participants, presymptomatic participants were not impaired in tests of egocentric or extrapersonal mental rotation tasks,

including the Roadmap Test (Brandt et al., 2002; Bylsma et al., 1992; Campodonica et al., 1996), the Shepard-Metzler mental rotation test (Wahlin et al., 2007), Extrapersonal Orientation test (Campodonica et al., 1996) and the Route Walking test (Bylsma et al., 1992).

Although the studies above consistently indicate that visuospatial abilities of presymptomatic participants are not impaired, other studies have shown that subtle visuospatial deficits are evident in presymptomatic participants who are closer to clinical onset. Wahlin et al. (2007) found individuals in a close to onset group (YTO<15 years) to be significantly impaired in a mental rotation task and the Rey Complex Figure Copy compared with control participants. In contrast, the far from onset group (YTO>15 years) showed no significant impairments in these tests. Brandt et al. (2002) found close to onset participants (YTO<8.11 years) had poorer performance on the Block Design test and Roadmap Test than far to onset participants (YTO>8.11 years). Similarly, Snowden et al. (2002) reported a close to onset group showed worse performance in Roadmap accuracy and completion times compared with a far from onset group. These findings indicate that subtle visuospatial deficits may occur before clinical onset.

Visuospatial deficits have typically been explained by models of striatal degeneration (Lineweaver et al., 2005; Brandt et al., 2005) or late-stage posterior cortical atrophy. However, evidence of changes in the parietal and occipital cortices in early and presymptomatic HD imply that posterior cortical degeneration may play a role in early visuospatial impairments in HD.

Language abilities

Language structure, including vocabulary, grammar and syntax, is usually preserved until advanced stages of the disease (Lezak, Howieson, & Loring, 2004; Podoll, Caspary, Lange, & Noth, 1988). Zakzanis (1998) found verbal skills were the least impaired cognitive functions in HD. Performance in confrontation naming, using the Boston Naming Test, is generally intact (Zakzanis, 1998), although mild naming impairments may be present (Smith, Butters, White, Lyon, & Granholm, 1988); these may be secondary to semantic processing deficits (Chenery, Copland, & Murdoch, 2002) or visual recognition deficits (Podoll, 1988).

However, speech becomes simplified, illustrated by utterances that are shorter and less informative (Murray, 2000). Articulation and prosody worsen as a result of involuntary respiratory or vocal movements (Brandt, 1991). With disease progression, and the loss of voluntary control over muscles of speech and breathing, people with HD eventually cease talking altogether (Lezak et al., 2004).

Mood and personality changes

Mood and personality changes often constitute the most distressing aspect of HD for patients and their families (van Duijn, Kingma, & van der Mast, 2007). They are complex and wide-ranging (Bates et al., 2002), and may include both psychiatric disorders as well as distinctive features of HD pathology (Rosenblatt, 2007). It is often difficult to determine whether the causes of HD psychiatric symptoms are a direct result of pathological changes, or are secondary responses to the difficulties inherent in HD.

Reviewing psychiatric changes in HD is difficult, because studies have used different assessment methods with varying definitions of psychiatric symptoms (van Duijn et al., 2007). However, these symptoms are unmistakably more common in HD than in the general population, and involve close to 100% of people in some studies (Paulsen, Ready, Hamilton, Mega, & Cummings, 2001). Depression is common, with approximately 30-40% having episodes that meet Diagnostic Statistical Manual (DSM) criteria for major depressive episodes (Rosenblatt, 2007). Depressed mood is reported in 35-69% of persons with HD, depending on the instrument used (Paulsen et al., 2001; Rosenblatt et al., 2007). The rate of suicide in HD is alarmingly high: about 5-10 times that of the general population, and subsequently the cause of 5-10% of HD deaths (Naarding, Kremer, & Zitman, 2001; Rosenblatt, 2007). Duff, Beglinger et al. (2007) found that subtle subclinical depressive symptoms were more common in presymptomatic participants compared with controls; however, more studies are required to assess rates of major depression in this group. No apparent relationship between depression and disease duration has been shown, although it may correlate negatively with cognitive symptoms, because of decreasing insight (van Duijn et al., 2007). Somatic symptoms, such as weight loss, insomnia and fatigue, may lead to over-diagnosis of depression in HD.

Obsessive-compulsive symptoms are also common in HD. These symptoms, including repetitive behaviours and speech, inflexibility, perseveration and preoccupation with idiosyncratic topics, may be caused by executive dysfunction, or may occur as an obsessive-compulsive disorder (Rosenblatt, 2007). Mania symptoms are more common in people with HD (5-10%) than in the general population (Rosenblatt, 2007). However, most studies have not used DSM-classification (Naarding et al., 2001), and personality changes common in HD such as disinhibition and irritability may confound these figures (Rosenblatt, 2007). Schizophrenia occurs in only a minority of individuals (3-6%), although psychotic symptoms may be seen in up to 30% of people with HD (Naarding et al., 2001). Anxiety is more common in HD (Paulsen et al., 2001), but a recent review of psychiatric disorders found no systematic studies of anxiety disorders in HD (van Duijn et al., 2007).

HD participants often present with behavioral and cognitive changes related to impaired striatal-frontal functioning, referred to as a dysexecutive syndrome. These symptoms may be difficult to define, but are considered inherent to the disease (Rosenblatt, 2007). People with dysexecutive syndrome may present as apathetic, irritable, disinhibited, impulsive, obsessional, and perseverative (Ho et al., 2006; Rosenblatt, 2007). Large-scale factor analyses of the Problem Behaviours Assessment have shown HD psychiatric symptoms to be divided into three primary domains: apathy, irritability and depression (Kingma, van Duijn, Timman, van der Mast, & Roos, 2008). Apathetic symptoms are most common in both symptomatic and presymptomatic HD, and include loss of energy and initiation, poor self-care and emotional blunting. Apathy disorders have been associated with the anterior cingulate, and accordingly it has been hypothesised that apathy in HD may result from degeneration in the striatal-anterior cingulate circuit (van Duijn et al., 2007). A low threshold for irritability and aggression is particularly common without prior history of a short temper (Paulsen et al., 2001). Irritability symptoms are common in presymptomatic HD (Berrios et al., 2002; Kirkwood et al., 2002) and often worsen with disease progression (van Duijn et al., 2007). The socially inappropriate behaviours apparent in HD, including aggression and disinhibition, are considered to result from degeneration in the striatal-orbitofrontal circuit (van Duijn et al., 2007).

Psychiatric impairments in HD are considered the most amenable symptoms to treat. Depression, psychosis, OCD, and irritability in HD respond readily to medical treatment. Moreover, behavioural management techniques and psychoeducation for people with HD and their caregivers are essential elements of good care (Rosenblatt, 2007).

Relationships between structural MRI and clinical measures in HD

A number of studies have investigated the relationship between brain changes in HD and measures of clinical functioning. This relationship can be examined using correlation or regression analyses between measures of brain volume and behavioural performance, or by comparing brain volumes in HD groups with varying levels of performance. Although most studies have only examined these relationships using the striatum, some studies have included cortical regions, using either region-of-interest (ROI) or whole-brain analyses. The large majority of these studies have included participants diagnosed with HD, rather than participants presymptomatic for HD. This section examines the relationships between brain changes and i) motor symptoms, ii) the Total Functional Capacity Scale, and iii) cognitive performance.

Relationship between brain changes and motor symptoms

A number of studies have correlated basal ganglia volumes with motor impairments, as assessed by the UHDRS motor rating scale, the Quantified Neurological Examination (QNE) motor scale, and fine motor tasks (Aylward et al., 1994; Aylward et al., 2004; Campodonico et al., 1998; Douaud et al., 2006; Harris et al., 1999; Muhlau et al., 2007). Correlational analyses are used to assess whether the variation in brain measures is associated with the variation in motor test scores. Douaud et al. (2006) found that volume loss in a number of subcortical regions, including the caudate, putamen, thalamus and globus pallidus (GP), was significantly correlated with increasing impairments on the UHDRS motor scale, the Purdue pegboard and the Hand-arm test. Similarly, Muhlau et al. (2007) reported striatal atrophy in symptomatic HD participants to be associated with UHDRS motor scores. Aylward et al. (2000) found caudate atrophy in symptomatic and presymptomatic participants to be associated with QNE scores at baseline and at a 37-40 month follow-up assessment, although

no correlation was found for the change in QNE scores between these sessions (for either symptomatic or presymptomatic participants).

Two studies using voxel based morphometry (VBM) investigated the relationship between motor symptoms and brain volumes in HD (Jech et al., 2007; Ruocco, Bonilha, Li, Lopes-Cendes, & Cendes, 2008). They both found UHDRS motor scores to be significantly correlated with the caudate and not the putamen. The two studies showed contrasting distributions of extra-striatal correlations, however. Ruocco et al. (2008) found performance in the UHDRS motor scale of symptomatic HD participants (including participants with juvenile HD) to be significantly correlated with atrophy within the thalamus, insula and frontal cortex. In contrast, Jech et al. (2007) found that UHDRS motor scores correlated with the calcarine fissure and the cerebellum.

Rosas et al. (2008) compared the distribution of cortical thinning in a subset of participants with predominant chorea symptoms and a subset with predominant bradykinesia, matched for age, gender and disease severity. They found that the chorea and bradykinesia groups correlated significantly with regional cortical thinning. The two groups showed overlap of cortical thinning in a number of cortical areas, including sensori-motor areas. Participants with more predominant bradykinesia demonstrated more extensive cortical thinning. This include the premotor and supplementary motor areas, which have a known role in planning and coordination of movement. In contrast, striatal volumes did not differ between the two motor phenotypes. These findings suggest that cortical thinning, in addition to striatum degeneration, may play an important role in motor impairment in HD.

Relationship between brain changes and the Total Functional Capacity Scale

The Total Functional Capacity Scale (TFC), a primary measure of disease progression in HD, also appears to be associated with atrophy in the basal ganglia and cerebral cortex. Rosas et al. (2003) found that the TFC to be significantly correlated with volumes in all selected regions of interest, including the caudate, putamen, GP, nucleus accumbens, hippocampus, amygdala, thalamus and brainstem. Similarly, Douaud et al. (2006) found that the TFC correlated with the caudate, putamen, GP and thalamus (Douaud et al., 2006). Aylward et al.

(2003) found caudate atrophy to be correlated with both baseline and follow-up TFC scores, but not with annual change in TFC scores.

Rosas et al. (2008) found a strong relationship between the TFC and regions of cortical thinning. These relationships were most evident in the sensori-motor and occipital cortices, areas that that were identified to be the first affected in this early-stage HD study. As expected, caudate atrophy also correlated with TFC decline. Not surprisingly, these results show a number of brain regions to be associated with functional impairment in HD. Because of the non-specific nature of the TFC however, the studies above do not determine how each of these brain regions contributes to specific functional changes in HD.

Relationship between brain changes and cognitive performance

A number of studies have investigated the relationship between MRI measures in the striatum and cortex and cognitive performance in HD. These analyses have included global brain measures and conventional ROIs, as well as voxel-based morphology and cortical thinning techniques.

Measures of global brain atrophy, such as total grey matter (GM), are not generally correlated with cognitive test performance in HD (Beglinger et al., 2005; Kassubek et al., 2005), probably because they are not sensitive to regional changes underlying cognitive symptoms. In contrast, ROIs within the striatum and other subcortical regions have shown significant correlations with a number of tasks. In a study with 20 early HD participants, Douaud et al. (2006) found that volume loss in the caudate, thalamus and GP, but not in the putamen, was correlated with performance on the Symbol Digit Modalities Test (SDMT), whereas only caudate atrophy was correlated with performance on the Stroop interference task. In contrast, a study with 10 early HD participants (Beglinger et al., 2005) found only modest, non-significant correlations (0.22-0.67, p values were all > .05) between striatal atrophy and the three UHDRS cognitive tests. Bamford et al. (1995) examined the relationship between changes in striatal volume and cognitive performance over 30- and 42-month follow-up assessments with early HD participants. Striatal volume loss in the HD participants was significantly correlated with poorer performance in ‘psychomotor index’ scores (consisting of

two timed tests: the Stroop and Trail-Making B), but not with measures of memory, visual construction abilities or semantic knowledge. In a small study with only five symptomatic HD participants and five controls, Backman et al. (1997) found 10 of 11 cognitive tasks (assessing psychomotor, executive and visuospatial abilities) were associated with striatal atrophy, and that four of the 11 tasks were associated with thalamic atrophy. Moreover, a measure of frontal lobe volume was correlated with all 11 cognitive tasks assessed, whereas temporal lobe volume did not correlate with any of the tasks. However, because of the small sample size in this study, data was collapsed across the HD and control group, and thus these associations may not be specific to HD pathology. Aylward et al. (1998) found frontal lobe volume, the only ROI used, was significantly correlated with performance in verbal and spatial tests, as well as the MMSE in a group of 20 HD participants in 'mild to moderate' stages of HD. However, these associations diminished when controlling for total brain volume.

Campodonica et al. (1998) investigated similar relationships in presymptomatic HD. They found performance in the SDMT and the HVLT for 13 presymptomatic HD participants showed marginally significant correlations with striatum atrophy ($r = .39$ and $r = .50$ respectively, using age and QNE as covariates), whilst performance on other tests, including the Stroop, Wisconsin Card Sorting Test (WCST), extrapersonal orientation test and the Roadmap Test, showed no correlations with the striatum. Correlational analyses with control participants showed no significant correlations between striatal volume and test performance, suggesting that the HD correlations did not simply represent relationships in the normal brain.

A small number of studies using voxel based morphology (VBM) have also investigated the relationship between brain changes and cognitive functioning in participants diagnosed with HD. VBM has been used to either identify regions-of-interest to be used individually in correlational analyses, or to perform a parametric analysis in which every voxel of the brain, both in subcortical and cortical regions, are systematically correlated with cognitive test scores. Ho et al. (2004) used VBM to correlate scores on a line bisection task with whole-brain MRI volumes with 40 HD participants (19 of whom were presymptomatic). Increased leftward error in this task was significantly correlated with decreased density in the angular

gyrus. No other subcortical or cortical correlations were reported. In another study using VBM, Kassubek et al. (2004) correlated a UHDRS 'total cognitive score' with ROIs showing small clusters of atrophy in a group of 44 early HD participants. Although the cognitive score was significantly correlated with three striatal clusters, it showed no significant correlation with an unidentified 'extrastriatal' cluster. Kassubek and colleagues also investigated the effect of brain changes on cognition by comparing brain atrophy in HD participants with mild and severe impairments in the UHDRS cognitive scale. Participants in the 'cognitive-mild' subgroup showed areas of grey matter density changes in the dorsal striatum and the hypothalamus. In the 'cognitive-severe' subgroup the striatal density changes were more robust and more extensive, extending into more ventral striatal areas, as well as atrophy in the hypothalamus, thalamus, and also cortical regions including the insula and the paracentral lobule.

A similar subgroup analysis was performed by Peineman et al. (2005), who divided 25 early HD participants into those who were least impaired and most impaired at each of three tests of executive functioning: the Stroop interference test, the Tower of Hanoi, and the modified WCST. The cognitive subgroups that were least impaired all showed only slight alterations to the striatum, with no apparent changes outside of the striaum. In contrast, each of the three cognitive subgroups that were most impaired showed extensive volume loss of grey matter throughout the entire striatum. Moreover, these three groups showed significant atrophy bilaterally in the insula, most pronounced in its dorsal part. Perhaps surprisingly, the most-impaired cognitive subgroups did not show greater frontal lobe atrophy. Although these groups were relatively small in size (n = 7-14), these results suggest that structural changes in both subcortical and cortical regions co-occur with a decrease in specific cognitive abilities in people with HD. Unfortunately, no VBM studies to date have assessed brain-behaviour relations in participants presymptomatic for HD.

The relationship between brain changes and cognitive performance in HD has also been investigated in cortical thinning studies. Rosas et al. (2008) regressed surface-based cortical thinning measures against the UHDRS cognitive measures with early-stage HD participants. Each test showed a distinct relationship with regional cortical thinning. For example, worse

performance on verbal fluency correlated with greater thinning measures in both hemispheres, including the precentral gyrus, superior temporal gyrus, posterior superior frontal gyrus, lingual gyrus, precuneus and cuneus. In contrast, worse performance on the SDMT correlated with greater thinning within the right pre-central gyrus and occipital regions including the cuneus. These results suggest that thinning in select cortical regions may contribute to specific cognitive deficits in HD. Interestingly, caudate volumes were correlated with performance on both Verbal Fluency and Symbol Digit, but unlike the cortex, the caudate did not correlate with the Stroop Color Word. This implies that the cortex may contribute to selective cognitive symptoms in HD, perhaps independently of the striatum.

Relationships between cortical thinning and cognitive performance may also be apparent in people presymptomatic for HD. Rosas et al. (2005) found that poorer performance on each of UHDRS cognitive tests was correlated with thinning in a large number of cortical regions throughout the frontal, parietal, occipital and temporal lobes (despite presymptomatic participants not performing significantly worse than controls). In contrast to the presymptomatic HD participants, the control group showed no significant correlations between cortical thickness and cognitive performance. Not surprisingly, the correlations for the presymptomatic HD group were less extensive than observed in the symptomatic study (Rosas et al., 2008). There was, however, considerable overlap in the distribution of correlations between these two studies. There were also discrepancies in the distribution of correlations between the studies, including correlations in the presymptomatic group in cortical regions that did not show correlations in the symptomatic group. These discrepancies may be caused by differences between the participant samples in these studies. For example, age and gender are associated with both cortical thinning (Salat et al., 2004) and cognitive performance (Lezak, 1995). Alternatively, discrepancies between studies may indicate heterogeneity in the distribution of cortical thinning between individuals with the HD gene, perhaps caused by variations in underlying pathological processes.

These brain-behaviour studies suggest that both striatal and cortical degeneration contribute to motor, functional and cognitive decline in HD. A number of factors however, complicate the interpretation of these findings. Firstly, the correlational design of these brain-behaviour

studies can be misleading, particularly given the progressive nature of the disease. As the disease advances, regional measures of brain structure and function may worsen simultaneously, and thus a correlation between these factors could reflect collinearity rather than a cause-effect relation. Accordingly, although striatal volumes consistently correlate with clinical measures, it is unclear whether clinical impairments are caused by striatal degeneration, or other factors associated with disease progression, for example, cortical atrophy.

Secondly, the distribution of cortical regions reported to be associated with clinical measures in HD differs considerably between studies, even for the same tests. Discrepancies between studies may be a result of variability between study methodology (e.g. MRI protocol, population size), variability between individuals (e.g. age, intracranial volume, CAG repeat length, duration of disease), and variability in the tests that were administered.

Thirdly, the cognitive tasks in these studies generally show low specificity for single cognitive constructs. Some studies combined cognitive tasks to yield a total cognitive score (e.g. Bamford et al., 1995; Kassubek et al., 2004). Because different cognitive functions are subserved by different cerebral networks, the combining of multiple tasks has limited validity or sensitivity for assessing regionally-specific brain-behaviour relationships. Most correlational studies with HD participants have used the three UHDRS cognitive tests. Although these tests often reveal early cognitive difficulties in people with HD, they are complex tasks that may draw on a multitude of cognitive domains. In addition, these tests are all timed, and thus may be influenced by slowed processing speed and/or psychomotor speed. Consequently, it is difficult to ascertain to which cognitive or neuropathological changes the brain-behaviour correlations in these tasks correspond.

Lastly, most correlational studies are not based on specific a priori hypotheses. Rather than calculate correlations between specific cognitive tests and the brain regions assumed to be subserved by these tests, they have tended to examine all/any significant correlations in the brain. Although this approach provides explorative information of brain-behaviour

relationships in HD, it lacks the validity and sensitivity that can be provided with a priori predictions.

In summary, studies investigating brain-behaviour relationships in HD have shown measures of the basal ganglia and the cortex to be associated with a number of neuropsychological measures. Only a small number of studies have assessed how cortical changes in HD relate to neuropsychological performance in HD, and even fewer with participants presymptomatic for HD. A number of other variables make it difficult to interpret the findings of these studies, including imprecise imaging measures, non-matched control participants, non-specific cognitive tasks, and limited a priori predictions. Ideally, to understand the onset and early development of the disease process in HD, brain-behaviour research is required for presymptomatic HD participants. These studies should include well-matched controls, cognitive measures subserved by specific regions of the brain, and high resolution imaging, using both a priori region-of-interest predictions and whole brain analyses.

Present study

The aims of this study are three-fold. The main objective is to determine the distribution of cortical thinning in pre-symptomatic HD with a larger sample than used by Rosas et al. (2005) and a well-matched control group. Based on earlier cortical thinning studies (Rosas et al., 2002; Rosas et al., 2005; Rosas et al., 2008), it is hypothesised that cortical thinning will be apparent in people with presymptomatic HD, and that thinning will be more apparent in posterior than anterior (or frontal) cortical regions, compared to age-, gender- and education-matched controls. In addition, to examine the onset and progression of cortical thinning in presymptomatic HD more precisely, participants will be divided into two groups. These will be based on their estimated proximity to clinical onset. Participants closer to clinical onset are predicted to present with greater cortical thinning.

The second aim of this study is to investigate whether cortical thinning in presymptomatic HD participants is accompanied by changes in neuropsychological functioning. To achieve this aim, cognitive tasks were selected based on those cortical regions that previous studies

have shown to be affected in early and presymptomatic HD patients (Rosas et al., 2002; Rosas et al., 2005; Rosas et al., 2008). The cognitive tasks are sensitive to specific cognitive abilities shown to be subserved predominantly by these regions of interest. It is predicted that the presymptomatic HD participants will score relatively lower on tasks sensitive to dysfunction of posterior cortical regions compared with controls. Moreover, it is hypothesised that the HD participants will have differentially lower scores on tasks sensitive to posterior cortical function than on tasks sensitive to frontal cortical function. This pattern of results is predicted to be greater in HD participants who are estimated to be closer to clinical onset.

Thirdly, the relationships between specific regions of cortical thinning and neuropsychological scores will be assessed using correlational analyses. To achieve this aim, both whole-brain and region-of-interest analyses will be conducted between neuropsychological tests and cortical thinning. It is hypothesised that poorer performance in the neuropsychological measures will be correlated with greater thinning in cortical regions that are important during performance of these tasks.

Finally, because psychological symptoms are a significant characteristic of the disease and are commonly experienced in presymptomatic stages of HD, mood assessments were also included. Explorative correlational analyses were used to better understand the relationship between psychological symptoms and cortical thinning.

Chapter Two General method

Participants

All participants were required to be 18 years or older, speak fluent English and be able to give fully informed consent. Participants were exluded from the study if they had a history of neurological conditions or illnesses other than Huntington's Disease (e.g. stroke, epilepsy, traumatic brain injury), a history or current episode of alcohol or drug abuse, or a current psychiatric disorder (e.g. Major Depressive Disorder, Schizophrenia). In addition, all participants were assessed for contraindications to MRI scanning (e.g. claustrophobia, pregnancy, cardiac pace-maker).

Presymptomatic HD participants

The presymptomatic HD (PreHD) group comprised 19 participants (11 males and 8 females) with a mean age of 41.84 years (SD = 11.93), ranging from 22 to 62 years of age. All PreHD participants had previously tested positive for the HD gene. The CAG repeat lengths in the PreHD group ranged from 38 to 45, with a median of 41 (see Table 1). In addition, all PreHD participants were assessed as presymptomatic at the time of the assessment by a clinical neurologist (R.R.) experienced in HD diagnosis, using the Huntington Study Group definition of clinical onset (Kieburtz et al., 1996). This requires the presence of extrapyramidal motor abnormalities, otherwise unexplained. HD gene carriers are considered to be presymptomatic at levels less than or equal to 2 (see Figure 5 for details of this). Of the 19 PreHD participants in this study, one participant was assessed as 0, 12 were assessed as 1, and 6 were assessed as 2 (mean = 1.26, SD = 0.56; see Table 1). The Unified Huntington's Disease Rating Scale (UHDRS) Motor Assessment (Kieburtz et al., 1996) was used to quantify motor abnormalities (a detailed description is provided under Screening tests). Their scores in the Total Motor Score ranged from 0 to 11, with a mean of 4.05 out of 124 (SD=2.68), showing that at most the HD participants had equivocal motor symptoms. The Total Functional Capacity Scale (TFC) of the UHDRS (Kieburtz et al., 1996; Shoulson & Fahn, 1979) was used to assess the functional abilities of the PreHD participants. Participants were included in the study if they had a TFC within Stage 1, i.e, a score of 11-13. Of the 19 PreHD

participants, 18 were assessed as 13/13, and one as 12/13. All of the Control participants were assessed as 13/13. The TFCS was assessed for all participants by the primary investigator (J.D). PreHD participants were recruited via the Auckland HD Community. Twenty-one presymptomatic HD participants enrolled in the study, however two were excluded: one participant scored above the presymptomatic cutoff range in the UHDRS diagnostic scale; and another, who was pregnant, was unable to undergo an MRI scan.

Table 1

Clinical characteristics of the PreHD group

	Mean (SD)	Range
Number of CAG repeats		
Mutant gene	41.44 (2.33)	38-46
Normal gene	18.53 (1.91)	16-22
Total Functional Score (0 - 13)	12.95 (0.23)	12-13
UHDRS Diagnostic Confidence Level (0 - 4)	1.26 (0.56)	0-2
UHDRS Total Motor Score (0 - 124)	4.05 (2.68)	0-11

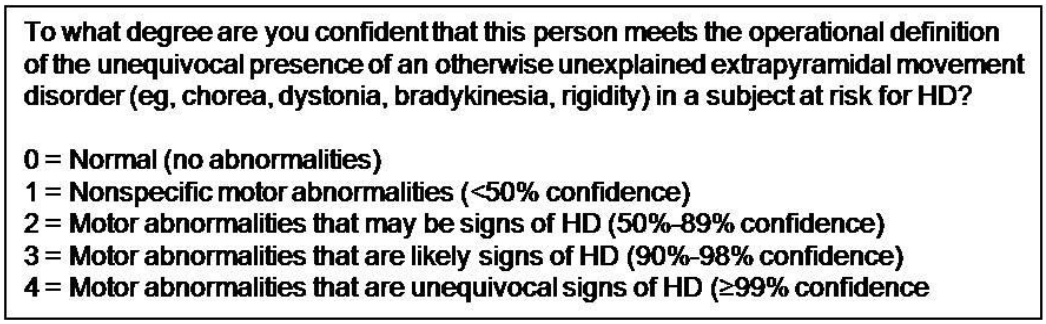

Figure 5: **Confidence rating of Huntington disease motor abnormalities (item 17 of Unified Huntington's Disease Rating Scale, 1998).**

Control participants

The Control group comprised 19 participants (11 males and 8 females) with a mean age of 42.47 years (SD = 12.21), ranging from 22 to 63 years of age. They had no family history of Huntington's disease. Each control participant was age-, sex- and education-matched to an individual PreHD participant. They differed by a maximum of two years of age and one year

of education to their HD counterpart. Control participants were recruited through two forums: word-of-mouth from participants with the HD gene already enrolled in the study; and word-of-mouth and emails from the author to personal contacts. Twenty control participants enrolled in the study, however one was excluded because she was claustrophobic, and consequently unable to undergo an MRI scan.

Demographic charateristics of the PreHD and Control groups are presented in Table 2. No significant differences were found between the two groups in age, t(36) = -0.16, p = .873, years of education, t(36) = -0.08, p = .934, gender, X^2 (1, n = 38) = .00, p = 1.00, or handedness, X^2 (1, n = 38) = 1.78, p = .180.

Table 2

Demographic characteristics for the PreHD and Control Groups

	PreHD group (n=19)	Control group (n=19)
Male: female ratio	11 / 8	11 / 8
Age: mean± SD (range)	41.84±11.93 (22-62)	42.47 ±12.21 (22-63)
Years of education: mean ± SD (range)	13.50±1.98 (10-17)	13.55±1.91 (10-17)
Handedness: right handed (%)	18 (95%)	14 (74%)

Proximity to onset subgroups

Two factors that contribute to the age of clinical onset of HD are years of age and CAG repeat length (Duyao et al., 1993). There was variability in the PreHD group on both of these measures, with age ranging from 22-63 and CAG repeat length ranging from 38-46. Consequently, some participants were more likely to be closer to onset of clinical symptoms (including cognitive changes) than others. To investigate whether estimated proximity to clinical onset affected cortical thinning and cognitive performance, the estimated years to onset (YTO) for each of the PreHD participants was calculated, using a website calculator *(http://www.hdni.org:8080/gridsphere/gridsphere?cid=HD Calculator*) based on data from Langbehn et al.'s (2004) study of HD disease progression. Although this process is discouraged for clinical use (because of the large variance when applied to individuals), it can

be useful in HD research for reducing the variance in test scores inherent in a group with wide ranges of age and CAG repeat length. The median YTO of the PreHD group was used to divide the PreHD participants into a 'close to onset' group (PreHDclose), and a 'far from onset' (PreHDfar). The YTO in the PreHD group ranged from 6.78 to 44.34, with a median of 14.69 years. As the median figure was below the mean, and numerically closer to the next lowest value, compared with the next highest value, this participant was added to the lower (PreHDclose) group. Consequently, the PreHDclose group had an estimated YTO of < 15 years, and the PreHDfar group had an estimated YTO > 15 years. One-way ANOVAs showed no significant differences between the PreHDclose, PreHDfar and Control groups on age, F (2, 37) = .164, p = .850, years of education, F (2, 37) = .010, p = .990, gender, X^2 (2, n = 38) = 2.77, p =.250, handedness X^2 (2, n = 38) = 3.52, p =.172 (see Table 3). As expected, the PreHDclose group had a significantly greater number of CAG repeats than the PreHDfar group, t (17) = -3.19, p = .005.

Table 3

Demographic characteristics for the PreHDfar, PreHDclose and Control groups

	PreHDclose group (n=10)	PreHDfar group (n=9)	Control group (n=19)
Male: female ratio	4 / 6	7 / 2	11 / 8
Age: mean± SD (range)	43.30±11.18 (31-62)	40.22±13.20 (22-61)	42.47 ±12.21 (22-63)
Years education: mean±SD (range)	13.45± 2.17 (10-17)	13.56±1.88 (10-16)	13.55±1.91 (10-17)
Handedness: right handed (%)	9 (90%)	9 (100%)	14 (74%)
Number of CAG repeats			
Mutant gene	42.70±1.83 (41-45)	40.11±1.69 (38-42)	N/A
Normal gene	19.20±2.74 (16-25)	18.33±1.94 (16-22)	N/A
Total Functional Score (0 - 13)	12.90±0.32 (12-13)	13±0 (13)	N/A
UHDRS Diagnostic Level (0 - 4)	1.10±0.57 (0-2)	1.44±0.53 (0-2)	N/A
UHDRS Total Motor Scale (0 - 124)	3.80±3.08 (0-11)	4.56±2.13 (2-8)	N/A

Screening tests

UHDRS motor scale

The Unified Huntington's Disease Rating Scale (UHDRS) Motor Assessment (Kieburtz et al., 1996) was used to quantify motor abnormalities. The UHDRS motor scale comprises standardised ratings of oculomotor function, dysarthria, chorea, dystonia, gait and postural stability. It has 31 items (0 = normal, 4 = severely impaired) providing a total score of 0-124

(see Appendix A). The UHDRS Diagnosis Confidence Level is used to assign HD gene carriers into one of five diagnostic levels ranging from 0 – 4, where 0 = normal and 4 = motor abnormalities that are unequivocal signs of HD (see Figure 5). HD gene carriers are considered to be presymptomatic at levels less than or equal to 2.

Total Functional Scale

The Total Functional Capacity Scale (TFC) of the UHDRS (Shoulson & Fahn, 1979) was used to assess the functional abilities of the PreHD participants. The TFC assesses a person's capacity in relevant functional domains, including employability, financial tasks, domestic responsibilities, and self-care skills. The scale relies on the clinician's assessment of the patient's capacity to perform rather than actual performance. The TFC score range is from 0 to 13, with higher scores indicating higher function. TFC scores are divided into five stages, with Stage 1 indicating high functioning and Stage 5 indicating poor functioning. Participants were included in the study if they had a TFC within Stage 1, i.e, a score of 11-13.

General Procedure

This study was approved by the Northern Y Regional Ethics Committee and informed consent (see Appendix B) was obtained from all participants prior to testing. The Auckland HD field officer informed potential PreHD participants from the Auckland HD Community about the study, and provided them with a Participant Information Sheet with contact details. Control participants were contacted directly by the author (J.D.) and were also provided with a Participant Information Sheet. All participants attended two sessions. Session One involved an MRI scan, which for the PreHD participants only was immediately preceded by the UHDRS motor assessment, performed by R.R. Session Two involved a structured interview and neuropsychological testing. The MRI analyses (Study 1) are described in the next chapter and the neuropsychological analyses (Study 2) are described in Chapter Four.

Chapter Three Study 1: Cortical thinning in presymptomatic HD

As previously discussed, it has been generally accepted that degeneration of the striatum and striatal-frontal circuits causes most of the neuropsychological symptoms experienced in HD (Brandt et al., 2002). A growing body of MRI and histological studies, however, have provided evidence of widespread cortical changes in HD (Montoya, Price et al., 2006). Recent mapping studies of cortical thickness have reported provocative results, showing significant cortical thinning in participants with early HD (Rosas et al., 2002; Rosas et al., 2008) and even presymptomatic HD (Rosas et al., 2005). Moreover, cortical thinning was most prominent in posterior regions of the brain, with relative preservation of anterior frontal regions.

The present study replicated the methodology of Rosas et al.'s (2005) cortical thinning study with a larger sample of presymptomatic HD participants and a control group individually matched for age, gender and education. To examine the onset and progression of cortical thinning more precisely, separate analyses were also conducted for the PreHDclose and PreHDfar groups. The distribution of cortical thinning was determined using two analyses: A surface-based analysis compared thickness measures vertex by vertex[2], and a cortical parcellation analysis compared mean thickness across neuroanatomical regions of interest. The segmentation of MRI data for this study was conducted by Rosas and colleagues in Boston, using identical automated MRI segmentation techniques to their previous studies (Rosas et al., 2005; Rosas et al., 2008). Based on these cortical thinning studies, it was hypothesised that cortical thinning would be apparent in participants with presymptomatic HD, and that thinning would be most prominent in posterior regions of the cortex. In addition, participants closer to clinical onset were predicted to present with greater cortical thinning.

[2] A vertex is a single point on the cortical surface, analogous to a voxel when referring to volume.

Methods

Materials

Scan acquisition

A Siemens Magnetom Avanto 1.5 T was used to obtain whole-brain high-resolution T1-weighted MPRAGE scans. Two scans were obtained for each participant. Image acquisition includes echo time (TE) = 3.31 ms, repetition time (TR) = 2730ms, 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 cortical thickness determination

Cortical reconstruction and thickness determination was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (*http://surfer.nmr.mgh.harvard.edu/*). The two MPRAGE scans for each subject were motion corrected, averaged to create a single image with high contrast-to-noise, and subsequently registered to standard space (van der Kouwe et al., 2005). The resulting averaged volume was used to segment and classify brain volumes into three major brain tissues: grey matter, white matter and CSF. The surface was deformed outwards from the grey/white matter boundary to locate the pial surface (see Figure 6). Estimates of cortical thickness were made by measuring (1) the shortest distance from each point on the white matter surface to the pial surface, and (2) the shortest distance from each point on the pial surface to the white matter surface (Fischl et al., 2001). Cortical thickness at each vertex was computed as the average of these two values. Thickness measures were mapped to the inflated surface of each brain reconstruction, allowing optimal visualization in both sulcul and gyral regions across the entire cortex without being obscured by cortical folding (see Figure 7). Sulcal and gyral features across individual subjects were aligned using a high-resolution surface-based averaging technique that morphs each subject's brain to an average spherical representation/atlas. This allows for accurate matching of morphologically homologous cortical locations among participants, while minimizing geometric distortion. The spherical atlas naturally forms a coordinate system in which point-to-point correspondence between subjects can be achieved. This coordinate system can then be used to create group maps (similar to how Talairach space is

used for volumetric measurements). A surface-based Gaussian smoothing kernel of full-width half maximum (equivalent to 485 iterations in an iterative nearest neighbour averaging procedure) was used to remove noise-induced variations in the measurements. Because the maps are created using spatial intensity gradients across tissue classes, rather than absolute signal intensity, they are not restricted to the voxel resolution of the original data and are therfore capable of detecting sub-millimeter differences between groups (Fischl & Dale, 2000). The output of this procedure is a mean measure of thickness at each vertex on the reconstructed surface for each participant. The technical details of these procedures are described in prior publications (Fischl & Dale, 2000; Fischl et al., 2004; Han et al., 2006; Salat et al., 2004).

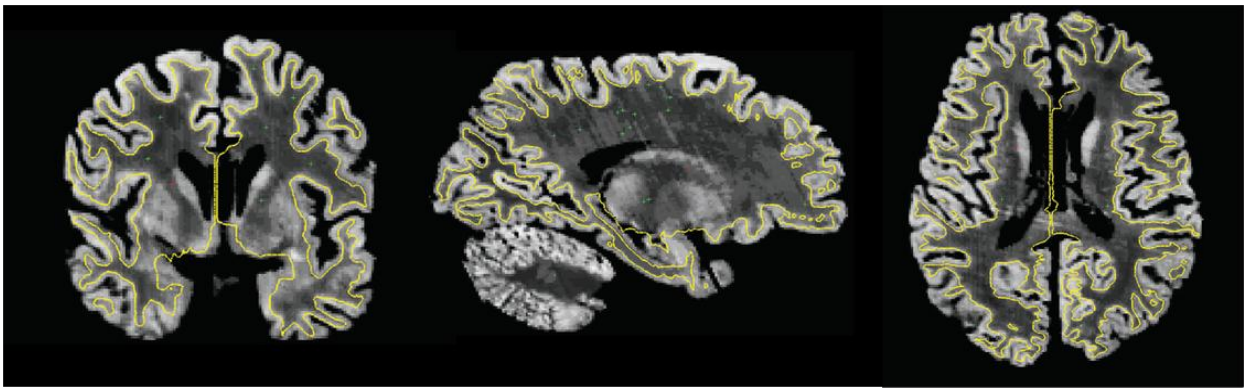

***Figure 6*: Image of a reconstructed MRI dataset from Fischl et al., (2008). The yellow line represents the grey matter/white matter surface, with cortical grey matter external to this line. Coronal, sagittal and axial views are presented from left to right.**

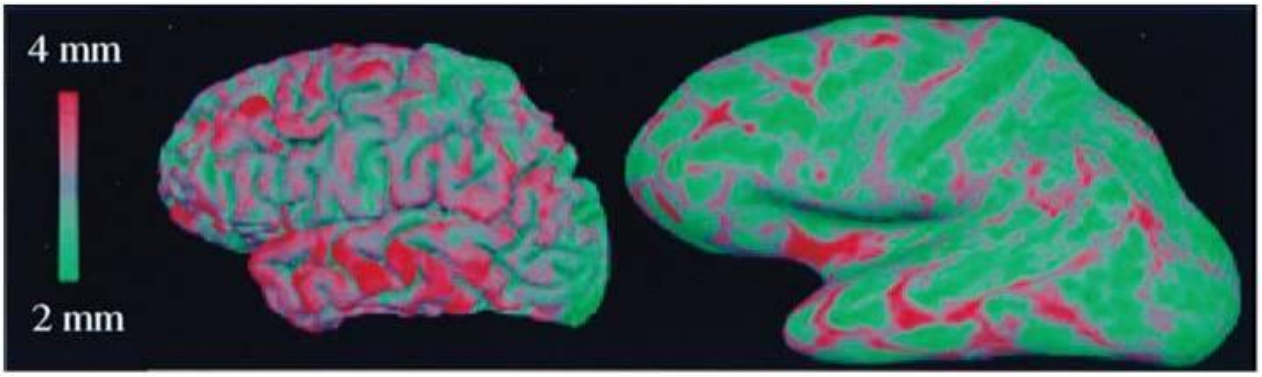

***Figure 7*: Lateral views of the pial surface (left) and inflated cortical surface (right) representations for a single participant. Cortical thickness measurements are overlaid in a red/green colour scale (2-4mm). Adapted from Fischl & Dale (2000).**

Procedure

All 38 participants underwent a 25 minute MRI scan, including set-up and set-down, at the University of Auckland Centre for Advanced MRI. Scanning was conducted in compliance with the relevant protocol and guidelines of the University of Auckland Advanced Centre for MRI (CAMRI). Participants completed an MRI screening and provided written, informed consent prior to scanning (see Appendix C). The screening form outlined exclusion variables for MRI scanning, including pregnancy, certain metallic implants, cardiac pacemaker, seizures, blood disorders, kidney disease and anaemia. Participants were informed that in the event of a clinical abnormality being detected in their MRI scan they would be informed and referred back to their general practitioner. No clinical abnormalities were detected in the MRI scans in this study.

