ATTENTIONAL DYSFUNCTION AS A PRODROME FOR HUNTINGTON'S DISEASE

By

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Preface

The idea for this study originated from observations made whilst working clinically with Huntington's disease patients. Several individuals and families reported that, over generations, they had noticed changes in family members who were later affected by the disease. Several families reported that they felt they could predict who was going to develop the disease, and when it had begun. These observations seemed to precede any testing, or the appearance of clinical symptoms. Although there was some variation in the content of what was reported many families returned to similar themes e.g. irritability, changes in previously established personality or behaviour, and obsessionality. Numerous discussions with colleagues in the Huntington's Disease Service revealed that they too had repeatedly heard such reports.

A discussion of these reports, their composition and significance, might constitute a lengthy study in itself. For the sake of this study however, these family mythologies about detection of the disease served to ignite an interest in more systematic approaches to identifying presymptomatic changes. Although the literature in this area is sparse it is growing, and this study has, due to practical constraints, selected one of the areas implicated by previous research and ignored others. Whilst one hopes to build on these existing theoretical foundations and contribute further to them, it also hoped that this study will have a degree of ecological validity for the clinicians with whom it originated.

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Abstract

Attentional dysfunction as a prodrome for Huntington's Disease

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The onset of choreiform movement disorder is the most widely used indicator for diagnosis of the onset of Huntington's disease. Research in recent years has investigated the possibility that onset of the disease may occur prior to this and is manifest in the form of cognitive impairment, but has been unable to identify the nature of this. Several previous studies have implied that attentional function may be affected. This study employed a more specific and sensitive test battery than had previously been used in this area to investigate the possibility that attentional function was impaired in presymptomatic gene carriers.

Eight carriers and fifteen at-risk non-carriers of the gene were recruited via the genetics services that had tested them for the gene. Two gene carriers were excluded from the analysis since they showed symptoms of movement disorder. These groups were compared in terms of response latency and errors on six sub-functions of attention: alertness, attentional set-shifting, inhibition of unwanted responses, integration of information from different sensory modes, divided attention, and vigilance. The two groups were of widely differing ages so a covariate analysis taking this into account was performed. Attentional set shifting and the integration of information from different sensory modes were found to be significantly impaired. The two symptomatic participants were compared qualitatively with other participants and appeared to have more impaired performances than either group.

The limitations of the study and its' implications clinically and for future research are discussed. This study offers the possibility that impairments in attention can be detected and that a more specific and sensitive testing procedure can be useful.

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1 Introduction

1.1 Early description of Huntington's disease

The literature on Huntington's disease (HD) began with George Huntington's paper "On Chorea", published in 1872, which was the first attempt to definitively describe it as separate from other types of chorea. This was not the first description of the disease, Elliotson in England described a hereditary chorea in 1832 and Lund described the 'chorea St Vitus' in Norway in 1860 (Hayden, 1981). The description given by Huntington stood out however, for its clarity, brevity and comprehensiveness, and it was quickly translated into other languages such that his name became widely attached to the disease.

George Huntington identified the disease in a specific static population, which enabled longitudinal observation and allowed for verification of his account. Like his father and grandfather who had preceded him as doctors in the same community he observed the heritability of the disease, the onset in adulthood and the association with mental health difficulties. Huntington identified that the disease seemed "to obey certain fixed laws" and that it was progressive such that the sufferer became "a quivering wreck of his former self" (Huntington, 1872, cited in Harper, 1996). He correctly identified that "if the thread was broken" i.e. the disease skipped a generation, then it did not re-emerge in subsequent generations of that family. There was marked and pervasive choreic movement disorder and a tendency to hyper-sexuality and/or disinhibition. Finally he noted that the chorea and the disease were without remission.

Huntington's account of the disease is still widely referred to in the literature and the on-going use of genealogical studies has been significant in the development of knowledge about the HD gene.

1.2 The Epidemiology of Huntington's Disease

Estimates of the prevalence of the disease range from 5 to 8 per 100 000 but the prevalence for people aged 40 to 55 years is around 12 per 100 000 (onset is usually

around this time)(Harper, 1996). Higher concentrations occur where communities, and hence 'gene pools', are quite static. The prevalence in these areas can be as high as 500-600 per 100 000 (e.g. Moray Firth in Scotland). The gene is present in all racial groups, with little variation (Lishman, 1994; Harper, 1996).

1.3 The Genetic Characteristics of Huntington's Disease

HD is identified genetically by an unstable trinucleotide expansion mutation at gene IT-15, the 'huntingtin' gene. The expansion is described in terms of the number of occurrences of a group of three nucleotides (cytosine, adenine and guanine) known as CAG repeats. In people who develop HD the number of repeats is over 37, in the rest of the population it is between 11 and 34 (Brandt and Butters, 1996). Higher numbers of repeats have been linked with paternal inheritance, earlier onset and greater severity (Duyao, Ambrose, Myers, Novelletto, Persichetti et al, 1993; Brandt, Bylsma, Gross, Stine, Ranen, and Ross, 1996). This gene was identified by a Collaborative Research Group comprising six teams from the UK and USA (HDCRG, 1993). This rather unique group studied a 'closed' community in the Zulia region of Venezuela where there was an unusually high rate of HD (originating from a single ancestor), whilst also providing much needed support to a poor and deprived community.

The Huntington's mutation is an autosomal dominant condition therefore if either parent carries the gene all of their offspring will stand a 50% chance of inheriting the gene. Anyone who inherits the gene will develop the disease barring premature mortality from other causes. Studies have sometimes found that there is no prior history of HD within families but this may be the result of several factors – the early death of a parent, illegitimacy, or concealment by other members of the family (Lishman, 1994).

It is worth noting that the HDCRG discovery of the HD gene was preceded by a DNA linkage analysis (Gusella, Wexler, Conneally, Naylor, Anderson, and Tanzi, 1983) which allowed prediction of the risk of carrying the HD genetic mutation e.g.

high (95%) versus low (5%). Hence, research on presymptomatic cognitive changes between 1983 and 1993 was able to control
for genetic status to some extent. Discovery of the gene, however, allowed study of the effects of HD in people who are pre-symptomatic to proceed in a way that would have previously been unlikely due to methodological problems arising from even minor uncertainty about genetic status.

1.4 Motor impairment in Huntington's disease

Huntington's disease is a degenerative disease of the central nervous system most commonly associated with choreiform movement disorder (Huntington's Chorea; chorea is derived from the Greek word meaning dance). Age of onset is usually in adulthood but is widely varied. For 76% of people with the HD gene onset occurs between the ages of 30 and 55, but the range extends from childhood to old age (Harper, 1996). In the early stages the movement disorder consists of randomly distributed and irregularly timed muscle jerks which are both brief and unpredictable, for example twitching of the fingers or fleeting facial grimaces, which can be mistaken for mannerisms. The movements usually start in the face, hands or shoulders, or can be detected as a subtle change in gait. Speech is often affected by slight dysarthria. As the disease progresses the pathological nature of the problem becomes more obvious as movements are abrupt, jerky, rapid and repetitive. They may be aggravated by voluntary movement, but can occur spontaneously, and are generally worse under stress (Lavers, 1981).

The face can show changes of expression and writhing contortions which give a grotesque appearance, the fingers twitch and the arms develop athetoid twisting movements. Gait is sometimes affected by a "dance-like ataxia which results from the variable choreic influences on the lower limbs" (Lishman, 1994, p396). Walking progress is difficult and interrupted and requires great effort. Rigidity is sometimes present (known as the 'Westphal variant') and can be associated with tremor and akinesia (Harper, 1996).

1.5 Psychiatric Problems in Huntington's Disease

Along with chorea and dementia, psychiatric problems form the triumvirate of difficulties most common in HD. George Huntington noted the occurrence of severe depression in his account in1872. It has been proposed that this triumvirate of movement disorder, dementia and depression, delineates diseases of the basal ganglia (Sano, 1991; Folstein, Peyser, Starkstein, and Folstein, 1991).

Brandt and Butters (1996) argue that there is considerable evidence that depression in HD is not just "an understandable reaction to the diagnosis of this incurable degenerative disease" (p. 326). The evidence they cite in support of this idea includes the onset of affective disturbances before cognitive or motor symptoms in naïve individuals and the existence of manic phases in 10% of depressed HD patients. These features are hard to reconcile with the suggestion that this is a reactive depression. It has also been noted that depression seems to run in families.

It has also been noted that depression can be observed in presymptomatic gene carriers but that severe psychiatric disturbances are rare (Rosenberg, Sorensen and Christensen, 1995). The existence of a serious presymptomatic mental health problem might be expected to have a significant influence on neuropsychological test performance (Zappacosta, Monza, Meoni, Austoni, Soliveri, et al, 1996).

Other affective difficulties include irritability, aggression, apathy, emotional lability, sexual disturbance, conduct disorder, substance abuse, and psychotic features (Lezak, 1995). One might argue that executive dysfunction, including disinhibition, is likely to contribute to the appearance of these difficulties.

1.6 Neuropsychological impairment in Huntington's disease

'Dementia' is another commonly discussed and defining feature of HD (Brandt and Butters, 1996). Onset of neuropsychological decline seems to be very gradual and may pre-date the onset of chorea by some years, hence this can be insidious. It has

been noted that a prevailing apathy can set in quite early which may impede cognitive functioning (Lishman, 1994), and in the early stages there is often general inefficiency at work and in the management of daily affairs (Hayden, 1981). This has actually been used as a criterion for the diagnosis of HD in some research projects (e.g. Starkstein, Brandt, Folstein, Strauss, Berthier et al, 1988). Focal features, such as dyslexia or dysphasia, are rare in comparison with other primary dementias. The special feature of dementia in HD, i.e. poor cognitive ability but without deterioration of language, suggests that it owes much to sub-cortical rather than cortical atrophy (Brandt and Butters, 1996).

In the early stages of the disease aspects of attention, procedural memory, visuo-motor and visuo-graphic skills, and executive functions (planning, programming, and monitoring activities, set shifting and mental flexibility) are likely to be most affected (Folstein, Folstein, and McHugh, 1975; Brandt and Butters, 1986; Brandt, 1991, Brandt and Bylsma, 1993). These abilities become progressively more impaired as the disease progresses. Primary sensory abilities and perceptual abilities, most aspects of language, non-motor spatial cognition and recognition memory are less likely to deteriorate, although they may not be completely spared. As the disease progresses executive dysfunction is one of the most common and problematic difficulties encountered. Intellectual deterioration in later stages is global, with marked distractibility (Lezak, 1995). The measurement of difficulties is often complicated by the occurrence of depression, which is frequent (Harper, 1996).

Memory impairment becomes more common as the disease advances, and is often discussed in the literature (see Section 1.9), but it is rarely as conspicuous as in Alzheimer's disease and can be submerged amidst general difficulties which include, attention, concentration, and organisation of thought (Lishman, 1994). The relative sparing of memory is consistent with the intact appearance of the limbic system on post-mortem (Lavers, 1981). Although there are undoubted memory problems it is unclear at times whether apparent difficulties might be due to other deficits e.g. attention (see Section 1.9)

The literature on longitudinal studies of Huntington's disease is surprisingly small and tends to focus on the progression of the disease following onset. Hence it does not generally consider the starting point of cognitive impairments. Brandt (1994) noted that attention and verbal learning were found to deteriorate across a period of one year in those patients who experienced early onset of the disease i.e. before age 40 (links between onset and severity are also related to inheritance see Section 1.8).

Certain aspects of the cognitive and movement disorders of HD have been found to relate particularly closely to each other. Cognitive performance was found to correlate with voluntary motor skill (Girotti, Marano, Soliveri, Geminiani, and Scigliano, 1988) and acquisition of limb motor skill (Heindel, Butters, and Salmon, 1988; Heindel, Salmon, Shults, Walicke, and Butters, 1989), but not the severity of involuntary movements. More recently Brandt (1994) found that the severity of voluntary motor impairment and memory impairment were more closely related to each other than to choreic movement disorder or duration of illness. Brandt (1994) suggested this supports the idea that although chorea is a distinguishing feature of HD, it is probably caused by separate brain mechanisms from those responsible for cognitive impairments. Discrete corticostriatal circuits sub-serving motor and cognitive functions have been identified in studies of monkeys (Alexander, DeLong and Strick, 1986)(for further discussion of the implications of this see section 1.7 on neuropathology).

It has been proposed that actual disability in HD is due more to progressive cognitive impairments (Bamford, Caine, Kido, Plassche and Shoulson, 1989), often along with depression (Mayeux, Stern, Herman, Greenbaum and Fahn, 1986), than movement difficulties. Several different measures of disability have been used e.g. total functional capacity, activities in daily living and neurological examination, all of which correlate more closely with cognitive impairment and loss of voluntary movement than with chorea (Brandt and Butters, 1996). This would seem to support the proposition that cognitive impairments (perhaps including for instance

the planning of movement) are more damaging than movement disorder per se. Thus early cognitive changes might be quite disabling.

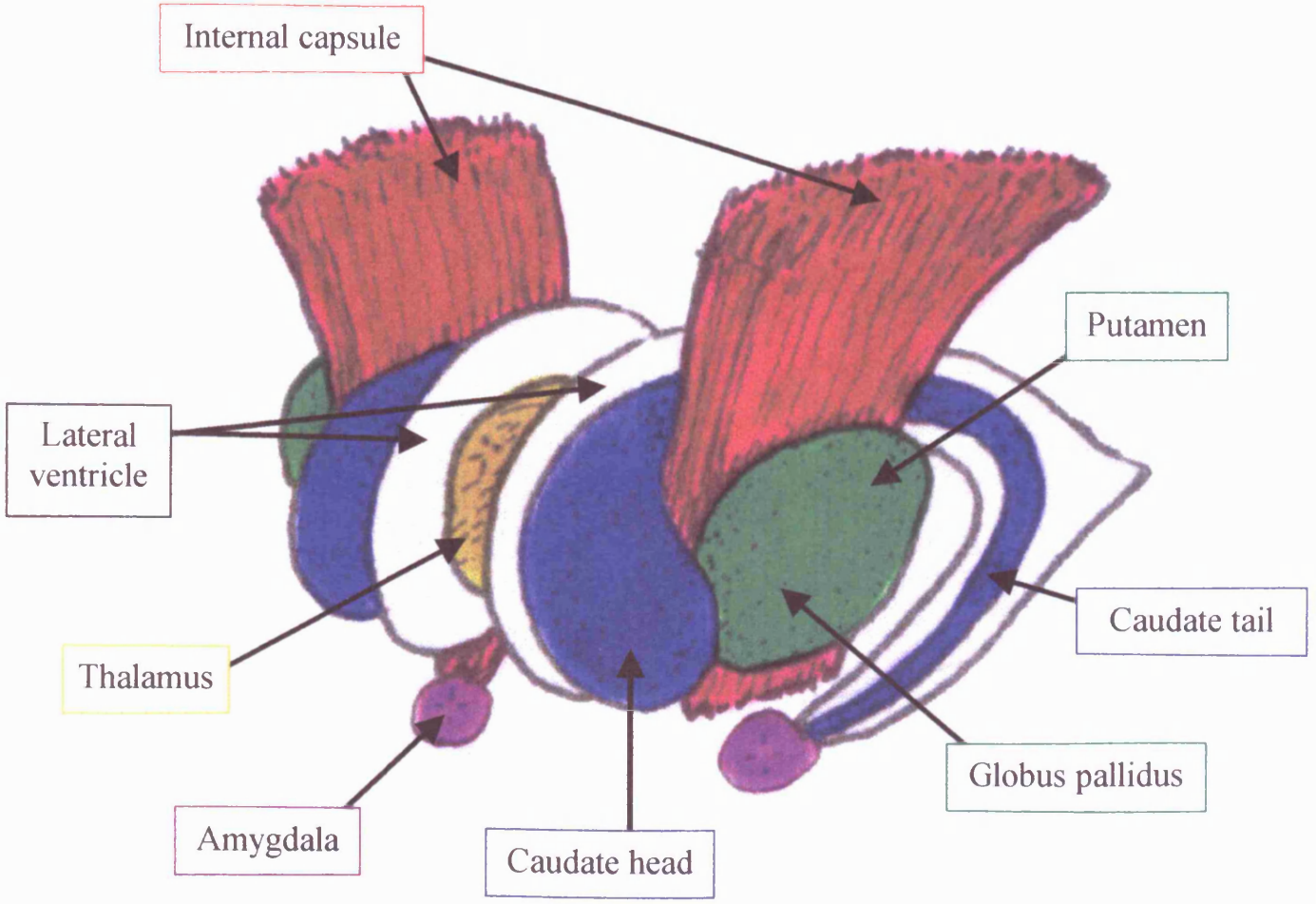
One weakness of some of these studies is that they measured cognitive ability using generalised dementia screening tools e.g. the Mini-Mental State Examination (Folstein et al, 1975), which are often not sensitive to disabling cognitive impairments that occur in HD (Brandt et al, 1996; Brandt, Bylsma and Gross, unpublished data cited in Brandt, 1994). The problem of how to measure changes in cognitive ability in Huntington's patients seems to have been a problem in several areas and will be discussed later (Section 1.9).

1.7 The neuropathology and neuroanatomy of Huntington's disease

Studies of neuropathology sometimes refer to, or have relevance for consideration of neuropsychological issues. This section will make some reference to these neuropsychological issues in relation to presymptomatic gene carriers but they will be discussed in more depth later (Section 1.9).

As has previously been implied the neuropathology of HD is mainly sub-cortical. Post-mortem of HD patients found that atrophy of the head of the caudate nucleus (see Figure One) was the most obvious feature, with wasting of the putamen also in evidence (Dom, Malfroid and Baro, 1976; Vonsattel, Myers, Stevens, Ferrante, Bird and Richardson, 1985; Starkstein et al, 1988; Starkstein, Brandt, Bylsma, Peyser, Folstein and Folstein, 1992; Campodonico, Aylward, Codori, Young, Krafft et al, 1998). On microscopic analysis it has been found that there is a loss of small spiny neurons in the dorso-medial aspect of the head of the caudate nucleus in the early stages of the disease. Involvement of the rest of the caudate and the putamen occurs as the disease progresses (Vonsattel et al, 1985) from the dorsal to the ventral aspect.

Figure One: Subcortical areas of the central nervous system



From Kapit & Elsan, 1993

Although the major neuropathological changes occur in these areas of the neostriatum, there is also evidence of cortical abnormality. A significant thinning of the cerebral cortex has been reported (Brandt and Butters, 1996). Comparison of the dorsolateral prefrontal cortex in normal and HD brains at post-mortem found a significant loss of neurons at various layers of the cortex (III, IV and V)(Hedreen, Peyser, Folstein, and Ross, 1991; Sotrel, Paskevich, Kiely, Bird, Williams and Myers, 1991). This suggests that the neuroanatomy of the frontal lobes may be affected and hence might be significant for our understanding of the presentation of the disease. It is as yet unclear whether loss of neurons in the cortex is a primary feature or secondary to the loss of striatal neurons that project to the cortex (Brandt and Butters, 1996).

Despite the evidence of atrophy in the cortex it is still likely that the cognitive impairments seen in HD result from degeneration of the caudate nucleus. Patients with bilateral lesions of the caudate display remarkably similar deficits to those found in HD, namely difficulties with attention, planning, sequencing and impairments of verbal recall but with preserved recognition (Mendez, Adams and Lewandowski, 1989; Caplan, Schmahmann, Kase, Feldman, Baquis, 1990). Furthermore, measures of caudate atrophy on CT and MRI correlate strongly with impairments on relevant tests such as sustained attention, processing speed, learning and memory, and cognitive flexibility (Starkstein et al, 1988 and 1992; Bamford et al, 1989; Campodonico et al, 1998) and with functional impairment (Starkstein et al, 1988; Bamford, Caine, Kido, Cox and Shoulson, 1995). Finally, functional imaging studies (e.g. PET and SPECT), blood flow (Reid, Besson, Best, Sharp, Gemmell and Smith, 1988), and glucose metabolism (Hayden, Hewitt, Stoessl, Clark, Ammann and Martin, 1987; Berent, Giordani, Lehtinen, Markel, Penney et al, 1988) show abnormalities in the caudate, but not in the cortex, which correlate highly with clinical severity.

1.7.1 Neuropathology in Presymptomatic Gene Carriers

Attempts at identifying neuropathological changes in the brains of presymptomatic gene carriers were largely inconclusive until Aylward et al (Aylward, Brandt, Codori, Magnus, Barta and Harris, 1994; Aylward, Codori, Barta, Pearlson, Harris and Brandt, 1996) used the first volumetric measure of caudate size, from a MRI (Magnetic Resonance Imaging) scan. They achieved 86% accuracy in identifying HD mutation carriers by changes in the structure of the caudate. This seemed to be because the volumetric measures allowed examination of the whole of the area and not just its size as delineated by its' boundaries. Hence this measurement was sensitive to changes in density caused by the premature atrophy of striosomes. The positions of the caudate and putamen within the sub-cortex can be seen in Figure One.

Campodonico, Codori and Brandt (1996) found that presymptomatic HD gene carriers showed subtle decline in sustained attention and mental speed over a two-year period, but remained in the normal range. These subtle changes were consistent with impairments seen in earlier studies of caudate atrophy in symptomatic carriers (e.g. Starkstein et al, 1992). In a later study Campodonico et al (1998) then went on to relate this to neuronal loss in the basal ganglia by demonstrating the existence of significant atrophy of the caudate and putamen. They provided a particularly interesting result, since they were among the first to study overall basal ganglia volume in relation to neuropsychological changes, finding slower mental processing speed, sub-clinical motor impairment and impaired verbal learning in presymptomatic gene carriers. Both of these studies do have limitations however, which are discussed along with those of other studies in this area in Section 1.9.