The MRI images were all analysed by research collaborators (H.D.R and S.L.) at the Massachusetts General Hospital Athinoula A. Martinos Center for Biomedical Imaging, Boston, USA. Following the completion of six MRI scans, the author (J.D.) and his primary supervisor (L.T.) travelled to Boston to check and calibrate the neuroimaging procedures. Following this, the remaining participants were scanned. A second trip to Boston was made by the author following the completion of all scans to discuss and analyse the MRI results.

Statistical analysis

Between-group comparisons of cortical thinning were analysed using a vertex-by-vertex procedure and a cortical parcellations ROI procedure.

Surface-based thinning

Comparing cortical thickness at each vertex of the reconstructed cortex is the most precise measure of cortical thinning. A vertex-by-vertex analysis was conducted using a multivariate general linear model to assess the main effects of group in cortical thickness, co-varying for age. This analysis was conducted for 1) the PreHD group (n = 19) and Controls (n = 19), 2) the PreHDfar group (n = 9) and corresponding control participants (n = 9), and 3) the PreHDclose group (n = 10) and corresponding control participants (n = 10). The latter two

comparisons were conducted to assess whether greater cortical thinning was apparent in participants estimated at closer proximity to clinical onset of HD. Thickness across subjects was modelled as [offset + (slope x age + slope x group) + an error term]. Maps showing differences in thickness were constructed using a t-statistic to compare the offsets at each vertex. Multiple comparisons were taken into account appropriately for all analyses, using a false discovery rate correction at 0.05 level of significance (Genovese, Lazar, & Nichols, 2002). To identify regions showing thinning, the thickness difference maps were aligned to an identically sized brain template with anatomical boundaries (see Figure 8), and regions showing differences in thickness were manually traced onto the template using Photoshop 5.0.

Cortical Parcellation analysis

Cortical parcellation analysis provides mean thickness for neuroanatomical regions of the cortex. Desikan et al. (2006) have recently developed a system specifically for surface-based MRI data that automatically quantifies cortical parcellations. This anatomic labelling system subdivides the cortex into 34 neuroanatomical regions per hemisphere (5 parietal, 4 occipital, 11 frontal, 4 medial temporal, 5 lateral temporal, and 5 cingulate; see Figure 8). Mean thickness for each region was calculated by averaging the mean cortical thickness measurements at each vertex within a given region. This parcellation method is valid when compared to manual procedures, with an average intra-class correlation (ICC) of 0.835 across all of the parcellations (Desikan et al., 2006). Moreover, it shows good intra- and inter-rater reliability with average ICC for all structures at 0.998 (Desikan et al., 2006). For a detailed description of the development and validation of this labelling system see Desikan et al. (2006).

Two of the 34 parcellations were excluded from analysis. The corpus callosum was excluded because it is a white matter structure and is only included in the methodology in order to better define the regions around it. The frontal pole was excluded because it is unreliable compared with manual measures (average ICC 0.26). It is probably unreliable because of its definition, namely the region in the most anterior portion of the brain that remains when all other regions near it are outlined (Desikan et al., 2006).

Independent t-tests were conducted to compare parcellation thicknesses in all 64 parcellations (32 in each hemisphere) between the PreHD group and the Control group. One-way ANOVAs were used to compare parcellation thicknesses between the PreHDclose, PreHDfar and Control groups. Because there was no significant difference between these three groups, it was not deemed necessary to divide the Control group into two separately matched groups for PreHDfar and PreHDclose groups. In order to reduce the likelihood of Type I errors associated with multiple comparisons, an alpha level of 0.01 was adopted for the parcellation analyses in this study.

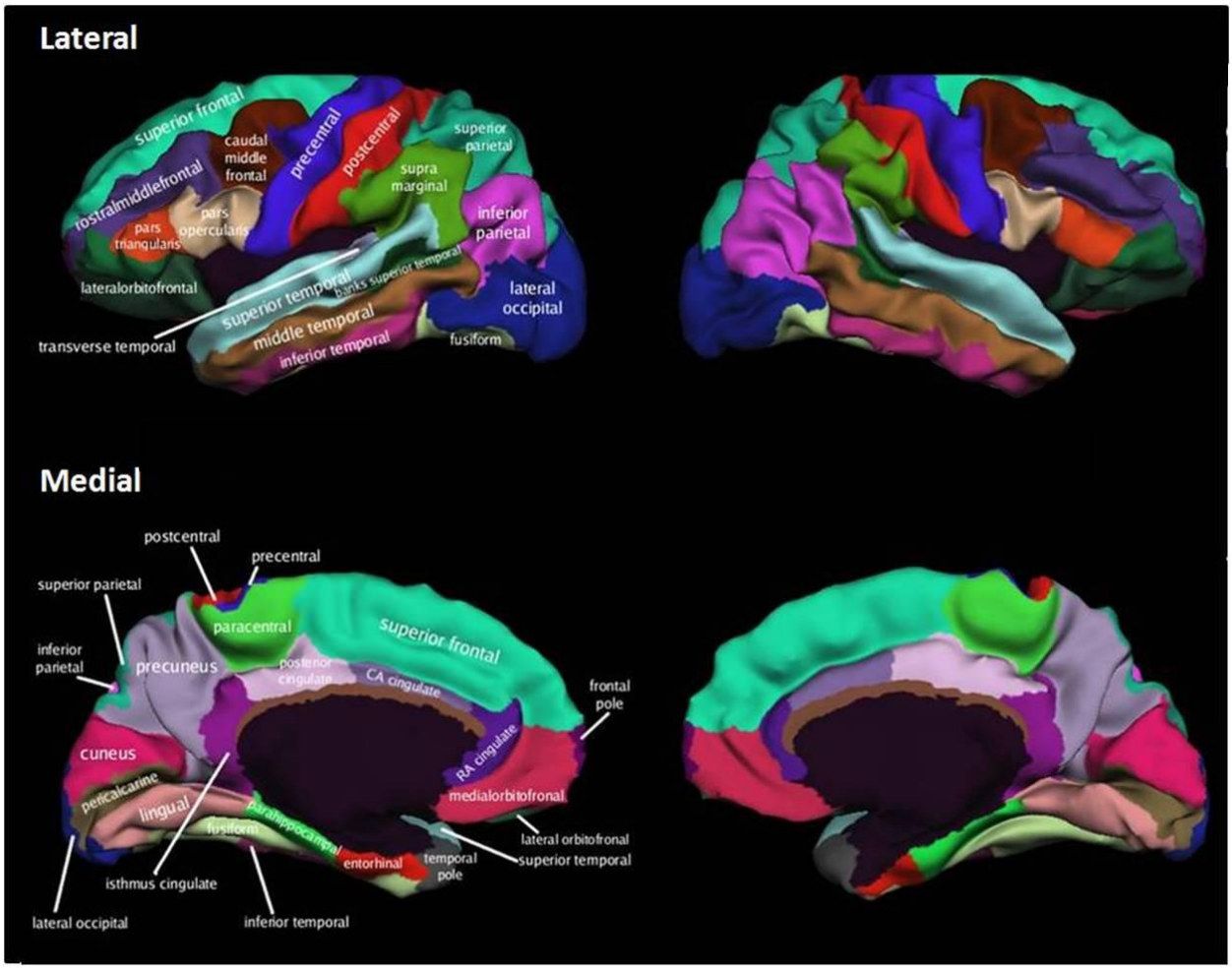

***Figure 8*: 68 Cortical parcellations, shown on a normal view of the brain (left) and an inflated view (right). From Desikan et al. (2006).**

Intracranial and striatal volumes

Intracranial (whole brain) volumes and striatal volumes (left and right caudate and putamen) were determined using an automated segmentation algorithm (see Fischl et al., 2002 for details). A significance level of p = 0.01 was used to reduce the likelihood of Type I errors.

To ensure that group differences in regional measures did not reflect group differences in brain size, a preliminary analysis compared groups in average cortical thickness and total intracranial volume (ICV). Average cortical thickness was calculated as the mean thickness of all 64 parcellations (Desikan et al., 2006). Table 4 shows the average cortical thickness and the intracranial volume for the PreHD group, the Control group, and the PreHDfar and PreHDclose sub-groups. There was no significant difference in average cortical thickness between the PreHD and Control groups, t (36) = .062, p = .775, or between the PreHDclose, PreHDfar and Control groups, F (2, 35) = .111, p = .896. Consequently, this measure was not used as a covariate for between-group cortical thinning analyses.

There was no significant difference in ICV between the PreHD and Control groups, t (36) = -.844, p = .404, although there was a significant difference in ICV between the PreHDclose, PreHDfar and Control groups, F (2, 35) = 5.49, p = .008. Post-hoc comparisons showed the PreHDclose group to have significantly smaller ICV than the PreHDfar group (p = .009) and Control groups (p = .046), whilst there was no significant difference in ICV between the PreHDfar and Control groups (p = .786). The potential confounding effect of the intracranial volume on regional brain volume analyses between these three groups was controlled by using it as a covariate in the statistical tests of striatal volume. Because brain size (i.e. ICV) is not correlated with cortical thickness, ICV was not used as a covariate for the cortical thinning analyses (Dickerson et al., 2008).

Table 4
Average cortical thinning and intracranial volumes

	Control group (n=19)	PreHD group (n=19)	PreHDclose group (n=10)	PreHDfar group(n=9)
Cortical thickness (mm^3): mean± SD	2.24 ± 0.09	2.23 ± 0.10	2.22 ± 0.07	2.23 ± 0.05
Intracranial volume (ml) : mean ± SD	2040 ± 214	1968 ± 307	1804 ± 3158	2149 ± 1703

Results

The cortical thinning results are divided into 1) surface-based analyses, 2) cortical parcellation analyses, and 3) striatal volume analyses.

Surface-based analyses

The vertex-by-vertex statistical maps comparing PreHD participants and Control participants is shown in Figure 9. The PreHD group showed significant cortical thinning in a small number of specific regions of the cortex. In support of our predictions, the most prominent region of cortical thinning was around 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 (approximate Brodmann's Areas[3] [BA] 37, 39, 19). Smaller regions of thinning were also present within the paracentral lobule/posterior superior frontal gyrus and the pars opercularis (approximate BA 44). In contrast, there were regions of thicker cortex in the right anterior cingulate and medial orbitofrontal cortex (approximate BA 12, 25 and 32), and within the left posterior cingulate cortex (approximate BA 23). All changes in cortical thickness were at a significance level of $p < .05$.

It was also hypothesised that participants who were estimated to be closer to clinical onset of HD would show greater cortical thinning. Separate surface-based analyses were performed for the PreHDclose and the PreHDfar groups. The thickness maps comparing the PreHDfar group ($n = 9$) with matched control participants ($n = 9$) is shown in Figure 10. The PreHDfar group showed no significant thinning at a significance level of $p < .05$. However, cortical thickening was present in the right medial orbitofrontal cortex (approximate BA 12). In contrast, the PreHDclose group showed significant thinning; this occurred almost exclusively in the right parieto-temporal-occipital junction, as identified in the PreHD group, with only a small region of thinning apparent in the pars opercula. Cortical thickening was also apparent

[3] Brodmann Areas (BA) are used to map cortical brain regions based on microanatomy and are commonly used for reporting brain regions in neuroimaging studies. Recent studies (Uylings et al., 2005; Amunts et al., 1999) however, have shown that the Brodmanns Areas may not reliably map onto macrostructures (i.e., gyri and sulci). Accordingly, the BAs provided in this study are termed 'approximate'. Devlin & Poldrack (2007) recommend reporting macrostructures which will be more readily identifiable in subsequent studies.

in the PreHDclose group within the right medial orbitofrontal cortex, anterior and isthmus cingulate cortices (approximate BA 12, 25, 32), and within the left posterior cingulate cortex (approximate BA23). Although Figure 10 also shows thickening in the corpus callosum, this is not a valid measure of actual thinning, as the cortical thinning procedures measure the volume between white and grey matter surfaces, and thus cannot be used to measure thinning in this region.

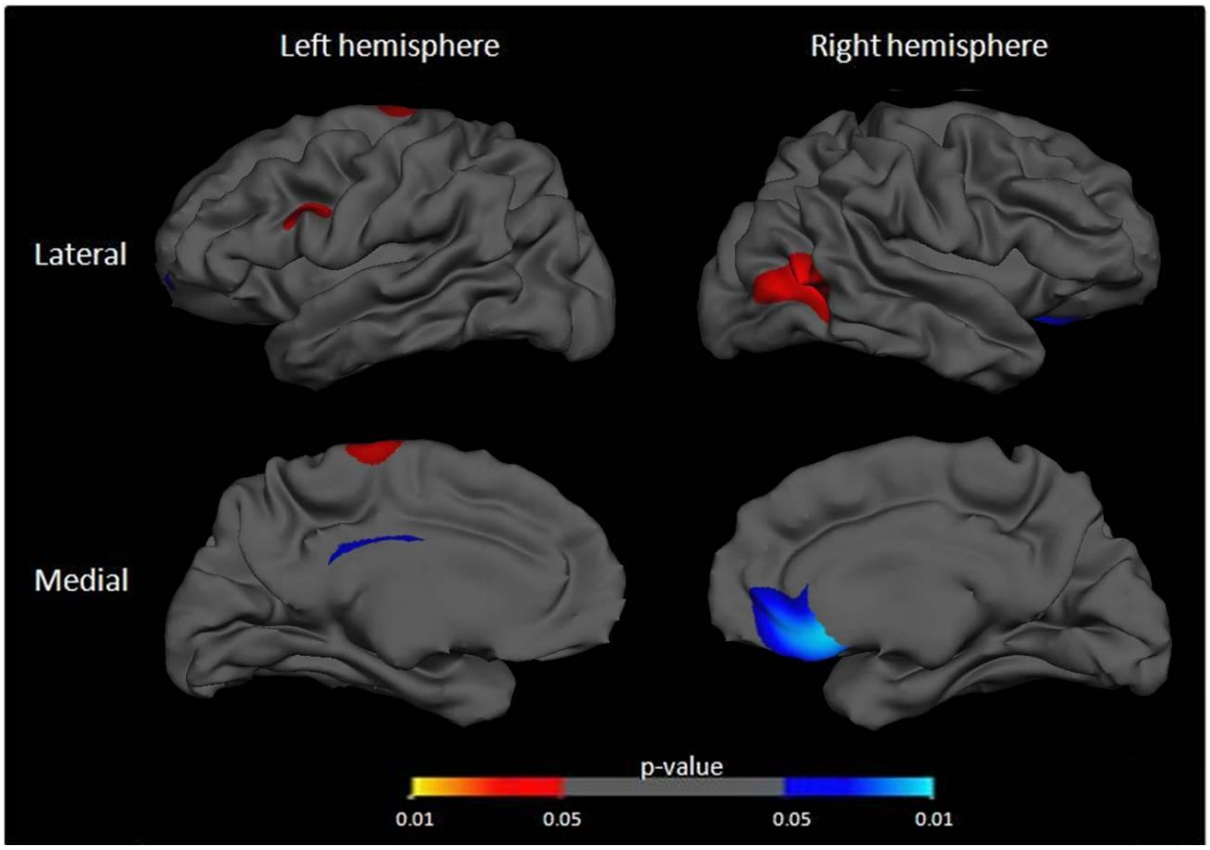

***Figure 9*: The topology of cortical thinning in the PreHD group (n = 19) compared to the matched control group (n = 19). Surface maps of cortical thinning were generated by using a general linear model at each vertex across the entire cortical mantle. Maps are presented on a semi-inflated cortical surface of an average brain. The colour scale at the bottom represents the significance of the thickness change, 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.**

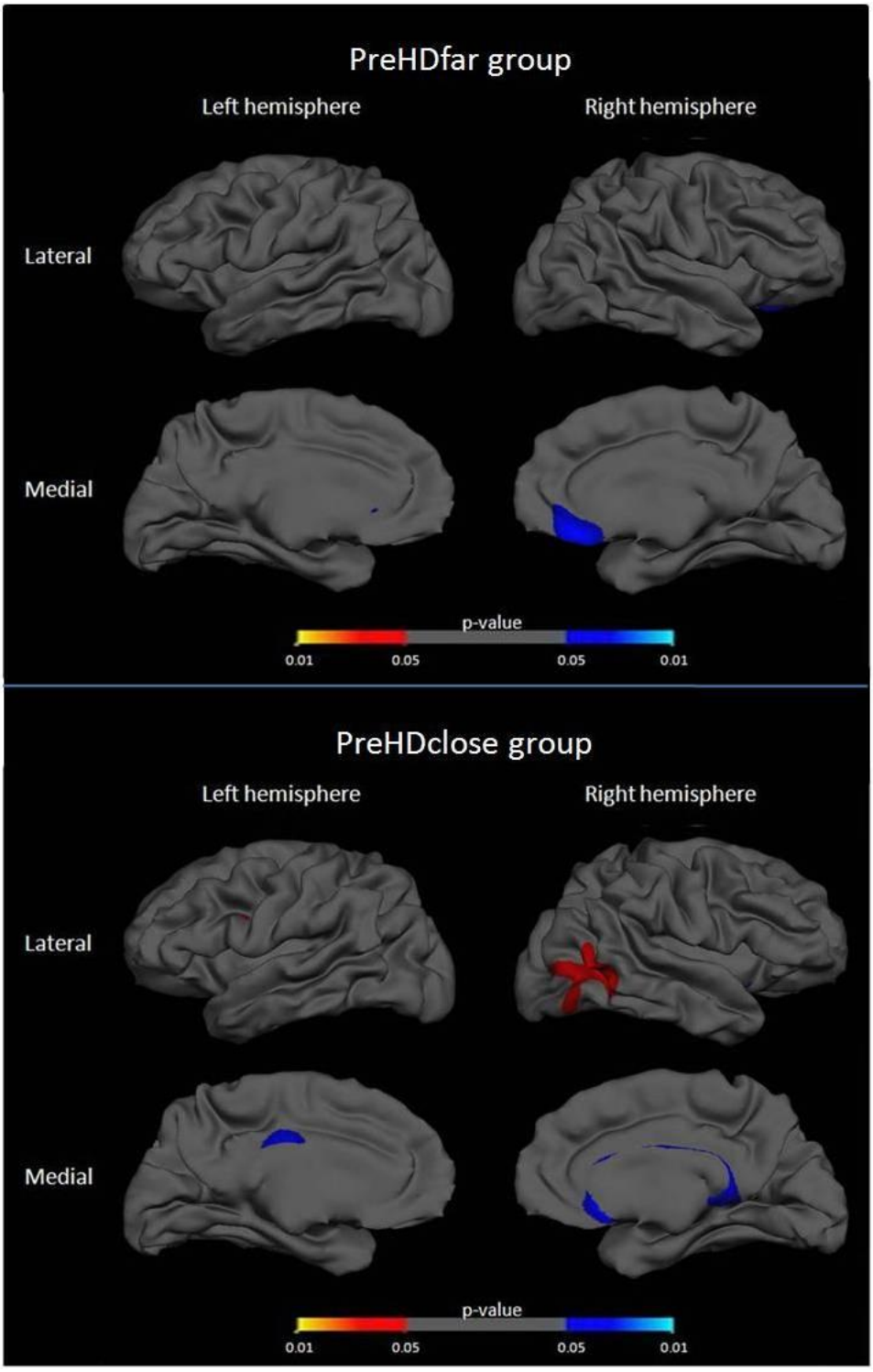

***Figure 10*: The topology of cortical thinning in the PreHDclose and PreHDfar groups. Top: PreHDfar group (n =9) compared with matched control participants (n = 9). Bottom: PreHDclose group (n = 10) compared with matched control participants (n = 10). The colour scale represents the significance of the thickness change, transitioning from $p < 0.05$ to $p < 0.01$. Red-Yellow corresponds to significant cortical thinning and blue/white corresponds to significant thickening.**

Cortical parcellations analyses

The means, standard deviations and between-group statistics for the parcellation thicknesses are presented in Appendix D and E. In contrast to the surface-based analyses, there were no significant differences in thickness between the PreHD and Control groups in any of the 64 cortical parcellations ($p < 0.01$). The average difference in parcellation thickness (mean ± SD) between the two groups was 0.04mm ± 0.03mm, with differences in mean thickness ranging from 0.01mm (right lingual gyrus) to 0.15mm (right entorhinal cortex). Similarly, there were no significant differences between the PreHDclose, PreHDfar and Control groups on any of the 64 parcellations (all p values > .01).

Striatal volume analyses

Although the means of the striatal volumes were all smaller in the PreHD group compared with controls, there were no significant differences between the two groups, (left caudate, t (36) = -1.317, p = .196, right caudate, t (36) = -1.608, p = .116, left putamen, t (36) = -1.547, p = .131, or right putamen, t (36) = -1.664, p = .105).

Based on earlier studies of striatal atrophy it was predicted that the PreHDclose group (YTO of < 15 years), but not the PreHDfar group, would show volume loss in the striatum. One-way ANOVAs were used to compare striatal volumes between the PreHDclose, PreHDfar and Control groups. There was a main effect of group for all four striatal measures: left caudate F (2, 35) = 7.49, p = .002, right caudate F (2, 35) = 5.24, p = .010, left putamen F (2, 35) = 7.44, p = .002, and right putamen F (2, 35) = 6.18, p = .005. In support of the predictions, post-hoc comparisons revealed that the volume of all four regions was significantly lower in the PreHDclose group than the PreHDfar and Control groups (all p-values < .05; see Figure 11). No significant differences were apparent between the PreHDfar group and the Control group (all p-values > 0.05). However, when intracranial volume was added as a covariate, the differences in striatal volume between the three groups reduced, leaving only trends towards differences in the left caudate (p = .095) and left putamen (p = .074).

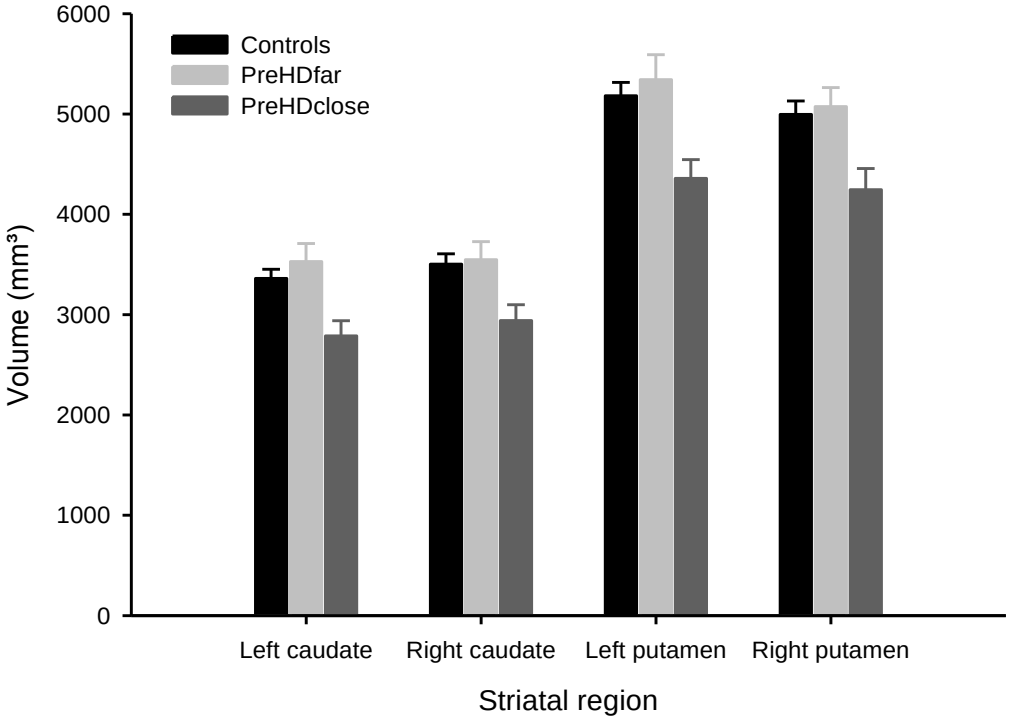

Figure 11: **Volume measures of the striatal regions in the PreHDclose, PreHDfar and Control groups. Volume measures were significantly smaller in the PreHDclose group in all four striatal regions compared with the PreHDfar and Control groups.**

Discussion

This study replicated the methodology of Rosas et al.'s (2005) cortical thinning study with a larger sample of presymptomatic HD participants and a control group individually matched for age, gender and education. It was hypothesised that cortical thinning would be apparent in presymptomatic HD participants, and that thinning would be most prominent in posterior regions of the cortex. It was also hypothesised that participants estimated at closer proximity to clinical onset would present with greater cortical thinning. These hypotheses were examined using both surface-based (vertex-by-vertex) and cortical parcellation analyses. Consistent with predictions, surface-based analyses showed regionally specific cortical thinning in the PreHD group, with the most significant thinning in the posterior cortices. Specifically, there was thinning in the right parieto-temporal-occipital (PTO) junction, extending into small portions of the inferior parietal cortex, the lateral occipital cortex, and the posterior middle temporal gyrus.

Despite using identical MRI methodology to that used by Rosas and colleagues in their presymptomatic study (2005), the results of the two studies showed a number of differences. In particular, the thinning was not as extensive in the present study, with little to no thinning in the superior parietal regions, medial occipital cortex, precentral gyri, middle and superior frontal regions, or the precuneus. Moreover, the distribution of posterior thinning was most prominent in medial, rather than lateral, parietal and occipital regions.

A number of factors may have contributed to the less extensive thinning in the present study. Although the participants in the two studies had similar mean ages and mean CAG repeat lengths, the present study included three PreHD participants with CAG repeat lengths within the 'incomplete penetrance' range of 36-39 repeats (Langbehn et al., 2004). The age of onset for people with CAG repeats within this range is highly variable, and may be significantly delayed compared with people with greater CAG repeat lengths. Therefore, the inclusion of these participants may have reduced the extent of thinning apparent in this study. The less extensive thinning in our study compared to Rosas et al. (2005) may also be explained by the large range in proximity-to-onset in the PreHD group (from 6 to 44 years). Unfortunately, Rosas et al. (2005) did not assess proximity to clinical onset and no direct comparison can be made. The differences in the distribution of thinning (e.g. medial versus lateral posterior thinning) may be indicative of heterogeneity between individuals with the HD gene.

Nevertheless, our results support findings of significant cortical thinning of posterior regions of the cortex in presymptomatic HD participants. Notably, the only VBM study comparing cortical changes in presymptomatic HD and control participants (Thieben et al., 2002) also reported the loss of regionally-specific grey matter in the right posterior cortex, specifically in the intraparietal sulcus.

The cortical regions thinned in the present study have also shown thinning in studies involving participants with early, and more advanced stage symptomatic HD (Rosas et al., 2002, 2008). Our findings are also consistent with a recent volumetric VBM study showing volume loss in middle and superior occipital gyri in early-stage HD (Muhlau et al., 2007). They are also consistent with stereological cell-counting studies that report pyramidal cell

loss in the inferior parietal cortex in post-mortem brain tissue from people with HD (Heinsen et al., 1994; Macdonald, Halliday, Trent, & McCusker, 1997).

Based on previous cortical thinning studies (Rosas et al., 2002; Rosas et al., 2005; Rosas et al., 2008), it was also hypothesised that cortical thinning in posterior brain regions would be greater than in anterior regions. Although small regions of thinning were apparent within the left frontal cortex, they were confined to posterior regions of the left inferior and superior frontal gyri and the paracentral lobule, with no thinning in anterior regions of the frontal lobe. The presymptomatic HD group in Rosas et al.'s (2005) study also showed thinning within the posterior superior and inferior frontal gyri, and, similarly to our study, this thinning was more predominant in the left hemisphere, with only small regions of thinning in the right frontal cortex. The thinning in their study was more extensive than in the present study, particularly in the middle and superior frontal regions, and the precentral gyrus.

Our results are strikingly similar to those of Rosas et al. (2008), who found participants with early-stage HD presenting with thinning in posterior frontal regions, including the paracentral lobule, with no thinning in anterior portions of the frontal cortex. Kassubek et al. (2004) also found paracentral lobule volumes to be smaller in participants with symptomatic HD than controls. Interestingly, the present study shows no sign of thinning in the precentral gyri, which have previously been reported as thinned in presymptomatic (Rosas et al., 2005) and symptomatic (Rosas et al., 2002; Rosas et al., 2008) HD participants, and atrophied in some symptomatic volumetric MRI studies (Kassubek et al., 2004; Douaud et al., 2006; Muhlau et al., 2007).

To assess whether presence or extent of cortical thinning was related to proximity to onset, the PreHD group was divided into close to onset and far from onset groups using the estimated years to onset formula of Langbehn et al. (2004). As predicted, the PreHDfar group in this study (>15 years from onset) showed no cortical thinning, whereas the PreHDclose group (<15 years from onset) had significant cortical thinning, almost exclusively in posterior regions of the cortex. These findings suggest that the cortex may begin to degenerate within 15 years before clinical onset, but changes are not evident before that. The progression from

no thinning in the PreHDfar group to significant thinning in the PreHDclose group provides tentative support for cortical thickness mapping as a valid method for assessing cortical changes in HD.

The PreHD group also showed regionally-specific cortical thickening. The right anterior cingulate and medial orbitofrontal cortices, and the left posterior cingulate, were significantly thicker than in controls. Although Rosas and colleagues did not report cortical thickening in their presymptomatic HD participants (Rosas et al., 2005), they found significant thickening in participants with early, moderate and advanced stages of symptomatic HD (Rosas et al., 2008). Interestingly, the cortical thickening in their study was also located in the anterior cingulate and medial orbitofrontal cortices. Other morphometric studies have also reported increases in brain volume in HD, for example slightly larger frontal lobe volume (Aylward et al., 1998) and increased volume of total grey matter (Paulsen, Magnotta et al., 2006).

It remains unknown whether increased cortical thickness is a pathological process or an adaptive process, or alternatively, an artifact of the imaging protocol. Cortical thickening has been reported in a number of neurological disorders, including spina bifida, medial temporal lobe epilepsy, ADHD, autism and depression (Juranek et al., 2008; McDonald et al., 2008). Rosas et al. (2008) has suggested that thickening of the cortical ribbon could be caused by gliosis, a process involving proliferation of astrocytes in damaged areas of the central nervous system. Indeed, a recent PET study reported increased microglial activation in the anterior cingulate and prefrontal cortices of symptomatic HD participants (Pavese et al., 2006).

Findings of increased thickness of grey matter can also result from decreased myelination (Sowell et al., 2008). Essentially, tissue that appears as cortical grey matter on MRI may actually be unmyelinated peripheral axonal fibres. Consistent with this idea, a number of MRI studies have illustrated white matter changes indicative of myelin breakdown in people both symptomatic (Bartzokis et al., 2007; Bartzokis & Tishler, 2000) and presymptomatic for HD (Paulsen, Magnotta et al., 2006; Reading et al., 2005).

Paulsen, Magnotta, et al. (2006) theorised that increased brain volume in HD could reflect aberrant brain development. In support of this theory, the PreHDfar group showed cortical thickening, but no thinning, indicating that this process could precede cortical thinning. Conversely, Rosas et al. (2005) found no cortical thickening (despite considerable thinning) in their presymptomatic HD participants, implying that thickening may not signify developmental neuropathology in HD.

Although longitudinal studies are required to assess changes in cortical thickening over time, current findings suggest that cortical thickening is not a precursor to cortical atrophy in HD. Firstly, the regions that show thickening in the present study appear to remain thickened in more advanced stages of the disease (Rosas et al., 2008). And secondly, cortical thickening does not appear to precede thinning in other cortical regions that become thinned in more advanced stages of HD (Rosas et al., 2002, Rosas et al., 2008). One possible, albeit speculative, explanation of cortical thickening in HD is that the anterior cingulate and orbitofrontal regions show a regionally-specific pathological process that does not occur in other cortical regions.

An alternative explanation of cortical thickening in HD is that increased cortical thickness is an adaptive process. Juranek and colleagues (2008) posited that cortical thickening in some regions of the brain may preserve neural functioning, and compensate for damage in other regions of the brain.

In contrast to the present study, other studies have reported that the anterior cingulate and prefrontal cortex is *reduced* in size in HD participants. One VBM study (Peinemann et al., 2005) reported the left anterior cingulate to be reduced in volume in participants with early HD, and a recent histological study (Thu, 2006) found neuronal loss in the anterior cingulate in post-mortem brains. It is possible, therefore, that the findings of thicker cortex in HD participants in the present study reflect a methodological artifact. In a study testing the reliability of cortical thickness mapping, Han et al. (2006) concluded that the close proximity of the two hemispheres often causes errors in localising the pial surface of the medial frontal cortex (and anterior temporal regions), resulting in larger variability in thickness measures.

This variability could contribute to the rather perplexing findings of cortical thickening in the PreHD group, and similar findings in Rosas et al. (2008). Replication of this study using VBM analyses could help to determine whether these findings are caused by the methodological artifacts of the cortical thinning protocol or reflect true cortical thickening in people who are presymptomatic for HD. Furthermore, longitudinal studies with presymptomatic HD participants will help ascertain the nature of these changes over time.

Subtle discrepancies between cortical thinning studies in HD could be partly explained by methodological factors. There are a number of instrument-related factors that have been shown to affect cortical thickness measurements based on MRI (Han et al., 2006). The precision of measurements of cortical thickness is constrained by the contrast-to-noise ratio of the MRI image, and can potentially produce unreliable results from one sample to the next. In particular, grey to white matter contrast is known to vary across the cortex, and is particularly reduced in areas that are highly myelinated, including the primary visual, primary motor and primary sensory cortices (Fischl & Dale, 2000; Han et al., 2006). This issue deserves attention because of the prominent thinning noted within these regions in earlier cortical thinning studies with HD (Rosas et al., 2002, Rosas et al., 2005, Rosas et al., 2008). In order to reduce the likelihood of such variations in image contrast, sequences were used that provided high spatial resolution and T1 contrast. Variations in contrast were also reduced by acquiring and averaging two MRI images for all participants in the study. To increase external validity between the cortical thinning HD studies, MRI protocols were used that were identical to Rosas et al. (2005, 2008). To increase internal validity in the between-group comparisons, all 38 participants in our study were scanned on the same scanner and with the same protocol and data processing methods. Moreover, to reduce the variability of cortical thickness associated with age and gender (Salat et al., 2004), and perhaps education, control participants were individually matched for these three variables. Although investigators were not blinded to the grouping of the participants, cortical thickness mapping is a completely automated process and is therefore free from bias. These factors increase the likelihood that our findings represent true cortical thinning in presymptomatic HD, rather than being methodological artifacts. Replication of this study by other research centres and scanners, however, would be a necessary test for reliability.

In contrast to the surface-based (vertex-by-vertex) thinning in the PreHD group, the parcellation analyses showed no significant between-group differences (in thinning or thickening) in any of the 64 parcellations. The parcellations involve relatively large cortical regions, in which the thickness of a large number of vertices are summed together to provide a mean measure of thickness. Although this measure may help identify significant cortical thinning in other neurological disorders, and perhaps more advanced stages of HD, they may be too coarse for assessing subtle changes in the presymptomatic stage of HD. Moreover, the neuroanatomical boundaries used for these parcellations may not correspond to the specific neural networks that degenerate in HD, and thus may not be sensitive to degeneration until thinning becomes more widespread.

Despite the PreHD group showing regions of significant cortical thinning, their striatal volumes were not significantly smaller than controls. The PreHDclose group, however, showed significant loss of volume in both the left and right caudate and putamen (although these significant differences became trends after controlling for intracranial volume). On the other hand, the PreHDfar group showed no differences from controls. This is consistent with other MRI studies that show gradual reductions in striatal volume beginning about 6-12 years before clinical onset, with no changes evident before this (Aylward et al., 1996, 2000, 2004, Harris, 1999).

Cortical changes are often assumed to be secondary to striatal degeneration, for example, by a process of retrograde degeneration of cortical neurons that project to the striatum (Sotrel et al., 1991). Conversely, other researchers have proposed that cortical degeneration may be a primary site of pathogenesis in HD (Wagster, Hedreen, Peyser, Folstein, & Ross, 1994). A recent cell-counting study (Thu, 2008) demonstrated significant neuronal loss in some regions of the cortex, but not others, even when the striatum showed little to no cell loss (using Vonsattel grades of striatal degeneration. This finding suggests that some cortical regions may degenerate earlier or more rapidly than the striatum. The results of our study reveal both cortical thinning and smaller striatal volumes in the PreHDclose group, but not in the PreHDfar group, indicating that changes to both the striatum and selected cortical regions

may occur within a similar timeframe. Longitudinal studies that include both cortical thinning and striatal measures are required to further examine the onset and progression of striatal and cortical changes in people presymptomatic for HD.

In summary, Study 1 supported previous cortical thinning studies showing thinning in the presymptomatic participants, and particularly the PreHDclose group, which was predominantly in posterior regions of the brain. Consistent with previous MRI studies, loss of striatal volume was apparent in participants relatively close to clinical onset.

Chapter Four Study 2: Neuropsychological changes in presymptomatic HD

Introduction

In Study 2 cognitive tests and psychological questionnaires were used to assess neuropsychological changes in presymptomatic HD. The selection of tests was guided by those cortical regions that have shown thinning in people with presymptomatic and early HD (Rosas et al., 2002, Rosas et al., 2005). Accordingly, the tests involved cognitive functions that are subserved primarily by posterior cortical regions. Decisions about tasks were based mainly on findings from functional neuroimaging studies with healthy individuals and neuropsychological lesion studies. Tests that were sensitive to specific regions of the frontal cortex were also used to provide a comparison between cognitive performance on tests heavily dependent on posterior regions and frontal regions. The detailed rationale for the selection of each test, and a table summarising current understandings of cortical regions mediating performance on these tests, are provided in Appendix F.

In addition to selecting tests that are sensitive to specific regions of the cortex, a number of other test criteria was taken into account. Tests that were deemed to show relatively high specificity for a single cognitive construct (e.g. letter mental rotation, unfamiliar face perception) were selected over those with less specificity and those that are more confounded by other perceptual, cognitive or motor components. To reduce potential motor speed confounds, tests were selected that were not dependent on speeded motor responses. Precedence was given to tests that were relatively short in duration and user-friendly, easy to understand and follow. Touch screen tests were included to make the tests more interactive and enjoyable for the participants, as well as to provide measures of motor speed. Brief mood assessments were also included because mood changes are a significant characteristic of the disease and commonly experienced in presymptomatic stages of HD.