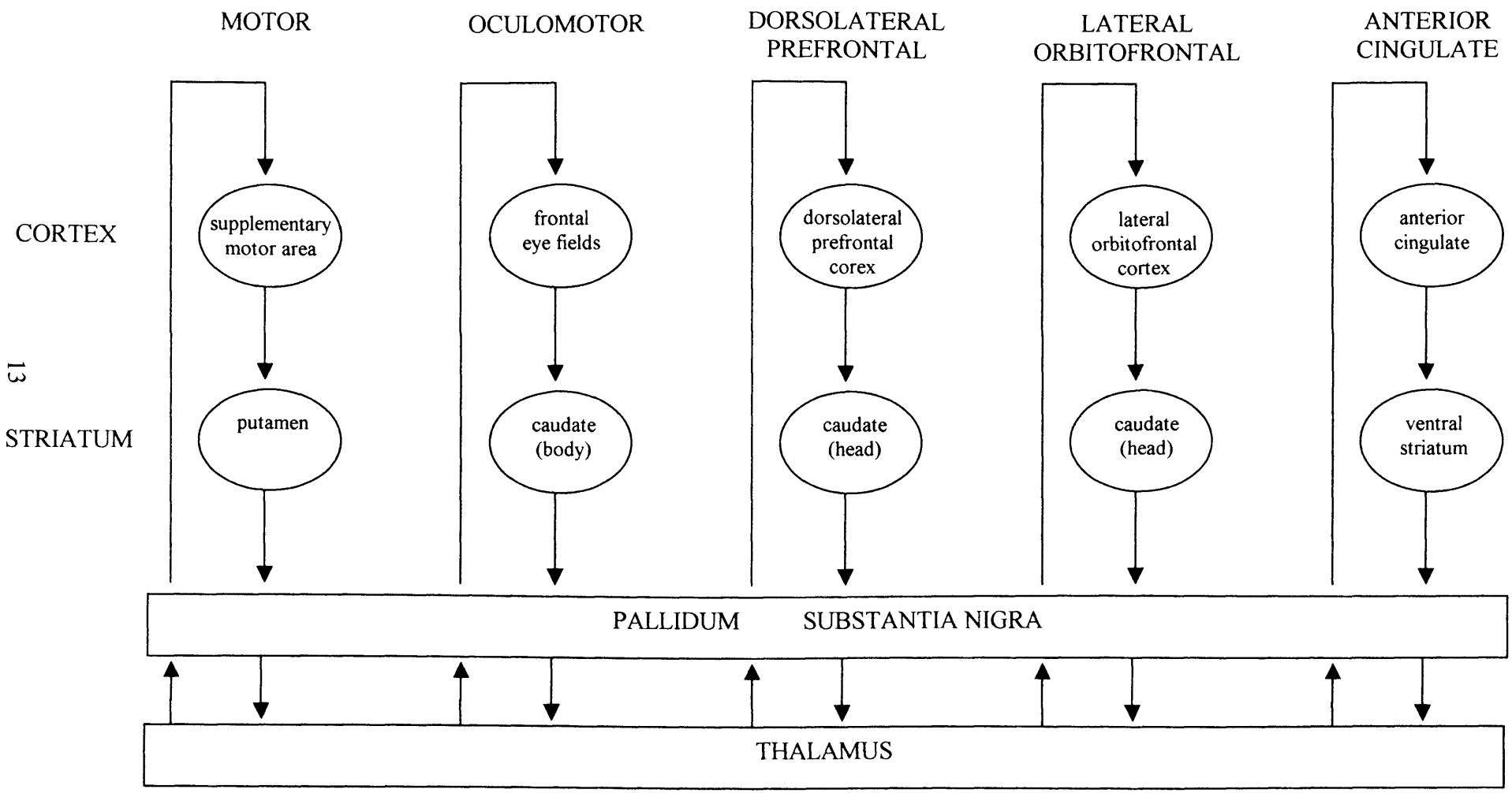
Lawrence, Sahakian, Hodges, Rosser, Lange and Robbins (1996) related the progression of impairments in attentional set shifting in HD patients to the dorsal-ventral progression of neuropathology throughout the striatum (Vonsattel et al, 1985; Hedreen and Folstein, 1995; Augood, Faull, Love and Emson, 1996). The

inputs to the striatum are arranged in a parallel 'loop' with the dorsal prefrontal cortex projecting to dorsal aspects of the caudate and the orbital prefrontal cortex projecting more ventrally. The path of these 'circuits' from cortex to striatum, as proposed by Alexander et al (1986), can be seen in Figure Two. Thus it would appear that those functions associated with the prefrontal cortex-striatal loop might be impaired before the onset of diagnosable symptoms such as movement disorder. The functions associated with the ventral loop are likely to become impaired as the neuropathological changes in the striatum progress from the dorsal to the ventral aspect.

This relates well to a number of studies, which consistently point to changes in the basal ganglia in pre-clinical HD. Albin, Reiner, Anderson, Dure, Handelin, et al (1992) demonstrated that neuronal damage could be present in the striatum before the appearance of diagnosable symptoms. Aylward et al (1994, 1996) showed by using structural MRI that HD gene carriers have reductions in the volume of the caudate head, putamen and globus pallidus many years before their predicted onset, which continue as onset approaches. PET studies have found decreases in basal ganglia glucose metabolism (Antonini et al, 1996) and dopamine receptor binding (Antonini et al, 1996; Weeks et al, 1996; Lawrence, Weeks, Brooks, Andrews, Watkins et al, 1998) in presymptomatic gene carriers. This suggests that pre-symptomatic impairments might be observed if sensitive enough cognitive markers could be identified.

A further significant finding is that recognition memory is normal in pre-symptomatic HD gene carriers who show impairment in other areas (Lawrence et al, 1998) but that it is impaired in early stage HD (Lawrence et al, 1996). This function is thought to be anatomically related to a loop between the temporal lobe and tail of the caudate and putamen (Middleton and Strick, 1996, cited in Lawrence et al, 1998). This suggests that functions associated with the tail of the caudate/putamen are less vulnerable to the earliest stages than the more dorsal areas of the striatum as would be expected given the dorsal to ventral progression proposed earlier.

Figure 2: A simplified form of proposed basal ganglia – thalamocortical circuits.



Adapted from Alexander et al, 198(

Campodonico et al (1998) found that verbal learning varied as a function of caudate size, while degree of motor abnormality was dependent on putamen size. Starkstein et al (1988) suggested that caudate pathology produces eye movement abnormalities (in saccadic movement) thereby impairing visual search and tracking. The caudate nucleus has strong reciprocal connections with dorsolateral pre-frontal neo-cortex and few connections with movement related cortical regions (DeLong, 1990). The putamen has anatomical and functional connections to the supplemental motor cortex (Alexander et al, 1986) and appears to be critically involved in movement (Berent et al, 1988; Starkstein et al, 1992)

Campodonico et al (1998) found that only volume of the putamen correlated with impairment on the QNE (Quantified Neurological Examination) and symbol digit modalities, whereas only caudate volume was associated with verbal learning. Campodonico et al (1996) had also used the symbol digit modalities test and found no impairment. Perhaps differences were found on the later study because it used older participants (5 years closer to onset) who were more likely to have atrophy of the putamen. Also the correlation of atrophy in the putamen with this deficit would suggest that it may be due to motor impairment rather than other cognitive abnormalities.

From the perspective of functional neuroanatomy it would be a mistake to view the basal ganglia in isolation. It makes better sense to attempt to ascribe behavioural functions to entire circuits of interconnected neural structures than to individual structures themselves (Alexander, DeLong, and Crutcher, 1992). The basal ganglia receive topographic projections from all areas of the cortex, and in turn project their own influences back upon areas of the frontal and temporal lobes via topographically organised pathways that pass through the thalamus (Alexander et al, 1992). The basal ganglia should be viewed as components of circuits organised in parallel and remaining largely segregated from one another (Strick, Dum and Picard, 1995). Alexander and Crutcher (1990) also point out that the basal ganglia is no longer considered to be organised in a serial fashion, but rather is seen as essentially parallel. If the pattern of atrophy proceeds dorsal to ventral as suggested

earlier then caudally mediated cognitive impairments would be expected to precede putamen related movement disorder impairments, and to be distinct from them.

Although there has been some debate about whether the cognitive impairments seen in presymptomatic HD are cortical rather than sub-cortical, the bulk of the evidence seems to point to a sub-cortical origin (Lawrence et al, 1998b). Given the interconnectedness of the basal ganglia and frontal lobes via discreet parallel circuits any difficulty in answering this question seems understandable.

The caudate can be described as a way station in the loop connecting the frontal and temporal cortices with the thalamus (Folstein, Brandt and Starkstein, 1992). While this loop might be partly involved in planning or sequencing movement it is also thought to be crucial for normal cognition. Folstein et al (1992) argue that deficits in HD can be related to pathology in the caudate if functional deficits can be correlated with the onset, time course and severity of lesions found elsewhere in the brain, such as the frontal cortex. They correlated atrophy of the caudate, atrophy of the frontal lobes and cognitive function and concluded that atrophy of the caudate is clearly related to function e.g. attention, sequencing and sustaining thoughts. Atrophy of the frontal lobes was not found to correlate.

The circuits of the basal ganglia have a role in modulating the operations of the entire frontal lobes (Alexander and Crutcher, 1990). They operate in parallel and by common mechanisms to influence such diverse 'frontal lobe' processes as the maintenance and switching of various attentional/behavioural sets (via the prefrontal and limbic circuits), and the planning and execution of limb and eye movements (via the motor and oculomotor circuits).

HD has been described as nature's experiment in disconnection of the caudate, and it is sometimes assumed that it provides a discrete picture of this phenomenon. This is evidently not the case. There is also a danger in assuming that anatomy demonstrates function or that it shows how lesions are transformed into symptoms since neither of these is the case.

1.7.2 Critique of the neuropathology

Many of the studies mentioned seem to make assumptions about the nature of the relationship between anatomy and function i.e. they locate functions in particular areas. Indeed this study is to some extent informed by possible relationships between neuropathology and functional neuroanatomy. This may appear to be an oversimplification and it must be acknowledged that certain difficulties exist in making this link.

The reason for this relates to the very nature of brain tissue and the localisation of function within that tissue. In studying the brain it has long been common to divide it into separate areas, with boundaries and discrete connections. However, Gregory pointed out as long ago as 1966 that "...the brain is like nothing so much as a lump of porridge...", which seems to render the idea of discrete divisions somewhat academic. A more constructive view is that connections within the brain and particularly those involving frontal areas form a complex and sometimes inter-dependant network, but that different tasks can act in a non-overlapping way.(Parkin, 1998). Alexander and Crutcher (1990) alluded to this when they pointed out the number of duplicated, parallel connections that seem to exist in frontal-striatal circuits. It may therefore be unhelpful to assume that certain functions are located in precise areas. This does not mean that neuroanatomical information is irrelevant, or that there is not evidence for the involvement of certain areas in specific functions.

If the relationship between neuropathology and neuropsychological change was entirely clear and precise then there might be no need for studies, such as this one, which examine cognitive factors. Neuroanatomical change is not, however, sufficient for diagnosis of onset.

Parkin (1998) further argues that assumptions are often made about a central executive that is treated as a single entity, but that different executive tasks are

quite clearly subsumed by different neural substrates. The work of Alexander et al (1986) seems to demonstrate just this point in relation to frontal-striatal areas. Attention, which will be discussed later, is perhaps a particularly good example of a functional concept that does not have any unitary definition or anatomical location but rather is multidimensional. The acknowledgement of this, and further study, have been proposed as a necessary condition for progression to a fuller understanding (Baddeley, 1998). Meanwhile the evidence that does exist, for instance for attentional dysfunction and dorsal caudate atrophy, needs further investigation.

1.8 The clinical relevance of study in this area

Before discussing the literature in the area of presymptomatic cognitive change, some of the reasons for studying this area will be considered.

As noted earlier (Section 1.3) the onset of HD is usually around 40 years of age but may occur across a broad range, thus individuals who are at-risk must live with the threat of the disease for a number of years. The insidious nature of HD is such that the exact onset may be difficult to spot. The early identification of symptoms is of paramount importance to gene carriers since diagnosis signals imminent and irreversible onset of the disease (de Boo, 1997).

Studies of 'presymptomatic' neuropsychological changes in HD were conducted before the gene was discovered. These studies aimed to provide a diagnostic tool, which would enable the identification of people suffering from the disease. Since the identification of the HD gene neuropsychological studies of presymptomatic gene carriers have continued. These studies aim to provide an insight into the possible existence and nature of presymptomatic neuropsychological changes. This could have implications for the sort of information that is given to gene carriers or for the stage at which intervention is offered.