Based on previous cortical thinning studies that show prominent posterior thinning early in HD (Rosas et al., 2002; Rosas et al 2005; Rosas et al 2008), it was hypothesised that participants with presymptomatic HD would perform more poorly than controls on measures of cognitive functions subserved by posterior cortical regions. It was also hypothesised that the PreHD participants would be less impaired on tests that are sensitive to frontal cortical functioning, than tests of posterior cortical functioning. This pattern of results was predicted to be greater in HD participants who were estimated to be closer to clinical onset.

Methods

Materials and procedure

Eleven cognitive tests were selected: six tests judged to be sensitive to posterior regions of cortical function, three tests sensitive to frontal cortical function, and two psychomotor speed tasks. The properties of these tests are summarised in Table 5 and are described in detail below. Of the 11 tests, 6 were computerised and 5 required verbal responses to visual stimuli. The computerised tasks were run on a Toshiba laptop with a 14" screen. Three of these six tasks required a touch screen monitor (15" TFT LCD). In addition to the cognitive tests, four psychological questionnaires were selected that required either written or verbal responses.

These tests are discussed under the following sections: psychomotor speed tasks, cognitive tasks sensitive to posterior cortical regions, cognitive tasks sensitive to frontal cortical regions, and psychological questionnaires.

Table 5

Properties of neuropsychological tests selected for this study

Tasks	Construct measured	Instruction modality	Response modality	Timed	Performance measures
Psychomotor Speed					
Motor Screening	Reaction time	Computerised	Touch screen	Yes	RT
Simple reaction time	Reaction time	Computerised	Touch screen	Yes	RT
Tests of posterior cortex					
Judgment of Line Orientation	Visual-spatial perception	Visual	Verbal	No	Accuracy
Hooper Visual Organisation Test	Visual-spatial integration; Object recognition	Visual	Verbal	No	Accuracy
Collision Judgement	Spatial-temporal integration	Computerised	Verbal	No	Accuracy
Benton Facial Recognition	Perception and recognition of unfamiliar faces	Visual	Verbal	No	Accuracy
Roadmap	Right-left orientation; Egocentric mental rotation	Visual	Verbal (Keypad by examiner)	Yes	Accuracy; RT
Letter Mental rotation	Extrapersonal rotation	Computerised	Keypad	Yes	Accuracy; RT
Tests of anterior cortex					
Iowa Gambling task	Decision-making abilities	Computerised	Touch screen	No	Accuracy
Stockings of Cambridge	Spatial planning (and motor control)	Computerised	Touch screen	Yes	Accuracy; RT
Hand Mental Rotation	Personal mental rotation	Computerised	Keypad	Yes	Accuracy; RT

Note: RT: Response time

Psychomotor speed tasks

Motor Screening Task (Lawrence et al., 1996)

A simple motor screening task provided a measure of psychomotor speed. It was also used to familiarise subjects with the testing process and to screen for visual, movement and comprehension difficulties. A flashing yellow and pink cross was presented in random locations on a black background. When touched, the cross disappeared and reappeared in a different location. The task consisted of thirteen trials. The mean response time was computed. Participants were asked to touch the cross on the touchscreen as quickly as possible.

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

This is a test of simple reaction time. A yellow dot appeared in the same location in each trial, within a small yellow circle in the middle of the touchscreen monitor. The time interval varied between each trial response and the onset of the stimulus for the next trial. The task consisted of eighteen trials. The mean response time was computed. Participants were asked to touch the yellow dot on the touchscreen as quickly as possible.

Cognitive tasks sensitive to posterior cortical regions

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

The Benton Judgement of Line Orientation Test (JLOT) is a test of basic visual perception. It assesses the ability of participants to judge the orientation of lines in space. This task was selected as a measure dependent upon the superior parietal cortex, as well as the precuneus and occipitotemporal regions (Dupont et al., 1998; Ng et al., 2001; Ng et al., 2000; Orban, Dupont, Vogels, Bormans, & Mortelmans, 1997; Warrington & Rabin, 1970).

The JLOT consists of a test booklet with 30 items (see Figure 12). For each item, participants were asked to identify which 2 of the 11 exemplar lines were the same orientation as the two stimulus lines. Participants verbally stated their chosen answer to the examiner. Five practice trials preceded the experimental trials. There were no time restrictions and no motor responses are required. Performance was assessed by the percentage of correct responses. The

JLOT has good split-half reliability (r = .84), and very good test-retest reliability (.90) over an interval ranging from 6 hours to 21 days (Benton, Sivan, & Hamsher, 1994).

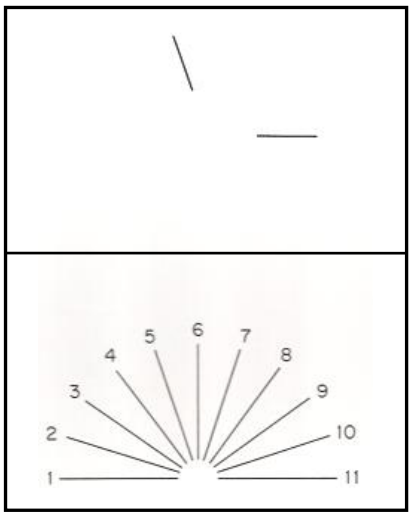

***Figure 12*: Judgment of Line Orientation Test. Participants were required to identify which of the eleven exemplar lines are the same orientation as the two stimulus lines.**

Hooper Visual Organisation Test (Hooper, 1983)

The Hooper Visual Organisation Test (HVOT) is a well-known test of visual-spatial ability and visual integration. Participants are required to mentally integrate and identify line drawings that have been fragmented into pieces (see Figure 13). This task was selected as a measure that reliably recruits bilateral superior occipital and superior parietal regions (Boyd, 1981; Fitz, Conrad, Hom, Sarff, & Majovski, 1992; Moritz, Johnson, McMillan, Haughton, & Meyerand, 2004; Wang, 1977).

The HVOT consisted of a test booklet with 30 line drawings, each showing puzzle pieces of a common object. Participants were instructed to mentally assemble the pieces into the original image and verbally identify the object. If several answers were offered participants were asked to decide on the most likely. Standardised scoring was used in which participants were given full credit if the right answer was given, or half credit if they provided the correct category but were unable to specify the exact object (such as *animal* rather than *cat*). There were no time restrictions. Performance was assessed by percentage of correct identifications. The HVOT has high internal consistency (r>.80) and interrater consistency (>.95) in adults

(Lopez, Lazar, & Oh, 2003), and high test-retest reliability (coefficient of concordance of .86) after a 6-12 month period (Lezak, 2004).

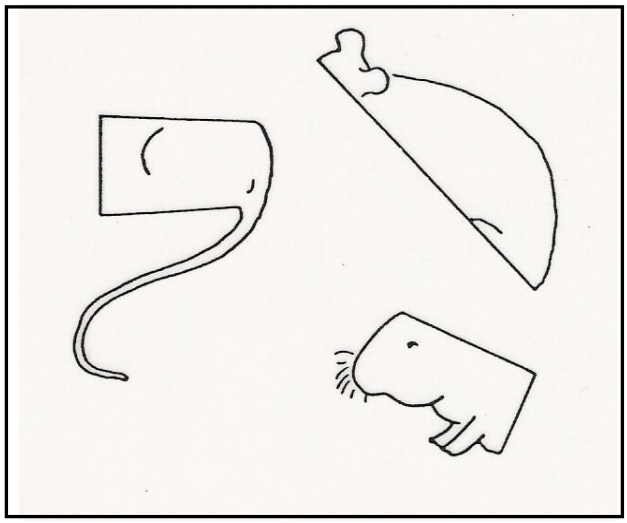

***Figure 13*: Item 22 (a mouse) from the Hooper Visual Organisation Test (HVOT). Participants are required to mentally integrate and identify line drawings that have been fragmented into pieces.**

Collision Judgments Task (Assmus et al., 2003)

The collision judgment task assesses the ability to mentally integrate spatial and temporal information. The participant is required to judge whether dots moving at constant speed are going to collide behind a centered square. This task was selected to assess functioning related to the left inferior parietal lobe, and particularly the left supramarginal gyrus (Assmus, Marshall, Noth, Zilles, & Fink, 2005; Assmus et al., 2003).

Stimuli for the Collision Judgment task were presented using Presentation 11.0 (Neurobehavioral Systems, CA, USA). The visual display of this task is presented in Figure 14. On each trial, two black dots start moving simultaneously from varying points of an outer square, and move to the opaque inner square behind which they 'disappear'. The dots move in straight lines at a constant speed. Participants responded with their index fingers by pressing one of two keys indicating a 'collision' or a 'miss'. Participants were informed that this was a task of accuracy not speed. They were not provided any feedback on their performance during the test. The speed of the dots, the angle that the dots travelled, and the

distance between the dots at the moment they passed each other varied between trials. The speed and the angle of the dots needed to be attended to and combined to correctly judge whether the dots would collide behind the inner square. A time limit of 20 seconds per trial was provided (although participants usually responded within 2-3 seconds), during which the dots were visible for about 1600ms (depending on the speed of the dots), and subsequently only the squares were visible. The task had a total of 90 trials, of which 50% of the dots collide and 50% miss. Performance was assessed as the percentage of correct judgments made.

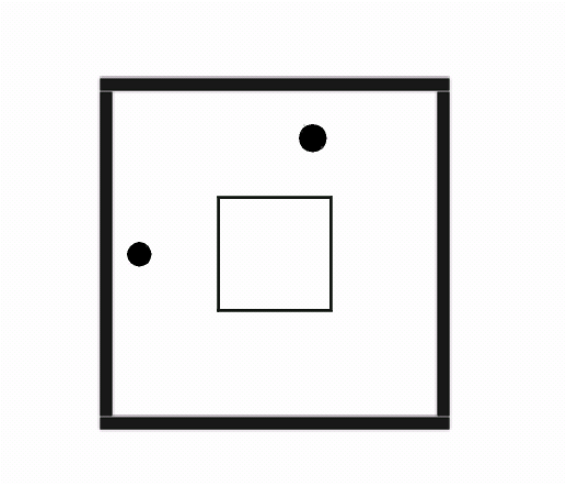

***Figure 14*: Collision Judgment task. Participants were required to judge whether dots moving at a constant speed were going to collide or miss behind the centered square.**

Facial Recognition Test (Benton, van Allen, Hamsher, & Levin, 1973)

The Facial Recognition Test (FRT) assesses the ability to identify and discriminate photographs of unfamiliar human faces. This test was selected as a measure that reliably recruits fusiform gyrus and adjacent occipitotemporal regions (Clark et al., 1996; Damasio, Tranel, & Damasio, 1990; Haxby, 1999; Haxby, Hoffman, & Gobbini, 2000; Haxby et al., 1994; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Sergent & Signoret, 1992).

The FRT stimuli are contained in an A4-sized booklet with 54 items. Each item consists of a stimulus picture of an unfamiliar face and its six exemplar faces, presented on two facing pages (see Figure 15). Participants were required to match the unfamiliar faces to the six exemplar faces. To respond, the participants pointed or verbally reported the numbers

corresponding to their answers. In the first six trials, participants were asked to match one of the exemplars to the target face; in the remaining trials, they were required to match three of the six exemplars to the target face. There were no time restrictions. Performance was assessed as the total percentage of correct matches. The long-form of the FRT shows adequate internal consistency (.72) and test-retest reliability (.71) over a 1-year period (Christensen, Riley, Heffernan, Love, & Maria, 2002).

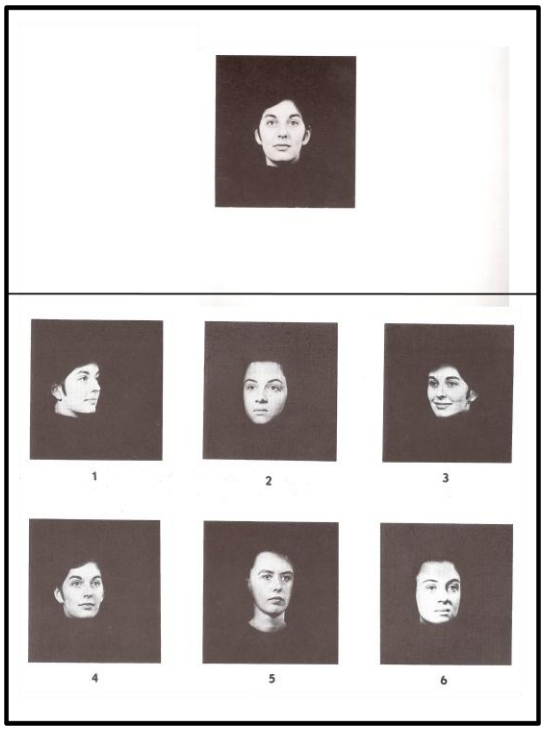

***Figure 15*: Facial Recognition Test. Participants were required to select the exemplar faces (bottom) that matched the target face (top).**

Modified Roadmap Test of Direction Sense (based on Money, Alexander, & Walker, 1965)

The Roadmap Test is a test of egocentric mental rotation and left-right discrimination. It assesses the ability to mentally orientate oneself through a schematic road map by judging the direction of each turn on a specified route (see Figure 16). This task was selected as a measure that reliably recruits the bilateral inferior and superior parietal lobes, and particularly the parieto-temporal-occipital (PTO) junction (Auer et al., 2008; Blanke et al., 2005; Creem-Regehr, Neil, & Yeh, 2007; Creem & Proffitt, 2001; Wraga, Shephard, Church, Inati, &

Kosslyn, 2005; Zacks, Gilliam, & Ojemann, 2003; Zacks, Rypma, Gabrieli, Tversky, & Glover, 1999).

The modified Roadmap Test consists of two schematic road-maps, one of which is an exact inverted version of the original roadmap. A dotted line shows a 'path' running through the maps. At times the path being traced is moving away from the participant when a judgment is required (unrotated turns), while at other times it is moving towards the participant (rotated turns). Judgments on unrotated turns need simple left-right visual orientation, whereas judgments on rotated turns involve left-right orientation plus egocentric mental rotation. The test route had a total of 64 turns, which can be classified into three turn types indicating the degree of egocentric mental rotation required (Vingerhoets, Lannoo, & Bauwens, 1996). Of the 64 turns, 18 required no mental rotation (no rotation, NR), 26 required a mental rotation of approximately 90° (half rotation, HR), and 20 turns required a mental rotation of between 90° and 180° (full rotation, FR). The two versions of the task were administered in random order for each participant. A short route of three turns was given as a practice to ensure the participant understood the nature of the task. Participants were instructed to follow the route drawn on the map, while indicating verbally whether the angle of the path turned to the left or the right. The map remained in a fixed position in front of the participant, and they were informed not to alter their body position to facilitate left-right judgments. Errors were corrected in the practice task, but no feedback was given during the test route. Performance was assessed by accuracy measures (percentage of correct turns for each of the three conditions [NR, HR and FR]) and a coarse measure of response time (average time taken for each of the three conditions). These measures were recorded by the *examiner* pressing a key corresponding to 'left' or 'right', in response to the participant's verbal responses.

The modified Roadmap Test was created for this study for two reasons. Firstly, to control for disproportionate numbers of left and right turns for each of the three conditions (in the second version the left turns become right turns and vice versa), and secondly, to provide a greater number of trials for more reliable comparisons between turn types, and greater sensitivity to error than the original Roadmap Test.

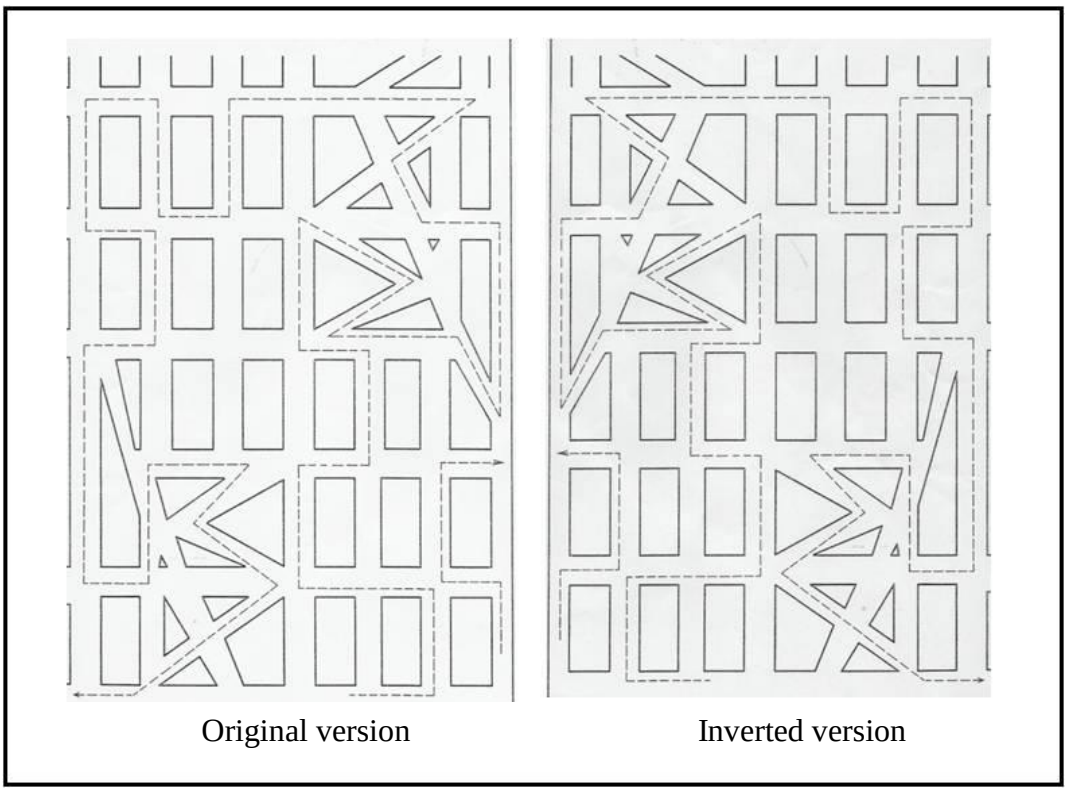

***Figure 16*: Modified version of the Roadmap Test of Directional Sense. The original version (left) and the inverted version (right) were both administered to all participants.**

Letter Mental Rotation Task (based on Alphanumeric Mental Rotation Task, Cooper & Shepard, 1973)

The letter mental rotation task assesses the accuracy and speed at which participants can mentally rotate misorientated letters to an upright position to judge whether the letter is normal or a mirror image (see Figure 17). This cognitive function is termed extrapersonal mental rotation. This task was selected as a measure that reliably recruits the inferior and superior parietal lobes (Alivisatos & Petrides, 1997; Farah & Hammond, 1988; Harris et al., 2000; Ng et al., 2000; Zacks, 2008).

The letter mental rotation task used in this study was based on Cooper & Shepherd's (1973) alphanumeric mental rotation task. It was designed and conducted using Eprime software (Schneider, Eschman, & Zuccolotto, 2002). Although the alphanumeric test usually includes multiple letters and/or numbers, only a single letter (F) was used in this study, to reduce

potential confounds of set-shifting, a cognitive function subserved primarily by frontal regions (Duncombe, Bradshaw, Iansek, & Phillips, 1994). In each trial the letter 'F' is presented in one of six different two-dimensional orientations separated by 60° (0°, 60°, 120°, 180°, 240°, 300°). Participants were asked to mentally rotate the letter 'F' to upright, and then judge whether it was in its normal position (facing forwards) or the mirror image of its normal version (facing backwards). They indicated their response by pressing one of two buttons corresponding to 'normal' and 'mirror image', with one index finger on each button. Participants were instructed to respond as quickly and as accurately as possible. They were informed not to turn their head to facilitate mental rotation judgments, and to mentally rotate the stimuli rather than mentally 'flip' the stimuli on a vertical axis (which would give an incorrect response).

A fixation cross appeared for one second prior to the stimulus, which in turn appeared either until the participant responded or for a maximum of 10 seconds. The stimuli were serially presented in random order. There were 20 trials for each orientation, making a total of 120 trials. In half of these trials the letter F was in a normal position when mentally rotated to upright, and on the other half it was a mirror image. Twelve practice trials preceded the experimental trials. Visual feedback ('correct' OR 'incorrect') was provided by the computer in the practice trails, but not the experimental trials. Reaction times that were less than 200ms were considered anticipatory and were disregarded. Reaction times greater than 4000ms were also excluded. Two performance measures were assessed in this task: the percentage of trials answered correctly in each orientation, and the mean reaction times for trials answered correctly in each orientation.

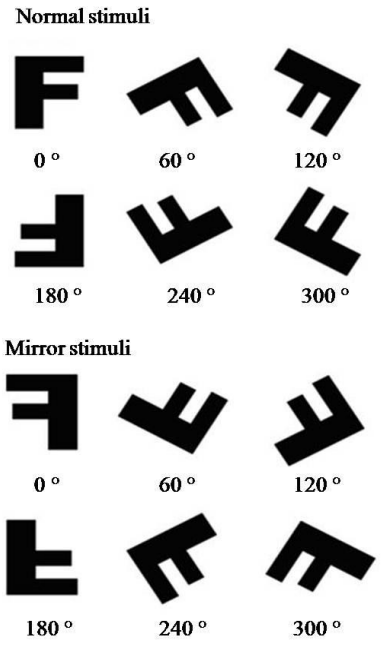

***Figure 17*: Letter mental rotation task stimuli including normal and mirror image 'F's in all six orientations. Participants were asked to mentally rotate the letter F to upright, and then judge whether it was in its normal position or the mirror image of its normal version.**

Cognitive tasks sensitive to anterior cortical regions

The Iowa Gambling Task (Bechara, Damasio, Damasio, & Anderson, 1994)

The Iowa Gambling Task (IGT) is a test of decision-making abilities. It assesses the ability to choose between cards with high monetary gains with a risk for even higher losses (disadvantageous cards), and cards with low monetary gains with a risk for smaller losses (advantageous cards). This task was selected as a reliable measure sensitive to functioning of the ventro-medial prefrontal cortex (VMPFC) (Bechara et al., 1994; Bechara, Damasio, Damasio, & Lee, 1999; Bechara, Damasio, Tranel, & Anderson, 1998; Bechara, Damasio, Tranel, & Damasio, 1997; Bechara, Tranel, & Damasio, 2000; Bolla et al., 2003; Ernst et al., 2002; Fukui, Murai, Fukuyama, Hayashi, & Hanakawa, 2005).

A computerised version of the IGT (Bechara et al., 1999) was used in this study (see Figure 18). Four decks of cards, labelled A, B, C and D, were presented on a touch-screen. Following a standardised set of verbal instructions (see Appendix G) participants were required to select one card at a time from any of the four decks by touching the card on the screen. Each card selection resulted in the participant winning an amount of money, while

after some selections they also lost an amount of money. The goal of the task was to win as much as possible and avoid losing as much as possible. Participants were informed that some of the decks are worse than others, and to win they should try to stay away from the bad decks. The task had a total of 100 trials. Decks A and B are termed disadvantageous decks: they are characterised by large wins (an average of $100) but occasional large punishments (e.g. $1250), which mean that participants will lose money over repeated selections. Decks C and D are termed advantageous decks: they are characterised by smaller wins (average of $50), but occasional smaller loses (e.g. $50), so that participants will make a profit over repeated selections. Decks A and B were equivalent in terms of overall net loss over the trials, and decks C and D were equivalent in terms of overall net gains.

The total number of advantageous card selections (from decks C and D) was used as a global measure of performance. In addition, because the early trials are considered learning trials, the total number of cards selected from the last three blocks (Selections 40-100) was used as a more sensitive measure of decision-making ability (Lakey, Goodie, Lance, Stinchfield, & Winters, 2007). To assess the learning in this decision-making task, the 100 card selections were divided into five time-blocks of 20 card selections. In each of these blocks the total number of advantageous selections (decks C and D) was calculated. In addition, the number of participants who selected >50 cards from the disadvantageous decks (i.e. more than expected by chance alone), was calculated (Bechara et al., 1998). The IGT has good split-half reliability using the total number of advantageous selections (r= 0.80) (Monterosso, Ehrman, Napier, O'Brien, & Childress, 2001). The last 50 trials of the IGT show a significant positive correlation with two other decision-making tasks, the Delay Discounting Procedure (r=0.37, p=0.04) and Rogers Decision-Making Task (r=0.36, p=0.04) (Monterosso et al., 2001).

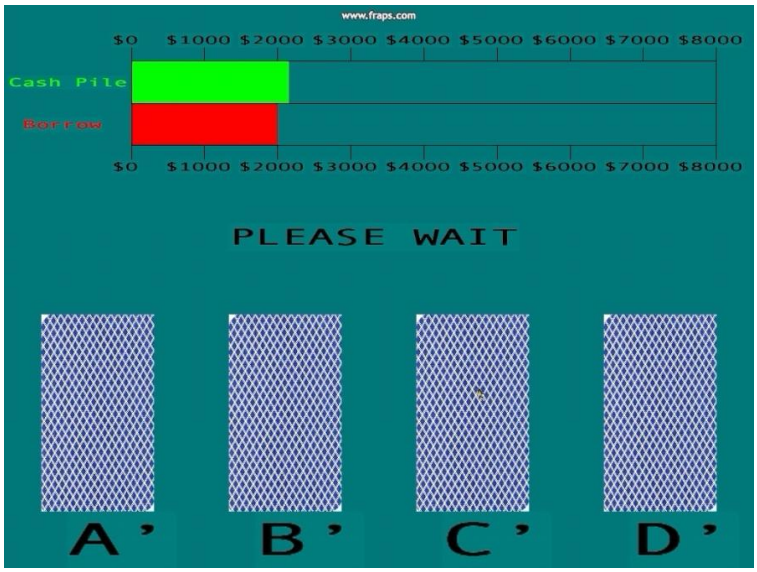

***Figure 18*: The Iowa Gambling Task. Participants were required to choose between cards with high monetary gains with a risk for even higher losses (disadvantageous cards, decks A and B), and cards with low monetary gains with a risk for smaller losses (advantageous cards, decks C and D)**

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

The Stockings of Cambridge task (SoC) is a spatial planning task, closely related to the Tower of London (ToL) task (Shallice, 1982). It assesses the ability to plan an increasing complexity of sequential moves. This task was selected as a reliable measure of the dorsolateral prefrontal cortex (DLPFC) (Dagher, Owen, Boecker, & Brooks, 1999; Lazeron et al., 2000; Owen et al., 1995; Rasmussen et al., 2006; Schall et al., 2003; Unterrainer & Owen, 2006; van den Heuvel et al., 2003).

The SoC was administered using a touch-screen monitor. Figure 19 shows the visual display for this task. On each trial, participants were instructed to rearrange the balls in the bottom display so that their positions matched the positions of the balls in the top half of the screen. On each trial the participant was verbally informed of the minimum number of moves in which the problem could be solved, and this number was also displayed on the screen. Participants could move a ball by first touching it and then touching an empty position in one of the other pockets. Participants were encouraged to mentally plan the entire sequence of moves to execute a correct solution before making their first move.

There were six practice problems which required a minimum of one or two moves. The experimental trials consisted of two each of two- and three-move problems and four each of four- and five-move problems, totalling twelve problem trials (these test problems corresponded exactly to those used in the original Tower of London task). The maximum moves allowed corresponded to twice the minimum number possible plus one or, in the case of five-move problems, plus two.

On completion of this main task, the participant did a motor control task. The participant was instructed to follow a sequence of single moves executed by the computer on the top half of the screen, by moving the corresponding ball in the lower half of the screen. Each move of this condition was an exact replication of the movements used by the participant in the corresponding test trial. Trials are divided into single moves so that the participant was not required to remember the sequence of moves. The motor control task also consisted of 12 trials. The number of moves, and the time taken to initiate and execute each trial was recorded. The ToL has test-retest reliability coefficients ranging from a low of .45 to a high of .74 (Atalay & Cinan, 2007; Lowe & Rabbitt, 1998).

Accuracy measures: The main accuracy measure was the proportion of problems solved in the minimum number of moves specified ("perfect solutions"). The average number of excess moves taken to complete each level ("excess moves") was also measured.

Latency measures: Four latency measures of performance are provided. The first two measures were provided by the motor control condition: The *motor initiation time* was the mean time between the onset of each problem and the completion of the first move (i.e., a correct touch of the required ball). The *motor execution time* was the time between touching the first ball and completing the sequence of single moves that comprise the whole problem. Since these control problems were yoked to the test problems, the total execution time was divided by the number of moves to provide an estimate of the average movement time per move. The task also provides two separate estimates of planning or "thinking" time, by subtracting the motor initiation and execution times from the total response times of the main task. In each problem, the *initial thinking time* was the time between the presentation of the

problem and the first touch minus the corresponding latency to make the same response on the yoked motor control task (i.e. total initiation time minus motor initiation time). The *subsequent thinking time* was the time between the selection of the first ball and the completion of the problem minus the total motor execution time from the corresponding control problem. Since this measure clearly varied with problem length, subsequent thinking time scores were divided by the number of moves to give an estimate of the 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, unconfounded by motor initiation or execution times.

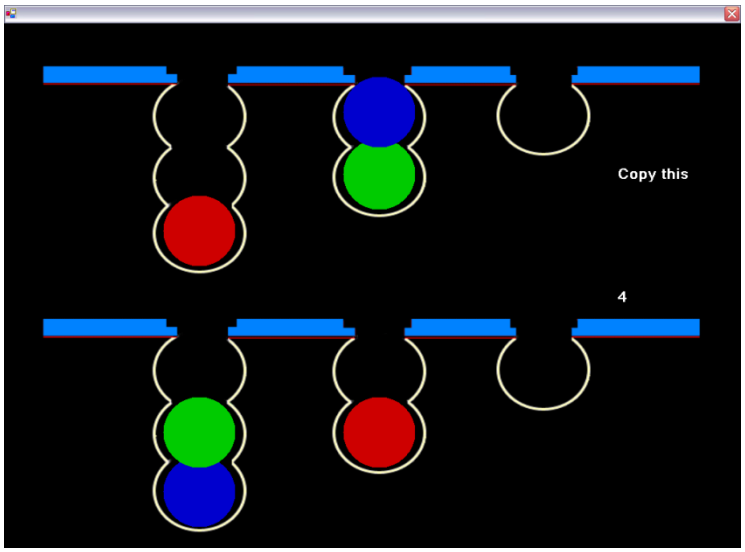

***Figure 19*: The Stockings of Cambridge task. Participants were required to move the balls on the bottom half of the touch-screen to mirror the positions of the balls in the upper half of the screen, in the least moves possible.**

Hand Mental Rotation task (modified from Ganis, Keenan, Kosslyn, & Pascual-Leone, 2000)

The hand mental rotation task assesses the accuracy and speed at which participants can mentally rotate the picture of a hand to an upright position to judge whether it is a left hand or a right hand. This task recruits frontal regions, including the precentral gyrus and the DLPFC, in addition to the posterior cortical regions recruited by the letter rotation task (Amick, Schendan, Ganis, & Cronin-Golomb, 2006; Creem-Regehr et al., 2007; Ganis et al., 2000; Kosslyn, Digirolamo, Thompson, & Alpert, 1998; Tomasino, Borroni, Isaja, & Rumiati, 2005).

The hand mental rotation task was designed and conducted using Eprime software (Schneider et al., 2002). This task used the same design as the letter rotation task to allow for a controlled comparison between frontal-posterior (hand rotation) and posterior (letter rotation) brain functioning. On each trial, a single computer-generated human hand was presented in one of six different 2D orientations separated by 60 degrees (0°, 60°, 120°, 180°, 240°, 300°; see Figure 20). Participants were asked to mentally rotate the pictures of hands to upright, and then judge whether they were a left hand or a right hand. They were told not to turn their head to facilitate mental rotation judgments, and to mentally rotate the stimuli rather than mentally 'flip' the stimuli on a vertical axis (which would give an incorrect response). Participants were instructed to respond as quickly and as accurately as possible. The participant indicated their response by pressing one of two buttons corresponding to 'left hand' and 'right hand' with one index finger on each button.

On each trial a fixation cross appeared for one second prior to the stimulus, which in turn appeared either until the participant responded or for a maximum of 10 seconds. The stimuli were serially presented in random order. There were 20 trials for each orientation, with a total of 120 trials. In half of these trials the hand was a left hand, and on the other half it was a right hand. Twelve practice trials preceded the experimental trials. Visual feedback ('correct' OR 'incorrect') was provided by the computer in the practice trials, but not the experimental trials. Reaction times less than 200ms were considered anticipatory and were disregarded. Reaction times greater than 4000ms were also excluded. As with the letter mental rotation task, performance measures included the percentage of trials answered correctly in each condition (rotation angles), and the mean reaction times for trials answered correctly in each condition.

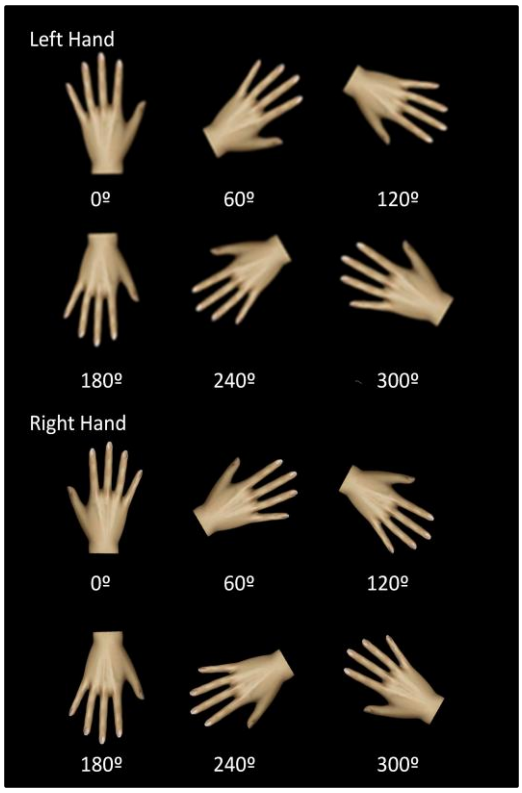

***Figure 20*: Hand Rotation Task stimuli including left and right hands in all six orientations.**

Mood Assessments

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

The Hospital Anxiety and Depression Scale (HADS) is a self-report questionnaire consisting of two subscales that are scored separately, one measuring anxiety (HADS-A) and one measuring depression (HADS-D) (see Appendix H). To reduce confounding by physical disorders, the scales do not include somatic symptoms such as dizziness, headaches, insomnia, and fatigue. Symptoms relating to serious psychiatric disorders were also excluded. The HADS-A and HADS-D each contain seven intermingled items. Each of these items has four-point (0-3) Likert responses, so the possible scores range from 0 to 21 for each scale. In addition, each of the mood states can be divided into four scoring bands: Normal (0-7), Mild (8-10), Moderate (11-14) and Severe (15-21). Completion time was about 3-5 minutes. In a review of 747 articles using the HADS, Bjelland et al. (2002) report good internal validity in the depression and anxiety scales with cronbach alpha coefficient means of .83 and .82 respectively.

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

The Inward Irritability and Outward Irritability subscales of the Irritability-Depression-Anxiety Scale (IDAS) were administered (see Appendix I). The Irritability construct is defined as 'reduced control over temper which usually results in irascible verbal or behavioural outbursts, although irritable mood may be present without observed manifestation' (Snaith & Taylor, 1985, p. 11). The inward and outward irritability subscales have four items each, all of which are based on four-point (0-3) Likert responses. The mood states can be divided into three scoring bands: Normal (0 - 4), Borderline (5 - 7), and Morbid (8 - 12). Unlike the *outward* irritability items, the four inward irritability items were not homogeneous (Snaith & Taylor, 1985), suggesting that they do not assess a single construct. Nonetheless, this subscale was included in this study because it includes clinically relevant items relating to self-harm and internalised anger that are not included in the other subscales. Because this subscale is not homogeneous, caution is required when interpreting the results of the inward irritability scale.

For both the HADS and IDAS scales participants were asked to read each item and circle or underline the reply that came closest to how they had been feeling in the past week. They were told that immediate reactions to each item will probably be more accurate than a long, thought-out response, and they were encouraged not to take too long over their replies.

Procedure of the testing session

Participants were tested individually in a quiet room, either in the Psychology Department at the University of Auckland or at their home — whichever they preferred. All tasks were administered by the author. Distractions and interference were minimized, for example by asking the participants to take their phone off the hook and to put their pets in another room. The duration of the testing sessions was 80 - 120 minutes, including a brief structured interview (see Appendix J), screening tests (TFC and Motor Screening test), neuropsychological testing, and psychological questionnaires. For the computer tasks, participants were seated at a comfortable distance from the computer screen and responded by pressing keypad buttons. On the touch screen tasks, responses were made by touching the

screen with their finger. Participants were encouraged to take breaks between tests when required to reduce discomfort and fatigue effects. Most assessments, for both PreHD and Control group participants, involved a 15-30 minute break in the middle of the session.

The tests were administered in the same order for all participants, except for the letter mental rotation and hand mental rotation tasks which were assessed in random order for each participant. The order of testing is presented below:

Order of tests

Interview using structured questionnaire
Total Functional Capacity Scale
Motor Screening Test
Reaction Time Task
Stockings of Cambridge Task
Iowa Gambling Task
Collision Judgments Task
Mental Rotation 1*
Standardised Roadmap Test
Judgement of Lines Test
Hooper Visual Organisation Test
Facial Recognition Test
Mental Rotation 2*
Hospital Anxiety and Depression Scale
Irritability-Depression-Anxiety Scale

*Mental rotation 1 and 2 refer to the Letter and Hand mental rotation tasks, which were administered in random order for each participant.

The testing session was conducted within two weeks of the MRI scan. However, eight participants (4 PreHD, 4 Controls) were unfortunately scanned with an incorrect scanning

protocol, and had to undergo repeat MRI scans. The repeat scans varied in their duration from the neuropsychological testing, with a mean (SD) of 6.67 (3.50) months.

Statistical Analysis

All analyses were performed with the statistical software package SPSS 14.0 for Windows (SPSS-Inc, 2006). When there was missing data in this study the cases were dropped on a variable by variable basis. The data was examined and corrected for possible outliers due to incorrect data entry. If outliers were deemed to be an accurate value they were included in the analysis. No outliers were removed from the dataset.

Independent t-tests and repeated-measures analyses of variance (ANOVA) were used to determine whether there were differences between the PreHD and Control groups on a number of different variables. When three groups were analysed (PreHDclose, PreHDfar and Controls), one-way ANOVAs were used instead of t-tests. Non-parametric statistics were used for variables with non-normalised distributions. For ordinal variables (e.g. test scores), Mann Whitney U tests were used. For nominal variables (e.g. gender), Pearson's Chi-Square tests were conducted. If within-subject variables were not normally distributed, logarithmic transformations were used to adapt the data for parametric statistical analysis. When the Mauchly's Test of Sphericity was violated in the repeated measures ANOVAs, the Greenhouse Geisser significance value was applied (Brace, Kemp, & Snelgar, 2003). When the Levene's test for homogeneity of variances was violated in the one-way ANOVAs, the Welch Robust test of Equality of Means was applied. The chi-square test of independence was used for between-group comparisons of categorical data. For 2x2 tables, the Continuity Correction was used to correct for overestimates of the chi-square value. For tables greater than 2x2, the Pearson contingency coefficient was used. If the 'minimum expected cell frequency' assumption was violated, the Fisher Exact Test value was used, rather than the Continuity Correction or the Pearson.

For the between-group analyses, a significance level of $p < 0.05$ was applied, without correction for multiple neuropsychological measures. This liberal significance level was used to increase sensitivity for detecting subtle changes in performance in presymptomatic

participants. Consequently, it is possible that some of these p-values may be inflated, as the risk of making a Type-I error increases with multiple comparisons. Exact p-values are reported for all statistical analyses unless the p value is less than .001 (reported as $p < .001$). All levels of significance reported are two tailed values, unless noted otherwise. Post-hoc comparisons for one-way ANOVAs and repeated-measures ANOVAs used Bonferroni corrections.

Results

Comparisons between total PreHD and Control groups

Psychomotor tasks

Table 6 presents the means and standard deviations of the psychomotor tasks for the PreHD and Control groups. There was no significant difference in the Simple Reaction Time task response times between the PreHD and Control groups, t (33) = 1.65, p = .109. In contrast, the PreHD group was significantly slower than the Control group on the Motor Screening Time task, t (36) = 2.54, p = .016.

Table 6

Mean response times (ms) and standard deviations on the motor screening and simple reaction time tasks for the PreHD and Control groups

	PreHD (n=19)	Controls (n=19)
Motor Screening: mean (SD)	1227.40 (328.59)	989.06 (244.70)
Simple Reaction Time: mean (SD)	504.91 (127.46)	443.89 (86.14)

Cognitive tasks sensitive to posterior cortical regions

Table 7 presents the means and standard deviations of four tests sensitive to posterior regions of the cortex: the Judgement of Lines Orientation test (JLOT), the Collision-Judgement test, the Facial Recognition Test, and the Hooper Visual Organisation Test (HVOT). The PreHD group had lower means than the Control group on all four measures. In support of the prediction that PreHD individuals would have impaired performance on tasks requiring

posterior brain regions, PreHD participants showed significantly poorer performance on the JLOT, *t* (36) = -2.123, p = .041, compared with controls. In addition, the PreHD participants showed a trend for performing worse on the HVOT, *t* (28.75) = -1.774, p = .087. However, contrary to predictions, there were no significant differences between the PreHD group and controls on the Collision-Judgments test, *t* (36) = -1.175, p = .325, or the Facial Recognition Test, *t* (36) = -.661, p = .513.

Table 7

Mean accuracy scores, standard deviations and ranges for four tasks sensitive to posterior cortical regions: the Judgment of Line Orientation task (JLOT), Hooper Visual Organisation Test (HVOT); Collision Judgment task and Facial Recognition Test.

Cognitive test	Test measure	PreHD Mean (SD)	Control Mean (SD)
JLOT	Accuracy (max 30)	25.95 (3.96)	28.34 (2.91)
	Range of scores	16 - 30	19 - 30
HVOT	Accuracy (max 30)	26.63 (2.40)	27.79 (1.39)
	Range of scores	22 - 30	25 - 30
Collision-Judgment	Accuracy (max 90)	73.68 (6.07)	75.84 (5.22)
	Range of scores	59 – 84	61 - 85
Facial Recognition	Accuracy (max 54)	46.68 (3.93)	47.42 (2.85)
	Range of scores	36 - 52	42 - 52

Roadmap Test

Table 8 presents the means and standard deviations for the PreHD and Control groups on the Roadmap performance measures. Accuracy and response time in the Roadmap Test were analysed seperately using repeated-measures ANOVAs. Group was used as a between-subjects factor (PreHD and Control) and turn-type as a within-subjects factor (turns requiring no mental rotation [NR], half rotation [HR], or full rotation [FR]).

The accuracy scores in this task did not differ significantly between the PreHD and Control groups, F (1, 36) = .90, p = .350. There was a significant main effect of turn-type, F (1.24, 44.74) = 14.60, p < 0.001, with both groups demonstrating poorer performance with increased mental rotation demands (all p-values < 0.05). There was no significant interaction between turn-type and group, F (1.24, 44.74) = .133, p = .771.

A similar result was found when both types of turns involving mental rotation (HR and FR) were combined and compared with NR turn types. There was no significant main effect of group, F (1, 36) = 1.21, p = .280. There was a significant effect of turntype, F (1, 36) = 16.45, p < .001, with poorer accuracy in rotated turns compared with non-rotated turns. There was no significant interaction between turn-type and group, F (1, 36) = .043, p = .838, indicating that the PreHD group did not perform differentially worse on turns involving mental rotation.

Table 8

Accuracy and response times on the Roadmap Test for the PreHD group and the Control group.

Measure	PreHD Mean (SD)	Control Mean (SD)
Accuracy		
Total	89.31 (13.62)	93.05 (10.80)
NR	95.68 (6.29)	98.84 (2.95)
HR	89.09 (14.85)	94.27 (11.44)
FR	83.05 (23.81)	86.05 (19.12)
HR+FR	86.07 (18.32)	90.16 (14.97)
Response time (ms)		
Total	2576.03 (1370.04)	1915.96 (856.33)
NR	1832.12 (977.20)	1445.70 (690.44)
HR	2485.87 (1258.90)	1796.23 (762.14)
FR	3410.09 (2106.97)	2505.94 (1220.35)
HR+FR	2947.98 (1634.52)	2151.08 (960.61)

Note: NR: no rotation turns; HR: half rotation turns; FR: full rotation turns; HR+FR: combined half and full rotation turns.

Response times in the Roadmap Test were also analysed using repeated-measures ANOVAs. There was a trend for a main effect of group, F (1, 35) = 3.05, p = .090. The PreHD were slower than Controls across all three turn types in this task. There was a significant effect of turntype, F (1.40, 49.07) = 38.035, p < .001, with both groups of participants responding more slowly with increased mental rotation demands (all p-values < .01). However, there was no significant interaction between turntype and group, F (1.40, 49.07) = 1.45, p = .242, indicating that the PreHD group was not differentially slower on turns requiring mental rotation. A similar result was found when both turns involving rotation were combined and compared with NR turn type. There was a trend for a main effect of group, F (1, 35) = 2.89, p = .098, with the PreHD group showing slower responses than controls on this task. There was a significant effect of turntype, F (1, 35) = 50.77, p < .001, with slower response speed for turns requiring mental rotation, but no significant interaction between turntype and group, F (1, 35) = 2.58, p = .117.

These results indicate that the PreHD group were slightly, but not significantly, slower than the Control group in the Roadmap Test, and they were no less accurate in performing the task. Moreover, the PreHD group's responses were not differentially slower on the rotated turns when compared to Controls.

Letter Mental Rotation task

Figure 21 shows that both the PreHD and Control groups demonstrated a pattern of response time similar to those described in previous studies of mental rotation (e.g. Hamm, Johnson, & Corballis, 2004; Shepard & Metzler, 1971). Specifically, RT increased in a curvilinear fashion as the angle of orientation increased from 0 to 180. Note that the data points in the figures for 0° and 360° of orientation are identical. These are presented to highlight the symmetry of the orientation effects around 180°, but they were not entered twice in the analysis.

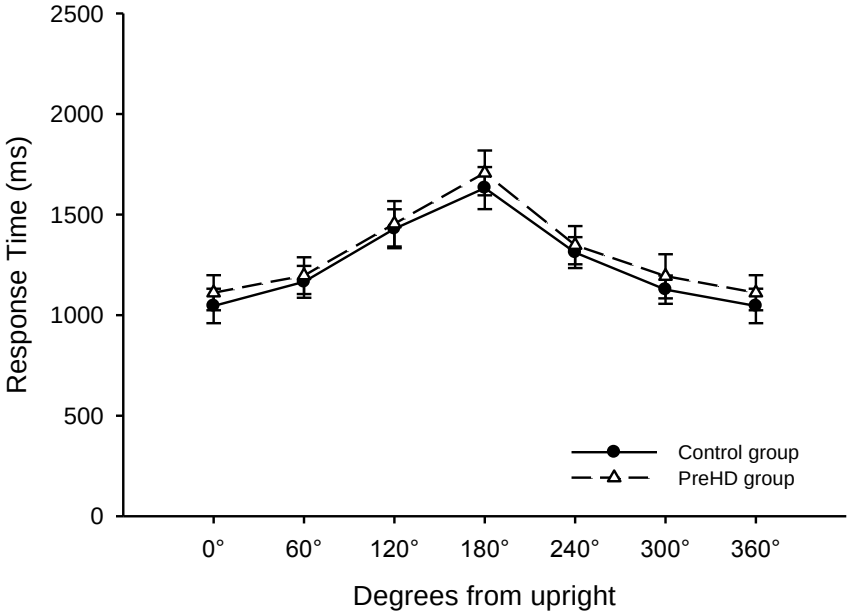

***Figure 21*: Mean response times for letter mental rotation task for the PreHD group and the Control group. Error bars indicate standard error of the mean.**

The mean response times were analysed using a three-way ANOVA, with orientation (6), condition (2: mirror, normal), and group (2) as factors. In keeping with other studies in the mental rotation literature (e.g. Shepard & Metzler, 1971, Lineweaver et al., 2005), data were collapsed across angles that required the same amount of rotation regardless of whether it was in a clockwise or a counter-clockwise direction. After collapsing about the 180°, planned contrasts were used to test for a linear, quadratic, and cubic trend component. The contrasts involving the linear trend component, indicating differences in rate of rotation, were of primary interest (see Appendix F for further details). When no significant contrast effects were apparent, only the linear contrast is reported. The results revealed no main effect of group, F (1, 36) = .17, p = .684. There was a significant main effect of orientation, both linear, F (1, 36) = 92.72, p < .001, and quadratic, F (1, 36) = 20.93, p < .001, indicating that RT increased for both groups as greater mental rotation was required (see Figure 21). As expected, there was a main effect of condition, F (1, 36) = 50.51, p < .001, with responses for the mirror condition taking longer than responses for the normal condition. There was a significant interaction between condition and group, F (1, 36) = 5.44, p = .025, with the PreHD group differentially slower than the control group on the mirror condition (see Figure

22). There was no significant interaction between group and orientation, *F* (1, 36) = .00, p=.987, condition and orientation, *F* (1, 36) = 2.26, p=.129, or condition and orientation and group, *F* (1, 36) = 1.54, p=.135. Thus, the PreHD group was proportionally slower at Mirror compared with Normal stimuli, but the magnitude of the increase over orientation (i.e., the rate of rotation) was not significantly different between the PreHD and Control groups (for either mirror or normal stimuli).

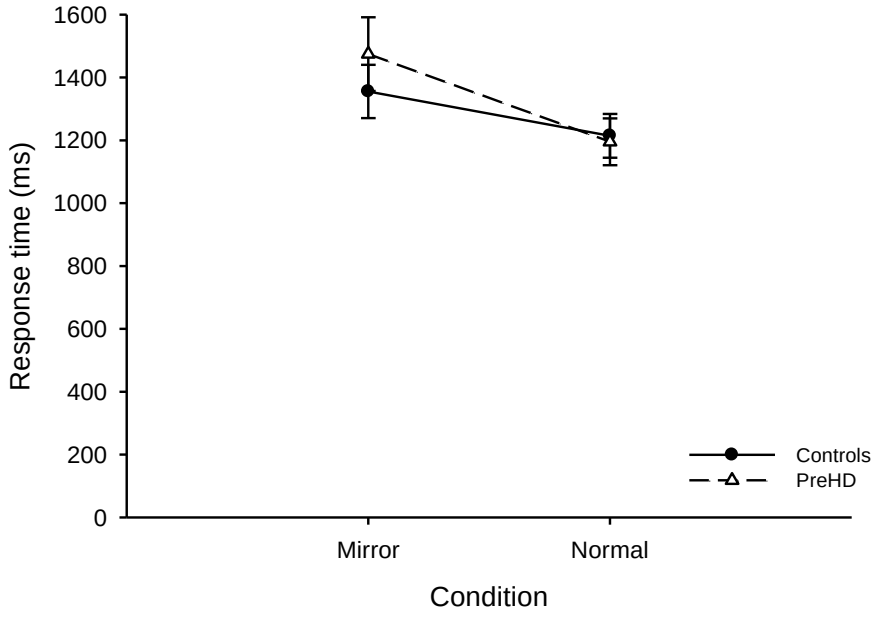

***Figure 22*: Mean response times for the Mirror and Normal conditions of the letter mental rotation task for the PreHD group and the Control group. Error bars indicate standard error of the mean.**

A repeated-measures ANOVA for mean accuracy revealed that the PreHD group performed significantly less accurately on the letter mental rotation task than the Control group, *F* (1, 36) = .17, p = .035. There was no significant main effect of orientation, *F* (1, 36) = .06, p = .816, indicating that the level of accuracy was not significantly different across the angles of rotations (see Figure 23). There was a trend for a main effect of condition, *F* (1, 36) = .06, p = .059, showing that, perhaps surprisingly, the participants performed slightly worse in the normal condition compared with the mirror condition (means ± SDs of 96.7±8.6 and 98.9±1.9 respectively). There was a significant interaction between condition and group, *F* (1, 36) = 4.80, p = .035, with the PreHD group performing differentially worse than controls on the Normal condition. There were no significant interactions between group and orientation *F* (1,

36) = .421, p = .520, condition and orientation, *F* (1, 36) = .014, p = .906, or condition and orientation and group, *F* (1, 36) = .004, p = .952, indicating that although the PreHD group performed more poorly than controls (in the normal condition), they did not show poorer performance than controls across increasing angle of orientation.

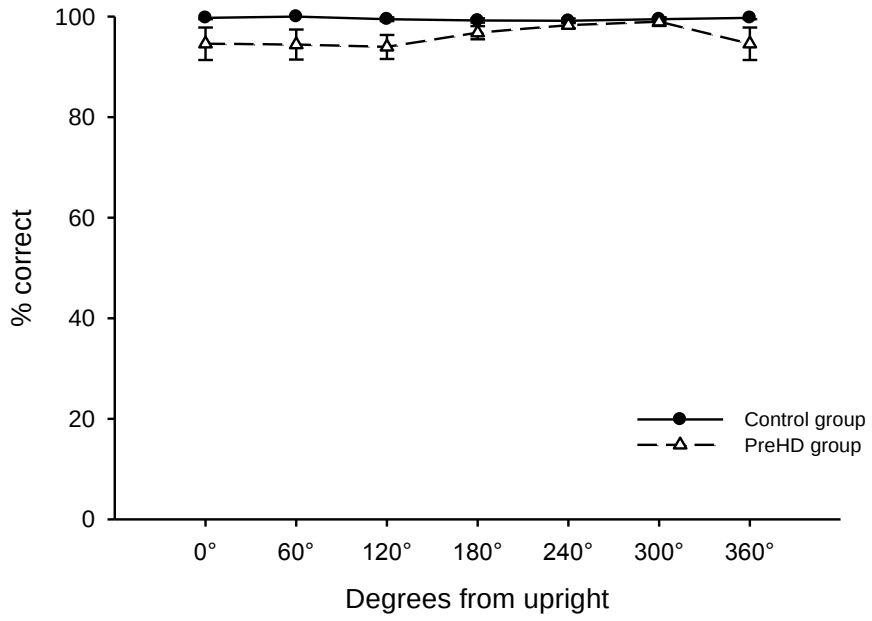

***Figure 23*: Mean accuracy for letter mental rotation task for the PreHD group and the Control group. Error bars indicate standard error of the mean.**

Cognitive tasks sensitive to anterior cortical regions

Hand Mental Rotation task

As shown in Figure 24, both the PreHD and Control groups demonstrated a curvilinear pattern of response time similar to those described in previous studies of mental rotation (Shepard & Metzler, 1971). The planned contrasts for this test were identical to those used for the letter mental rotation analyses.

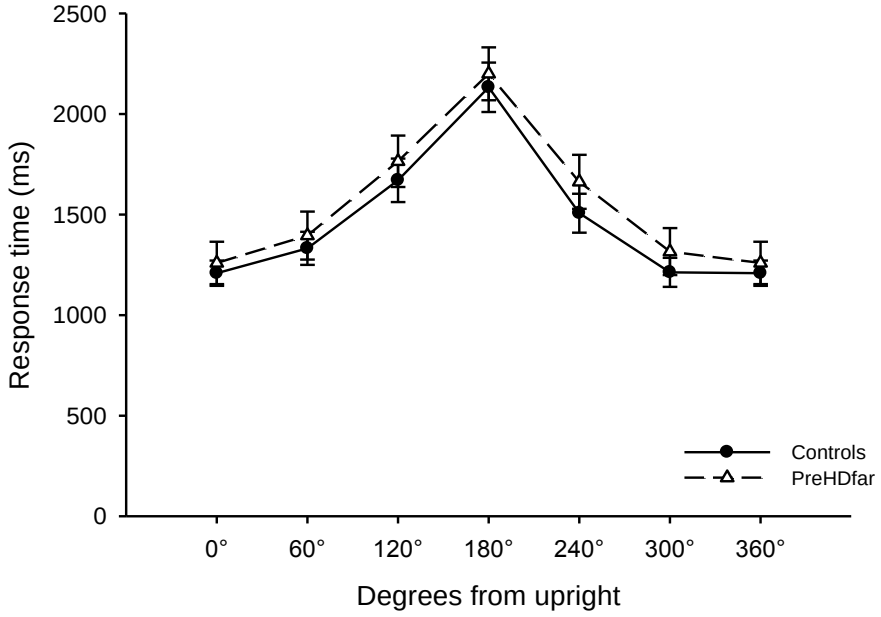

***Figure 24*: Mean response time for hand mental rotation task for the PreHD group and the Control group. Error bars indicate standard error of the mean. Note that the data point for 0° is duplicated at 360° to highlight the symmetry of the orientation effects around 180°.**

The mean response times were analysed using a three-way ANOVA, with orientation (6), condition (2: left hand and right hand stimuli), and group (2) as factors. As with the letter mental rotation analyses, data were collapsed across angles that required the same amount of rotation regardless of whether it was in a clockwise or a counter-clockwise direction. A preliminary analysis indicated no significant differences between clockwise and counter-clockwise orientations. There was no significant main effect of group, F (1, 34) = .421, p = .542. There was a significant main effect of orientation, both linear, F (1, 34) = 196.87, p < .001, and quadratic, F (1, 34) = 53.59, p < .001, indicating that RT increased for both groups as greater mental rotation was required (see Figure 24). There was a main effect of condition, F (1, 34) = 6.15, p = .018, with responses for the left hand condition taking longer than responses for the right hand condition. However, there were no two- or three-way interactions (all p-values > 0.05), indicating that the effects of orientation and condition were not significantly different between the PreHD and Control groups.

A repeated-measures ANOVA for mean accuracy on the hand mental rotation task showed no significant main effect of group F (1, 34) = .1.97, p = .170. There was a significant effect of

orientation, both linear, F (1, 36) = 13.16, p = .001 and quadratic, F (1, 36) = 12.11, p = .001, with participants performing less accurately as greater mental rotation was required (see Figure 25). There was a significant main effect of condition, F (1, 36) = 5.68, p = .023, with participants performing worse with left hand stimuli than right hand stimuli. A significant linear interaction between condition and orientation (F (1, 36) = 4.35, p = .045) indicated that responses for left hands showed a larger increase over orientations than responses for right hands. However, there were no significant interactions between group and orientation, F (1, 36) = .890, p = .352, condition and group F (1, 34) = 1.25, p = .272, or condition and orientation and group, F (1, 36) = .1.17, p = .199, indicating that the greater increase over orientations observed for the left hand condition was not significantly different between PreHD and Control groups. Thus, participants performed less accurately with increasing angle of rotation, and more poorly with left hand than right hand stimuli, but the PreHD group did not perform significantly differently to controls.

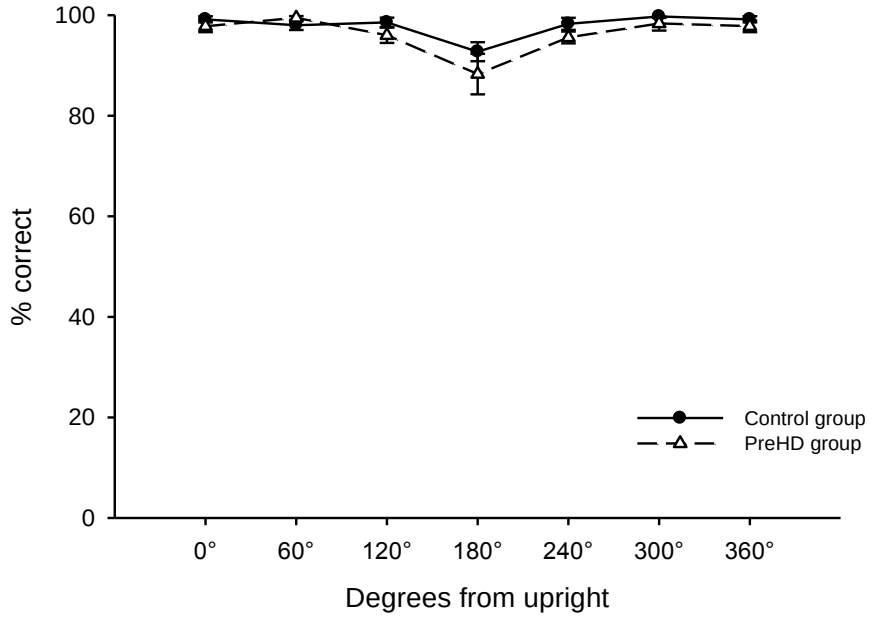

***Figure 25*: Mean accuracy for hand mental rotation task for the PreHD group and the Control group. Error bars indicate standard error of the mean.**

Iowa Gambling Task

A repeated-measures ANOVA was conducted to compare the total number of advantageous card selections over five consecutive time-blocks between the PreHD group and the Control

group. There was no main effect of group, F (1, 35) = 1.34, p = .255, indicating that the overall performance of the two groups in this task was not significantly different. There was a main effect of time-blocks, F (3.17, 111.01) = 10.50, p < .001. Participants showed a quick learning curve over the first 2-3 blocks, with no significant changes after this (see Figure 26). There was no significant interaction between time-blocks and group, F (3.17, 111.01) = 1.765, p = .155.

The total number of cards selected from the last three blocks (Selections 40-100) was used as a more sensitive measure of decision-making ability. An independent t-test showed no significant difference between the PreHD (M = 36.74, SD = 11.88) and Control groups, M = 42.83, SD = 10.44; t (35) = -1.65, p = .107.

To assess whether a subgroup of HD participants were significantly impaired on this task, the number of participants who selected greater than 50 cards from the disadvantageous decks was calculated. Six of the 19 (31.60%) PreHD participants, and 2 of the 18 (11.10%) Control participants, performed in this range. A chi square test for independence indicated no significant association between group and good/poor performance, X^2 (1, 37) = 1.24 , p = .232.

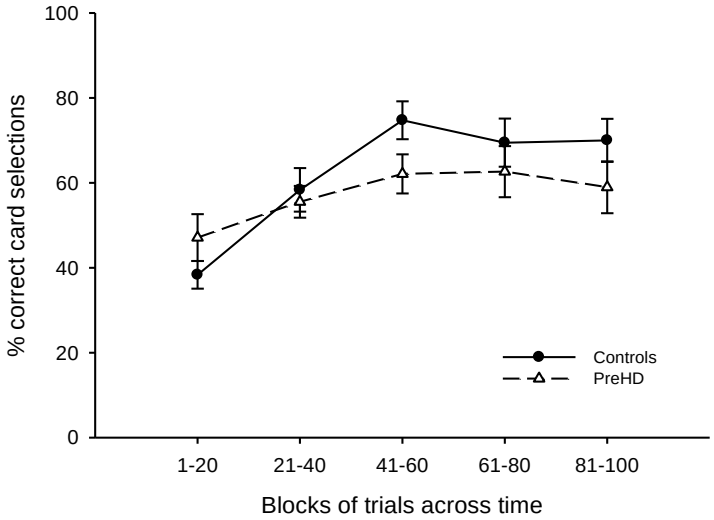

***Figure 26*: Mean percent correct (advantageous card selections from deck C and D) across the five time-blocks of the Iowa Gambling task for the PreHD group and the Control group. Error bars indicate standard error of the mean.**

Stockings of Cambridge task

Repeated measures ANOVAs were used for the two accuracy measures and the four latency measures of the Stockings of Cambridge task, with problem difficulty level (1 - 4) as a within-subject factor and group as a between-subject factor. There was no significant main effect of group for either the proportion of perfect solutions (i.e., those solved using the minimum number of moves), F (1, 36) = .017, p = .897, or the number of excess moves to achieve a correct solution, F (1, 36) = .009, p = .925. As expected, there was a significant effect for difficulty level for both the proportion of perfect solutions, F (1, 36) = 68.47, p < .001, and excess moves to completion, F (1, 36) = 52.98, p < .001. For both groups, the proportion of perfect solutions decreased with increasing problem difficulty, and the number of excess moves increased with increasing problem difficulty (p-values < .05), with the exception of no significant differences between levels 4 and 5 for either of these measures (p values > .05; see Figure 27). The interaction between group and difficulty level was not significant for either the proportion of perfect solutions or the number of excess moves, F (2.52, 90.81) = 1.14, p = .333, and F (1.65, 59.40) = .554, p = .545 respectively.

Consistent with other studies (e.g. Owen et al., 1995) the SoC response time data was not normally distributed and data was transformed using reverse logarithm. The PreHD group and the Control group did not differ significantly in their initial thinking times, F (1, 34) = .10, p = .325 or their subsequent thinking times, F (1, 34) = .10, p < .754. There was a significant effect of difficulty level for both the initial thinking times, F (2.01, 68.29) = 92.08, p < .001, and the subsequent thinking times, F (2.25, 76.53) = 37.88, p < .001. Participants in both groups tended to have slower initial and subsequent thinking times with increasing problem difficulty (see Figure 28). However, there was no significant interaction effect between group and difficulty for either the initial or subsequent thinking times (F (2.01, 68.29) = .38, p = .68 and F (2.25, 76.53) = .837, p = .449 respectively), indicating that the PreHD group did not perform differentially more slowly than controls with increasing demands of planning.

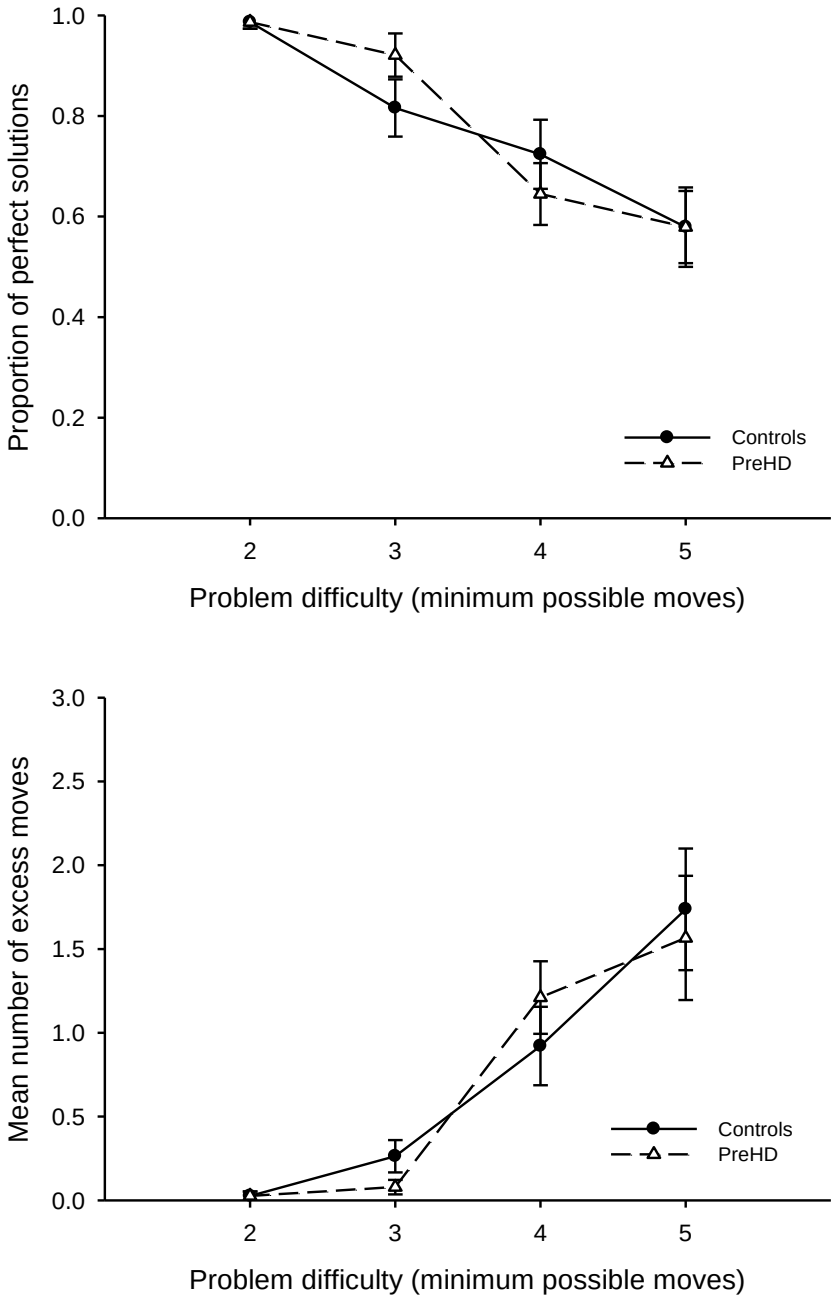

***Figure 27*: Mean proportion of perfect moves (top) and mean number of excess moves to completion (bottom) across the four problem difficulty levels of the Stockings of Cambridge task for the PreHD group and the Control group. Error bars indicate standard error of the mean.**

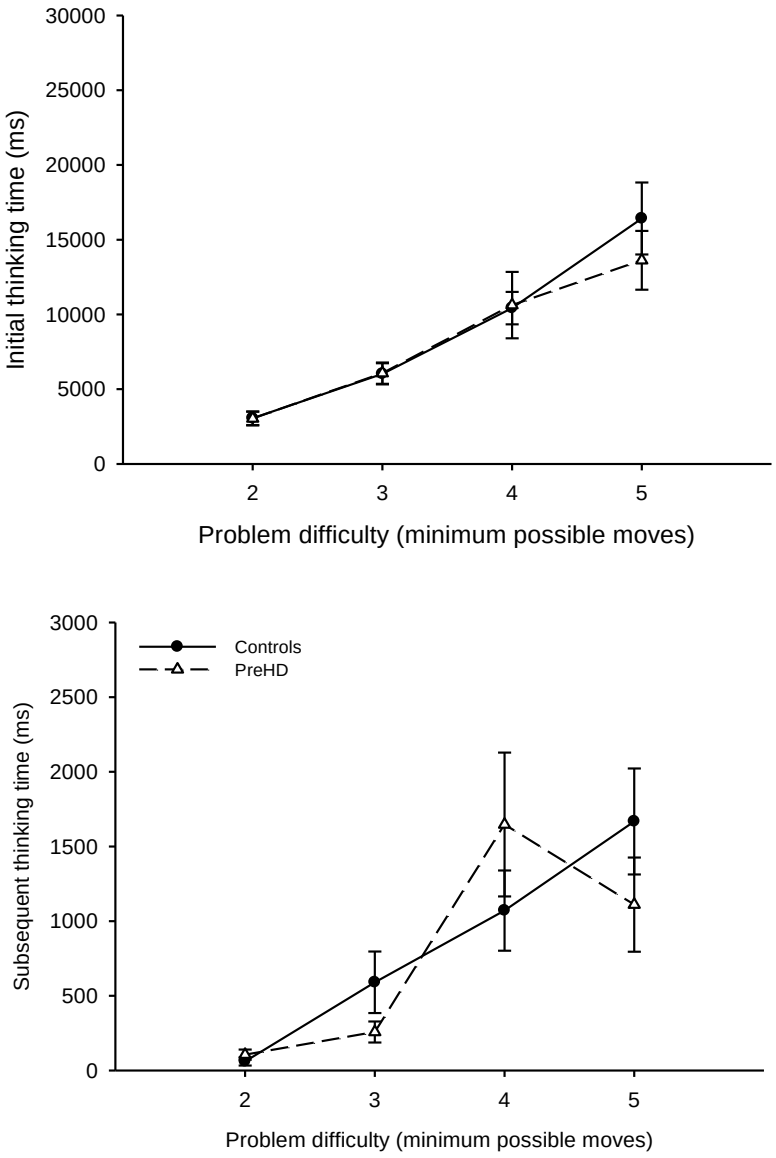

***Figure 28*: Mean initial thinking time (top) and subsequent thinking time (bottom) across the four problem difficulty levels of the Stockings of Cambridge task for the PreHD group and the Control group. Error bars indicate standard error of the mean.**

The motor control task for the SoC provided measures of motor initiation times and motor execution times. There was no significant main effect of group in the motor initiation times, F (1, 34) = 1.36, p = .252. There was a significant effect of difficulty level, F (2.50, 85.04) = 18.19, p < .001, with both groups of participants initiating movements more quickly with increasing problem difficulty, probably as a result of practice effects over time (see Figure

29). Similarly, there was no significant main effect of group in motor execution times, *F* (1, 34) = .008, p = .928. There was a significant main effect of difficulty level, *F* (2.27, 77.33) = 110.22, p < .001. Post-hoc comparisons showed that all levels were significantly different (all p values < .001) except levels 4 and 5 (p = 1.000). The motor execution times for both groups of participants increased from problem difficulty level 2 to 3, and then decreased for levels 4 and 5 (see Figure 29). There were no significant interaction effects between group and difficulty level in either motor initiation times, *F* (2.50, 85.04) = .91, p = .42, or motor execution times, *F* (2.27, 77.33) = 2.79, p = .061.

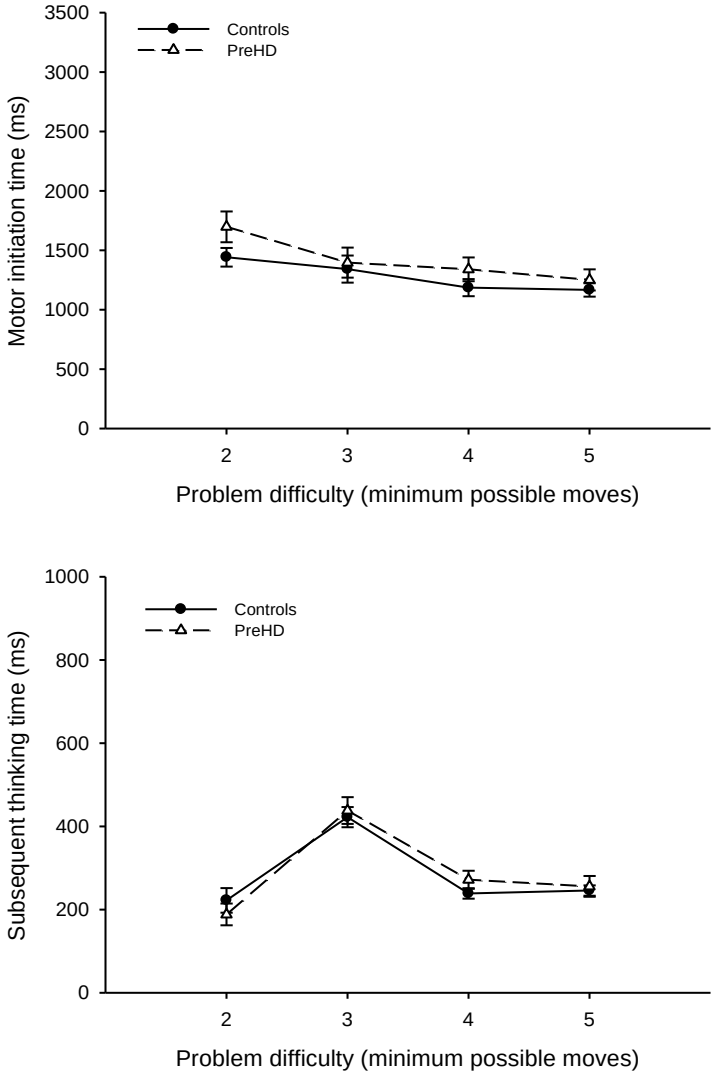

***Figure 29*: Motor initiation times (left) and motor execution times (right) in the Stockings of Cambridge task for difficulty levels 2-5 for the PreHD group and the Control group. Error bars indicate standard error of the mean**

Mood assessments

Table 9 presents the means and standard deviations on the four psychological assessments for the PreHD and Control groups. The PreHD group scored significantly higher on the IDAS Outward Irritability Scale, t (31.15) = 2.51, p = .018, and the IDAS Inward Irritability Scale, t (36) = 2.06, p = .047, indicating greater levels of outward and inward irritability. In contrast, no differences were found between the two groups in the Hospital Depression Scale, t (36) = .26, p = .796, or the Hospital Anxiety Scale t (36) = 1.24, p = .225.

Chi Square analyses assessed whether PreHD participants were more likely than controls to score in the mild, moderate and severe ranges. Because the number of participants in the moderate and severe range of these tests was smaller than required for Chi Square analyses, the psychological scores were divided into either the normal range or an 'abnormal range' that encompassed scores that fell in the mild, moderate and severe ranges. A chi square test for independence showed a trend for an association between group and outward irritability, X^2 (1, 38) = 2.80, p = .090, indicating that the proportion of PreHD participants with 'abnormal' outward irritability was slightly, but not significantly, greater than that of Control participants. In contrast, group was not significantly associated with inward irritability, X^2 (1, 38) < .001, p = 1.000, depression, X^2 (1, 38) < .001, p = 1.000, or anxiety, X^2 (1, 38) = .122, p = .727.

Table 9

Means and standard deviations for PreHD and Control groups on the four mood assessments.

	PreHD (n = 19)	Controls (n = 19)
Outward Irritability Scale (0-12)		
Total score: mean (SD)	3.37 (2.14)	1.89 (1.41)
% in abnormal range	31.60	5.30
Inward Irritability Scale (0-12)		
Total score: mean (SD)	2.11 (1.67)	1.16 (1.07)
% in abnormal range	5.30	0.00
Depression Scale (0-15)		
Total score: mean (SD)	3.21 (1.72)	3.05 (2.01)
% in abnormal range	0.00	5.30
Anxiety Scale (0-15)		
Total score: mean (SD)	6.95 (5.11)	5.16 (3.70)
% in abnormal range	36.80	26.30

Comparisons between PreHDclose, PreHDfar and Control groups

Psychomotor speed tasks

Table 10 presents the means and standard deviations for the Motor Screening task and the Simple Reaction Time task for the PreHDclose, PreHDfar and Control groups. There was a significant main effect of group on the Motor Screening task, F (2, 16.2) = 4.77, p = .027. Post-hoc comparisons indicated that PreHDClose average reaction times were significantly slower than Controls (p = .025), whereas the PreHDFar reaction times were not significantly different from either PreHDClose (p = .698) or Controls (p = .585). In contrast, there was no significant difference between the three groups on the Simple Reaction Time test, F (2, 32) = 1.34, p = .26.

Table 10

Means response times (ms) and standard deviations on the motor screening and simple reaction time task for the PreHDclose, PreHDfar and Control groups.

	PreHDclose (n=10)	PreHDfar (n=9)	Controls (n=19)
Motor Screening: mean (SD)	1303.48 (254.03)	1142.88 (386.31)	989.06 (244.70)
Reaction Time: mean (SD)	514.30 (59.77)	495.52 (175.37)	443.89 (86.14)

Cognitive tasks sensitive to posterior cortical regions

Table 11 presents the means and standard deviations of the PreHDclose, PreHDfar and Control groups for four tasks sensitive to posterior cortical regions. A one-way ANOVA showed a significant main effect of group on the Judgment of Line Orientation test, F (2, 35) = 3.30, p = .049. In support of predictions, post-hoc comparisons indicated that PreHDClose obtained significantly lower scores than Controls (p = .044), whilst PreHDFar did not differ significantly from either PreHDClose (p = .508) or Controls (p = 1.000).