As stated in Section 1.6 cognitive impairments are the most influential factor in terms of disability and hence it seems of paramount importance to map the nature of these impairments. This is to some extent reinforced by clinical observations that many people with the HD gene report changes in their daily lives which pre-date onset of diagnosable symptoms. For example finding work increasingly difficult to cope with for no specified reason, or feeling increasingly irritable have both been reported clinically.

Lawrence et al (1998) suggest that the issue of detecting pre-clinical manifestations of HD is of profound importance given current developments in treatment strategies. For instance the administration of possible therapies aimed at either replacing damaged neural tissue (Dunnett, 1995) or at disabling or slowing the time course of mechanisms of cell death (Kieburtz et al, 1996).

Research into the existence of presymptomatic neuropsychological changes may also indicate whether the HD gene is minimally active throughout life rather than switching on when triggered or at a pre-determined time of life. This would require further clarification perhaps by longitudinal follow-up of gene carriers from discovery of the gene onwards. Any such study would have to take into account the possible time to onset, which can be estimated using the regression equation developed by Rubinsztein, Leggo, Chiano, Dodge, Norbury and Rosser (1997) where information about the number of CAG repeats is available.

The results obtained in previous studies (e.g. Lawrence et al, 1998) indicate that the cognitive sequelae of basal ganglia dysfunction can be observed prior to the appearance of diagnosable symptoms which in turn implies that the Huntington's gene has a continuous rather than discontinuous mode of action. Bhide, Day, Sapp, Schwarz, Sheth and Kim (1996) found mutant huntingtin in developing brains and propose that neurons might be affected during brain development. As Lawrence et al (1998) note this is not to suggest that cognitive dysfunction is the first presentation of HD since there is the possibility that psychiatric disturbances may present prior to the onset of movement disorder.

Lawrence et al (1988) offer the possibility that an attentional set shifting task may be useful clinically in tracking the cognitive decline seen in HD. An improvement in diagnostic sensitivity, whether it was this or something else, would have useful implications. It could enable testing of interventions earlier in the course of the disease, where they are most likely to be effective (Campodonico et al, 1998), as well as helping to determine when they should start and measuring their effects. Siemers, Foroud, Bill, Sorbel, Norton, and Hodes (1996) suggest that only through further longitudinal study can conclusions be reached about the staging of decline in individuals who carry the HD mutation, and whether abnormalities occur from early life or only on approaching onset.

If cognitive changes can be reliably detected in carriers of the HD gene, the point at which they become evident could be investigated and thus might provide information about the nature of the gene e.g. whether it has an effect throughout life or switches on at some point.

1.9 Previous studies in this area.

The difficulty of early detection of HD has been acknowledged as a problem for some time, but there does seem to be a presymptomatic phase where subtle changes can be detected even as early as pre-adolescence (Wilson and Garron, 1979). Also it has been noted that intellectual deterioration is evident from early in the disease process (e.g. Butters, Sax, Montgomery and Tarlow, 1978; Brandt and Butters, 1986; Blackmore, Simpson and Crawford, 1995).

A number of studies of pre-symptomatic neuropsychological changes were conducted before the identification of the HD gene (see Brandt and Butters, 1996 for a review). But these studies were limited by the inability to classify at-risk participants as having HD or not, and are often difficult to interpret (Lawrence et al, 1998).

It is worth noting that these studies all used controls who were people at-risk of developing HD who were considered to be low risk or who had been tested and found not to carry the gene. Blackmore et al (1995) argue that it may not be valid to compare gene carriers with normal controls, as at-risk groups are subject to a different kind of stress not experienced by normal groups and there is evidence that stress can impair cognitive ability. People at-risk often have the added stress of a parent or grandparent already affected by HD, and may be nervous in the test situation if they believe that the results of cognitive assessments could give an indication as to whether or not they are experiencing symptoms of onset. Prior to the widespread use of the genetic test participants would also have had the stress that testing might have revealed whether they had the disease or not. This issue leads to a problem, in that there is a lack of standardisation data for this population.

Some earlier studies used the DNA linkage analysis (Gusella, Wexler, Conneally, Naylor, Anderson and Tanzi, 1983) which allowed high (>95%) versus low (<5%) risk of carrying the HD mutation to be determined. Whilst certain studies found an impairment, most did not (e.g. Rothlind et al, 1993; Giordani et al, 1995). However, many of these have been criticised (Strauss and Brandt, 1990; Brandt and Butters, 1996) for their inability to reliably assign participants to the correct groups. It has been suggested (Lawrence et al 1998; Diamond, White, Myers, Mastromauro, Koroshetz et al, 1992) that they could in fact point to pre-symptomatic cognitive dysfunction in HD if the data was re-analysed with the benefit of reliable predictions about genetic status (e.g. Jason, Pajurkova, Suchowersky, Hewitt, Hilbert et al, 1988).

It would seem that this issue is far from resolved. Studies that compare cognitive function in pre-clinical mutation positive versus mutation negative at-risk subjects have found inconclusive results. A number of studies (Campodonico et al, 1998; Lawrence et al, 1998; Gray et al, 1997; Siemers et al, 1996; Rosenberg, Sorensen and Christensen, 1995; Foroud, Siemers, Klindorfer, Bill, Hode and Norton, 1995) report pre-clinical cognitive impairment in mutation carriers on various measures such as psychomotor speed, memory, emotion recognition, attentional set-shifting

and eye movement abnormalities. Other studies (de Boo et al, 1997; Campodonico et al, 1996; Gomez-Tortosa, Del Barrio, Barroso and Garcia Ruiz, 1996; Blackmore et al, 1995) report no differences between mutation positive and mutation negative subjects.

Campodonico et al (1996) point out that despite the often inconclusive results the hypothesis is far from disproven. The discrepant findings in these studies might well be explained by differences in population sizes, mean age, test sensitivity, and the inclusion/exclusion criteria used in relation to symptoms. Studies that used the high versus low-risk categorisation lose statistical power due to the possibility that individuals may have been assigned to the wrong groups. Studies that used direct gene testing whilst not vulnerable to this effect may have other sources of variance. Four later studies (Rosenberg et al, 1995; Giordani et al, 1995; Blackmore et al, 1995; Campodonico et al, 1996) which reported no differences between groups, had gene positive participants who were younger than the gene negative, and younger than have been used elsewhere. They used gene positive groups with a mean age in the early thirties, whereas Foroud et al (1995) and Lawrence et al (1998) had gene positive groups in their mid-to-late thirties and found differences between groups on cognitive indicators. Age differences are perhaps inevitable if symptomatic participants are screened out since this is likely to eliminate at least some of any cohort aged over 35-40 years.

Campodonico et al (1998) found that striatal volume was inversely associated with age in gene carriers. Assuming, therefore, that subtle changes in performance might appear or become increasingly obvious as participants approached the age of onset this difference of a few years at a critical age could be important. This can be a particular problem where studies have used a longitudinal design but have not followed participants over a long enough period of time, e.g. only one or two years (Campodonico et al, 1996). This might produce a false negative result, which could be given more credence because of the design. Participant age cannot however account for all of the variation since participants in both the Campodonico et al (1996) and Lawrence et al (1998) studies were an average of 10 years from onset,

and these studies produced conflicting results. Also Rosenberg et al (1995) found a negative correlation between age and test scores, which suggests that the difference between groups is explained by cognitive decline.

Age and QNE were used by Campodonico et al (1998) among others as covariates, in order to screen out those with mild symptoms. The use of age as a covariate rests on the assumption that HD follows a continuous course that worsens with age. This has yet to be confirmed and it may be that the disease is discontinuous and has an irregular course. This obviously raises methodological issues for the current and other studies. However the effects of age in such studies may still be worth investigating.

Criteria for inclusion and exclusion on the basis of symptoms may also be a source of variance. Lawrence et al (1998) pointed out that, at that time, there were no strict criteria for early motor signs in HD. Hence differences in criteria used may contribute to discrepancies in the published literature. Most studies have relied upon the subjective, albeit expert, opinions of one, or at most two, neurologists to identify motor symptoms and only a few (e.g. de Boo et al, 1997) have used motor assessments as part of their methodology. Some studies have attempted to control for minor neurological abnormalities (Campodonico et al, 1998), especially where they included participants who were symptomatic (de Boo et al, 1997).

It might be argued that any differences found between gene positive and gene negative groups are due to normal differences in the brain. It has been found however that brain morphometry, in the form of basal ganglia volumes, does not correlate with neuropsychological test performance in non-gene carriers (Campodonico et al, 1998)

Further difficulties exist with the precise nature of cognitive tests used. Lawrence et al (1998) found significant differences in semantic verbal fluency, which had not previously been tested although letter fluency had been tested and found to be unimpaired by Blackmore et al (1995). Perhaps because this is still a relatively

open area there has been little agreement between studies about which measures to use. Table 1 shows a sample of the tests that have been used in this area. It is noticeable that Foroud et al (1995), the study with by far the largest sample, used only the WAIS-R and yet found significant differences between gene carriers and non-carriers.

Many studies (e.g. Campodonico et al, 1998; Lawrence et al, 1998) selected tests that were sensitive to symptomatic HD. This seems the most logical starting point if one assumes that presymptomatic changes will take the same form as those observed later in the disease. However, there may be a difficulty in using the same measure to assess clinical and pre-clinical populations, since the latter are by definition unlikely to score outside of the normal range. This leads to uncertainty about whether results indicate natural variation or pathological change. Neuropsychological assessments which have been designed to be used with clinical populations might be especially difficult to interpret since ceiling effects will be observed where participants are only minimally impaired. Campodonico et al (1998) note that the anatomical and neuropsychological changes that they observed, even where significant, were in the sub-clinical range but paralleled those found in some studies of symptomatic HD patients (e.g. Starkstein et al 1988 and 1992). Despite this it would be premature to criticise existing studies for poor test selection since they have effectively ruled out the existence of any reliable pathognomonic impairment on a number of measures that are sensitive to early changes in symptomatic patients. For instance the WAIS-R, the Trail Making Test, the Stroop Test, the Tower of London.

Given the predicted small size of changes the sensitivity of measures is vital, apparently sensitive standardised tests may not be designed with this sort of population in mind. For instance, Campodonico et al (1996) report no significant differences between carriers and non-carriers but on closer examination found a trend towards worse test performance on sustained attention and processing speed for gene positive participants who were closer to onset. This was obscured by the inability of tests to discriminate effectively between gene carriers and non-carriers.

Table 1: Tests of cognitive ability used in previous research

Study	Test
Jason et al, 1988	Weschler Adult Intelligence Test-Revised (WAIS-R), Trail Making Test, Weschler Memory Scale (WMS), Rey-Osterrieth Figure, Free Drawing, Wisconsin Card Sorting Test (WCST), Stroop Test, Word Fluency, Design Fluency, Dot Discrimination, Speed of Reading, Object Naming, Language Comprehension, Spelling
Blackmore et al, 1995	WAIS-R, National Adult Reading Test (NART), California Verbal Learning Test (CVLT), Corsi Blocks and Supraspan, Digit Supraspan, Cognitive Estimations, WCST, Verbal Fluency, Purdue Peg Board, Benton Visual Retention Test, Trail Making Test, Pursuit Rotor Test, Finger Tapping, Word completion, Judgement of Line Orientation, Paced Auditory Serial Addition Task.
Foroud et al, 1995	WAIS-R
Rosenberg et al, 1995	Trail Making Test, WAIS-R, WMS, CVLT, Modified Card Sorting Test, Rorschach Test, Tower of Toronto, Rupp's Test of Spatial Ability, Andersen's Test of Visual Memory
Campodonico et al, 1996	WAIS-R, Hopkins Verbal Learning Test, Stroop Test, WCST
de Boo et al, 1997	WAIS, WMS, WCST, Stroop Test, CVLT, Benton Visual Retention Test, Figure Copying, Schufried Motor Performance Test (e.g. line tracking, timed choice)
Campodonico et al, 1998	Symbol Digit Modalities, Hopkins Verbal Learning Test, Standardised Road Map Test of Directional Sense, Extrapersonal Orientation test, Stroop Test, WCST
Lawrence et al, 1998	WAIS-R, Letter fluency, CANTAB, Corsi Block Span, Spatial Working Memory, One-Touch Tower of London, Visual Discrimination Learning/Attentional Set-Shifting

A further question is whether the measures chosen are the most appropriate. The Wisconsin Card Sorting Test (WCST) has been used by a number of researchers (Strauss and Brandt, 1990; Blackmore et al, 1995; Rosenberg et al, 1995; Campodonico et al, 1996 and 1998; de Boo et al, 1997) but the only effect was found by Jason et al (1988) in a group of high-risk individuals. The WCST however, is a multi-component task which can be solved using a number of strategies and does not necessarily have the psychological and neural specificity of

an attentional set-shifting task (Downes, Sharp, Costall, Sagar and Howe, 1993, Grafman et al, 1990; Owen et al, 1991 cited in Lawrence et al, 1998). For example the WCST also involves hypothesis testing and conceptual reasoning. A more specific task might be more reliable and sensitive in identifying processes that are vulnerable in HD. Lawrence et al (1998) suggest that tests sensitive to early-stage Huntington's may not be sensitive to pre-symptomatic changes for this reason i.e. they are not specific enough and can be solved using various strategies. Also some tests may be more sensitive to cortical rather than sub-cortical changes.

Blackmore et al (1995), Giordani et al (1995) and Gomez-Tortosa et al (1996) all investigated short-term visual memory and found no impairments. Planning was assessed by Rosenberg et al (1995) and by Lawrence et al (1998), although it was only the latter study that required an entire solution to be formulated before it was executed. Neither of these studies found any impairment. Lawrence et al (1998) posit that the absence of impairment found on these difficult tasks suggests that difficulty alone is not sufficient explanation for the differences that were found. Also, letter fluency is considered to be more effortful than semantic fluency (Martin, Wiggs, Lalonde and Mack, 1994) and yet differences were found only on the latter. This is consistent with the lack of impairment in general intellectual function (Foroud et al, 1995; Lawrence et al, 1998) and points, again, to more specific deficits.

Rosenberg et al (1995) found that gene carriers were impaired on psychomotor speed, attention and concentration but only on more difficult tasks. They noted that half of the gene positive group had previous episodes of depression but did not investigate this systematically.

Lawrence et al (1998) found that on their motor screening task the gene positive group had slower mean response latencies although this did not reach statistical significance. More interestingly Lawrence et al (1998) found evidence of a specific pattern of cognitive impairment in presymptomatic HD gene carriers consisting of difficulties with semantic verbal fluency and visual discrimination

learning/attentional set shifting. Both of these tasks have previously been found to be sensitive to early stage HD (Hodges et al, 1990; Lawrence et al, 1996). Thus this study points to a very specific difference between presymptomatic gene positive and gene negative groups.

Lawrence et al (1998) found differences between gene carriers and non-carriers on attentional set-shifting and semantic verbal fluency, and found that scores on these two tests correlated quite highly with each other. Although these tasks seem quite different it can be argued that the category shift required in changing from letter verbal fluency to semantic verbal fluency is similar to an attentional set-shifting task (Downes et al, 1993; Lawrence et al, 1998). Furthermore, Lawrence et al (1998) suggest that the negative correlation which they found between errors on the attentional set-shifting task and the number of examples generated on the semantic fluency task points to the possibility of a unitary deficit affecting both tasks.

This raises a question as to the cause of this impairment on attentional set shifting. Owen, Roberts, Hodges, Summers, Polkey and Robbins (1993) demonstrated that impairment on this sort of task in symptomatic HD gene carriers resulted from perseveration i.e. difficulty inhibiting responses. This is consistent with the proposal that the striatum has a role in inhibitory control (Mink, 1996) and is affected in presymptomatic HD gene carriers (Section 1.7.1). The striatum seems to have similar roles in inhibitory control in both movement and cognition (Mink, 1996).

Siemers et al (1996) used a computerised test battery to investigate issues such as visual processing, movement and reaction time in gene carriers and non-carriers. They found significant differences on an alternating button tapping task, in movement time, movement time with decision making, auditory reaction time and visual reaction time with decision making. They also found significant correlations between the number of CAG repeats and alternating button tapping, movement time with decision making and visual reaction time with decision making. They did however include people with mild symptoms in these calculations; when only pre-

symptomatic gene carriers were considered movement time with decision making was still significantly correlated. This study claimed to have demonstrated subtle sub-clinical changes in motor-function and reaction time in pre-symptomatic gene carriers. The average age of this group was 37 years, which is older than in some studies and in the optimum range for onset of chorea, hence it might be the case that this study has measured sub-clinical symptoms of onset.

Rosenberg et al (1995) reported a statistically significant difference on half of the tests used, and a trend for poorer performance by gene carriers in all others. Psychomotor speed and attention were the most affected areas. Other studies (Diamond et al, 1992) have found impairments in learning and memory but in symptomatic patients this could be related to inefficient planning, and Rosenberg et al (1995) suggest that in pre-symptomatic patients it may be related to attentional difficulties. Although all of the tests used in this study and others could be vulnerable to stress, such as that caused by living with at-risk status, it is clear that gene carriers still perform below the level that might be expected, thus indicating greater likelihood of neuropsychological impairment.

Foroud et al (1995) note that previous studies have often used small numbers of participants and many different tests but have not adjusted the level of significance to account for multiple testing. Hence some significant results might be expected by chance. Foroud et al (1995) had 394 participants which was a notable increase in size from previous studies which tend to have 25-40, but a number of this cohort were symptomatic individuals. Foroud et al (1995) found that gene carriers scored lower on all tests, significantly so on digit symbol and picture arrangement even if symptomatic carriers were excluded. They also found that CAG repeats correlate with deficits in pre-symptomatic gene carriers. This seems to uphold the suggestion that higher CAG repeats relate to severity and earlier onset of problems.

The study by Jason et al (1988) highlights further difficulties with this type of research. They found deficits in gene carriers in functions normally associated with the frontal lobes and that general intelligence, motor skills, verbal memory and

language abilities appeared unaffected. However samples were very small (7 gene positive) and came from only 3 pedigrees, hence differences could have arisen from genetic factors other than the gene. Jason et al (1988) failed to include statistical control for type 1 errors when analysing the data. Also they used some measures which are scored subjectively (e.g. Rey figure, Free Drawing) and do not necessarily identify specific functions.

If subtle cognitive decline is the earliest sign then clinical diagnosis of onset will remain problematic. At present it would seem that although effects have been found, they could not be pinned down reliably. One might argue that in order to progress there is a need for greater specificity in the area investigated and greater sensitivity in testing. Lawrence et al (1998), Campodonico et al (1996 and 1998), and Gomez-Tortosa et al (1996), all found that presymptomatic gene carriers had problems with attention. This might be the basis for under-performance in other tests and seems worthy of further attention.

1.10 Attentional function and Huntington's disease.

The concept of attention has denied definition for some years but is of undoubted importance since it is interacting and integrated with all other cognitive functions (Zimmermann, North and Fimm, 1993). Sohlberg and Mateer (1987) suggest that it is not a unitary concept, (which may contribute to the difficulty in definition), but a multidimensional system of related but semi-independent processes. 'Level of activation' and 'selectivity' are widely recognised as different dimensions, which also have further complexities e.g. internally versus externally modulated 'level of activation' i.e. vigilance and alertness respectively (Sprengelmeyer, Lange and Homberg, 1995). Other examples of sub-functions of attention are the ability to shift focus between competing stimuli or suppress unwanted responses.

Attention is such a complex task that test procedures must be designed to suit highly specific functions since complex tasks do not add to our understanding (Zimmermann et al, 1993). A test battery for this purpose has been designed using

as its' basis the Multi-Component Theory of Attention (Posner and Boeis, 1991, cited in Zimmermann et al, 1993). The Zimmermann et al (1993) battery has developed and evolved through several stages owing partly to the very problem of definition mentioned earlier, and a process of refinement. This battery formed the core of the assessments used by Sprengelmeyer (1995) in assessing the pattern of attentional deficits in Huntington's disease.

The battery used by Sprengelmeyer et al (1995) covered the following functions.

Alertness looked at the ability to control the level of activation in response to external stimuli. This task sometimes included a 'pre-condition' warning and hypothesised that this would raise arousal and improve response time. The neuroanatomical basis hypothesised for this function is the mesencephalic reticular formation (Foote et al, 1991, cited in Sprengelmeyer et al, 1995). This function has not been found to be impaired in early HD (Sprengelmeyer, Zimmermann, Lange and Homberg, 1993; Sprengelmeyer et al, 1995), which is unsurprising if the neuroanatomical model is correct.

Vigilance is closely related to alertness but is modulated internally rather than externally. Vigilance requires the ability to attend to only a few stimuli over a lengthy period of time. The neuroanatomical basis of this function is believed to lie in frontal and limbic structures (Pardo, Fox and Raichle, 1991). Sprengelmeyer et al (1993 and 1995) did find impairments in this area but did not offer a causal explanation. Interestingly there is consistency between the anatomical model proposed for this function and the atrophy expected in HD.

Divided attention depends on the ability to monitor dual tasks simultaneously. In this case (Zimmermann et al, 1993; Sprengelmeyer et al, 1995) these tasks involved separate input-channels i.e. visual and acoustic. HD patients were found by Sprengelmeyer et al (1993 and 1995) to have poorer performance on this task. The measure of divided attention used in this battery places disproportionate loads on these separate channels, since the visual task requires more, and more demanding,

sub-processes such as preparation and execution of eye movements and visual-perceptual processing.

Response flexibility presupposes the ability to selectively focus attention and tests the ability to maintain and switch focus at will. Dysfunction in this area may be seen as perseveration and rigidity, or high distractibility and flights of ideas (Zimmermann et al, 1993). HD patients have been found to be significantly impaired in this area (Sprengelmeyer et al, 1993 and 1995; Roman, Delis, Filoteo, Demadura, Paulsen et al, 1998). They suggest that since the selective shifting of the focus of attention is essential to many everyday skills it is unsurprising that people with HD have so many difficulties in planning, organising and sequencing.

Response inhibition requires the ability to limit responses to target conditions, ignoring others. This skill has been implicated in problems controlling voluntary actions (Luria cited in Zimmermann et al, 1993) and has been reported in patients with frontal lobe lesions (Zimmermann et al, 1993). Sprengelmeyer et al (1995) found only mildly impaired performance on this test, but Roman et al (1998), in a comparable study, found that HD patients were very poor at inhibiting certain types of response.

Inter-modal integration relies on the selective control of attention across different sensory channels and the integration of information from both. Integration of information may involve a separate underlying mechanism that is not modality specific (Mirsky, 1989; Wagensonner and Zimmermann, 1991; both cited in Zimmermann et al, 1993). HD patients exhibited significant impairment on this task (Sprengelmeyer et al, 1993 and 1995).