Table 11

Mean accuracy, standard deviation and range for the PreHDclose, PreHDfar and Control groups on four tasks sensitive to posterior cortical regions

Cognitive test	Test measure	PreHDclose Mean (SD)	PreHDfar Mean (SD)	Control Mean (SD)
JLOT	Accuracy (max 30)	24.90 (4.25)	27.11 (3.48)	28.34 (2.91)
	Range of scores	16 - 30	20 - 30	19 - 30
HVOT	Accuracy (max 30)	26.35 (1.63)	27.00 (2.13)	27.79 (1.39)
	Range of scores	23 - 29	22 - 30	25 - 30
Collision-Judgment	Accuracy (max 90)	72.30 (5.42)	75.22 (6.70)	75.84 (5.22)
	Range of scores	65 - 84	59 - 82	61 - 85
Facial Recognition	Accuracy (max 54)	46.90 (4.89)	46.44 (2.79)	47.42 (2.85)
	Range of scores	36 - 52	43 - 50	42 - 52

Note: JLOT: Judgement of Line Orientation Test; HVOT: Hooper Visual Organisation Test

There was no significant main effect of group on the Hooper Visual Organisation Test, F (2, 35) = 1.81, p = .179, despite a trend towards group differences on this test in the two-group analyses. Similarly to the two-group comparisons, there were no significant differences between the three groups on the Collision Judgments test, F (2, 35) = 1.33, p = .277, or the Facial Recognition test, F (2, 35) = .254, p = .777.

Roadmap Test

Table 12 presents the means and standard deviations of the Roadmap Test for the PreHDclose, PreHDfar and Control groups. For the Roadmap accuracy scores, there was a trend towards a main effect of group, F (2, 35) = 3.14, p = .056. The PreHDclose group performed more poorly (albeit not significantly) than the Control group and the PreHDfar group. There was a significant main effect of turn-type, F (1.63, 44.21) = 13.23, p < 0.001, with poorer performance for turns requiring mental rotation (all p-values < .05), but no significant interaction between turn-type and group, F (2.53, 44.21) = .1.76, p = .176.

When both turns involving mental rotation were combined and compared with the no-rotation turns, a significant main effect of group was apparent, F (2,35) = 2.31, p = .048. Post-hoc comparisons showed a trend for the PreHDclose group to perform more poorly than the PreHDfar group (p= .083) and the Control group (p= .094), whilst there were no significant differences between the PreHDfar and Controls (p = 1.000). There was also a significant effect of turntype, F (1,35) = 15.91, p < .001, with all three groups of participants performing more poorly on the turns requiring mental rotation than the non-rotation turns (see Figure 30). However, there was no significant interaction between group and turn-type accuracy, F (2, 35) = 2.21, p = .125, indicating that the PreHD group did not perform more poorly on turns requiring mental rotation.

Table 12

Accuracy and response times on the Roadmap Test for the PreHDclose, PreHDfar and Control groups.

Test measures	PreHDclose Mean (SD)	PreHDfar Mean (SD)	Control Mean (SD)
Accuracy			
Total	83.52 (16.04)	95.74 (6.27)	93.05 (10.80)
NR	93.89 (8.05)	97.67 (2.77)	98.84 (2.95)
HR	83.16 (16.34)	95.67 (10.15)	94.27 (11.44)
FR	73.30 (28.89)	93.89 (9.28)	86.05 (19.12)
HR+FR	78.23 (21.43)	94.78 (8.73)	90.16 (14.97)
Response time (ms)			
Total	2827.93 (1339.46)	2296.13 (1427.39)	1915.96 (856.33)
NR	1915.70 (866.75)	1739.25 (1133.57)	1445.70 (690.44)
HR	2810.70 (1381.44)	2124.96 (1067.95)	1796.23 (762.14)
FR	3757.40 (2035.51)	3024.19 (2238.07)	2505.94 (1220.35)
HR+FR	3284.05 (1648.68)	2574.58 (1629.50)	2151.08 (960.61)

Note: NR: no rotation turns; HR: half rotation turns; FR: full rotation turns; HR+FR: combined half and full rotation turns.

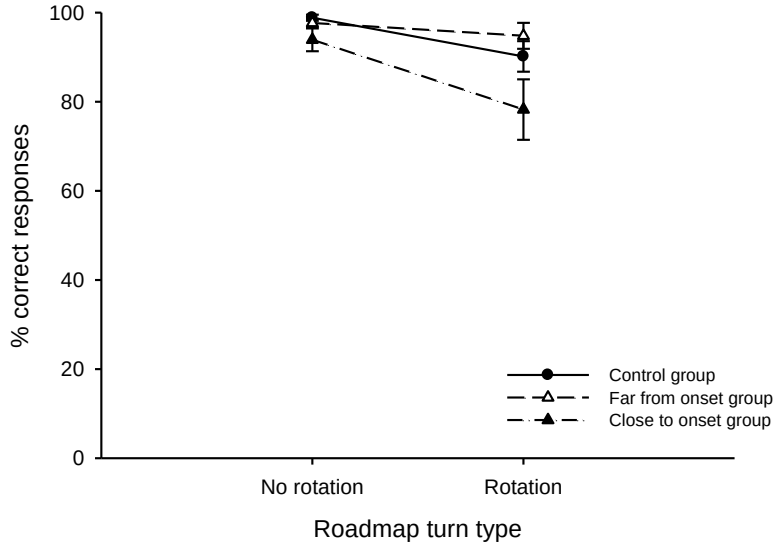

***Figure 30*: Mean percentage of correct turns for the no rotation (NR) and the rotation turns (HR and FR combined) of the Roadmap Test for the PreHDclose, PreHDfar and Control groups. Error bars indicate standard error of the mean.**

For the Roadmap response times there was no main effect of group, F (2, 34) = 2.03, p = .147. There was a significant effect of turntype, F (1.40, 46.83) = 38.81, p = < .001, with participants in all three groups showing slower response times with increased demands on mental rotation. There was no significant interaction between turntype and group, F (2.80, 46.83) = 1.25, p = .301. A similar result was found between the rotated and non-rotated turn types. There was no main effect of group, F (2, 34) = 1.85, p = .173; there was a significant effect of turntype, F (1, 34) = 54.53, p < .001, with poorer performance on rotated compared with non-rotated turns; and there was no significant interaction between group and turn-type, F (2, 34) = 2.49, p = .098.

Letter Mental Rotation task

Similarly to the two-group analyses, the mean response times were analysed using a three-way ANOVA, with orientation (6), condition (2), and group (3) as factors. The results revealed no significant main effect of group, F (2, 35) = .094, p = .910. There was a significant main effect of orientation, both linear (F (1, 35) = 84.23, p < .001) and quadratic (F (1, 35) = 20.23, p < .001), indicating that RT increased for all three groups as greater mental rotation was required (see Figure 31). There was a significant main effect of condition, F (1, 35) = 55.18, p < .001, with responses for the mirror condition taking longer than responses for the normal condition. Although there was no significant interaction between group and orientation (F (2, 35) = .54, p = .589), there were trends for linear interactions between condition and group, F (2, 35) = 2.83, p = .072, and condition and orientation, both linear, F (1, 35) = 3.41, p = .073 and quadratic, F (1, 35) = 4.09, p = .051. There was also significant linear interaction between condition and orientation and group (F (2, 35) = 4.73, p = .015). To investigate which pairs of groups contributed to the significant interaction, the interaction was computed for each pairing and tested against the error term from the original analysis. These results showed a significant interaction only between the PreHDclose and Control group. Paired-group post-hoc comparisons showed that the PreHDclose group had a differentially slower rate of rotation in the normal condition than the mirror condition, compared to the Control group (F (1, 27) = 7.67, p = .022). However, the groups did not show a significantly different rate of rotation in either the normal condition F (1, 27) = .30, p = .586) or the mirror condition (F (1, 27) = 2.58, p = .120).

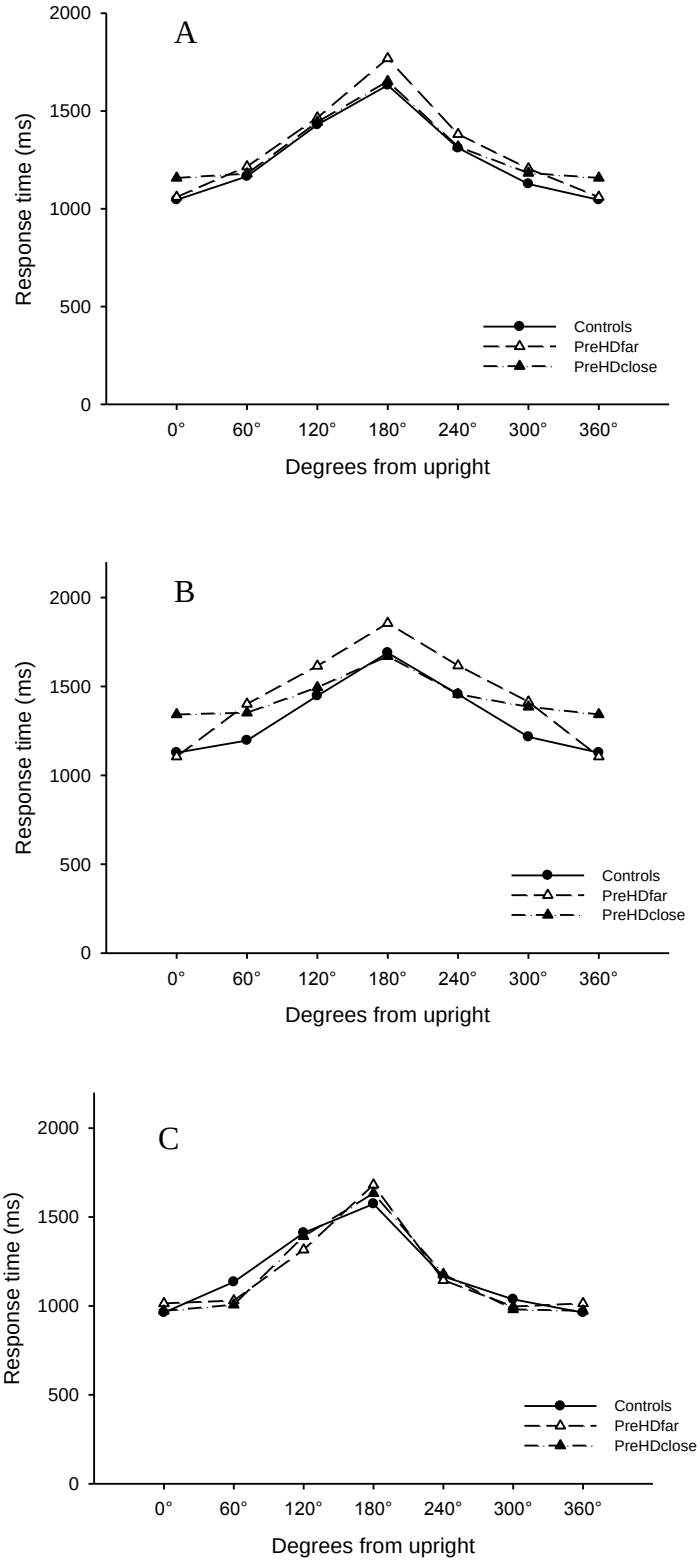

***Figure 31*: Mean response times for (a) total letter mental rotation task, (b) mirror condition, and (c) normal condition, for the PreHDclose, PreHD far and Control groups.**

Figure 32 presents the mean accuracy scores in the letter mental rotation task for the PreHDclose, PreHDfar and Control groups. There was a trend towards a main effect of group, F (2, 35) = .2.72, p = .080, with the PreHDclose group with the lowest mean accuracy. There was no significant main effect of orientation, F (1, 35) = .238, p = .629, indicating that participants did not perform significantly differently across the angles of rotations. There was a significant main effect of condition, F (1, 35) = .6.24, p = .017, with participants less accurately rotating normal stimuli compared with mirror stimuli. There was a trend for an interaction between condition and group, F (2, 35) = .3.03, p = .061, with Figure 33 showing the PreHD groups, and particularly the PreHDclose group to perform less accurately (albeit not significantly) on normal compared with mirror stimuli. However, there was no significant interaction between group and orientation F (2, 35) = .98, p = .386, condition and orientation, F (1, 35) = .010, p = .921, or condition and orientation and group, F (2, 35) = .014, p = .986, indicating that mental rotation accuracy in the three groups did not differ significantly across orientations.

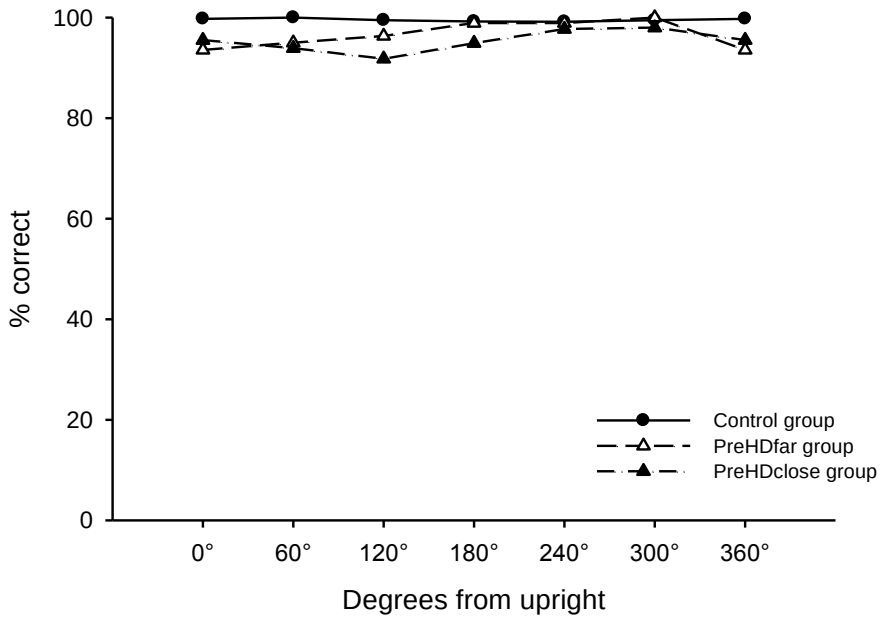

***Figure 32*: Mean accuracy for letter mental rotation task for the PreHDclose, PreHD far and Control groups. Error bars indicate standard error of the mean.**

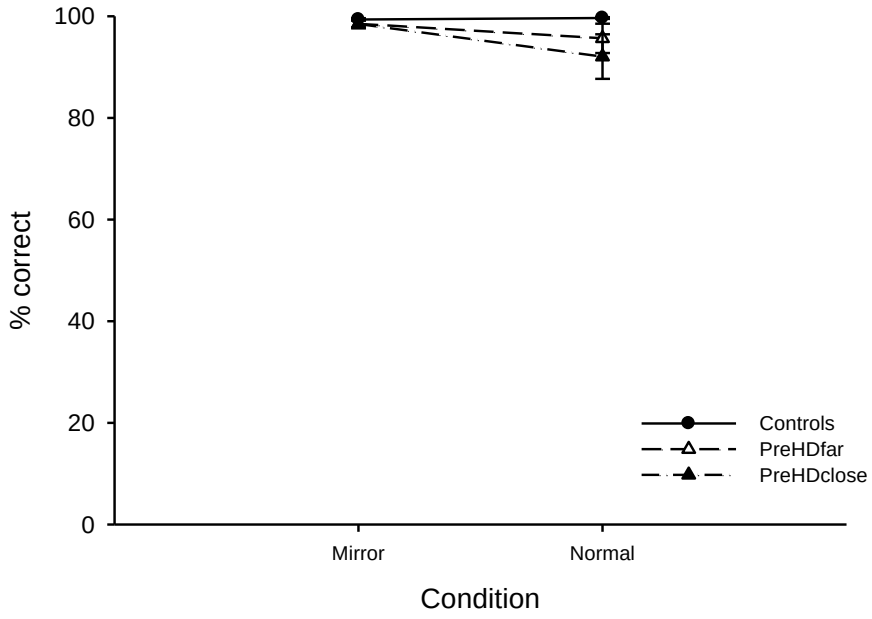

***Figure 33*: Mean accuracy for the mirror and normal conditions of the letter mental rotation task for the PreHDclose, PreHD far and Control groups. Error bars indicate standard error of the mean.**

Cognitive tasks sensitive to frontal cortical regions

Hand Mental Rotation task

As with the letter mental rotation task, the mean response times were analysed using a three-way ANOVA, with orientation (6), condition (2), and group (3) as factors. The results revealed no significant main effect of group, F (2, 33) = .28, p = .758. There was a significant main effect of orientation, both linear (F (1, 33) = 193.90, p < .001) and quadratic (F (1, 33) = 52.61, p < .001, indicating that response times increased for all three groups as greater mental rotation was required (see Figure 34). There was a significant main effect of condition, F (1, 33) = 5.17, p = .030, with all groups taking longer to respond to left hand stimuli than right hand stimuli (see Figure 35). However, there were no significant two-way or three-way interactions. Thus, there were no significant group differences in RT increase over orientations, indicating a similar rate of mental rotation (of hands) in these groups.

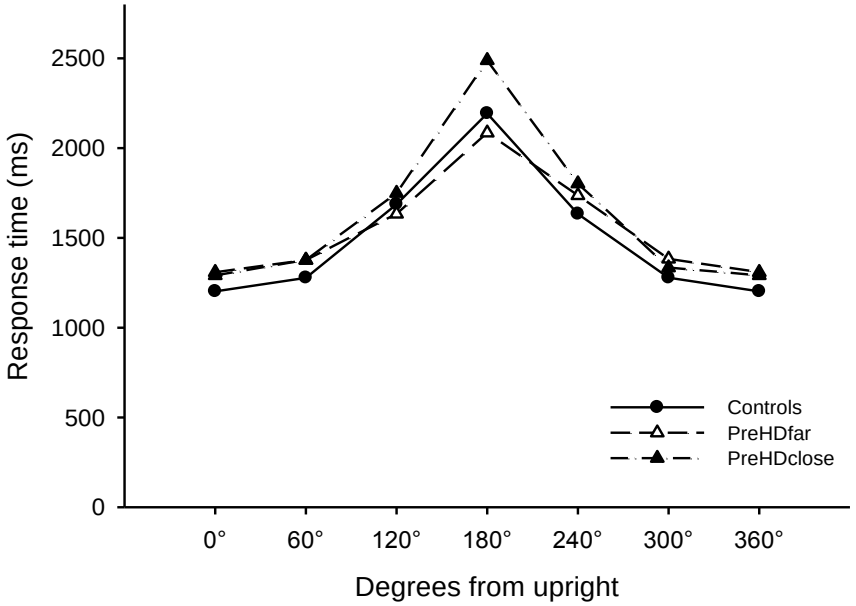

***Figure 34*: Mean response times for Hand mental rotation task for the PreHDclose, PreHD far and Control groups. Error bars indicate standard error of the mean.**

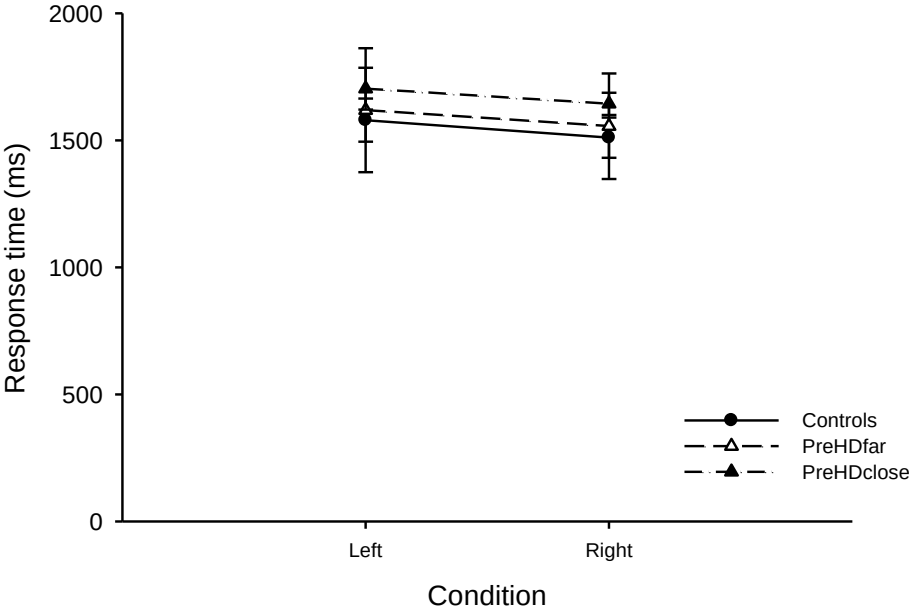

***Figure 35*: Mean response times for the left and right hand stimuli of the hand mental rotation task for the PreHDclose, PreHD far and Control groups. Error bars indicate standard error of the mean.**

A repeated-measures ANOVA for mean accuracy on the hand mental rotation task was also conducted. There was no significant main effect of group, $F(2, 33) = .96$, $p = .394$. There was a significant effect of orientation, both linear, $F(1, 33) = 14.01$, $p = .001$ and quadratic, $F(1, 33) = 12.78$, $p = .001$. Participants in all three groups performed less accurately as greater mental rotation was required (see Figure 36). However, there was no significant interaction between group and orientation, $F(2, 33) = .96$, $p = .392$), indicating that the increase in magnitude across orientations was not significantly different between the three groups.

There was a significant main effect of condition, $F(1, 33) = 9.15$, $p = .005$, with participants performing worse in the left hand condition compared with the right hand condition. There was also a significant interaction between condition and group, $F(2, 33) = 7.09$, $p = .003$. Post-hoc comparisons showed that although the three groups did not perform significantly differently on either the left hand condition (all p–values > .05) or the right hand condition (all p–values > .05), only the PreHDclose group performed significantly more poorly on the left hand condition (mean ± SD of 93.5 ± 0.05) compared with the right hand condition (mean ± SD of 98.1± 0.02) ($p < .001$). There was a significant linear interaction between condition and orientation, $F(1, 33) = 5.91$, $p = .021$, with the responses for left hand stimuli showing a larger decrease in accuracy over orientation than responses for right hand stimuli. However, there was no significant interaction between condition and orientation and group, $F(1, 36) = .1.17$, $p = .199$, indicating that effect was not significantly different between the three groups.

In summary, the only significant difference between the three groups was that the PreHDclose group (but not the PreHDfar or Control groups) performed significantly more poorly on the left hand condition than the right hand condition.

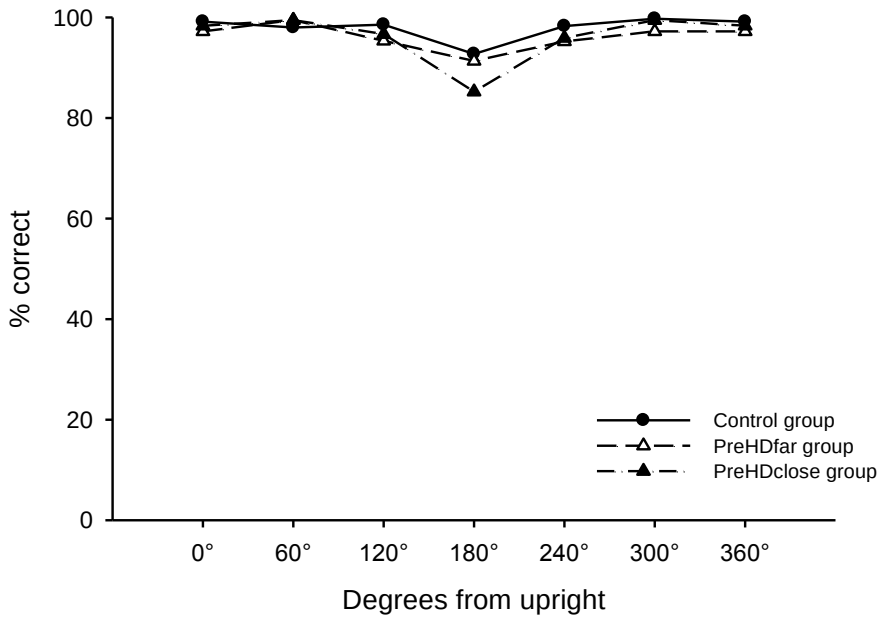

***Figure 36*: Mean accuracy for hand mental rotation task for the PreHDclose, PreHD far and Control groups. Error bars indicate standard error of the mean.**

Iowa Gambling Task

Table 13 presents the performance measures in the Iowa gambling task for the PreHDclose, PreHDfar and Control groups. Similarly to the two-group analysis, there was no significant main effect of group for the total number of advantageous card selections, F (2, 34) = 1.02, p = .373. There was a significant main effect of time-blocks, F (3.17, 107.93) = 7.38, p < .001. Post-hoc comparisons showed participants chose significantly more advantageous cards in time-blocks 3, 4 and 5 than in time-block 1 (all p-values < .05; see Figure 37). There was no significant interaction between group and time-blocks, F (6.35, 107.93) = 1.47, p = .194.

As in the earlier analyses, the total number of cards selected from the last three blocks (Selections 40-100) was used as a more sensitive measure of decision-making ability. A one-way ANOVA showed no significant difference between the three groups F (2, 34) = 2.01, p = .149.

The number of participants who selected >50 cards from the disadvantageous decks (i.e. more than expected by chance alone), was also calculated. A chi square test for independence

indicated no significant association between group and good/poor performance, X^2 (2, 37) = 3.17, p = .205. However this test did violate the recommended minimum cell counts.

Table 13

Performance measures for the Iowa gambling task

	PreHDclose (n=10)	PreHDfar (n=9)	Controls (n=19)
% correct Mean (SD)	54.90 (14.10)	59.89 (14.90)	62.17 (11.18)
% correct, last 60 trials Mean (SD)	56.67 (19.33)	66.30 (20.19)	71.39 (17.41)
% of participants with >50 cards from disadvantageous decks	40.00	22.20	11.10

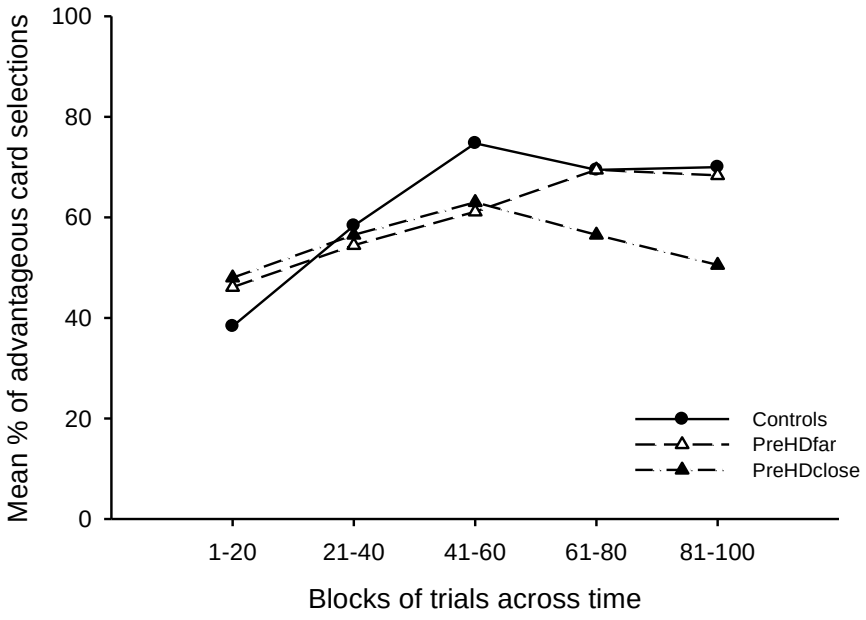

***Figure 37*: Mean percent of advantageous card selections (from Deck C and D) across the five time-blocks of the Iowa Gambling task for the PreHDclose, PreHDfar and Control groups.**

Stockings of Cambridge task

Repeated-measures ANOVAs were used for the two accuracy measures and the four latency measures of the Stockings of Cambridge task. There was no significant main effect of group for either the proportion of perfect solutions, F (2, 35) = .093, p = .911, or the number of excess moves, F (2, 35) = .201, p = .819, indicating that the performance in this task was not

significantly different between the three groups. As expected, there was a significant effect for difficulty level for both the proportion of perfect solutions, F (1, 35) = 62.51, p < .001, and excess moves, F (1, 35) = 46.16, p < .001 (see Figure 38). The interaction between group and difficulty level was not significant for either the proportion of perfect moves or the number of excess moves, F (5.05, 88.41) = 1.87, p = .106, and F (3.21, 56.24) = 1.11, p = .355 respectively.

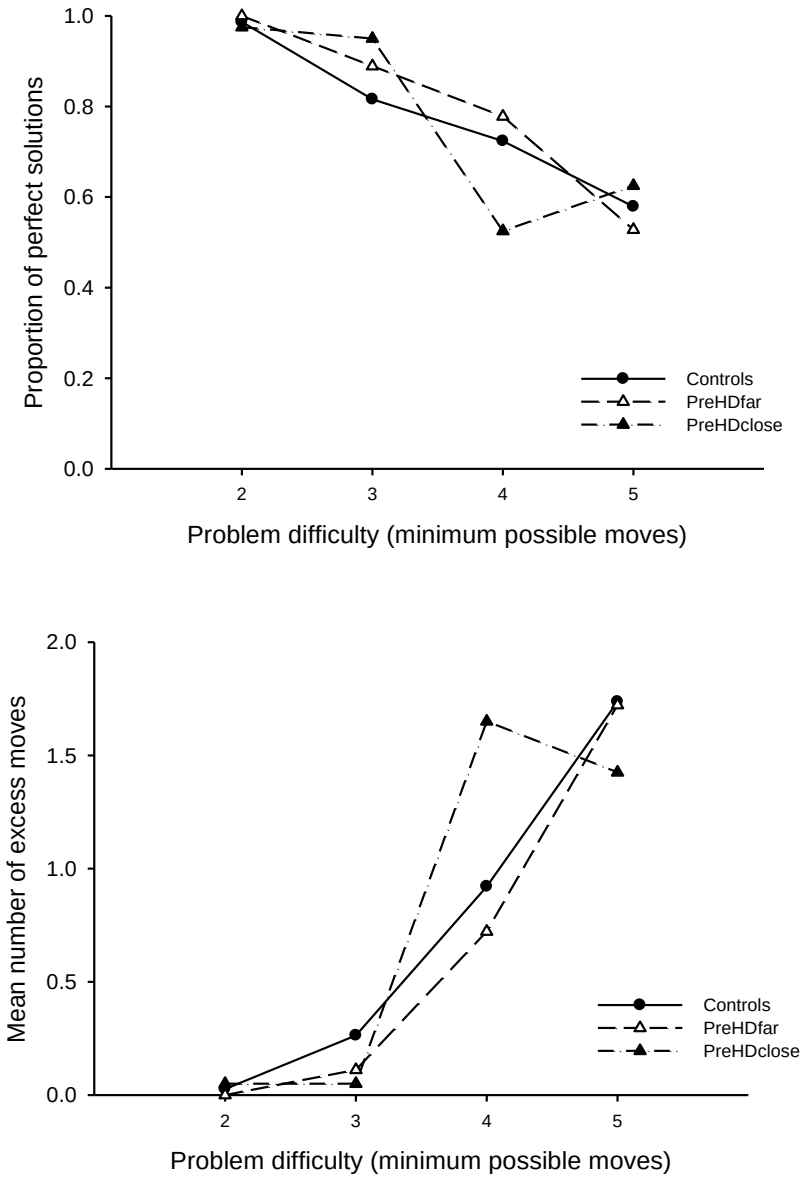

***Figure 38*: Mean proportion of perfect moves (top) and excess moves (bottom) for difficulty levels 2-5 of the Stockings of Cambridge task for the PreHD group and the Control group. Error bars indicate standard error of the mean.**

The PreHDclose, PreHDfar and Control groups did not differ significantly in their initial thinking times, F (2, 33) = .71, p = .499. There was a significant main effect of problem difficulty, F (1.97, 64.95) = 80.63, p < .001, with participants showing slower initial thinking times with increasing problem difficulty (all p values < .001), but the interaction between group and difficulty was not significant (F (3.94, 64.95) = .50, p = .733; see Figure 39). Similarly, there was no significant main effect of group for subsequent thinking times, F (2, 33) = .87, p = .428. There was an expected significant main effect of problem difficulty, F (2.11, 69.76) = 32.09, p < .001. There was no significant interaction between group and problem difficulty, F (4.23, 69.76) = .1.49, p = .211.

For the motor initiation times of the SoC, there was no significant main effect of group, F (2, 33) = .671, p = .518. There was a significant effect of difficulty level, F (1, 33) = 48.73, p < .001, with participants in all three groups initiating movements more quickly with increasing problem difficulty, probably as a result of practice effects over time (see Figure 40). There was no significant interaction between group and difficulty level, F (5.01, 82.56) = .47, p = .80.

For the motor execution times (see Figure 40), there was also no main effect of group, F (2, 33) = .18, p = .83. There was a significant effect of difficulty level, F (2.34, 77.32) = 114.08, p < .001 and a significant interaction effect between group and difficulty level, F (4.89, 77.32) = 3.48, p = .008. To investigate which pairs of groups contributed to the significant interaction, the interaction was computed for each pairing and tested against the error term from the original analysis. Although these results showed significant interactions between PreHDfar and Controls, and PreHDfar and PreHDclose, paired-group post-hoc comparisons showed that the three groups did not differ significantly from one another on any of the four levels of difficulty (all p-values > .05). Figure 40 illustrates the similarity in motor execution times between the three groups.

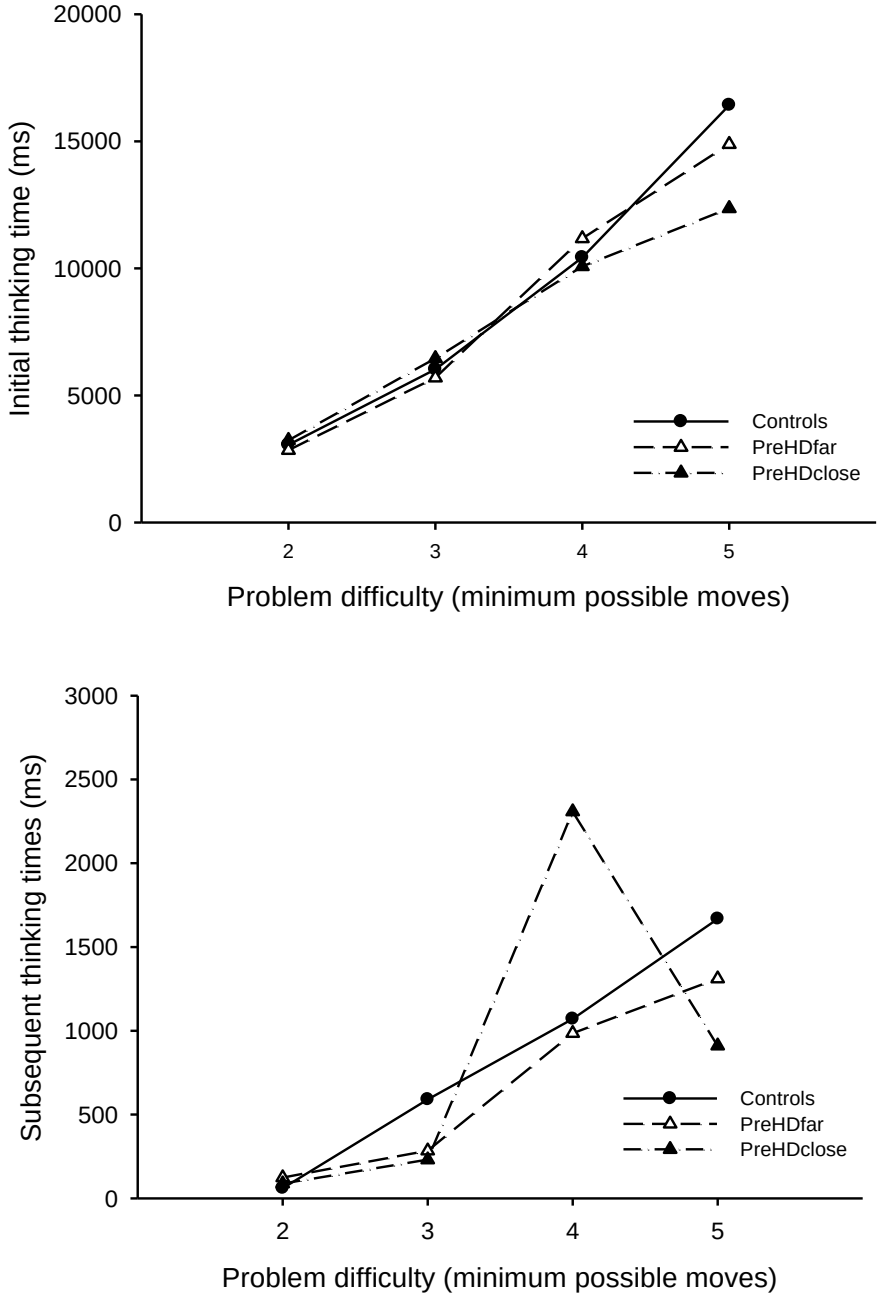

***Figure 39*: Mean initial thinking time (top) and subsequent thinking time (bottom) across for difficulty levels 2-5 of the Stocking of Cambridge task for the PreHDclose, PreHDfar and Control groups. Error bars indicate standard error of the mean.**

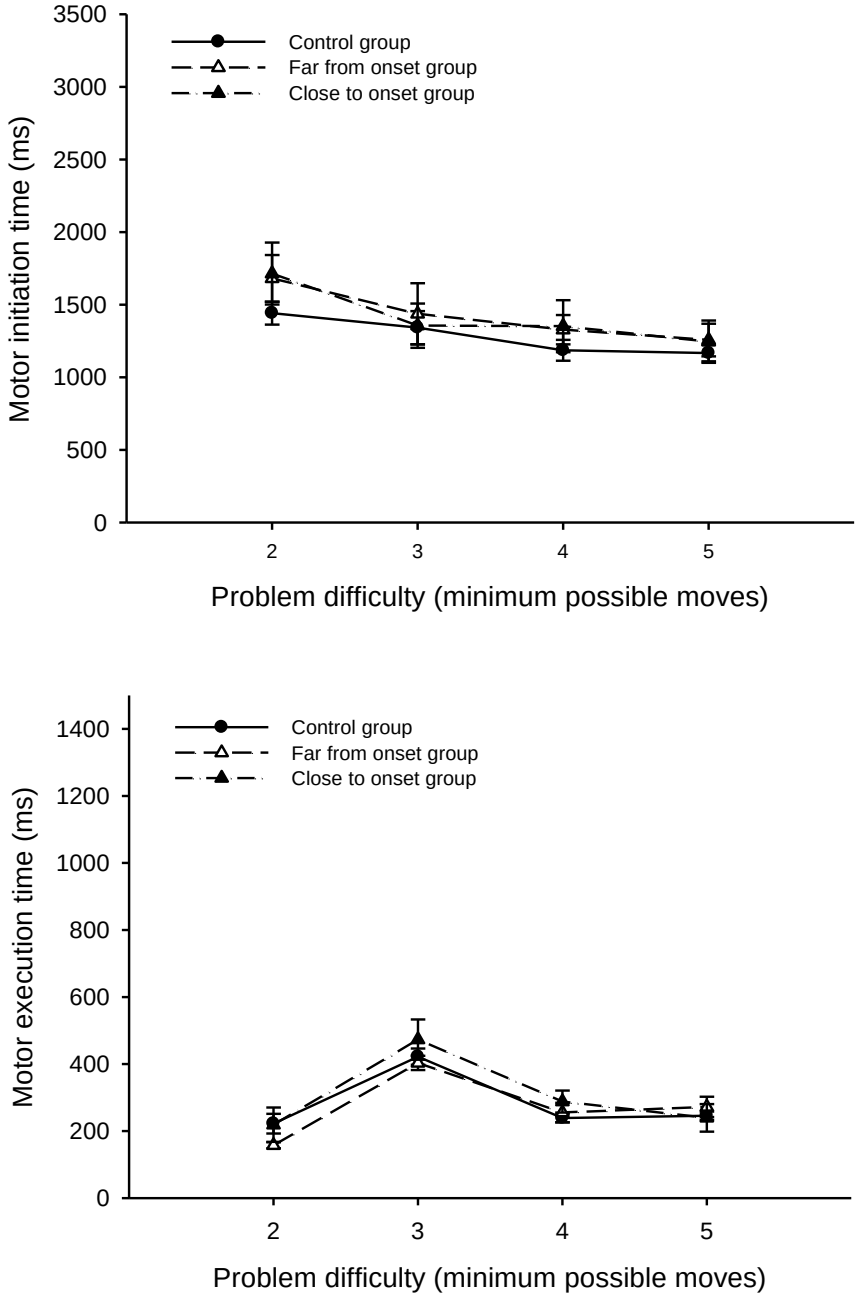

***Figure 40*: Mean motor initiation times (left) and motor execution times (right) in the Stockings of Cambridge task for difficulty levels 2-5 for the PreHD group and the Control group.**

Mood assessments

Table 14 presents the means and standard deviations for the PreHDclose, PreHDfar and Control groups on the four psychological measures. There was a significant main effect of group on the Outward Irritability Scale, F (2, 35) = 3.47, p = .042, with post-hoc comparisons

revealing that the PreHDclose group have significantly higher scores (i.e., higher levels of irritability) than the Control group (p = .047). No significant differences were apparent between the PreHDfar group and the PreHDclose group (p = 1.000) or the Control group (p = .427). In contrast, no significant differences were found between the three groups on the Inward Irritability Scale F (2, 35) = 2.28, p = .117, the Hospital Depression Scale F (2, 35) = 1.12, p = .339 or the Hospital Anxiety Scale F (2, 35) = 1.63, p = .211.