Response inhibition, response flexibility and inter-modal integration are all cognitive processes taping into executive functions. These functions, involving non-routine and attention-demanding tasks are believed to be under the control of the 'Supervisory Attentional System' (Shallice, 1988). This system is linked to a frontal-striatal circuit between the anterior cingulate and ventral striatum (DeLong

et al, 1992). Given the aforementioned expected progression of neuropathology through the striatum (dorsal to ventral) these functions might be affected in HD, although perhaps not at the very earliest stage.

Sprengelmeyer et al (1995) conclude that attentional functions are impaired in HD but that the arousal function is not. They included in this the 'posterior' attentional system (Posner and Dehaene, 1994), which is associated with superior parietal cortex and is believed to be responsible for both stimulus location and shifting from one stimulus to the next. They also suggest that 'higher' cognitive deficits observed in HD might be explained to some degree by problems in attention, and that studies which do not control for this should be viewed with caution.

Roman et al (1998) also observed impaired attentional function in HD, particularly in selectively focusing attention when irrelevant or distracting information was present. This study used a more traditional, clinically oriented, set of tests, which revealed a less intricate picture of attentional function. Roman et al (1998) went on to note that this methodology may not be the most effective at delineating deficits in attention in HD patients, and suggested that a more experimental approach might be useful.

Sprengelmeyer et al (1995) can also be criticised for certain assumptions they make in analysing their data. For instance they assume that the measurement of errors is continuous, i.e. they assign the same value to the difference between each point on the error scale, and seem to ignore what the potential meaning of differences might be. Although their calculations seem intuitively correct they assign gravity to error scores which, although significant, are actually in very a narrow band.

It must also be noted that Sprengelmeyer et al (1995) used their test battery with symptomatic HD patients who may have different patterns of neuropathology from presymptomatic gene carriers. However attention has been mentioned by several authors as a likely and actual area of dysfunctional processes in presymptomatic

gene carriers (see Section 1.9). It seems likely that if attentional processes are effected early in presymptomatic gene carriers then this battery of tests, based on a conceptual typology of attentional function, will provide a useful insight.

1.11 Hypotheses.

The hypotheses to be tested were as follows.

Hypothesis One

There will be no significant differences between presymptomatic gene carriers and non-carriers on the alertness task.

Hypothesis Two

Presymptomatic gene carriers will have significantly poorer performance than non-carriers on the response flexibility task

Hypothesis Three

Presymptomatic gene carriers will have significantly poorer performance than non-carriers on the intermodal integration task.

Hypothesis Four

Presymptomatic gene carriers will have significantly poorer performance than non-carriers on the response inhibition task.

Hypothesis Five

Presymptomatic gene carriers will have significantly poorer performance than non-carriers on the divided attention task.

Hypothesis Six

Presymptomatic gene carriers will have significantly poorer performance than non-carriers on the vigilance task.

2 Method

2.1 Design

In total, 23 participants took place and were divided into three groups. These were presymptomatic gene carriers (N=6), gene negative people from at-risk families (N=13), and symptomatic gene carriers (N=2). These groups are smaller than had been hoped for and the implications of this will be discussed further in Section 4.3.1, however there is a precedent within the literature for groups of approximately this size e.g. Jason et al (1988), N=7, deBoo et al (1997), N=9; Campodonico et al (1998), N=13.

This design allowed for the gene carriers to be compared with an at-risk group who might have been similarly affected by stresses such as the expectation of developing Huntington's disease, or living with an affected relative.

The same procedures and tests were used with all participants.

2.2 Participants

Details of the participant group, incorporating the results of tests of intellectual ability etc., will be presented in the results (Section 3.1).

2.2.1 Ethical Approval

Leicester University Research Ethics Committee (June, 1999), Leicestershire and Rutland NHS Trust Research Ethics Committee (February, 2000) and Nottingham City Hospital Research Ethics Committee (January, 2000) approved the study. Participants were not informed of the exact hypotheses but were told that the study was investigating the possible subtle effects of the gene for Huntington's disease on specific cognitive functions. All participants gave informed written consent (a copy of the written consent form can be found in Appendix 1).

The Leicester Ethics Committee required that all potential participants were written to asking whether they would be willing to receive information about research and that information about this study was sent only to those who responded to this in the affirmative. Other than this the same procedures were used with all participants.

Copies of the invitation to participate and the information sheet are given in Appendix 2.

2.2.2 Gene tested participants

The nature of this study necessitated the recruitment of people who had been tested for the Huntington's gene but were considered free from symptoms. The only reliable point of contact with services for this group of people was through the genetics departments that tested them for the HD gene. Hence participants were recruited through genetics departments. Although this group could not be ensured to be free of symptoms, the request for volunteers stated this as a requirement and the procedure involved screening for symptoms.

Testing for the Huntington's gene is considered to be highly confidential and so no information was passed to the researcher until after participants had volunteered. In addition to conducting the initial recruitment the genetics services helped to screen out, as far as was possible, individuals who would be excluded because of onset of symptoms or other difficulties, such as drug abuse.

The participants for this study were recruited via Leicester Royal Infirmary Clinical Genetics and Nottingham City Hospital Medical Genetics. Criteria for inclusion were that the person must have been tested for the Huntington's gene more than three months but less than three years ago. The genetics services suggested this time frame since they felt that a significant proportion of people tested more than three years ago would have experienced onset of the disease. It was also believed that those tested in the preceding three months who were gene

positive would not have had time to adjust to living with this insidious threat. People with either positive or negative test results were included.

Exclusions were made if volunteers had symptoms of onset such as movement disorder, mental health problems or obvious cognitive dysfunction (i.e. to the extent that it impaired their usual daily functioning). Any volunteers who exhibited or reported other factors, current or historical, that might confound the collection or quality of the data were excluded from the analysis e.g. heavy alcohol use, head injury, significant mental health problems. The method for collection of this data is described in Section 2.4.1.

Several of the participants were related to each other, the details of these relationships are given in Appendix 3, and the implications are considered in the discussion (Section 4.3.5).

2.3 Experimental Procedure

The tests were run in one session lasting approximately one hour and thirty minutes. The tasks were presented in the same order for each participant; interview, Unified Huntington's Disease Rating Scale (UHDRS), National Adult Reading Test (NART), Hospital Anxiety and Depression Scale (HADS), Alertness, Inhibition, Flexibility, Inter-modal Integration, Divided Attention, and Vigilance. Data was collected on the relevant forms and in data files on a laptop computer.

Before testing began the researcher went through the consent form with each participant to ensure that they had read the information sheet and had been given the opportunity to ask questions or clarify any aspect of the testing. All participants were reminded that they could withdraw from the study at any time. All participants were then asked to sign the consent form.

The UHDRS, NART and HADS were administered according to the standard procedure given in the respective manuals. All tests of attention were administered

in the same fashion. Participants were seated in a chair at a standard height dining table and the laptop computer was placed on the table with the screen approximately 50cm away from them. The button box was placed on the table between the participant and the computer in a central position. All participants were instructed to use the index finger of their dominant hand for tasks requiring one response button and the index finger of each hand for tasks requiring two.

Verbal instructions were given on how to complete each task (Appendix 4).

The testing equipment can be seen in Figure 3. A guide to the procedure was used throughout to ensure uniformity, a copy of which can be seen in Appendix 5.

2.4 Equipment and Tests

In order to provide data to inform the inclusion or exclusion of participants, and to enable description of the participant group, a number of measures were used. These are detailed below.

2.4.1 Interview

The interview schedule was designed to collect basic demographic information that might influence inclusion/exclusion.

A copy of the interview schedule can be found on the procedure guide in Appendix 5.

2.4.2 National Adult Reading Test

The National Adult Reading Test (Nelson, 1991) was developed to provide an estimate of pre-morbid IQ in people who may be suffering from dementia. It relies on two factors: (i) reading ability is highly correlated with general IQ level and (ii) reading ability in dementing patients is maintained at or near it's pre-morbid level

(Nelson and McKenna, 1975 in Nelson, 1991). Although participants in this study would not be expected to display dementia the NART was selected because it provides a reliable estimate of IQ and is relatively quick and simple to administer.

Figure 3: The computer and button box arrangement used to test attention

The NART consists of 50 words selected on the basis that they cannot be decoded using common rules e.g. phonetic decoding, hence the participant would only be expected to give a correct response if they were familiar with the word. The words

are also short enough that a dementing patient would not have difficulty processing the information. Participants were asked to read aloud each word on the list and were scored on their pronunciation using the guidelines given in the NART manual.

The NART has been standardised against the Weschler Adult Intelligence Scale (WAIS) and gives a predicted WAIS IQ score (Nelson, 1991). It has been validated as a measure of pre-morbid IQ and is recommended as a criterion for matching research participants (Nelson, 1991).

2.4.3 The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS, Zigmond and Snaith, 1983) is a 14 item self-assessment scale that has been used with both psychiatric and non-psychiatric populations (Snaith and Zigmond, 1994). The HADS is designed to record the present state of anxiety and depression, which are recorded and scored separately.

The internal consistency and test-retest reliability of the HADS have been found to be satisfactory (Clark and Fallowfield, 1986; Snaith and Zigmond, 1994). The face, construct and concurrent validity of the HADS and the validity of the separation of the two sub-scales have also been investigated and found to be satisfactory (Moorey et al, 1991; Bramley et al, 1988; Aylard et al, 1987 all in Snaith and Zigmond, 1994; Zigmond and Snaith, 1983).

The HADS was selected for use in this study because it provides a relatively quick and simple measure of anxiety and depression without sacrificing reliability and validity.

2.4.4 Unified Huntington's Disease Rating Scale

The Unified Huntington's Disease Rating Scale (UHDRS) (Huntington Study Group, 1996) is an instrument developed by the Huntington Study Group and used at designated research centres. It provides a neurological screening assessment of motor skills, cognitive ability, behaviour, generalised functioning and independence. Much of this scale would be redundant for use with a population of people considered pre-symptomatic, and so items relevant to the detection of onset of Huntington's Chorea were selected with the advice of a neurologist. These were:

Ocular Pursuit
Saccadic Suppression
Dysarthria
Finger Tapping
Pronation/Supination of the hands
Luria (a sequence of hand movements)
Rigidity of the arms
Bradykinesia
Chorea
Gait.

These items were tested and observed by the researcher following training, and practice, in their use by a Consultant Neuro-psychiatrist.

2.4.5 Assessment of Attention

Each client was also assessed on six different attentional functions. All of these tests were presented on a Toshiba T4400C Model laptop computer and used a purpose built button box, of a type recommended for use with the software used to generate the tests, to record responses (Figure 3). A button box was used because the laptop computer did not continuously sample keyboard responses but only

registered collected information put in via the keyboard every 25-100 milliseconds. Hence any key press would be subject to a possible error of the same magnitude. The button box, and the software that was used to run the experiment, allowed the time of each response to be collected to within 1 millisecond. Since reaction time was an important variable for the tests this was a significant requirement. All of the tests were based on software written in the MEL experiment designer system. For each of these tests the same data was recorded; reaction time, errors and omissions.

The measures were as follows.

Alertness

This test of alertness consisted of a cross (12 point font size was used for all characters) presented in the middle of the screen with the instruction to participants that they should press a designated button as quickly as possible after they saw the cross. 80 trials were presented, 40 of which were preceded by a tone. The tone was included by Sprengelmeyer et al (1995) and it was expected that patients with HD might be unable to suppress anticipatory responses and would therefore have higher error scores on this task. There is no evidence to suggest that this is the case in this group but the inclusion of tones served to vary the task and hopefully prevent boredom.