Chi square tests for independence were used to compare the number of participants in each group that scored in the 'normal' and 'abnormal' ranges of the psychological measures. There was a trend for a significant association between group and outward irritability, X^2 (2, 38) = 537, p = .068, indicating that the PreHDclose group had slightly, but not significantly, more participants with 'abnormal' irritability. There was no significant association between group and inward irritability, X^2 (2, 38) = 2.88, p = .237, depression, X^2 (2, 38) = 1.03, p = .598, or anxiety, X^2 (2, 38) = 2.18, p = .336. However, these analyses did violate the recommended minimum cell counts.

Table 14

Means and standard deviations on four mood assessments for the PreHDclose, PreHDfar and Control groups.

Psychological measures	PreHDclose (n = 10)	PreHDfar (n = 9)	Control (n = 19)
Outward Irritability Scale (0-12)			
Total score: mean (SD)	3.70 (2.21)	3.00 (2.12)	1.89 (1.41)
% in abnormal range	40.00	22.20	5.30
Inward Irritability Scale (0-12)			
Total score: mean (SD)	2.30 (1.89)	1.89 (1.54)	1.16 (1.07)
% in abnormal range	10.00	0.00	0.00
Depression Scale (0-15)			
Total score: mean (SD)	3.80 (1.62)	2.56 (1.67)	3.05 (2.01)
% in abnormal range	5.30	0.00	0.00
Anxiety Scale (0-15)			
Total score: mean (SD)	8.20 (4.73)	5.56 (5.43)	5.16 (3.70)
% in abnormal range	50.00	22.20	26.30

Discussion

Study 2 investigated whether people presymptomatic for HD differ from matched controls on a range of neuropsychological tests that are subserved primarily by specific posterior or anterior cortical regions. Based on previous cortical thinning studies, that showed prominent posterior thinning early in HD (Rosas et al., 2002; Rosas et al., 2005; Rosas et al., 2008), it was hypothesised that participants with presymptomatic HD would perform more poorly than controls in cognitive functions that are subserved by posterior cortical regions. In support of these predictions, the PreHD group, and particularly the PreHDclose group, performed more poorly than controls on two of the six tests subserved primarily by posterior regions (the Judgment of Line Orientation Test and the Roadmap Test) and showed a trend towards poorer performance on the Hooper Visual Organisation Test. No differences were evident between the groups on the tests that are subserved primarily by frontal regions.

The Judgment of Line Orientation Test (JLOT) is a test of basic visual perception that requires participants to judge the orientation of lines in space. The PreHD group performed less accurately than the Control group in this test, and as predicted, the PreHDclose group performed more poorly than both the PreHDfar and Control groups. This suggests that subtle changes in visuospatial perception may be evident prior to clinical onset of the disease, and worsen with increasing proximity to onset. The JLOT task has previously been found to be impaired in people with symptomatic HD (Lineweaver et al., 2005; Soliveri et al., 2002), although two presymptomatic HD studies have found no differences from controls (Soliveri et al., 2002; Blackmore et al., 1995). Discrepancies between these two presymptomatic HD studies and the present study may result from less precisely matched control groups. The presymptomatic HD group was significantly more educated than controls in Soliveri et al.'s (2002) study, and an average of seven years younger than controls (although not significantly different) in Blackmore et al.'s (1995) study. In addition, Soliveri et al. (2002) and Blackmore et al. (1995) had fewer participants presymptomatic for HD (n = 17 and n = 13 respectively) than in the present study, and thus had lower power for detecting significant effects.

The Roadmap Test assesses left-right discriminations and egocentric mental rotation. The PreHD group did not perform less accurately than the controls on the Roadmap, and they

performed only slightly more slowly than the control group ($p = 0.09$). However, the PreHDclose group performed significantly worse on this task compared with the PreHDfar and Control groups, with no significant difference in response times. The PreHDclose group performed poorly across all turn types, but did not show significantly poorer performance with increasing demands of mental rotation. This may be indicative of difficulty with left-right discriminations, but not egocentric mental rotation abilities per se. Poorer accuracy on the Roadmap is unlikely to be a result of a speed-accuracy trade-off, as the PreHDclose group did not respond more quickly than PreHDfar or Control groups. Snowden et al. (2002) reported similar results to the present study: their total presymptomatic HD group performed similarly to controls on the Roadmap Test; but when they later compared the original scores of participants who had become clinically affected ($n = 15$) with those still presymptomatic ($n = 9$), the participants who had been closer-to-onset performed significantly worse on the Roadmap than those further-from-onset.

Other studies using the Roadmap Test with participants presymptomatic for HD have shown no differences from controls (Bylsma et al., 1992; Campodonica et al., 1996). However, these studies did not specifically assess participants close to clinical onset, who appear to be more impaired in this task. Moreover, in the Roadmap Test used in our study, an inverted version of the roadmap was administered in addition to the original version. This extended version of the Roadmap Test may have greater sensitivity to detect errors, and thus provide a better measure for detecting subtle changes in presymptomatic HD. A number of studies have reported participants with symptomatic HD to perform worse than controls in the Roadmap Test (Snowden et al., 2001; Lineweaver et al., 1999; Brouwers et al., 1984). Consistent with our study, Snowden et al. (2001) found HD participants performed less accurately, but not more slowly, than controls on this task.

The Hooper Visual Organisation Test (HVOT) is a test of visual-spatial ability and visual integration. PreHD participants showed a trend towards poorer performance on this task. Although the PreHDclose group performed worse than the PreHDfar and Control groups, this difference did not reach significance. The subtlety of these differences should be highlighted

however, as 18 of the 19 participants in both the PreHD and Control groups scored greater than 25/30, considered the 'normal range' in this test (Gomez-Tortosa et al., 1996).

Contrary to predictions, the PreHD group did not perform worse than controls in three other tasks that assessed functioning of posterior cortical regions: the letter mental rotation task, the facial recognition test or the collision judgment task. The PreHD participants performed remarkably similarly to controls in the letter mental rotation task, with no differences in rates of rotation. There is a dearth of research on mental rotation in HD, particularly with presymptomatic HD. The results of this study show no evidence for extrapersonal mental rotation impairments in presymptomatic HD, even in participants close to clinical onset. Normal performance on the facial recognition task is consistent with another presymptomatic HD study that also found no between-group differences on this task (Diamond et al., 1992). Other studies have indicated that impairments in facial recognition and mental rotation are manifest in symptomatic HD participants (Lineweaver et al., 2005; Jacobs et al., 1995; Sprengelmeyer et al., 1996).

It was hypothesised that the PreHD participants would be less impaired on tasks sensitive to frontal cortical functioning, than tasks of posterior cortical functioning. Consistent with this, the PreHD group showed no significant differences from controls on the Stockings of Cambridge task, the Iowa Gambling task, or on the Hand mental rotation task (a measure subserved by both frontal and posterior cortical regions). Moreover, the PreHDclose group did not perform significantly worse on these tasks than controls. Normal performance in the SoC is consistent with Lawrence et al. (1999) who found no differences between presymptomatic HD participants and controls on measures of accuracy and latency in the one-touch ToL.

There are no reports of the use of the Iowa Gambling test and the Hand mental rotation test in presymptomatic HD participants. The present study provides no evidence of impaired decision-making abilities or mental rotation of hands, functions typically associated with prefrontal regions, in presymptomatic HD. Although these findings of poorer performance in tasks that are subserved by posterior regions but not in those subserved by anterior regions

support our hypotheses, it is important to note that more posterior tests were used in this study (6 versus 3).

Some of the neuropsychological tests showed ceiling effects and limited range in scores, rendering them less sensitive for detecting differences in functioning. In particular, on the letter mental rotation task and the hand mental rotation tasks, more than half of the PreHD group obtained accuracy scores higher than 95%. Although the primary measure of these tests is rate of rotation, not accuracy, the ceiling effects in these tests indicate that the demands on mental rotation in this task may be too easy. Future studies may benefit from using cognitive tasks with higher levels of difficulty (for example mental rotation of complex 3D shapes rather than the letter 'F'; Shepard & Metzler, 1971), which may yield a greater range of scores.

Impairments in psychomotor speed are often apparent in presymptomatic HD participants (Lemiere et al., 2002, 2004; Witjes-Ane et al., 2003), and this can affect test performance, particularly in timed tasks. The PreHD group performed significantly more slowly than controls on one measure of psychomotor speed, the Motor Screening task. However, the PreHD group (and the PreHDclose group) did not show slower response times than controls on other measures of psychomotor speed, including the Simple Reaction Time Task, the motor initiation or motor execution subtasks of the SoC, the Roadmap Test, or the Hand and Letter mental rotation tasks. The slower performance of the PreHD participants on the simple reaction time task may indicate very mild motor slowing in this group, may reflect a false positive result.

Mood assessments

The PreHD group showed significantly greater levels of irritability than the control group on both outward and inward irritability scales, whereas no differences were apparent between the two groups on anxiety and depression scales. Interestingly, only the PreHDclose, and not the PreHDfar group, showed greater outward irritability than controls. Irritability symptoms are common in participants with both symptomatic and presymptomatic HD (Kirkwood et al., 2002; Berrios et al., 2002) and often worsen with disease progression (van Duijn et al., 2007).

Although irritability may be a secondary response to difficulties inherent in HD, it may also be a direct result of pathological changes. Impairments in irritability and anger are often associated with changes in the limbic system (particularly the amygdala) and the orbitofrontal and anterior cingulate cortices (Siever, 2008). Accordingly, in HD these symptoms are hypothesised to result from degeneration of the striatal-orbitofrontal (van Duijn et al., 2007) and/or striatal-cingulate circuits (Afifi, 1994).

The use of current psychiatric diagnoses of major depression and anxiety disorders as exclusion criteria could potentially result in lower scores in the depression and anxiety scales. No participants were excluded on this basis, however, suggesting that these results are a reliable measure of mood symptoms in this sample of individuals presymptomatic for HD.

In summary, Study 2 showed that the PreHD participants, and particularly the PreHDclose participants, performed significantly more poorly than controls on two of the six neuropsychological tests subserved primarily by posterior cortical regions. These results are consistent with other neuropsychological studies in HD that have detected significant differences in visuospatial tasks in participants close to onset, but not far to onset (Wahlin et al., 2007; Snowden et al., 2002). There were no significant differences between the PreHD and Control participants on tests subserved primarily by frontal cortical regions.

Chapter Five Study 3: Clinical correlates of brain measures

Introduction

Study 1 (Chapter 3) reported significant cortical thinning in PreHD participants (and particularly PreHDclose participants) that was most prominent in the posterior regions. Cortical thickening was also present in frontal and anterior cingulate regions. Study 2 (Chapter 4) showed that the PreHD participants (and particularly PreHDclose participants) performed more poorly than controls in selective neuropsychological tests that were subserved primarily by posterior cortical regions of the brain. Accordingly, Study 3 sought to investigate the relationship between cortical thinning and cognitive performance in the PreHD group.

Surface-based regressions were used to investigate whether there were significant associations across the entire cortex. In addition, region-of-interest (ROI) analyses were conducted by correlating selected cortical parcellations with each cognitive task. It was hypothesised that poorer performance in the neuropsychological tests would be associated with greater thinning in cortical regions that subserve these measures. It was also hypothesised that these correlations would be more apparent in cognitive tasks subserved primarily by posterior cortical regions, compared with tasks subserved primarily by frontal cortical regions. Because the striatum is a primary site of pathology in HD, correlational analyses were also conducted between caudate and putamen volumes and each neuropsychological measure. No a priori predictions were made for the psychological measures. However, as there was a significant between-group difference in scores on the Outward Irritability Scale (Study 2), an explorative surface-based regression was conducted for this scale.

Method

Statistical analysis

Surface-based regressions with neuropsychological scores

Cortical thickness was regressed on a vertex-by-vertex basis against selected neuropsychological test scores. This analysis was conducted for the PreHD participants only (n = 19). Because of the small sample size, correlational analyses were not conducted for the separate PreHDclose and PreHDfar groups. Four cognitive tasks were selected for regression analysis: the Judgment of Line Orientation Task and the Roadmap Test, on which the PreHD group performed more poorly than controls; and the Iowa Gambling task and the Stockings of Cambridge task, in which PreHD participants were not impaired. In addition, a regression analysis was conducted for the Outward Irritability Scale, in which the PreHD group showed significantly higher levels of irritability than controls. Each score was modelled independently, using the following model of thickness for each subtest: [offset + (slope x test score) + (slope x age) + an error term]. The offset and slope were subject-independent regression coefficients estimated separately for each vertex using a general linear model. Pearson correlation coefficients were calculated from the slope and mapped on the surface. *T* Statistics at each vertex were used to test the hypothesis that the slope coefficient was equal to zero. This procedure has been found to be highly reliable for identifying relationships between regional cortical thickness and neuropsychological performance, in terms of both spatial localisation and magnitude of absolute cortical thickness measurements (Dickerson et al., 2008).

Cortical parcellation correlations with neuropsychological scores

Correlation coefficients were also calculated between the neuropsychological test scores and cortical parcellation thickness measures. A preliminary analysis involved conducting a partial correlation matrix between the neuropsychological test measures (including 16 cognitive measures and the 4 psychological measures) and the mean thickness measures of all 64 cortical parcellations, with age as a covariate. This analysis was conducted separately for the PreHD and Control groups. Chi-square tests were used to calculate whether the number of significant correlations in the PreHD and Control groups was greater than expected by

chance, and whether the PreHD group showed more correlations than the Control group. An identical analysis was conducted between the same neuropsychological test measures and the total caudate and total putamen volumes.

Using the correlation matrix generated as described above, selected regions of interest (ROIs) were examined that were deemed crucial to performing each cognitive task (based on analyses from neuropsychological lesion studies and functional imaging studies; see Chapter 3 and Appendix F). Table 15 presents the ROIs examined for each cognitive measure. This ROI analysis was completed for the PreHD group only. Age was used as a covariate in all correlational analyses because it has been associated with both cognitive performance (Benton et al., 1994) and cortical thinning (Salat et al., 2004) in normal adults, and because there was marked variability in age within the groups. Two-tailed tests were used because of the limited current understanding of the relationship between cortical thinning and cognitive functioning in HD. To reduce Type-I error for multiple comparisons, correlations were considered significant only if $p < 0.01$.

Table 15

Cortical parcellation regions of interest (ROIs) associated with cognitive test measures.

Cognitive tests	Measures	Cortical parcellation ROIs
JLOT	Accuracy	Superior parietal; precuneus, lingual; cuneus; lateral occipital
HVOT	Accuracy	Cuneus; lateral occipital; superior parietal; fusiform
Collision Judgement	Accuracy	Left supramarginal gyrus; *left inferior parietal*
Facial Recognition	Accuracy	Fusiform, lateral occipital, *superior temporal*
Roadmap	Rotation turns only: Response time; accuracy	Inferior and superior parietal cortex
Letter Mental rotation*	Response time; accuracy	Inferior and superior parietal cortex
Iowa Gambling task	Percentage advantageous cards in last 60 trials	Medial and lateral orbitofrontal; *pars orbitalis, pars triangularis, pars opercularis*
Stockings of Cambridge	Perfect moves; initial thinking times; subsequent thinking times	Superior frontal; rostral middle frontal; Caudal middle frontal, *pars orbitalis, pars triangularis, pars opercularis*
Hand Mental Rotation*	Response time; accuracy	Precentral gyri; premotor gyri; caudal middle frontal; superior frontal (in addition to inferior and superior parietal)

Note: Primary ROIs are in normal font; secondary ROIs are in italics. All ROIs include bilateral measures, unless otherwise noted. JLOT: Judgement of Line Orientation Test; HVOT: Hooper Visual Organisation Test.
* To obtain 'pure' measures of mental rotation response times for the correlational analyses, data was collapsed about 180° and a regression line was fitted to the remaining four data points (0°, 60°, 120°, 180°), which provided a measure of rate of rotation (ms/deg). For mental rotation accuracy measures the data for the 0° angle of orientation was excluded.

Results

Surface-based regressions

The following neuropsychological variables were included for surface-based regressions: JLOT (total accuracy); Roadmap Test (accuracy of rotation turns); SoC task (proportion of perfect solutions); Iowa Gambling task (percentage advantageous cards in last 60 trials); and the Outward Irritability Scale (total score). Significant correlations were evident between each neuropsychological measure and selective cortical thinning in the PreHD group. Consistent with predictions, worse performance on the Judgement of Line test was correlated with thinner cortex (see Figure 41). Significant correlations were evident in the right supramarginal gyrus, and perhaps surprisingly, in the left pars opercularis and precentral gyrus.

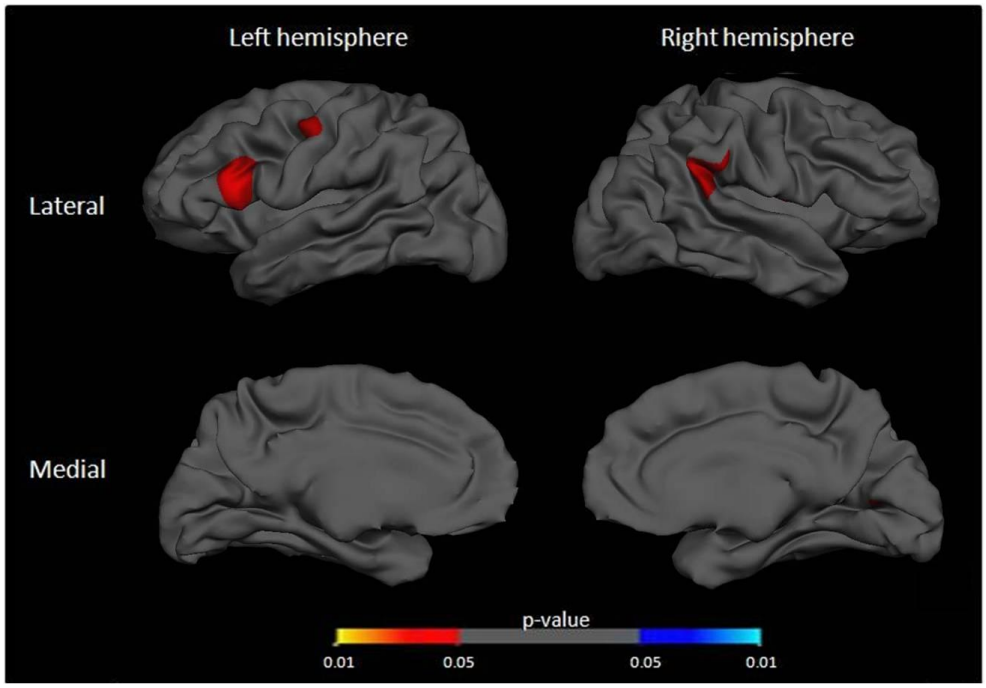

***Figure 41*: Significant correlations between JLOT total accuracy scores and selective cortical thinning in the PreHD group. P-values range in value from 0.05 to 0.01, with yellow/red corresponding to significant positive correlations and blue corresponding to significant negative correlations. Worse scores in the JLOT were associated with thinner cortex.**

Poorer performance on the Roadmap significantly correlated with thinner cortex in a number of regions (see Figure 42). These included the left caudal middle frontal gyrus, right inferior and middle temporal gyri, and the temporal poles. Small correlation clusters were also visible

in the right pars triangularis and lateral occipital gyrus. Contrary to predictions, poorer performance on the Roadmap was also significantly correlated with thicker cortex, predominantly in the right orbitofrontal gyrus and bilaterally in the precuneus.

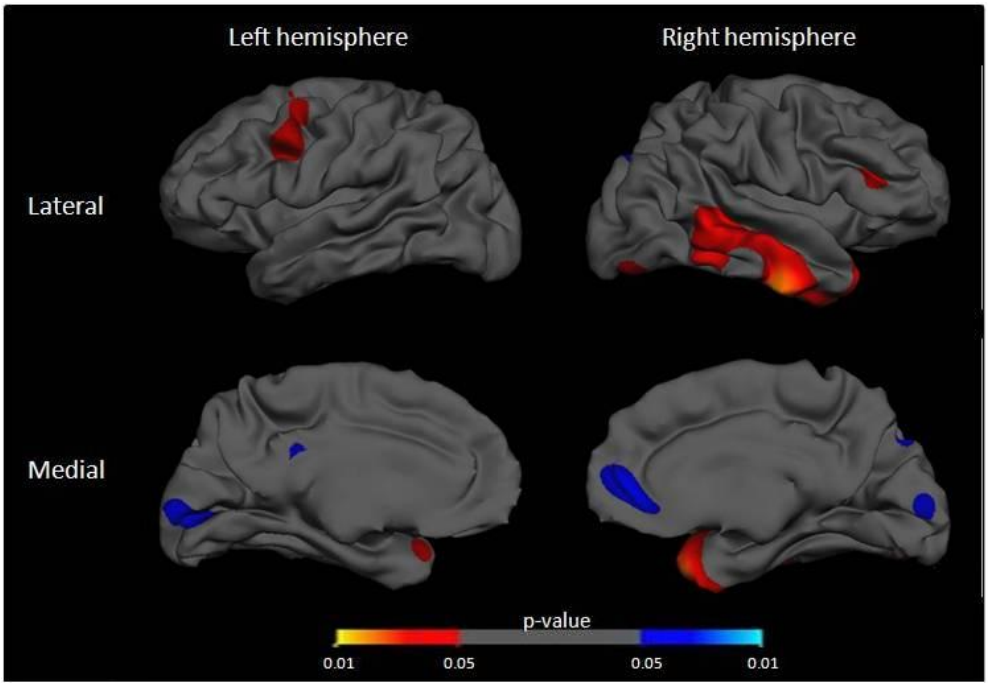

***Figure 42*: Significant correlations between Roadmap accuracy scores (rotation turns only) and selective cortical thinning in the PreHD group. P-values range in value from 0.05 to 0.01, with yellow/red corresponding to significant positive correlations and blue corresponding to significant negative correlations. Worse scores in the Roadmap were associated with both thicker and thinner cortex in different regions.**

Consistent with predictions, poorer performance in the Stockings of Cambridge task was significantly correlated with thinner cortex in a number of frontal regions, including the pars triangularis, pars opercularis, precentral, superior frontal and medial orbitofrontal gyri (see Figure 43). Significant correlations were also apparent within the precuneus and cuneus, as well as the right inferior, middle and superior temporal gyri. Figure 44 presents a scatter plot which illustrates the relationship between performance on the SoC and cortical thickness in a selected ROI within the right pars triangularis ($r = .58$, $n = 19$, $p = .009$), with poorer scores associated with thinner pars triangularis.

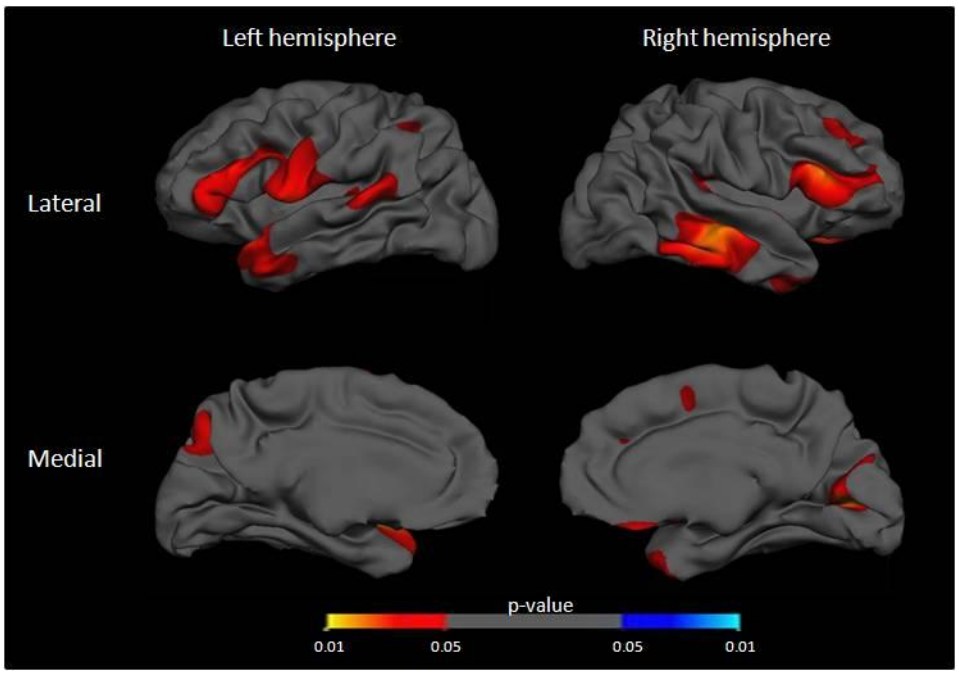

***Figure 43*: Significant correlations between Stockings of Cambridge task (proportion of perfect solutions) and selective cortical thinning in the PreHD group. P-values range in value from 0.05 to 0.01, with yellow/red corresponding to significant positive correlations and blue corresponding to significant negative correlations. Worse scores in the SoC task were associated with thinner cortex.**

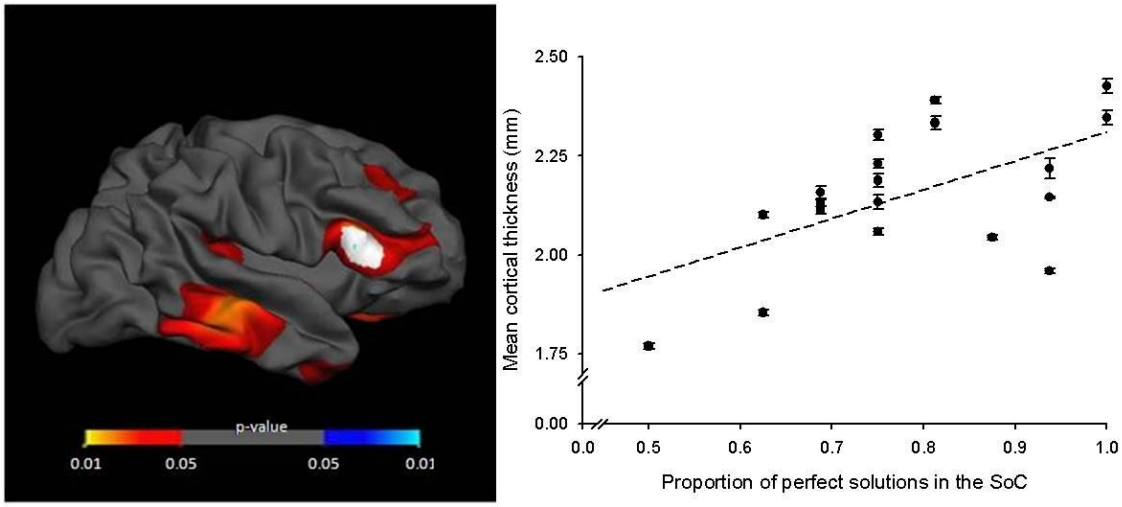

***Figure 44*: Scatter plot illustrating the correlation between performance on the Stockings of Cambridge task and a manually selected ROI within the right Pars Triangularis. P-values range in value from 0.05 to 0.01, with yellow/red corresponding to significant positive correlations and blue corresponding to significant negative correlations. Error bars indicate standard error of the mean.**

Similarly to the SoC task, poorer performance in the Iowa Gambling task was significantly correlated with thinner cortex in a number of frontal regions (see Figure 45). Significant correlations were apparent bilaterally in the superior frontal, caudal middle frontal, and precentral gyri, as well as the left pars opercula and paracentral gyrus, and the right pars triangularis. Significant correlations were also apparent within the right middle and inferior temporal gyri, the left inferior parietal gyrus and the precuneus. Contrary to predictions, the Gambling task was also correlated with thicker cortex, specifically in the right lateral orbitofrontal cortex and the left occipital cortex (including the cuneus, pericalcarine and lingual gyri).

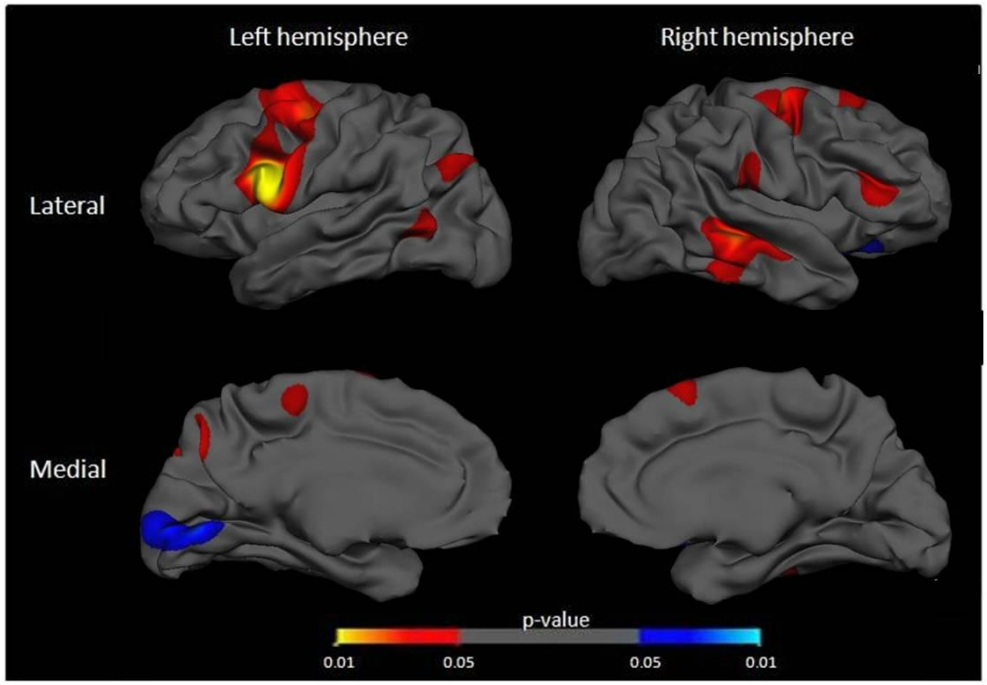

***Figure 45*: Significant correlations between Iowa Gambling task (percentage of advantageous cards in last 60 trials) and selective cortical thinning in the PreHD group. P-values range in value from 0.05 to 0.01, with yellow/red corresponding to significant positive correlations and blue corresponding to significant negative correlations.**

Contrary to predictions, worse scores on the Outward Irritability Scale (i.e., higher levels of irritability) were significantly correlated with *thicker* cortex in the anterior cingulate cortex (see Figure 46). This relationship is illustrated on a scatter plot in Figure 47 ($r = .56$, $n = 19$, $p = .014$).

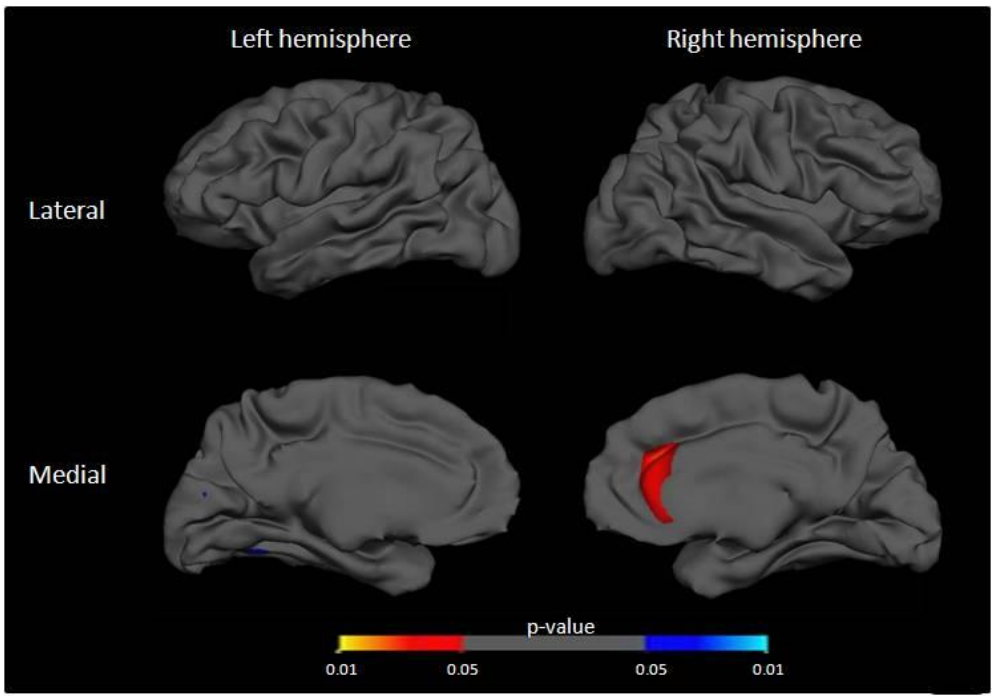

***Figure 46*: Significant correlations between Outward Irritability Scale total scores and selective cortical thinning in the PreHD group. P-values range in value from 0.05 to 0.01, with yellow/red corresponding to significant positive correlations and blue corresponding to significant negative correlations. Higher scores (i.e., higher levels of irritability) in the Outward Irritability Scale were associated with thicker cortex.**

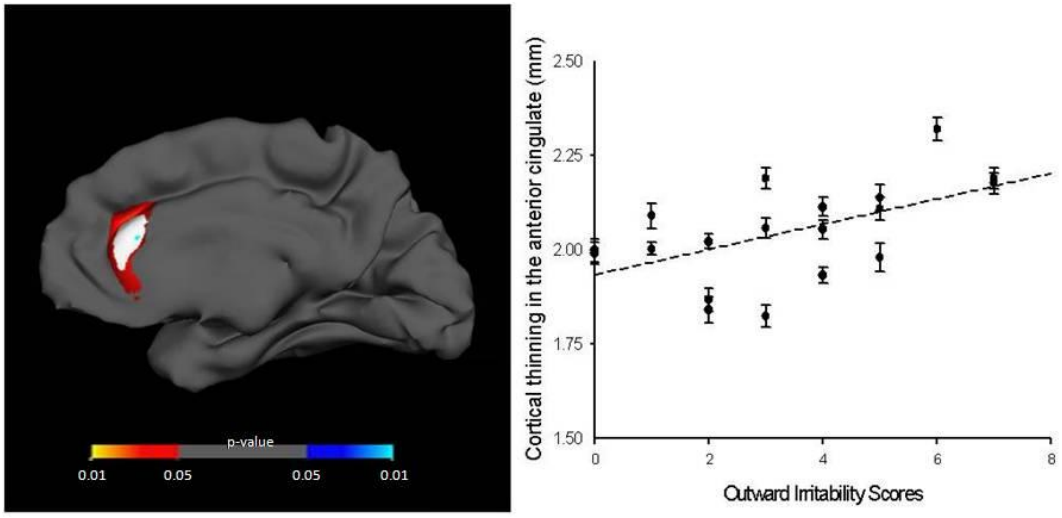

***Figure 47*: Scatter plot illustrating the correlation between performance on the Outward Irritability Scale and an ROI within the right anterior cingulate cortex. P-values range in value from 0.05 to 0.01, with yellow/red corresponding to significant positive correlations and blue corresponding to significant negative correlations. Error bars indicate standard error of the mean.**

Correlations between cortical parcellations and neuropsychological test scores

A partial correlational matrix was calculated between neuropsychological test scores and all cortical parcellations, with age as a covariate. With a significance level of 0.01 we would expect 12.8 significant correlations by chance (0.01 x 20 tests scores x 64 parcellations). The Control group had 12 significant correlations, no more than expected by chance, X^2 (1, 19) = .157 p = .692. In contrast, the PreHD group had 21 significant correlations, significantly more than the Control group, X^2 (1, 19) = 6.81, p = .009, and the number of correlations expected by chance, X^2 (1, 19) = 4.29, p = .038.

From the partial correlational matrix generated, correlations were also conducted between the cognitive test scores and selected ROIs that were deemed crucial to performing each task (See Appendix K) were examined. There were 14 cognitive test measures (as mood measures were not included), and each measure was correlated with between 2 and 6 parcellations, totalling 48 correlations. With a significance level of 0.01, we would expect 0.48 significant correlations by chance (0.01 x 48 correlations). Only one of the 48 correlations between the tests scores and the ROIs was significant for the PreHD group. The accuracy score (percentage of advantageous cards in last 60 trials) of the Iowa Gambling test was significantly correlated with the left pars opercula, in the ventral prefrontal cortex (r = .79, n = 19, p < .001; see Figure 48). The Control group showed no significant correlation between performance in the Iowa Gambling test and the left pars opercula (r = -.153, n = 19, p < .558), or between any of the test scores and selected ROIs (all p-values > .01).

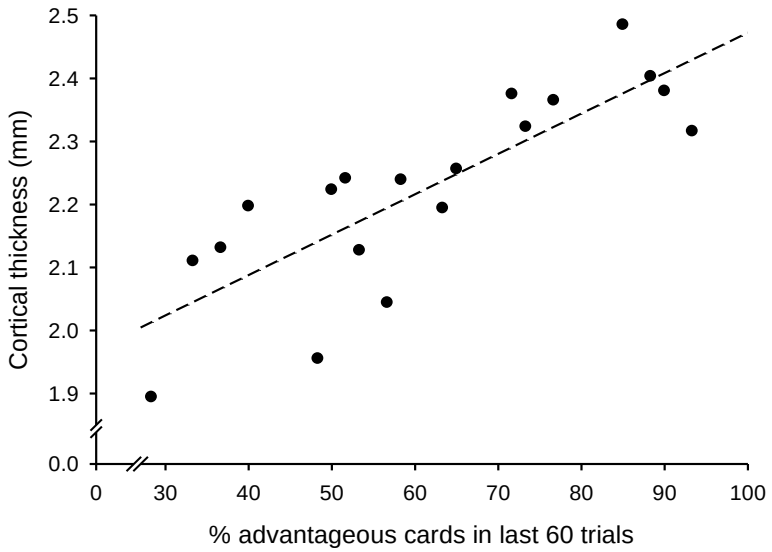

***Figure 48*: Scatter plot illustrating the positive correlation between Iowa Gambling task accuracy scores (percentage of advantageous cards in last 60 trials) and cortical thickness in the left pars opercula.**

Correlations between striatal volume and neuropsychological tests scores

A partial correlational matrix was also calculated between the neuropsychological tests scores and the caudate and putamen volumes. With a significance level of 0.01 we would expect 0.40 significant correlations by chance (0.01 x 20 test scores x 2 striatal measures). Unexpectedly, the Control group showed two significant correlations, significantly more than expected by chance, X^2 (1, 19) = 5.19 p = .023. The PreHD group also showed two significant correlations; no more than the Control group. The striatal measures in the PreHD group were significantly correlated with cognitive tests subserved primarily by posterior cortical regions, and not tests subserved primarily by frontal regions. Caudate volume was correlated only with Roadmap accuracy (r = .679, n = 19, p = .002; see Figure 49). Putamen volume was correlated with accuracy on the Roadmap (r = .675, n = 19, p = .002) and the Judgment of Line Orientation task (r = .492, n = 19, p = .003; see Figure 50). The caudate and putamen measures of the Control group correlated with only the facial recognition task (p=001 and .008 respectively). However, when intracranial volume was added as a covariate the correlations for both groups diminished (all p-values > .01).

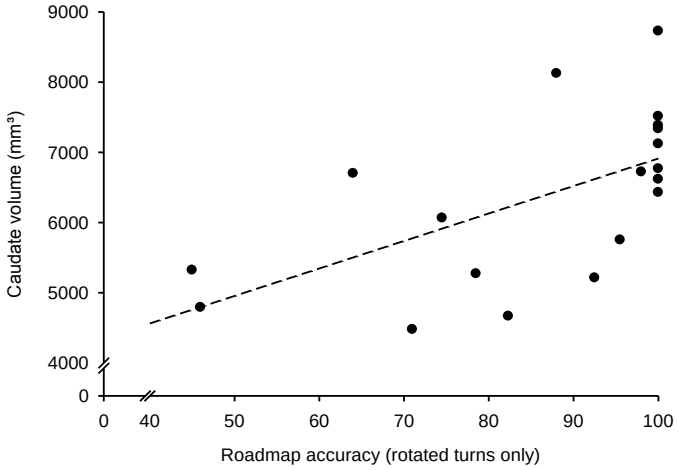

***Figure 49*: Scatter plot illustrating the positive correlation between caudate volume and Roadmap accuracy scores for the PreHD group.**

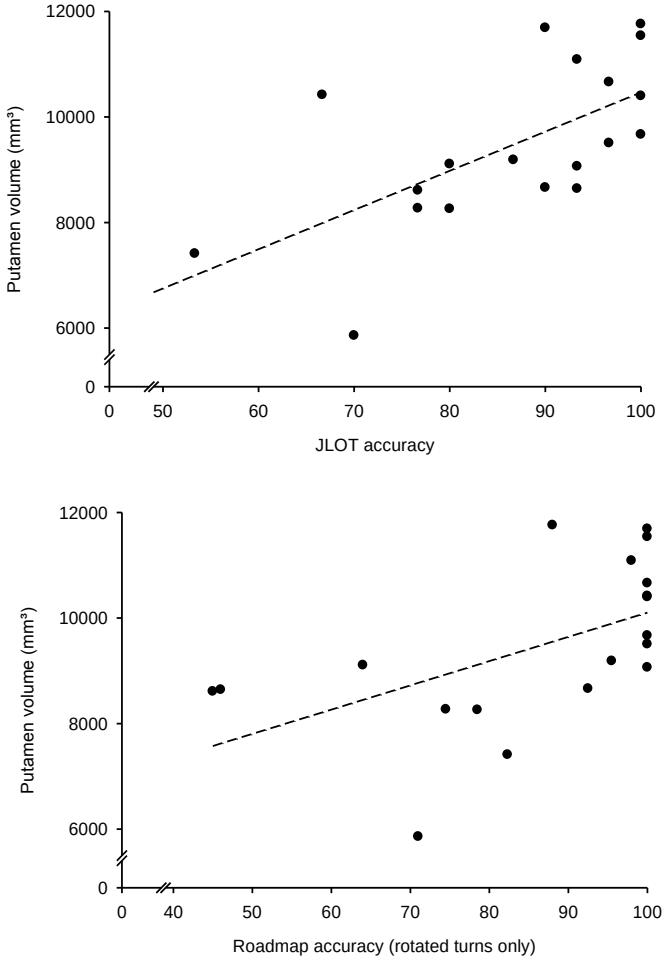

Figure 50: Scatter plots illustrating the positive correlation between putamen volume and JLOT accuracy scores (top) and Roadmap accuracy scores (bottom) for the PreHD group.

Discussion

Study 3 used correlational analyses to assess the relationship between specific regions of cortical thinning and cognitive performance in the PreHD group. It was hypothesised that poorer performance on the cognitive measures would be associated with greater thinning in cortical regions that are hypothesised to subserve these tests. Surface-based regressions were used to illustrate significant regressions across the entire cortex. In addition, region-of-interest (ROI) analyses were conducted by correlating cortical parcellations selected a priori with each cognitive task.

The surface-based regressions were conducted for four selected cognitive tasks, the JLOT and Roadmap Tests (which showed significant between-group differences), and the Iowa Gambling Task and the Stockings of Cambridge (which showed no between-group differences). All four tasks showed significant relationships with regional thinning. Worse performance in the JLOT was significantly correlated with greater thinning in the inferior parietal cortex, inferior frontal gyrus and precentral gyrus. A small number of functional imaging studies have shown activations of these regions (particularly the inferior parietal cortex) during performance on JLOT-like tasks (Faillenot, Sunaert, Van Hecke, & Orban, 2001; Orban et al., 1997). These tasks are predominantly associated with the occipitotemporal and superior parietal cortices (Dupont et al., 1998; Faillenot et al., 2001; Hannay et al., 1987; Herrmann, Ehlis, Wagener, Jacob, & Fallgatter, 2005; Ng et al., 2001; Ng et al., 2000; Orban et al., 1997; Vandenberghe et al., 1996) which did not correlate with JLOT performance in this study. Despite significant thinning in the occipito-parietal cortex in the PreHD group, there were again no significant correlations between these regions and JLOT performance.

Unexpectedly, poorer performance on the Roadmap Test was associated with both cortical thinning and cortical thickening in the PreHD group. Poorer performance correlated with thinning in frontal and temporal cortices, with no apparent correlations in the parietal regions that are predominantly associated with this task. Again, no significant correlations were apparent in the parieto-temporal-occipital junction (PTO) which showed thinning in the between-group thinning analyses and has been associated with similar tasks involving egocentric rotation and right-left discrimination (Creem-Regehr et al., 2007; Creem &

Proffitt, 2001; Zacks, Vettel, & Michelon, 2003). Roadmap correlations with cortical *thickening* were apparent within both posterior (cuneus, pericalcarine and superior parietal gyrus) and frontal cortical regions. Although the posterior regions have been associated with similar tasks (Creem-Regehr et al., 2007; Zacks et al., 1999), the negative relationship between task performance and cortical thinning is perplexing (negative brain-behaviour relationships are discussed further in Chapter 6).

Surface-based regressions for the two tasks subserved primarily by frontal regions, Iowa Gambling and SoC, both showed significant correlations between performance and cortical thickness, despite the PreHD group performing similarly to controls on these tasks. Consistent with predictions, correlations in the Iowa Gambling task were most prominent in frontal regions, particularly the pars opercula. This region, which showed thinning in the PreHD group, is situated within the ventral lateral prefrontal cortex, one of the regions that has been associated with performance on this test (Clark, Manes, Nagui, Sahakian, & Robbins, 2003; Ernst et al., 2002). No correlations were found, however, between test performance and thinning in the ventral medial prefrontal cortex (VMPFC), which is most commonly associated with this task (Bechara et al., 1999; Bechara et al., 2000; Bechara et al., 2001; Bolla et al., 2003). Contrary to predictions, poorer performance in the Iowa Gambling task was also associated with thicker cortex, both in the lateral orbitofrontal gyrus and the occipital cortex. As discussed above, these relationships may represent pathological cortical thickening. Although the orbitofrontal cortex is commonly associated with this task (Fellows, 2007), correlations in the occipital cortex are more difficult to make sense of.

In the SoC task, correlations were apparent in frontal regions of the brain associated with performance in this task (Lazeron et al., 2000; Rasmussen et al., 2006; van den Heuvel et al., 2003). Correlations were also apparent in temporal, parietal and occipital regions. Indeed, although the dorsolateral prefrontal cortex (DLPFC) is considered the crucial region mediating performance on this task, most neuroimaging studies reveal a frontal-parietal network activated during this task, with some tasks also showing activation in occipital regions (e.g. Dagher et al., 1999; van den Heuvel et al., 2003; Unterrainer et al., 2005). The parietal and occipital areas are thought to be associated with the visual processing demands of

the task, but not the planning components of this task, because they do not show increases in activation with increasing levels of difficulty in the SoC (Dagher et al., 1999; Wagner et al., 2006). However, in our study extensive correlations were also visible bilaterally in the temporal cortices, regions that do not appear to be required for this task.

Consistent with the present study, other cortical thinning studies have also shown cognitive performance (as assessed by the UHDRS tasks) to be associated with thinning in a large number of regions across the cortex, both in presymptomatic (Rosas et al., 2005) and symptomatic (Rosas et al., 2008) HD participants. Whilst Rosas and colleagues (2005) did not report any *negative* correlations between cortical thickness and task performance in presymptomatic participants, Rosas et al. (2008) found performance on the symbol digit in symptomatic HD participants to be associated with thickening in the anterior cingulate cortex.

Methodological artifacts may have influenced cortical thinning measures, tests performance measures, and/or the relationships between these variables. Firstly, five of the PreHD participants were scanned with an incorrect scanning protocol, and had to undergo a repeat MRI scan. The time difference between the neuropsychological assessment and the repeat scan (mean ± SD of 6.0 ± 3.5 months) could have confounded the association between these measures for these participants. Although the disease process of HD progresses slowly, particularly in presymptomatic stages, subtle changes in cortical thickness over this time could influence the correlations in Study 3. Three of the five participants were in the PreHDfar group, which showed no thinning, so we should not put too much weight on these effects.

Secondly, the ceiling effects and limited range in scores in some of the neuropsychological tests may have reduced the size of the correlations. For example, more than half of the PreHD group obtained accuracy scores higher than 90% on the JLOT task and 95% on the Roadmap Test. Future studies would benefit from using cognitive tasks with higher levels of difficulty, which yield a greater range of scores.

Thirdly, 9 of the 19 PreHD participants were estimated to be a long way from onset of the disease. The inclusion of these participants increases the likelihood of null results due to too much of the sample being at 'ceiling' level of cortical thickness. Unfortunately, excluding far from onset individuals from this sample and only examining the correlations in the PreHDclose group would have resulted in a smaller sample size of only 10 participants, and consequently insufficient power to detect significant correlations.

Fourthly, the significance level used in the surface-based regressions ($p < .05$) may have been too liberal. Consequently, rather than reflecting real brain-behaviour relationships, some of the correlations in Study 3 may have simply occurred by chance. This significance level was selected by our collaborators and is commonly used in other cortical thinning studies (McDonald et al., 2008; Rosas et al., 2008; Sowell et al., 2008). A more conservative significance level would provide lower sensitivity to detecting early changes in the disease, but may also reduce spurious findings.

Lastly, our sample size of 19 may have been too small to detect meaningful relationships between thinning and task performance. Although this sample size was sufficient to detect group differences in cortical thickness (Study 1) and in neuropsychological performance (Study 2), the combination of cortical thickness measures and neuropsychological scores significantly increases inter-individual variance; correlational analyses of these variables may require a larger number of participants.

Optimally, I would have liked to have explored further the cortical thinning and correlational data. Further analysis could include examining i) the variability and magnitude of thinning in both control and PreHD participants, ii) undue influence of outlier participants, and iii) the effects of covariates on the surface-based regressions. Because control of the data analysis was shared between two centres, the extent to which results could be explored and verified was limited (this is discussed in more detail in the General Discussion section).

A region-of-interest correlation analysis was also performed with the parcellation data. Correlations between cognitive test scores and a priori selected regions of interest (ROIs)

deemed crucial to performing each task were examined. Contrary to predictions, there were no significant correlations between task performance and selected ROIs for tasks sensitive to posterior cortical regions. However, consistent with the surface-based regressions in this study, the Iowa Gambling test correlated significantly with the left pars opercula. However, the significance level for these correlations was relatively liberal ($p < .01$) considering the number of comparisons, and longitudinal studies are required to clarify the significance of this correlation.

These findings indicate that there are few correlations between the cognitive tasks and the selected ROIs. There are possible explanations for this. The probability of detecting significant correlations may have been reduced by the imprecise nature of the parcellations. As discussed in Chapter 3, the parcellations provide coarse measures of mean thickness across large cortical regions. For example, the *lateral occipital* parcellation includes the entire lateral occipital cortex, inclusive of BA 17, 18 and 19. The parcellations may incorporate several neuroanatomical regions, each subserving different functions. Accordingly, the summation of these regions may reduce the sensitivity of detecting specific brain-behaviour relationships. This may be illustrated by significant correlations in the surface-based regressions and not in the parcellation analyses. In addition, the probability of detecting significant correlations may have been constrained by limited variability in cortical thinning measures between participants, and the restricted range of cognitive scores, particularly after controlling for age.

Correlational analyses were also conducted between striatal volumes and cognitive performance. This recognised that the striatum is a site of primary pathology in HD, and neuropsychological symptoms in HD are often ascribed to degeneration in this region (Lawrence et al., 1998). We might expect that the striatum would correlate more strongly with tasks of frontal lobe function than posterior cortical function, given the significant projections from the striatum into the frontal cortex (Middleton & Strick, 1998, 2000). Surprisingly, striatal volume measures in the PreHD group were significantly correlated with the JLOT and the Roadmap Test (both of which are subserved primarily by posterior cortical regions). Interestingly, these were the same two tests that PreHD participants showed poorer

performance on in Study 2. Equally surprising, the striatal measures in the Control group were correlated with scores on the Facial Recognition Test. No correlations were evident between striatal volume and performance on tasks subserved primarily by frontal regions (in either the PreHD or Control groups).

Although a number of MRI studies have reported significant correlations between striatal measures and performance in the UHDRS cognitive tests (Douaud et al., 2006; Rosas et al., 2008), only a small number of studies have correlated striatal measures with tests subserved primarily by posterior cortical regions. One study with presymptomatic participants reported no significant association between striatal measures and performance in either the Roadmap Test or an extrapersonal rotation task (Campodonica et al., 1998).

The correlations in the present study may simply reflect collinearity between striatal volumes and performance measures, rather than a cause-effect relationship. Indeed, these striatal correlations diminished when intracranial volume was used as a covariate, indicating that extra-striatal brain changes, or differences in total brain size, may contribute to these effects. Moreover, the Control group showed the same number of correlations between striatal measures and cognitive tasks as the PreHD group. This suggests that the observed correlations either represent relationships in the normal brain, or occur by chance, particularly given the relatively liberal significance level that was used.

No a priori predictions were made for cortical regions subserving the psychological scales, and thus ROI correlational analyses were not conducted. However, because the PreHD group scored significantly more poorly than controls on the Outward Irritability Scale, a surface-based regression was used to explore the relationship between scores on this scale and cortical thickness in the PreHD group. Heightened levels of outward irritability were correlated with thickening in the right anterior cingulate cortex only. As discussed earlier, thickened cortex could be indicative of neuronal pathology, and therefore cortical thickening in this region could potentially contribute to a lower threshold of irritability. Indeed, the anterior cingulate has been associated with irritability (Siever et al., 2008) and the striatal-cingulate circuit has been hypothesised to cause irritability symptoms in HD (Afifi et al.,

1994). However, more research is required to understand the cellular processes in HD that underlie cortical thickening. Longitudinal studies may help clarify the relationship between these regions and levels of irritability over time.

In summary, surface-based regressions for both posterior and frontal cognitive tasks showed a number of correlations that indicate that the cortex may directly contribute to cognitive changes in presymptomatic HD. However, the distribution of the correlations did not provide strong support for the hypotheses in this study. In particular, performance in tasks primarily subserved by posterior cortical regions showed little to no association with cortical thinning in these regions.

Chapter Six General Discussion

The aims of this thesis were threefold: Firstly, we aimed to determine the distribution of cortical thinning in HD gene-positive individuals who were presymptomatic. The second aim was to investigate neuropsychological changes that may be associated with cortical changes in these participants. Thirdly, we aimed to examine the relationship between cortical thinning and neuropsychological performance in this group.

This discussion provides a brief summary of the findings of these three studies. It then discusses issues and recommendations that emerged from these studies, and the overall significance of this thesis.

Summary of findings

Study 1 replicated the methodology of Rosas et al.'s (2005) study by using an identical automated MRI method for mapping the thickness of the cortex. We used a larger sample which included 19 participants who were presymptomatic for HD and 19 control participants who were individually matched for age, gender and education. It was hypothesised that cortical thinning would be evident in people presymptomatic for HD, and that thinning would be more apparent in posterior than frontal cortical regions. Consistent with predictions, surface-based analyses showed regionally-specific cortical thinning in the PreHD group, with the most significant thinning in the posterior cortices, centred on the right parieto-temporal-occipital (PTO) junction. Small regions of thinning were apparent within the posterior frontal gyri (left paracentral lobule and pars opercularis), but there was no thinning in anterior regions of the prefrontal lobe. Interestingly, the PreHD group also showed regionally specific cortical *thickening* within the orbitofrontal and cingulate cortices.

A model of proximity to onset was used to make inferences about closeness to clinical onset and the progression of cortical thinning in presymptomatic HD. As predicted, the PreHDfar group (>15 years to onset) showed no cortical thinning, whereas the PreHDclose group (<15 years to onset) had significant cortical thinning, almost exclusively in posterior regions of the

cortex. These findings provide evidence that the cortex may begin to degenerate within 15 years before clinical onset of HD, with little to no thinning before this.

There was a trend towards striatal volume loss in the PreHDclose group, but not the PreHDfar group. This is consistent with other MRI studies that have shown gradual reductions in striatal volume which begin about 6-12 years before clinical onset, with no changes evident before this (Aylward et al., 1996; Aylward et al., 2000; Aylward et al., 2004; Harris, 1999).

Study 2 investigated whether the PreHD participants showed poorer performance on neuropsychological tests that have been associated with the integrity of posterior regions of the cortex. It was also hypothesised that the PreHD participants would perform more poorly on tasks that are sensitive to posterior cortical functioning than tasks of frontal cortical functioning. In support of our predictions, the PreHD group, and particularly the PreHDclose group, performed more poorly than controls on two of the six tests subserved by posterior regions (the Judgment of Line Orientation Test and the Roadmap Test), and showed a trend towards poorer performance on the Hooper Visual Organisation Test. Poorer performance on these tasks is generally consistent with the reduced cortical thickness in posterior regions observed in these participants in Study 1. No differences were evident between the groups on the tests that are subserved primarily by frontal regions.

Study 3 used correlational analyses to assess the relationship between neuropsychological performance and thinning in specific regions of the cortex in the PreHD group. It was hypothesised that poorer performance in the cognitive measures would be associated with greater thinning in cortical regions that are important during performance of these tests. Although a number of correlations were evident between cortical thinning and performance on the neuropsychological tests, these correlations did not generally support our specific hypotheses. Firstly, there was no convincing evidence of a link between specific regions of the posterior cortex showing thinning and poorer performance on tests hypothesised to be sensitive to these regions. Secondly, there were significant correlations in a number of regions of the brain that showed no thinning in the PreHD group and that are not typically associated with performance on these tests. And thirdly, some of the neuropsychological tests

showed negative correlations, in which poorer task performance was associated with regions of *thicker* cortex.

A number of interesting questions have emerged from the study's findings, particularly with respect to the relationship between cortical changes and neuropsychological performance. The discussion below is primarily centred on the perplexing nature of the correlations in Study 3. I will also discuss some other areas of interest, and provide recommendations for future studies.

Understanding correlations between cortical thinning and neuropsychological scores

The study of brain-behaviour relationships using cortical thinning as an indicator of cortical integrity is a relatively new field. There is limited understanding of how changes in cortical thickness are associated with neuropsychological functioning, either in people with the HD gene, or in the normal population. Study 3 in this thesis is based on an assumption that significant thinning in specific regions of the cortex will result in poorer performance in tests that normally recruit these regions. The results of this study, however, failed to find such associations and raised several issues related to studying brain-behaviour relationships using this approach. Five issues are discussed below.

Complexity of brain processes in presymptomatic HD

The last few decades of brain-behaviour research have shown that cognitive abilities and emotions are not easily assigned to limited regions of the brain, but rather are associated with distributed, interconnected networks of neural regions (Cacioppo, Berntson, & Nusbaum, 2008; Haxby et al., 2001; Poldrack, 2008). Certainly, functional neuroimaging studies rarely show activations corresponding to single regions of the brain, despite the images presented following subtraction paradigms (Devlin & Poldrack, 2007). The complexity of these brain circuits and the complex disease processes in HD, may make it difficult to establish simple one-to-one correlations between isolated brain regions and specific neuropsychological functions in individuals who are presymptomatic for HD.

Brain reorganisation and compensation may affect brain-behaviour relationships in individuals with the HD gene. For example, when specific regions within a neural circuit begin to degenerate, the brain may do its uttermost to recruit other regions of the brain to perform these tasks (Hillary, 2008; Price & Friston, 1999). These compensatory processes in HD may make it more difficult to detect localised brain-behaviour relationships, particularly using a structural measure of the brain. Functional neuroimaging techniques could be used to determine whether people with the HD gene employ different regions of the brain than controls do when performing cognitive tasks, and what the relationships are between these regions and those showing changes in cortical thickness in the same participants.

At this point however, it is difficult to provide a compelling explanation as to why there are significant correlations in regions of the cortex that are not thinned in the PreHD group and that are not typically considered to be important in the performance of these tests. It is possible that the correlations revealed in Study 3 simply occur by chance or are a result of methodological artifacts. As discussed in Chapter 5, it is more difficult to detect significant correlations with a small sample size, particularly when there is limited variation and range in the variables being correlated — in this case the neuropsychological scores and thinning measures.

Cortical thinning and neuropsychological performance in the normal population

An alternative possibility is that the correlations in Study 3 may reflect normal, rather than disease-related, brain (cortical thickness)-behaviour relationships. Correlational analyses between the parcellation data and behavioural performance were conducted separately for the Control and PreHD groups. These analyses showed control participants had no more significant correlations than expected by chance, whereas the PreHD group had significantly more significant correlations than controls, and than expected by chance. These results provide some support for the view that at least some of the relationships between cortical thinning and test performance are related to the disease process. Importantly, the PreHD group had only twice the number of significant correlations; this indicates that half of these could represent normal brain-behaviour relationships, or occur by chance.

The current study followed others on clinical populations by conducting surface-based regressions (which map significant correlations across the cortex) only with participants who were presymptomatic for HD (Juranek et al., 2008; McDonald et al., 2008; Rosas et al., 2008). It remains unknown whether the distribution of correlations seen in participants with the HD gene might be apparent if the same surface-based regressions had been conducted with the control data.

Only a small number of studies have investigated whether there are relationships between cortical thickness and neuropsychological performance in normal participants (Dickerson et al., 2008; Sowell et al., 2008). Interestingly, these studies have found significant relationships between cortical thickness measures and performance on a number of cognitive tasks, including the Trail-Making Test, the CVLT and the Rey Complex Figure. Because the above studies used different neuropsychological tests from the present study, we cannot directly compare the distribution of these correlations. Nevertheless, the findings of Dickerson et al. and Sowell et al. illustrate that significant relationships between thinning and neuropsychological performance can be found in normal samples. These findings highlight the need to conduct separate surface-based regressions for PreHD and Control participants in order to understand whether brain-behaviour relationships are normal or disease-related.

Poorer neuropsychological performance is associated with both thinner and thicker cortex

Our findings of both positive and negative correlations between cortical thickness and neuropsychological performance in the PreHD group present another challenge to interpreting brain-behaviour relations in this population through such methods. These findings indicate that both thinning and thickening of the cortex may be associated with poorer neuropsychological performance in presymptomatic HD. While cortical thinning in HD is generally assumed to result from dysfunction and loss of cells or other cellular components within the cortical ribbon, processes that cause cortical thickening are more poorly understood. It is also unclear whether thickening of the cortex reflects a pathological or an adaptive process, or alternatively, an artifact of the imaging protocol.

The most marked thickening in the PreHD group was in the medial orbitofrontal and anterior cingulate cortices. The Iowa Gambling Test is primarily subserved by the medial orbitofrontal cortex, but there were no correlations between performance in this task and thickening (or thinning) in this region. No neuropsychological tests were selected a priori to assess functioning of the anterior cingulate cortex. This region however, has been associated with irritability and anger (Siever et al., 2008); it is interesting that heightened levels of 'outward irritability' in the PreHD group were correlated with thickening in the right anterior cingulate cortex only. These results suggest that cortical thickening may reflect a pathological process in presymptomatic HD. Importantly, however, these interpretations have been made following exploration of the data, and are not based on predictions of region-of-interest.

Recent studies using surface-based regressions with normal participants may cast some light on why poorer performance is associated with thicker cortex in the present study (Dickerson et al., 2008; Sowell et al., 2008). Interestingly, these studies show that poorer performance is associated with both thinning and thickening of cortical regions in the normal population. Dickerson et al. (2008) found performance on a test of verbal learning (CVLT) in 15 normal adults to be positively correlated with thickness of the medial temporal region and negatively correlated with the cingulate sulcus; whilst performance on the Trail-Making Test (TMTB) was correlated negatively with the lateral parietal cortex. In a group of 21 children, adolescents and adults, Sowell et al. (2008) found performance on the CVLT to be positively correlated with cortical thickness in dorsal frontal regions, whilst performance on a measure of visuospatial functioning (the Rey Copy) was negatively associated with large areas of the frontal, parietal and temporal lobes. While cortical thinning is generally assumed to reflect pathological processes inherent to clinical populations (Juranek et al., 2008; McDonald et al., 2008; Rosas et al., 2008), these studies reveal that thinning occurs in normal populations and can be associated with *better* behavioural performance. Similar findings have been reported in volumetric MRI studies with normal participants, in which smaller volumes of grey matter are commonly associated with better performance in executive functioning and memory tasks. This occurred both in young adults (Chantome et al., 1999; Foster et al., 1999) and older adults (Duarte et al., 2006; van Petten, 2004).

It is suggested that relationships between better neuropsychological performance and thinning in cortical regions reflects the normal developmental process of neural pruning which occurs predominantly during childhood and adolescence (van Petten., 2004). This process involves pruning of unnecessary or underutilised synaptic connections, and is associated with increased cortical efficiency and functioning (Nordeen & Nordeen, 1997). Therefore, the relationships between better performance and thinner regions of the cortex in the present study may be attributed to normal variation in neural pruning between the PreHD participants. Clearly, this relationship would not occur in an indefinite linear fashion. *Pathological* thinning (which is likely to occur on a larger scale) would negatively affect cortical functioning, at some point, and thus impact on neuropsychological functioning. In other words, both processes may be evident in individuals with the HD gene: normal levels of cortical thinning may have a positive influence on cognitive performance, but thinning associated with the disease process may be deleterious.

Longitudinal studies will help to ascertain the nature of these relationships in people with the HD gene over time. These studies can test whether changes in thickness in specific regions of the cortex are associated with better or poorer performance in neuropsychological tests that are sensitive to these regions.

A priori selection of neuropsychological tasks

Tasks for this thesis were selected because there was evidence to suggest that they recruit those regions of the brain that previous studies had shown to be affected in early and presymptomatic HD participants (Rosas et al., 2002; Rosas et al., 2005; Rosas et al., 2008). One limitation of this a priori approach is that it is dependent on participants in the current study showing cortical thinning in the same regions as in previous studies. As seen in Study 1 of this thesis, the distribution of cortical thinning in our PreHD group shows subtle differences from earlier cortical thinning studies. Although cortical thinning studies have all illustrated significant posterior changes, the specific regions of thinning appear to be heterogeneous both between, and within, microanatomic (gyral and sulcal) regions. Therefore, the tests selected for this study may not have been optimal for the regions actually changed in this sample of participants. For example, the Facial Recognition Test was selected

as a measure that reliably recruits the inferior temporal gyrus, which was significantly thinned in previous studies. As this region was not significantly thinned in the present study, this test may have been a poor measure of neuropsychological change for these participants. Nonetheless, the range of cognitive tests selected for this study provides a reasonable coverage of the posterior cortices (see Table 15). Although some of the individual tests may not specifically relate to regions of thinning in the present sample, when taken together they generally cover the various posterior regions that have showed thinning in participants presymptomatic for HD. Quantifying the relationships between neuropsychological functioning and specific regions of the cortex is not determined solely by the precise selection of tests. For example, the regions judged to be crucial for performing the Roadmap Test (the parieto-temporal-occipital junction) showed the most significant thinning in the PreHD group, but there was no correlation between performance on this task and thinning in this region.

Basal ganglia and neuropsychological performance

Impairments in neuropsychological functioning in HD are often attributed to degeneration in the basal ganglia (Lawrence et al, 1998). It is possible that striatal changes in our PreHD group contributed to poorer scores in the JLOT and Roadmap Tests.This could explain the absence of a correlation between scores on these tests and thinner posterior regions. Although a number of studies have reported relationships between striatal measures and neuropsychological functioning in symptomatic HD (e.g. Douaud et al., 2006; Peineman et al., 2005; Rosas et al., 2008), research into these relationships for presymptomatic HD participants is scarce. Campodonica (1999), in a presymptomatic HD sample, found no relationships between striatal measures and visuospatial tasks, including the Roadmap Test and an extrapersonal orientation test. The extensive neuroanatomical connections between the cortex and the basal ganglia, and the complex pathological relationship between these structures in HD, can make it exceedingly difficult to determine the contributions of the basal ganglia to specific neuropsychological changes. Although the present study showed no significant correlations between striatal measures and performance on any of the neuropsychological tests, changes in the basal ganglia may still, to some extent, be a mediating force in the poorer performance evidenced in these participants.

A number of brain regions were not measured in this study, and therefore we cannot discount the possibility that degeneration in these areas may also contribute to poorer cognitive performance in HD. Poorer cognitive performance in UHDRS tests, for example, has been associated with volume loss in the globus palladium, as well as in other subcortical regions, including the thalamus (Douaud et al., 2006). A decreased volume of white matter may also be associated with poorer performance in these tests (Beglinger et al., 2005). Until we better understand the relationships between cortical thinning and neuropsychological performance, future studies may benefit from including structural measures of these brain regions, using volumetric imaging and diffusion tensor imaging.

We are left, therefore, with a number of possible explanations of the relationships between cortical thinning and neuropsychological functioning, but no conclusive answer. Future studies are required to further our understanding of these issues. This includes expanding the present study into a longitudinal study with the same participants.

Validity of the proximity to onset model

This is the first MRI study to compare whole-brain cortical changes in participants with HD at different stages of proximity to clinical onset. Langbehn et al.'s (2004) proximity to onset model divides participant groups into close to onset and far from onset groups based on age and CAG repeat length. This enables cross-sectional studies to assess more precisely the onset and progression of the neurological and neuropsychological changes in participants presymptomatic for HD. Some caveats about Langbehn et al.'s (2004) model are worth noting, however. Firstly, it is based on the predicted proximity to clinical onset, assessed solely by motor symptoms, and does not incorporate the onset of cognitive and mood symptoms. Because different domains of functioning do not decline in a uniform fashion, the accuracy of this model for assessing clinical disease onset and progression is limited. Secondly, the predictive formulae for Langbehn et al.'s model have not yet been validated with prospective data (although this is currently underway with PREDICT-HD, a large

international prospective study). And lastly, this model is not exact and shows large variance on an individual level (Langbehn et al., 2004).

It is possible that in the present study the PreHDclose and PreHDfar groups in fact overlap to some degree, with some participants in the PreHDfar group who are closer to onset than some participants in the PreHDclose group, and vice versa. Nevertheless, nearly all neuropsychological tests showed the expected direction of means: the PreHDclose participants performed worse than the PreHDfar participants, and the PreHDfar group did not perform significantly worse than the PreHDclose group on any performance measures. The use of Langbehn et al.'s method of estimating closeness to onset is also supported by the cortical thinning results, in which the PreHDclose group showed significant thinning, whilst the PreHDfar group showed no thinning.

Future studies may benefit from using the proximity to onset model to select greater numbers of participants who are closer to clinical onset (< 15 YTO), in whom this study has indicated structural brain changes and cognitive changes are most evident. Although this cross-sectional study has shown significant thinning in participants who were estimated at 15 years or fewer to clinical onset, it has not illustrated the onset or progression of cortical thinning *within* this 15-year timeframe. Future studies with this group of participants will better characterise when and where in the cortex these changes first occur, and how they progress.

Contributions to scientific research and implications for clinical trials

Cortical thickness mapping provides a useful tool for investigating brain-behaviour relationships in HD. It provides efficient, highly accurate whole-cortex analyses, which enable both region-of-interest analyses and the exploration of brain-behaviour relationships across the entire cortex. In the future, longitudinal studies based on this method should be used to further define the distribution, magnitude and temporal course of cortical thinning, and the relationship between thinning and neuropsychological functioning. A longitudinal study is currently underway with the participants from this study. The concurrent use of other functional and structural imaging techniques with cortical thinning would help to clarify the

degree to which regional cortical, white matter and subcortical changes are associated with each other, or whether they reflect distinct underlying degenerative processes in HD.

The results of the current study have contributed to a better characterisation of the cortical and neuropsychological changes in presymptomatic stages of the Huntington's Disease. The findings support a systems model of HD, in which both cortical and subcortical regions are affected and contribute to neuropsychological changes in HD, even in presymptomatic stages of the disease. This model may provide a more satisfactory explanation of the varied and progressive symptoms that are experienced in HD, and that are unlikely to be caused solely by changes in the basal ganglia.

The ultimate goal in HD research is to develop neuroprotective therapies that can delay or prevent illness for people at risk of HD, or slow progression for those clinically affected. With the first pilot intervention studies with neuroprotective compounds already underway (Huntington Study Group, 2009), there is a critical need to develop valid, reliable and efficient measures, or 'biomarkers', for predicting and monitoring the effect of interventions (Paulsen et al., 2008; Rosas & Goldstein, 2004). The present study indicates that cortical thinning may provide a sensitive measure of brain changes. Structural MRI measures of the striatum have been proposed as biomarkers for HD (Aylward et al., 2003), and indeed have been incorporated into the PREDICT-HD study (Paulsen, Hayden et al., 2006), the largest international prospective multisite study aimed at identifying presymptomatic HD biomarkers. If cortical changes are confirmed to occur reliably before the onset of clinical symptoms in HD, cortical thinning measures may be integrated with striatal volumes to provide a set of biomarkers, both for preventative therapeutic intervention trials and for scientific characterisation of the disease. Results of this thesis indicate that regionally-specific changes in cortical thickness may be detected at least as early as the loss of striatal volume. This means that these measures may provide a particularly sensitive measure of onset of the disease.

Before establishing cortical thinning as a biomarker in pharmacological interventions, however, a greater understanding of cortical thinning in HD is required. This includes better

characterisation of i) the onset and progression of cortical thinning and thickening in presymptomatic HD, ii) the underlying pathological or non-pathological processes causing cortical thinning and thickening, iii) the variability of cortical thickness between individuals with the HD gene and normal controls, and iv) the clinical and neuropsychological correlates of these processes.

Importantly, neuroimaging biomarkers only capture part of the disease process, and are not necessarily predictive of significant clinical changes later in the disease. Ideally, these biomarkers would be teamed up with neuropsychological assessments that are sensitive to presymptomatic HD brain changes.

Reflections on an international collaboration

The collaboration with the Massachusetts General Hospital Centre for Biomedical Imaging in Boston provided the opportunity to study simultaneously two different aspects of Huntington's Disease — brain morphology and neuropsychology. The Boston team's high level of expertise in cortical thickness mapping with HD enabled us to combine these aspects at a level that would not otherwise have been possible. There were also challenges in completing a doctoral thesis within a long-distance collaboration. Because control of the data analysis was shared between two centres, the extent to which results could be explored and verified was limited. Queries or suppositions were often discussed with the Boston team through email, rather than being addressed immediately on the spot in Auckland. This process placed some limitations on data exploration (particularly with analyses involving both cortical thinning and neuropsychological data), and created significant time restraints. Errors in data transfer between teams, however minor, also delayed data analysis. The author's two trips to Boston were crucial for checking and calibrating the neuroimaging procedures, gaining a better understanding the cortical thinning protocol and process, discussing and analysing results, and sustaining our collaborative relationship. Despite the challenges, the overall success of this open collaboration with the Boston group is apparent in the joint decision to follow up the results of this study with a longitudinal study.

Conclusions

This thesis has produced significant findings in four areas. Firstly, it has replicated findings of cortical thinning in individuals presymptomatic for Huntington's Disease, by using a larger sample size than previously used, and a well-matched control group. Consistent with findings in previous thinning studies, thinning was most prominent in posterior regions of the brain. Secondly, this is the first MRI study to examine cortical changes in participants at different stages of proximity to onset. Interestingly, cortical thinning occurred in individuals up to 15 years prior to clinical onset, with little to no thinning before this. Furthermore, cortical thinning (and thickening) was apparent at least as early as the loss of striatal volume. Thirdly, the study provides new evidence for impairments in selective cognitive functions that are subserved primarily by posterior cortical regions: this indicates that thinning in these regions may contribute to poorer performance in these tasks. Moreover, these impairments were more apparent in participants estimated to be at closer proximity to clinical onset. Lastly, correlational analyses showed a number of regionally-specific relationships between thinning and cognitive performance; this supports a role for the cortex in HD symptomology. Because some correlations did not accord with our predictions, it is suggested that other factors (pathological or non-pathological) may also contribute to these associations.

The results contribute to a better characterisation of the cortical and neuropsychological changes that occur early in the development of HD, and provide tentative support for cortical thickness mapping as a valid and sensitive measure for assessing cortical changes in presymptomatic HD. Longitudinal studies, with a greater number of participants at closer proximity to clinical onset, will further characterise the distribution, magnitude and temporal course of cortical thinning, and the relationship between thinning and neuropsychological functioning. Ultimately, cortical thinning may provide a biomarker of disease severity that could be included in therapeutic trials.

Although Huntington's Disease arises from only a single gene mutation, this study illustrates again its complex pathology and clinical phenotype, even in presymptomatic stages. This study adds another small step towards characterising the pathogenesis of this devastating disease, defining the biomarkers for the disease, and ultimately finding a cure for HD.