Response Flexibility

The response flexibility task examined participants' ability to change the focus of attention between stimuli. There were 3 conditions. In each condition a letter X and a number 7 appeared simultaneously on opposite sides of the screen equidistant from the midpoint. The side that each character appeared on varied in a random order. Participants were instructed to use a designated button to refer to each side of the screen. In Condition One participants were to push the button on the same side as the letter. In Condition Two participants were to push the button

on the same side as the number. In Condition Three participants were to alternate between letter and number and therefore push the button on the same side as first the letter and then the number, and continue alternating for the rest of the task. Participants were also instructed that if they lost track of the sequence they should restart by responding to the next letter.

This task consisted of 20 trials of conditions one and two and 40 trials of condition three.

Response Inhibition

In this task participants' ability to attend to stimuli and appropriately inhibit responses was investigated. Participants were presented with two visual stimuli, which resembled a letter r and its' mirror image in the centre of the screen. The task was to respond to the former but not the latter of these stimuli.

There were 100 presentations requiring a response and 20 that required inhibition.

Inter-modal Integration

The inter-modal integration task was used to investigate participants' ability to integrate information from two different sensory modes. This task consisted of visual information in the form of an arrow pointing up or down and auditory information in the form of a high or low pitched tone. Participants were to respond as quickly as possible using a designated button when an arrow pointing up was accompanied by a high pitched tone or when an arrow pointing down was accompanied by a low pitched tone, and not to respond in any other circumstances. This task involved 80 presentations, 40 of which 'matched' and therefore required a response.

Before the presentation of the main block of trials participants were presented with a sample of high and low tones each of which was accompanied by the relevant label, "High tone" or "Low tone", on the screen.

Divided Attention

This test of divided attention consisted of two parallel tasks, one using visual information, the other auditory. In the visual task groups of two letters were presented in the centre of the screen, which were either XX, XY, YX, or YY. Participants were asked to press a designated button when XX or YY appeared. In the auditory task two tones were presented 100ms after the two letters which were either two high pitched tones, two low pitched tones or one high and one low pitched tone. Participants were to respond when two tones of the same pitch were presented.

In this task there were 40 presentations in each modality.

Vigilance

In this task participants were presented with three possibilities; a letter X would appear, sometimes on the left side of the screen, and sometimes on the right, and occasionally two X's would appear, one on each side. Participants were to respond as quickly as possible, using a designated button, when two X's appeared.

There were 120 trials, divided into 20 target stimuli (requiring a response) and 100 non-target stimuli.

2.5 Ethical concerns

In the design and execution of this study ethical concerns were of considerable importance. Issues around genetic testing are treated in a strictly confidential manner and it was seen as essential that participants were not identified to others as

being at risk of HD. Furthermore, taking part in the research, and expectations about diagnosis through participation were potentially problematic. The following points were considered to be particularly important:

- Information about the study was provided before potential participants met with the researcher. All participants were given the opportunity to ask questions about the study and provided with a contact who was not involved in the study in case they had any questions or concerns.
- It was made clear that participation would not effect any current or future care they might receive, and that they could drop out of the study at any time.
- Participants were reassured that their anonymity would be protected, and that the identity of participants would be known only to the main researcher and contact at the genetics department where they were tested.
- Confidentiality was maintained throughout the study. Participants were only identified by a number on all forms, except the consent form. All forms were kept in a locked filing cabinet, with consent forms kept separately. Data was coded before being entered into a computer.
- Participants were informed that this study would not be able to diagnose or predict the onset of HD, and that the results of the study would not be made available to individuals.
- One concern was that this study would identify individuals who exhibited symptoms of onset who were not aware of this. A procedure for directing individuals to the appropriate services was agreed with the ethics committees. Both of the symptomatic participants who were recruited did have an awareness of their difficulties and had contact with appropriate services.

3 Results

3.1 Data describing the participants

Following the collection of data from participants the results were scrutinised before formal analysis began. Two participants in the gene carrier group scored 3 on the UHDRS, indicating definite signs of onset. These took the form of eye movement abnormalities, specifically difficulty suppressing saccadic movements, tremor of the hands, and bradykinesia (motor slowness). The data pertaining to these participants has been excluded from all analyses, although their scores are included where tables are given and will be discussed individually. These participants were noticeably older than the average for the other groups. All other participants scored zero on the UHDRS. A summary of demographic and descriptive information is given in Table 2.

Table 2: Descriptive statistics for the participant group.

Genetic Status		Age	Years in Education	Estimate IQ	HADS Anxiety	HADS Depression
Non-carriers (N=15)	Mean	42.3	10.9	115.3	6.3	3.3
	Minimum	22	9	108	1	0
	Maximum	62	13	125	15	9
Gene Carriers (N=6)	Mean	29	11	109.2	9	5
	Minimum	21	10	97	1	1
	Maximum	38	12	115	17	13
Symptomatic Gene carrier 1		62	11	95	9	9
Symptomatic Gene carrier 2		75	9	114	18	9

In terms of ethnic origin all of the participants were classed as white European.

The average age of gene carriers was 13.3 years younger than that of non-carriers. Average number of years in education was similar and the estimated average IQ of the two groups was within 6.2 IQ points, with carriers being the lower. One gene carrier and one non-carrier were left-handed, all other participants were right-handed. There were 4 female and 2 male gene carriers and 7 female and 8 male non-carriers.

The average HADS Anxiety score for gene carriers was 9 falling in the 'mild' range (8-10) and 6.3 for non-carriers which lies in the 'normal' range (0-7). The average depression scores were 5 and 3.3 for carriers and non-carriers respectively, both of which fall in the 'normal' range (0-7). Two individual participants scored in the 'severe' range for anxiety, one gene carrier and one non-carrier. The latter of these had received one year of psychotherapy one year ago for Post Traumatic Stress Disorder and reported some minor residual problems. One further non-carrier reported a recent bereavement at interview, but scored in the 'mild' and 'moderate' ranges on anxiety and depression respectively. Symptomatic gene carrier 2 scored in the 'severe' range for anxiety but reported few problems at interview.

Given that the mean ages of the gene carriers and non-carriers were so far apart it was decided to perform a covariate analysis with age. The greater power of a parametric method was preferred over a non-parametric one, but given the small group sizes the data was examined graphically to ensure that this was appropriate. ANCOVA's were performed, the results of which are given below.

Raw means and standard deviations for latency are given in Table 3 and for error in Table 4. The adjusted means and standard errors for latency and error, covaried for age, are given in Table 5 and Table 6 respectively.

Table 3: Means and standard deviations of response latency for each participant group.

	Mean (Standard Deviation) Latency		Mean (Range) Latency	
Task	Gene carriers	Non-carriers	Symptomatic carriers	
			1	2
Alertness	821.2 (78.5)	807.9 (26.5)	1056 (375-778)	1155 (383-2128)
Response Flexibility	473.5 (52.3)	468.2 (56.9)	543 (260-692)	621.9 (412-699)
Response Inhibition	394.3 (53.3)	409.1 (48.3)	506.7 (300-694)	541.3 (367-696)
Inter-modal Integration	633.5 (85.3)	667.0 (122.2)	--	0
Divided Attention	489.6 (76.3)	463.9 (151.0)	--	693.4 (235-978)
Vigilance	447.8 (31.3)	407.65 (123.5)	--	657.6 (575-699)

3.2 Hypothesis One

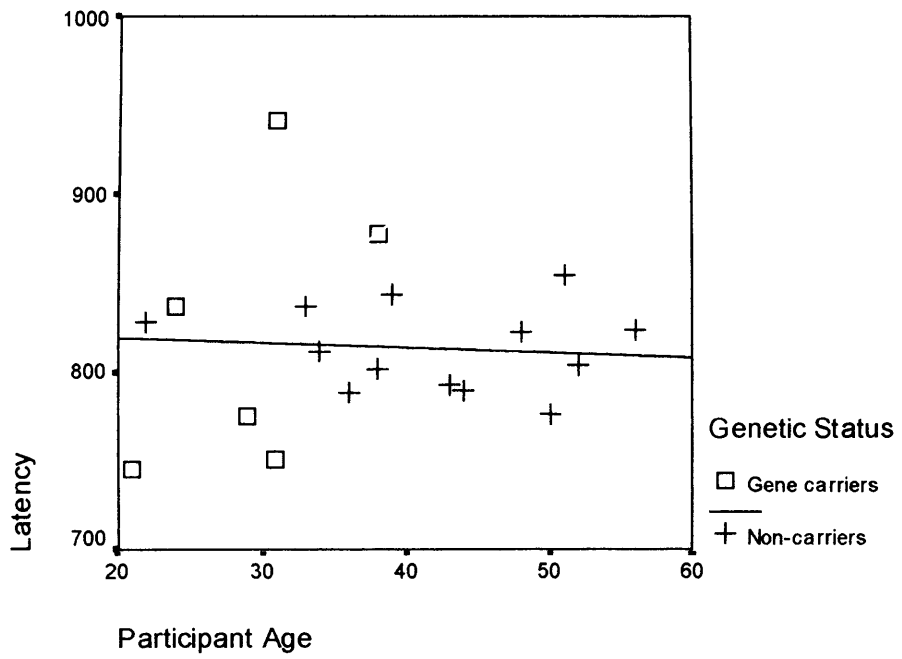
The alertness task tested the ability of participants to respond to externally generated stimuli. Table 3 shows the mean response latencies for gene carriers and non-carriers, which are quite close together, and it can be seen in Table 5 that this remains so in the means adapted for covariation.

Analysis of covariance showed no significant effect of age on response latency [$F(1) = 0.292$, $P = 0.595$]. With age removed as a covariate, there was no significant difference between the gene positive and gene negative groups for latency [$F(1) = 0.610$, $P = 0.445$].

There were no errors on the alertness task.

The scatterplot (Graph 1) illustrates the relationship between latency and age on the alertness task for the two groups. There does not seem to be a strong relationship between these variables nor is there an obvious difference between the groups on latency, which is consistent with the test result.

<u>Graph 1:</u> Scatterplot of latency and age for the alertness task



This appears to uphold the hypothesis that gene carriers and non-carriers will not differ in alertness.

Table 4: Means and standard deviations of error score for each participant group.

Test	Mean (Standard Deviation) Latency			
	Gene carriers	Non-carriers	Symptomatic carriers	
			1	2
Response Flexibility	13.16 (9.2)	12.8 (9.9)	89	119
Response Inhibition	9 (9.9)	3.9 (3.4)	15	31
Intermodal Integration	1.33 (1.2)	1.3 (1.5)	--	--
Divided Attention	2.2 (2.9)	3.3 (5.5)	--	30
Vigilance	1 (0.8)	0.46 (0.77)	--	15

3.3 Hypothesis Two

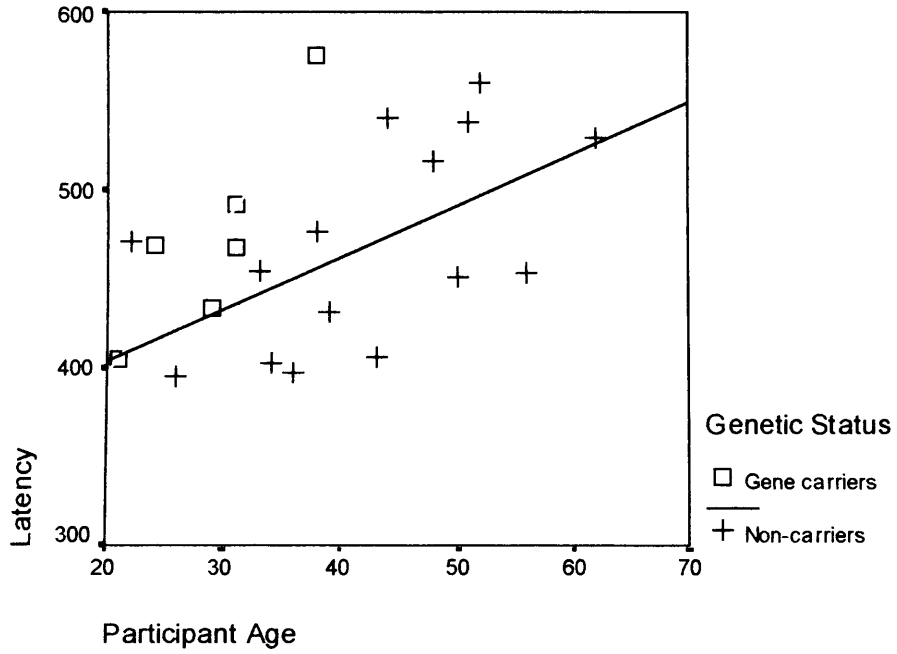
Attentional set shifting was examined using the response flexibility task. Table 3 shows the mean response latencies for each group on this task, which do not seem to differ significantly. However in Table 5, where the means adapted for covariation are shown the difference is larger.