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Appendix A: UHDRS motor scale

9|9 Draft

[STUDY NAME]
UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99
(MOTOR)

3|2

SUBJECT ID | | | | | 0 0 0 0 VISIT NO. V | |

INITIALS | | | SITE NO. | | | VISIT DATE | | MM | | DD | | | | YYYY

I. MOTOR ASSESSMENT

1. OCULAR PURSUIT — Horizontal 1a. | | Vertical 1b. | |
   0 = complete (normal)
   1 = jerky movement
   2 = interrupted pursuits/full range
   3 = incomplete range
   4 = cannot pursue

2. SACCADE INITIATION — Horizontal 2a. | | Vertical 2b. | |
   0 = normal
   1 = increased latency only
   2 = suppressible blinks or head movements to initiate
   3 = unsuppressible head movements
   4 = cannot initiate saccades

3. SACCADE VELOCITY — Horizontal 3a. | | Vertical 3b. | |
   0 = normal
   1 = mild slowing
   2 = moderate slowing
   3 = severely slow, full range
   4 = incomplete range

4. DYSARTHRIA — 4. | |
   0 = normal
   1 = unclear, no need to repeat
   2 = must repeat to be understood
   3 = mostly incomprehensible
   4 = anarthria

5. TONGUE PROTRUSION — 5. | |
   0 = can hold tongue fully protruded for 10 seconds
   1 = cannot keep fully protruded for 10 seconds
   2 = cannot keep fully protruded for 5 seconds
   3 = cannot fully protrude tongue
   4 = cannot protrude tongue beyond lips

6. FINGER TAPS — Right 6a. | | Left 6b. | |
   0 = normal (≥ 15/5 sec.)
   1 = mild slowing and or reduction in amplitude (11-14/5 sec.)
   2 = moderately impaired. Definite and early fatiguing.
   May have occasional arrests in movement (7-10/5 sec.)
   3 = severely impaired. Frequent hesitation in initiating movements
   or arrests in ongoing movements (3-6/5 sec.)
   4 = can barely perform the task (0-2/5 sec.)

 (7/1/05)

Draft

[STUDY NAME]
UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99
(MOTOR)

0 0

0 0

SUBJECT ID

0 0 0 0

VISIT NO. V

I. MOTOR ASSESSMENT (CONT)

7. PRONATE/SUPINATE-HANDS
0 = normal
1 = mild slowing and/or irregular
2 = moderate slowing and irregular
3 = severe slowing and irregular
4 = cannot perform

Right 7a. Left 7b.

8. LURIA (fist-hand palm test)
0 = ≥ 4 in 10 seconds, no cue
1 = < 4 in 10 seconds, no cue
2 = ≥ 4 in 10 seconds with cues
3 = < 4 in 10 seconds with cues
4 = cannot perform

8.

9. RIGIDITY - ARMS
0 = absent
1 = slight or present only with activation
2 = mild to moderate
3 = severe, full range of motion
4 = severe with limited range

Right 9a. Left 9b.

10. BRADYKINESIA - BODY
0 = normal
1 = minimally slow (? normal)
2 = mildly but clearly slow
3 = moderately slow, some hesitation
4 = markedly slow, long delays in initiation

10.

11. MAXIMAL DYSTONIA
0 = absent
1 = slight/intermittent
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged

11a. TRUNK
11b. RUE
11c. LUE
11d. RLE
11e. LLE

Draft

0 0

[STUDY NAME]
UNIFIED HUNTINGTON'S DISEASE RATING SCALE '99
(MOTOR)

0 0

SUBJECT ID | | | | |

0 0 0 0

VISIT NO. V | | |

I. MOTOR ASSESSMENT (CONT)

12. MAXIMAL CHOREA
0 = absent
1 = slight/intermittent
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged

12a. FACE
12b. BOL
12c. TRUNK
12d. RUE
12e. LUE
12f. RLE
12g. LLE

13. GAIT
0 = normal gait, narrow base
1 = wide base and/or slow
2 = wide base and walks with difficulty
3 = walks only with assistance
4 = cannot attempt

13.

14. TANDEM WALKING
0 = normal for 10 steps
1 = 1 to 3 deviations from straight line
2 = > 3 deviations
3 = cannot complete
4 = cannot attempt

14.

15. RETROPULSION PULL TEST
0 = normal
1 = recovers spontaneously
2 = would fall if not caught
3 = tends to fall spontaneously
4 = cannot stand

15.

17. DIAGNOSIS CONFIDENCE LEVEL
To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e. g., chorea, dystonia, bradykinesia, rigidity) in a subject at risk for HD?
0 = normal (no abnormalities)
1 = non-specific motor abnormalities (less than 50% confidence)
2 = motor abnormalities that may be signs of HD (50% - 89% confidence)
3 = motor abnormalities that are likely signs of HD (90% - 98% confidence)
4 = motor abnormalities that are unequivocal signs of HD (≥ 99% confidence)

17.

18. **Motor Examiner**

18. | | | | |
STAFF CODE

Appendix B: Study consent form

CONSENT FORM
PARTICIPANTS WITH THE HD GENE

Title of Project: Early brain changes and level of functioning in people with Huntington's disease

Principal Researcher: John Davison
Name of Participant: _____ **Age: _____** years
Participant Number: _____

English: I wish to have an interpreter	Yes	No
Maori: E hiahia ana ahau ki tetahi tangata hei korero Maori ki ahau	Ae	Kao
Samoan: Oute mana'o e iai se fa'amatala upu	Ioe	Leai
Tongan: 'Oku fiema'u ha fakatonulea	Io	Ikai
Cook Island: Ka inangaro au i tetai tangata uri reo	Ae	Kare
Niuean: Fia manako au ke fakaaoga e tagata fakahokohoko vagahau	E	Nakai

I ……. have read and understand the participant information sheet dated 29/11/05. 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.

This study has been approved by the Northern Y Regional Ethics Committee on ……

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: John Davison
Project role: Primary Investigator
Signature…….. Date…….

Appendix C: 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.

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.

Do you consent to the use of contrast? ☐yes ☐no Signature _____

FEMALE PATIENTS

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

DO YOU HAVE ANY OF THE FOLLOWING?

Implanted cardiac defibrillator	☐yes	☐no
Implanted electronic or magnetic device	☐yes	☐no
Metallic stent, filter or coil	☐yes	☐no
Cochlear implant or other ear implant	☐yes	☐no
Heart valve prosthesis	☐yes	☐no
Any type of prosthesis (eye, limb etc)	☐yes	☐no
Joint replacement	☐yes	☐no
Screws, plates or wires in bones or joints	☐yes	☐no
Shunt (spinal, intraventricular, or heart)	☐yes	☐no
Vascular or drug access port or catheter	☐yes	☐no
Radiation seeds or implants	☐yes	☐no
Medication patches (Nicotine or hormone)	☐yes	☐no
Tattoo or permanent makeup	☐yes	☐no
Dentures or partial plate	☐yes	☐no
Hearing aid	☐yes	☐no
Shrapnel, bullets or other metal	☐yes	☐no

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.

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
- 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 _____

Appendix D: Mean thicknesses of the cortical parcellations in the PreHD and Control groups

Parcellations	PreHD mean (SD)	Controls mean (SD)	t	P-value
lh-bankssts	2.14 (0.15)	2.16 (0.19)	-0.379	0.707
lh-caudalanteriorcingulate	2.34 (0.35)	2.31 (0.23)	0.311	0.758
lh-caudalmiddlefrontal	2.24 (0.19)	2.29(0.15)	-0.878	0.386
lh-cuneus	1.66 (0.12)	1.68 (0.09)	-0.468	0.643
lh-entorhinal	3.02 (0.47)	3.04 (0.23)	-0.155	0.878
lh-fusiform	2.33 (0.14)	2.34 (0.14)	-0.263	0.794
lh-inferiorparietal	2.12 (0.15)	2.13 (0.15)	-0.374	0.711
lh-inferiortemporal	2.52 (0.16)	2.49 (0.17)	0.484	0.632
lh-isthmuscingulate	2.46 (0.17)	2.39 (0.17)	1.149	0.258
lh-lateraloccipital	1.93 (0.12)	1.96 (0.12)	-0.936	0.356
lh-lateralorbitofrontal	2.39 (0.15)	2.34 (0.14)	1.052	0.3
lh-lingual	1.85 (0.14)	1.82 (0.09)	0.759	0.453
lh-medialorbitofrontal	2.03 (0.15)	1.96 (0.18)	1.332	0.191
lh-middletemporal	2.56 (0.15)	2.58 (0.16)	-0.309	0.759
lh-parahippocampal	2.11 (0.28)	2.16 (0.33)	-0.538	0.594
lh-paracentral	1.99 (0.16)	2.03 (0.17)	-0.666	0.51
lh-parsopercularis	2.22 (0.16)	2.30 (0.12)	-1.569	0.125
lh-parsorbitalis	2.36 (0.20)	2.34 (0.19)	0.375	0.71
lh-parstriangularis	2.10 (0.17)	2.08 (0.15)	0.457	0.65
lh-pericalcarine	1.41 (0.11)	1.39 (0.08)	0.594	0.556
lh-postcentral	1.78 (0.15)	1.70 (0.13)	-0.34	0.736
lh-posteriorcingulate	2.29 (0.13)	2.22 (0.15)	1.511	0.139
lh-precentral	2.20 (0.20)	2.27 (0.18)	-1.131	0.266
lh-precuneus	2.00 (0.12)	2.02 (0.15)	-0.61	0.546
lh-rostralanteriorcingulate	2.38 (0.26)	2.34 (0.30)	0.434	0.667
lh-rostralmiddlefrontal	2.01 (0.12)	1.98 (0.12)	0.78	0.44
lh-superiorfrontal	2.37 (0.16)	2.39 (0.15)	-0.494	0.625
lh-superiorparieta	1.83 (0.15)	1.87 (0.13)	-0.933	0.357
lh-superiortemporal	2.49 (0.18)	2.51 (0.16)	-0.272	0.787
lh-supramarginal	2.19 (0.18)	2.27 (0.16)	-1.533	0.134
lh-frontalpole	3.45 (0.24)	3.38(0.33)	0.693	0.493
lh-temporalpole	2.03 (0.33)	2.11 (0.32)	-0.719	0.477
lh-transversetemporal	2.23 (0.25)	2.27 (0.17)	-0.575	0.569

Parcellations	PreHD mean (SD)	Controls mean (SD)	t	P-value
rh-caudalanteriorcingulate	2.22 (0.17)	2.24 (0.17)	-0.476	0.637
rh-caudalmiddlefrontal	1.66 (0.12)	1.72 (0.13)	-1.488	0.145
rh-corpuscallosum	3.18 (0.36)	3.33 (0.39)	-1.266	0.214
rh-cuneus	2.35 (0.18)	2.38(0.11)	-0.824	0.415
rh-entorhinal	2.13 (0.15)	2.18 (0.11)	-1.261	0.215
rh-fusiform	2.55 (0.13)	2.53(0.13)	0.348	0.73
rh-inferiorparietal	2.39 (0.17)	2.41 (0.15)	-0.355	0.725
rh-inferiortemporal	1.94 (0.14)	2.00 (0.14)	-1.403	0.169
rh-isthmuscingulate	2.27 (0.12)	2.23 (0.11)	0.907	0.37
rh-lateraloccipital	1.88 (0.13)	1.89 (0.10)	-0.317	0.753
rh-lateralorbitofrontal	2.06 (0.20)	1.93 (0.12)	2.244	0.031
rh-lingual	2.58 (0.15)	2.63 (0.13)	-1.085	0.285
rh-medialorbitofrontal	2.24 (0.25)	2.28 (0.19)	-0.558	0.58
rh-middletemporal	2.02 (0.16)	2.05 (0.16)	-0.459	0.649
rh-parahippocampal	2.22 (0.20)	2.26 (0.17)	-0.616	0.542
rh-paracentral	2.43 (0.21)	2.37 (0.18)	1.016	0.316
rh-parsopercularis	2.11 (0.18)	2.09 (0.15)	0.315	0.755
rh-parsorbitalis	1.41 (0.08)	1.43 (0.09)	-0.722	0.475
rh-parstriangularis	1.78 (0.18)	1.81 (0.15)	-0.582	0.564
rh-pericalcarine	2.35 (0.18)	2.29 (0.12)	1.316	0.196
rh-postcentral	2.15 (0.18)	2.23 (0.18)	-1.395	0.172
rh-posteriorcingulate	2.00 (0.17)	2.04 (0.14)	-0.745	0.461
rh-precentral	2.37 (0.30)	2.41 (0.25)	-0.43	0.669
rh-precuneus	1.93 (0.09)	1.92 (0.13)	0.373	0.712
rh-rostralanteriorcingulate	2.38 (0.17)	2.40 (0.18)	-0.379	0.707
rh-rostralmiddlefrontal	1.84 (0.14)	1.87 (0.14)	-0.689	0.495
rh-superiorfrontal	2.51 (0.18)	2.55 (0.14)	-0.813	0.422
rh-superiorparietal	2.20 (0.19)	2.26 (0.15)	-1	0.324
rh-superiortemporal	3.54 (0.42)	3.65 (0.23)	-1.055	0.298
rh-supramarginal	2.02 (0.30)	2.05 (0.29)	-0.268	0.79

Note: lh: left hemisphere, rh: right hemisphere. See Desikan et al. (2006) for parcellation descriptions

Appendix E: Mean thicknesses of the cortical parcellations in the PreHDclose, PreHDfar and Control groups

Parcellations	Controls mean(SD)	PreHDfar mean(SD)	PreHDclose (mean(SD)	F statistic	P-value
lh-bankssts	2.16 (0.19)	2.13 (0.15)	2.15 (0.15)	0.10	0.902
lh-caudalanteriorcingulate	2.31 (0.23)	2.29 (0.31)	2.38 (0.39)	0.28	0.757
lh-caudalmiddlefrontal	2.29(0.15)	2.21 (0.19)	2.26 (0.20)	0.58	0.565
lh-cuneus	1.68 (0.09)	1.66 (0.11)	1.66 (0.13)	0.11	0.898
lh-entorhinal	3.04 (0.23)	3.00 (0.23)	3.03 (0.63)	0.03	0.971
lh-fusiform	2.34 (0.14)	2.32 (0.06)	2.33 (0.19)	0.06	0.942
lh-inferiorparietal	2.13 (0.15)	2.13 (0.18)	2.10 (0.12)	0.21	0.810
lh-inferiortemporal	2.49 (0.17)	2.55 (0.10)	2.49 (0.20)	0.47	0.631
lh-isthmuscingulate	2.39 (0.17)	2.50 (0.19)	2.42 (0.16)	1.08	0.352
lh-lateraloccipital	1.96 (0.12)	1.92 (0.13)	1.93 (0.11)	0.43	0.653
lh-lateralorbitofrontal	2.34 (0.14)	2.33(0.11)	2.44 (0.16)	1.86	0.171
lh-lingual	1.82 (0.09)	1.88 (0.14)	1.82 (0.13)	1.11	0.341
lh-medialorbitofrontal	1.96 (0.18)	1.97 (0.16)	2.08 (0.12)	1.86	0.171
lh-middletemporal	2.58 (0.16)	2.57 (0.18)	2.55 (0.13)	0.08	0.927
lh-parahippocampal	2.16 (0.33)	1.97 (0.29)	2.23 (0.23)	1.97	0.154
lh-paracentral	2.03 (0.17)	2.00 (0.17)	1.98 (0.16)	0.25	0.780
lh-parsopercularis	2.30 (0.12)	2.25 (0.18)	2.20 (0.13)	1.54	0.228
lh-parsorbitalis	2.34 (0.19)	2.30 (0.20)	2.42 (0.19)	1.05	0.360
lh-parstriangularis	2.08 (0.15)	2.09 (0.22)	2.12 (0.12)	0.18	0.834
lh-pericalcarine	1.39 (0.08)	1.38(0.08)	1.44 (0.13)	1.04	0.364
lh-postcentral	1.70 (0.13)	1.81 (0.17)	1.75 (0.14)	0.50	0.613
lh-posteriorcingulate	2.22 (0.15)	2.27 (0.14)	2.31 (0.14)	1.27	0.292
lh-precentral	2.27 (0.18)	2.19 (0.23)	2.21 (0.17)	0.66	0.525
lh-precuneus	2.02 (0.15)	2.02 (0.13)	1.98 (0.11)	0.36	0.700
lh-rostralanteriorcingulate	2.34 (0.30)	2.35 (0.20)	2.41 (0.31)	0.21	0.814
lh-rostralmiddlefrontal	1.98 (0.12)	1.99 (0.14)	2.03 (0.12)	0.45	0.644
lh-superiorfrontal	2.39 (0.15)	2.33 (0.16)	2.41 (0.16)	0.70	0.504
lh-superiorparieta	1.87 (0.13)	1.83 (0.17)	1.83 (0.14)	0.42	0.658
lh-superiortemporal	2.51 (0.16)	2.52 (0.21)	2.47 (0.15)	0.19	0.831
lh-supramarginal	2.27 (0.16)	2.20 (0.20)	2.18 (0.16)	1.20	0.312
lh-frontalpole	3.38(0.33)	3.49 (0.22)	3.41 (0.26)	0.41	0.669
lh-temporalpole	2.11 (0.32)	2.19 (0.38)	1.89 (0.22)	2.34	0.111
lh-transversetemporal	2.27 (0.17)	2.33 (0.28)	2.15 (0.19)	1.88	0.167

Parcellations	Controls mean(SD)	PreHDfar mean(SD)	PreHDclose (mean(SD)	F statistic	P-value
rh-bankssts	2.49 (0.22)	2.42 (0.24)	2.58 (0.23)	1.08	0.350
rh-caudalanteriorcingulate	2.24 (0.17)	2.23 (0.19)	2.21 (0.15)	0.14	0.873
rh-caudalmiddlefrontal	1.72 (0.13)	1.68 (0.13)	1.64 (0.12)	1.35	0.272
rh-corpuscallosum	3.33 (0.39)	3.18 (0.26)	3.18 (0.45)	0.78	0.467
rh-cuneus	2.38(0.11)	2.44 (0.13)	2.26 (0.18)	4.21	0.023
rh-entorhinal	2.18 (0.11)	2.16 (0.16)	2.10 (0.14)	1.46	0.247
rh-fusiform	2.53(0.13)	2.60 (0.12)	2.50 (0.12)	1.55	0.226
rh-inferiorparietal	2.41 (0.15)	2.37 (0.20)	2.41 (0.15)	0.18	0.834
rh-inferiortemporal	2.00 (0.14)	2.00 (0.14)	2.00 (0.13)	2.62	0.087
rh-isthmuscingulate	2.23 (0.11)	2.24 (0.13)	2.30 (0.10)	1.10	0.344
rh-lateraloccipital	1.89 (0.10)	1.92 (0.14)	1.85 (0.10)	1.16	0.326
rh-lateralorbitofrontal	1.93 (0.12)	2.02 (0.17)	2.09 (0.23)	2.96	0.065
rh-lingual	2.63 (0.13)	2.65 (0.17)	2.51 (0.10)	3.34	0.047
rh-medialorbitofrontal	2.28 (0.19)	2.17 (0.26)	2.31 (0.23)	1.07	0.355
rh-middletemporal	2.05 (0.16)	2.03 (0.18)	2.02 (0.15)	0.11	0.893
rh-parahippocampal	2.26 (0.17)	2.18 (0.24)	2.25 (0.17)	0.52	0.597
rh-paracentral	2.37 (0.18)	2.39 (0.25)	2.47 (0.17)	0.85	0.435
rh-parsopercularis	2.09 (0.15)	2.12 (0.22)	2.09 (0.13)	0.12	0.887
rh-parsorbitalis	1.43 (0.09)	1.39 (0.07)	1.43 (0.10)	0.59	0.558
rh-parstriangularis	1.81 (0.15)	1.80 (0.20)	1.75 (0.17)	0.40	0.676
rh-pericalcarine	2.29 (0.12)	2.36 (0.21)	2.34 (0.15)	0.86	0.430
rh-postcentral	2.23 (0.18)	2.15 (0.19)	2.15 (0.18)	0.95	0.397
rh-posteriorcingulate	2.04 (0.14)	2.02 (0.17)	1.99 (0.18)	0.36	0.701
rh-precentral	2.41 (0.25)	2.41 (0.20)	2.33 (0.37)	0.29	0.748
rh-precuneus	1.92 (0.13)	1.95 (0.11)	1.92 (0.06)	0.19	0.830
rh-rostralanteriorcingulate	2.40 (0.18)	2.37 (0.21)	2.39 (0.13)	0.09	0.910
rh-rostralmiddlefrontal	1.87 (0.14)	1.85 (0.14)	1.83 (0.15)	0.29	0.751
rh-superiorfrontal	2.55 (0.14)	2.54 (0.22)	2.48 (0.13)	0.69	0.510
rh-superiorparietal	2.26 (0.15)	2.25 (0.22)	2.16 (0.16)	1.17	0.322
rh-superiortemporal	3.65 (0.23)	3.55 (0.25)	3.52 (0.54)	0.57	0.572
rh-supramarginal	2.05 (0.29)	2.01 (0.37)	2.03 (0.24)	0.04	0.959

Note: lh: left hemisphere, rh: right hemisphere. See Desikan et al. (2006) for parcellation descriptions

Appendix F: Rationale for cognitive tests used in this study

This appendix describes the rationale for selecting each cognitive test in this study. 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 et al., 2001; Hannay et al., 1987; Herrmann et al., 2005; Ng et al., 2001; Ng et al., 2000; Orban et al., 1997; Vandenberghe 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 et al., 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; 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 et al., 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, 1997), and adjacent occipitotemporal regions are often associated with an inability to recognise faces, termed prosopagnosia (Damasio et al., 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 et al., 1994; McCarthy et al., 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 (based on 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 (e.g.Creem-Regehr et al., 2007; Creem & Proffitt, 2001; Zacks, Vettel 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 et al., 1999; Zacks, Vettel et al., 2003).

Letter Mental Rotation Task (modified alphanumeric 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; Podzebenko, 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 (see Cooper & Shepard, 1973; Hamm et al., 2004). Differences in the slope of linear and curvilinear function can be used to compare the relative mental rotation abilities across different groups.

The Iowa Gambling Task (Bechara et al., 1994)

Patients with lesions in the ventro-medial prefrontal cortex (VMPFC) consistently performed more poorly on the Iowa Gambling Task (IGT) than normal controls (Bechara et al., 1994;

Bechara et al., 1997; Bechara et al., 1999; Bechara et al., 2000 Bechara et al., 2001) and brain-damaged controls with occipital lobe, temporal lobe or dorsolateral prefrontal lobe damage (Bechara et al., 1994; Bechara et al., 1998). In an event-related fMRI study of the IGT, Fukui et al. (2005) subtracted the brain activation during advantageous card selections from the activation during disadvantageous card selections to investigate the area of brain involved in anticipating risk, a core component of decision-making. They found exclusive activation in the medial frontal gyrus (which is richly interconnected with the VMPFC), and a significant correlation between activation in this region and task performance. In a PET study of the IGT a number of brain regions were activated during task performance, including the prefrontal cortex, anterior cingulate cortex, insula, thalamus inferior parietal cortex, and cerebellum (Ernst et al., 2002) However, the only regions in which rCBF was significantly correlated with performance scores included the right ventrolateral PFC, the right anterior insula, and right head of the caudate nucleus. Another PET study reported better performance in the IGT to be associated with greater activation in the orbitofrontal cortex, but not the right or the left dorsolateral prefrontal cortex (DLPFC) (Bolla et al., 2003) These studies demonstrate the crucial role of the prefrontal cortex for the Iowa gambling task, and particularly the VMPFC, although some studies have also suggested that the DLPFC also plays an important role in this task (Fellows & Farah, 2005; Manes et al., 2002).

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

Ample evidence from lesion and neuroimaging studies suggests that specific areas of the prefrontal lobe are involved in higher executive function of planning. Shallice & Burgess (1992) 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 (e.g. 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 (rrCBF) 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 et al., 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, Doyon, Petrides, & Evans, 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.

Hand Mental Rotation task

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 et al., 2006; Creem-Regehr et al., 2007; Kosslyn et al., 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 et al., 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).

Table 16

Cortical regions considered crucial to mediating cognitive task in the study

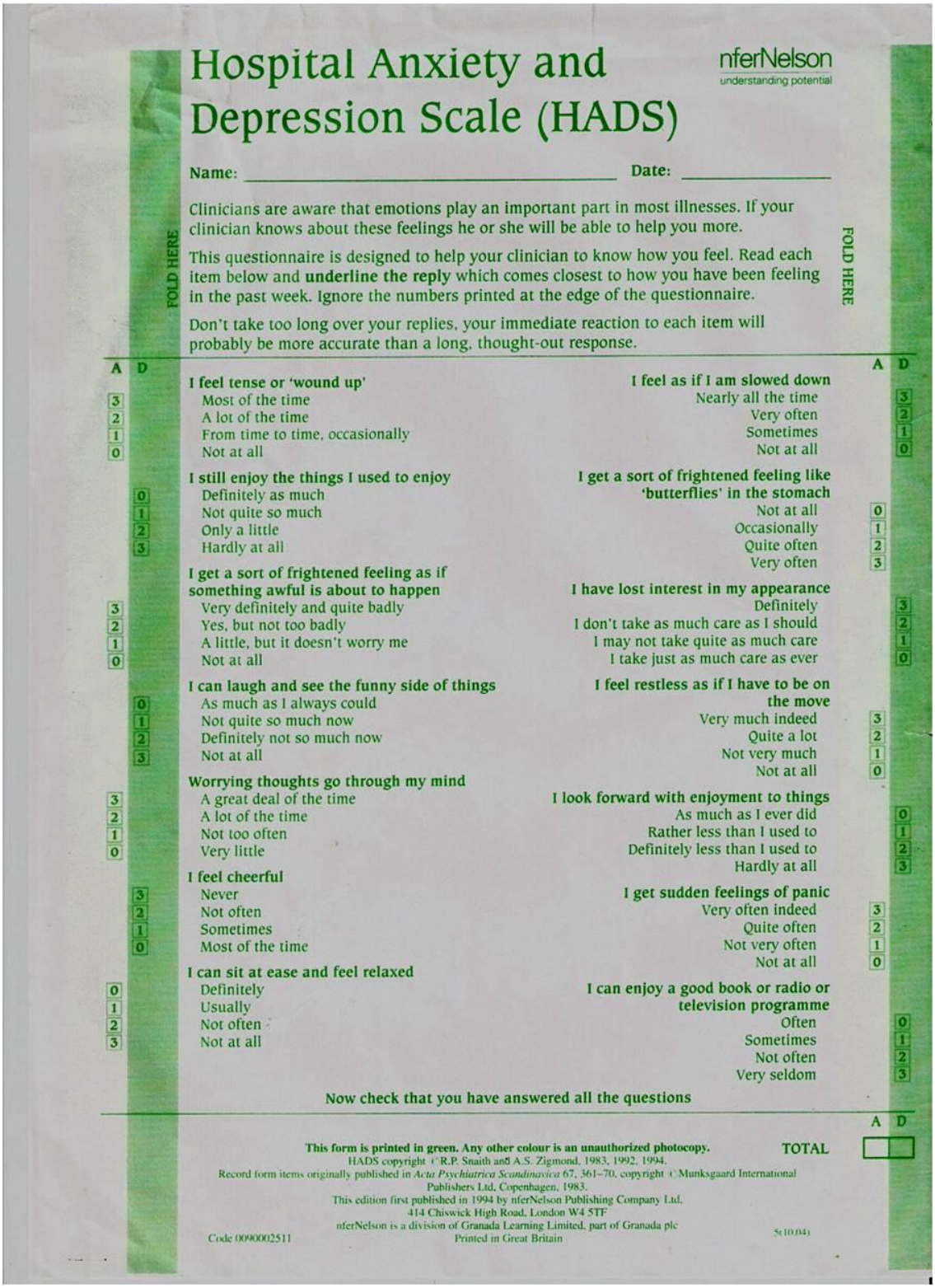
Cognitive Tasks	Cortical regions
Posterior tests	
JLOT	Superior parietal; precuneus; occipital temporal; extrastriate gyri
HVOT	Superior occipital; posterior superior parietal; fusiform gyrus
Collision Judgement	Left supramarginal gyrus
Benton Facial Recognition	Inferior and superior temporal; inferior occipital
Roadmap	Inferior and superior parietal cortex
Letter Mental rotation	Inferior and superior parietal cortex
Frontal tests	
Iowa Gambling task	Ventromedial prefrontal cortex (VMPFC)
Stockings of Cambridge	Dorsal-lateral prefrontal cortex (DLPFC)
Hand Mental Rotation	Precentral, premotor, caudal middle and superior frontal (in addition to inferior and superior parietal cortex)

Appendix G: Standardised instructions for the Iowa Gambling Test

Instructions for Subject

1. In front of you on the screen, there are 4 decks of cards: A, B, C, and D.
2. When we begin the game, I want you to select one card at a time by clicking on a card from any deck you choose.
3. Each time you select a card, the computer will tell you that you won some money. I don't know how much money you will win. You will find out as we go along. Every time you win, the green bar gets bigger.
4. Every so often, when you click on a card, the computer will tell you that you won some money as usual, but then it will say that you lost some money as well. I don't know when you will lose or how much. You will find out as we go along. Every time you lose, the green bar gets smaller.
5. You are absolutely free to switch from one deck to the other at any time, and as often as you wish.
6. The goal of the game is to win as much money as possible and avoid losing as much money as possible.
7. You won't know when the game will end. Simply keep on playing until the computer stops.
8. I am going to give you $2000 of credit, the green bar, to start the game. The red bar is a reminder of how much money you borrowed to play the game, and how much money you have to pay back before we see whether you won or lost.
9. The only hint I can give you, and the most important thing to note is this: Out of these four decks of cards, there are some that are worse than others, and to win you should try to stay away from bad decks. No matter how much you find yourself losing, you can still win the game if you avoid the worst decks.
10. Also note that the computer does not change the order of the cards once the game begins. It does not make you lose at random, or make you lose money based on the last card you picked.

Appendix H: Hospital Anxiety and Depression Scale



Hospital Anxiety and Depression Scale (HADS)

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understanding potential

Name: _____ **Date:** _____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

FOLD HERE

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		3
2		A lot of the time		2
1		From time to time, occasionally		1
0		Not at all		0
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		

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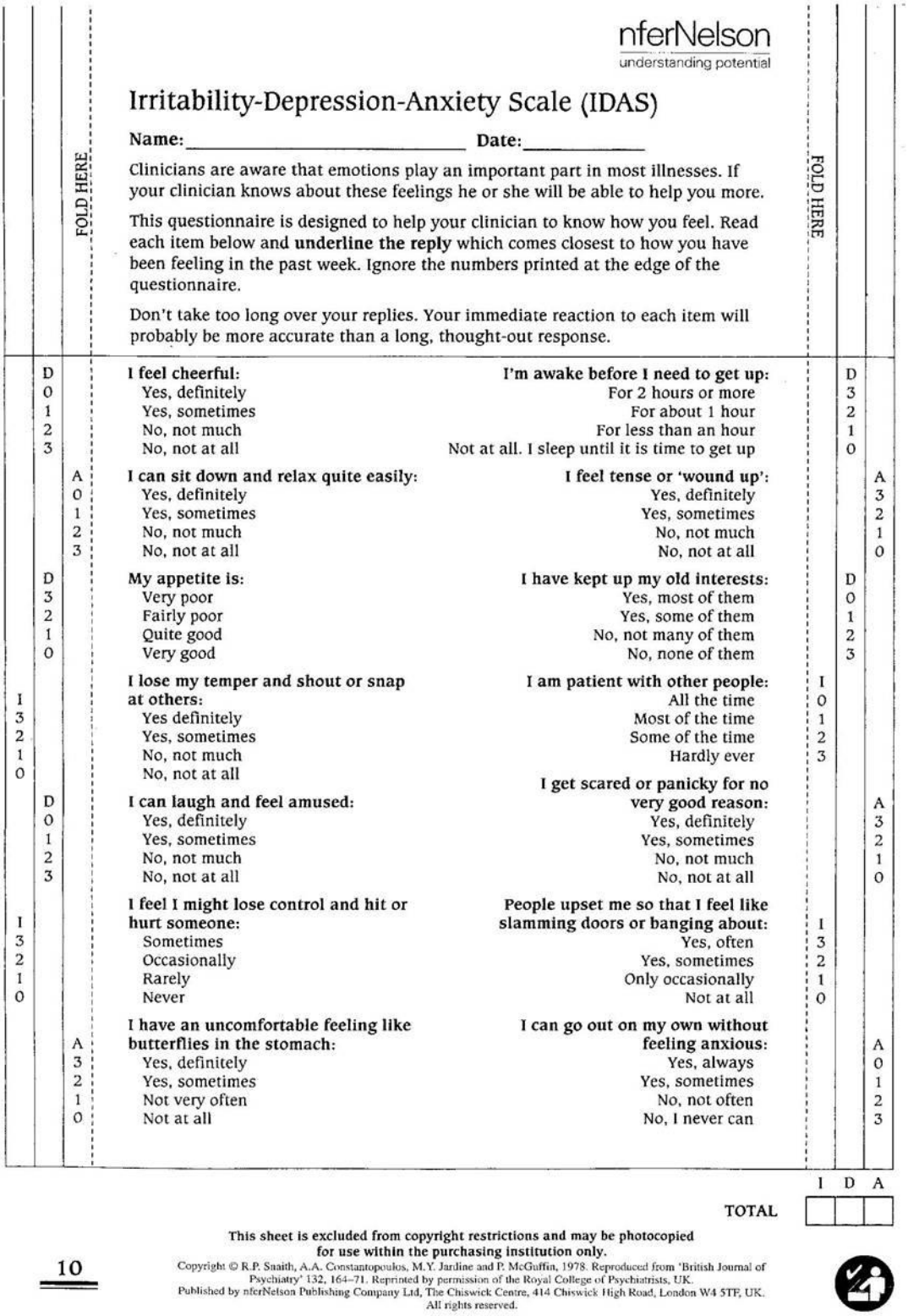
Appendix I: Irritability-Depression-Anxiety Scale (IDAS)



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Irritability-Depression-Anxiety Scale (IDAS)

Name:_____ **Date:**_____

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies. Your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

I feel cheerful:
D
0 Yes, definitely
1 Yes, sometimes
2 No, not much
3 No, not at all

I can sit down and relax quite easily:
A
0 Yes, definitely
1 Yes, sometimes
2 No, not much
3 No, not at all

My appetite is:
D
3 Very poor
2 Fairly poor
1 Quite good
0 Very good

I lose my temper and shout or snap at others:
I
3 Yes definitely
2 Yes, sometimes
1 No, not much
0 No, not at all

I can laugh and feel amused:
D
0 Yes, definitely
1 Yes, sometimes
2 No, not much
3 No, not at all

I feel I might lose control and hit or hurt someone:
I
3 Sometimes
2 Occasionally
1 Rarely
0 Never

I have an uncomfortable feeling like butterflies in the stomach:
A
3 Yes, definitely
2 Yes, sometimes
1 Not very often
0 Not at all

I'm awake before I need to get up:
D
3 For 2 hours or more
2 For about 1 hour
1 For less than an hour
0 Not at all. I sleep until it is time to get up

I feel tense or 'wound up':
A
3 Yes, definitely
2 Yes, sometimes
1 No, not much
0 No, not at all

I have kept up my old interests:
D
0 Yes, most of them
1 Yes, some of them
2 No, not many of them
3 No, none of them

I am patient with other people:
I
0 All the time
1 Most of the time
2 Some of the time
3 Hardly ever

I get scared or panicky for no very good reason:
A
3 Yes, definitely
2 Yes, sometimes
1 No, not much
0 No, not at all

People upset me so that I feel like slamming doors or banging about:
I
3 Yes, often
2 Yes, sometimes
1 Only occasionally
0 Not at all

I can go out on my own without feeling anxious:
A
0 Yes, always
1 Yes, sometimes
2 No, not often
3 No, I never can

FOLD HERE

I D A
TOTAL

10

Appendix J: 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)?
_____

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

8. 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

_____

9. Are you presently unemployed or working less because of your health? (check the reasons for this)
_____

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 that 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 K: Correlations between cognitive test scores and mean thicknesses in the cortical parcellation regions of interest in the PreHD and Control groups

Cognitive tests	Cognitive measures	Cortical parcellation ROIs	Hemisphere			
			Left		Right	
Tests of posterior cortex			*r*	*p*	*r*	*p*
JLOT	Accuracy	Superior parietal	0.14	0.566	0.16	0.516
		Precuneus	0.15	0.549	0.30	0.234
		Lingual	0.21	0.408	0.19	0.456
		Lateral occipital	0.02	0.936	0.14	0.571
		Cuneus	0.01	0.970	0.04	0.879
HVOT	Accuracy	Cuneus	0.08	0.752	0.00	0.997
		Lateral occipital	0.24	0.340	0.42	0.080
		Superior parietal	0.24	0.343	0.01	0.982
		Fusiform	0.20	0.434	0.36	0.145
Collision Judgement	Accuracy	Left supramarginal	0.04	0.881	n/a	n/a
		Left inferior parietal	*0.10*	*0.704*	*n/a*	*n/a*
Facial Recognition	Accuracy	Fusiform	0.12	0.646	0.03	0.912
		Superior temporal	0.13	0.603	0.30	0.229
		Lateral occipital	0.08	0.751	0.14	0.575
	Response time	Inferior parietal	0.02	0.945	0.05	0.851
		Superior parietal	0.28	0.258	0.09	0.731
Roadmap	Accuracy	Inferior parietal	0.19	0.458	0.02	0.924
		Superior parietal	0.05	0.836	0.31	0.204
	Response time	Inferior parietal	0.05	0.846	0.28	0.258
		Superior parietal	0.10	0.699	0.23	0.355
Letter Mental rotation*	Accuracy	Inferior parietal	0.04	0.872	0.14	0.576
		Superior parietal	0.08	0.741	0.19	0.449
	Response time	Precentral gyri	0.18	0.498	0.10	0.698
		Caudal middle frontal	0.29	0.253	0.25	0.335

Cognitive tests	Cognitive measures	Cortical parcellation ROIs	Hemisphere			
			Left		Right	
Tests of anterior cortex			*r*	*p*	*r*	*p*
Iowa Gambling task	% correct (last 60 trials)	Medial orbitofrontal	0.24	0.339	0.41	0.092
		Lateral orbitofrontal	0.11	0.678	0.37	0.128
		Pars opercularis	*0.79*	*0.000*	*0.17*	*0.512*
		Pars orbitalis	*0.24*	*0.340*	*0.03*	*0.912*
		Pars triangularis	*0.02*	*0.947*	*0.34*	*0.162*
Stockings of Cambridge	Perfect moves	Superior frontal	0.06	0.814	0.12	0.641
		Rostral middle frontal	0.03	0.893	0.29	0.238
		Pars opercularis	*0.38*	*0.117*	*0.12*	*0.644*
		Pars orbitalis	*0.05*	*0.831*	*0.01*	*0.968*
		Pars triangularis	*0.50*	*0.034*	*0.37*	*0.135*
	Initial thinking times	Superior frontal	0.09	0.726	0.21	0.421
		Rostral middle frontal	0.02	0.947	0.07	0.803
		Pars opercularis	*0.03*	*0.903*	*0.01*	*0.973*
		Pars orbitalis	*0.19*	*0.467*	*0.30*	*0.238*
		Pars triangularis	*0.13*	*0.631*	*0.02*	*0.947*
	Subsequent thinking times	Superior frontal	0.32	0.208	0.36	0.157
		Rostral middle frontal	0.47	0.056	0.47	0.056
		Pars opercularis	*0.45*	*0.067*	*0.05*	*0.837*
		Pars orbitalis	*0.25*	*0.330*	*0.28*	*0.282*
		Pars triangularis	*0.49*	*0.047*	*0.39*	*0.118*
Hand Mental Rotation*	Accuracy	Superior frontal	0.48	0.053	0.55	0.022
		Precentral gyri	0.14	0.586	0.03	0.915
		Caudal middle frontal	0.10	0.708	0.02	0.951
		Superior frontal	0.31	0.231	0.61	0.100

Note: JLOT: Judgement of Line Orientation Test; HVOT: Hooper Visual Organisation Test.

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