Analysis of covariance showed a significant effect of age on response latency [$F(1) = 5.96$, $P < 0.05$] and error rate [$F(1) = 4.409$, $P = 0.05$]. With age removed as a covariate, there was significant difference between the gene positive and gene negative groups for latency [$F(1) = 10.617$, $P < 0.01$] but not error rate [$F(1) = 1.408$, $P = 0.251$].

Graph 2 shows the relationship between age and latency on the response flexibility task for each group. Allowing for the variation of latency with age, the gene carriers still look to have higher than expected latency.

This supports that hypothesis that gene carriers will be slower on this task than non-carriers.

Graph 2: Scatterplot of latency and age for the response flexibility task



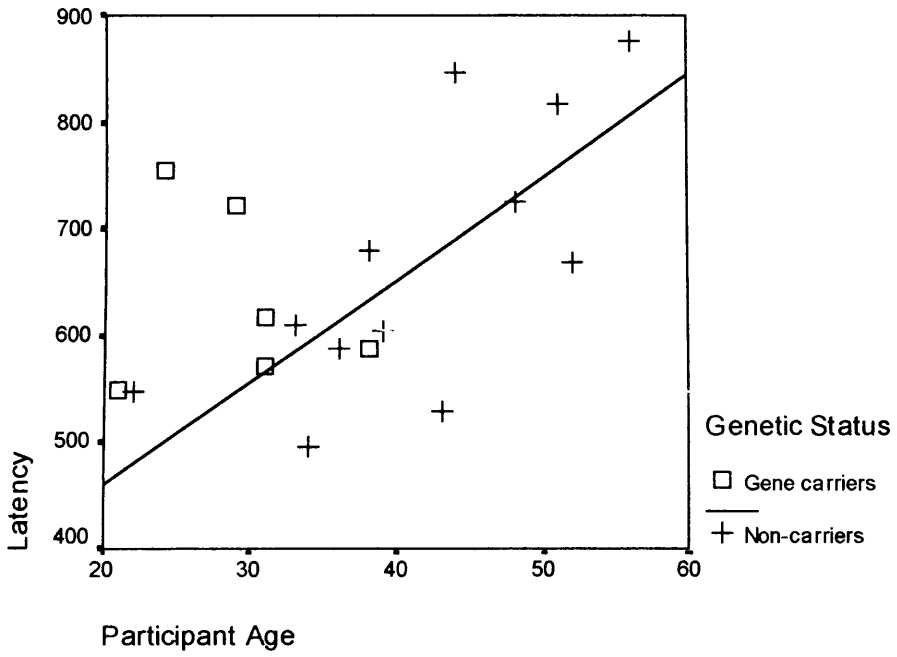
3.4 Hypothesis Three

The integration of information from separate sensory modes was tested using the inter-modal integration task. The data in Table 3 shows the difference in mean response latency. When covaried for age (Table 5) the difference between gene carriers and non-carriers appears quite large.

Analysis of covariance showed a significant effect of age on response latency [$F(1) = 5.969$, $P < 0.05$] but not on error rate [$F(1) = 0.012$, $P = 0.891$]. With age removed as a covariate, there were significant differences between the gene positive and gene negative groups for latency [$F(1) = 7.25$, $P < 0.05$] but not error rate [$F(1) = 0.012$, $P = 0.915$].

Graph 3 shows the relationship between age and latency on the intermodal integration task for each group. Allowing for the variation of latency with age, the gene carriers still look to have higher than expected latency.

<u>Graph 3:</u> Scatterplot of latency and age for the intermodal integration task



This supports the hypothesis that gene carriers will have poorer performance than non-carriers on tasks requiring the integration of information from separate sensory modes.

Table 5: Adjusted means and standard deviations of response latency for each participant group when covaried for age.

	Mean (Standard Error) Latency	
Task	Gene carriers	Non-carriers
Alertness	826.7 (21.8)	805.7 (12.8)
Response flexibility	506.1 (21.7)	455.8 (12.0)
Response inhibition	412.7 (21.7)	401.8 (12.8)
Inter-modal integration	691.3 (46.8)	640.3 (29.5)
Divide	482.0 (64.1)	466.9 (37.8)
Vigilance	407.0 (48.7)	425.1 (29.3)

Table 6: Adjusted means and standard deviations of error scores for each participant group when covaried for age.

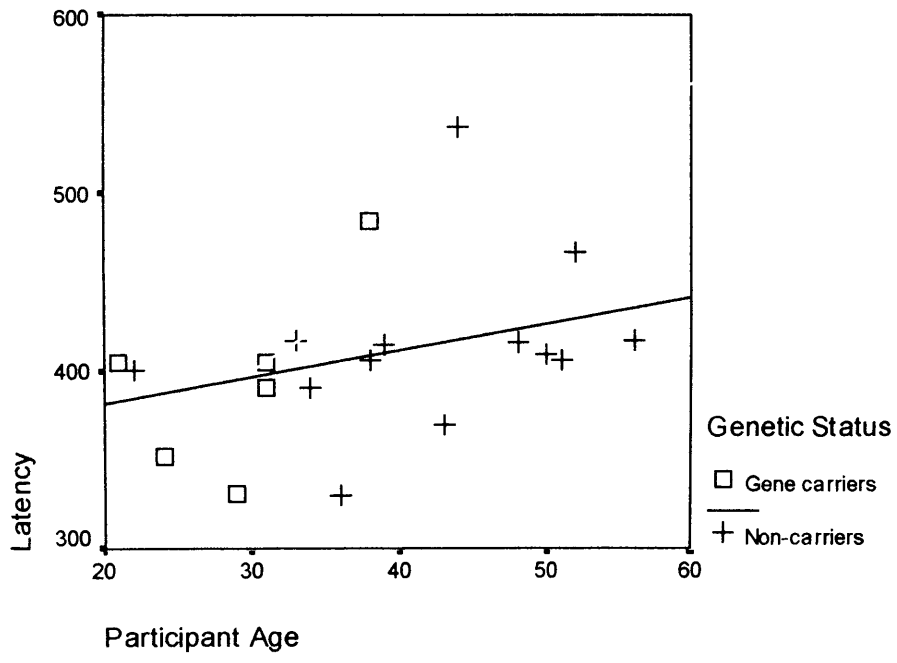
	Mean (Standard Error) errors	
Task	Gene carriers	Non-carriers
Alertness	--	--
Response flexibility	17.25 (4.15)	11.2 (2.5)
Response inhibition	9.4 (2.8)	3.75 (1.6)
Inter-modal integration	1.4 (0.7)	1.3 (0.45)
Divide	3.4 (2.25)	2.8 (1.3)
Vigilance	1.13 (0.39)	0.4 (0.25)

3.5 Hypothesis Four

The ability to inhibit unwanted responses was tested on the response inhibition task. The difference in mean response latency between gene carriers and non-carriers seen in Table 3 is small, and this is maintained when the means are adapted for covariation with age (Table 5).

Analysis of covariance did not show a significant effect of age on response latency [F(1) = 3.260, P = 0.088] or error rate [F(1) = 0.117, P = 0.736]. With age removed as a covariate, there was no significant difference between the gene positive and gene negative groups for latency [F(1) = 0.165, P = 0.690] or error rate [F(1) = 2.748, P = 0.115].

Graph 4: Scatterplot of latency and age for the response inhibition task



Graph 4 shows the relationship between age and latency on the response inhibition task for each group. There does not seem to be a strong relationship between these

variables. There is no obvious difference between the groups in terms of latency, which is consistent with the test result.

The hypothesis that gene carriers will have more difficulty inhibiting unwanted responses that non–carriers has not been upheld.

3.6 Hypothesis Five

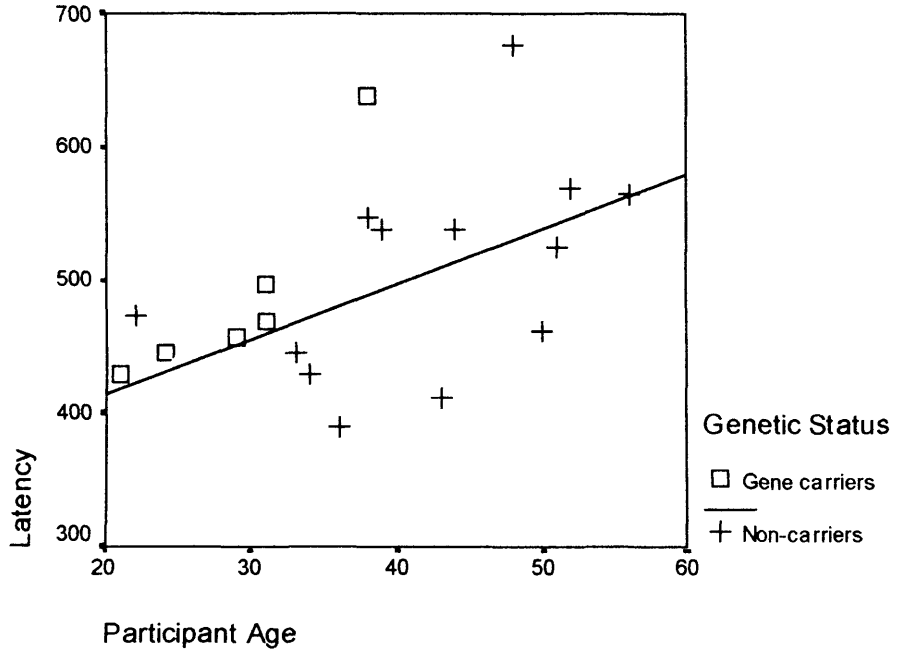
The test of divided attention required two tasks in separate modalities to be performed simultaneously. The differences in mean response latency between gene carriers and non-carriers (Table 3), and the differences in means adapted for covariation (Table 5) do not appear to be of a significant magnitude.

Analysis of covariance did not show a significant effect of age on response latency [$F(1) = 0.065$, $P = 0.802$] or error rate [$F(1) = 1.306$, $P = 0.268$]. With age removed as a covariate, there was no significant difference between the gene positive and gene negative groups for latency [$F(1) = 0.036$, $P = 0.851$] or error rate [$F(1) = 0.045$, $P = 0.834$].

Graph 5 shows the relationship between age and latency on the divided attention task for each group. Age does not seem to have a strong relationship to latency. There is no obvious difference between the groups in terms of latency. This is consistent with the test result.

This does not support the hypothesis that gene carriers will have poorer performance than non-carriers on a test of divided attention.

Graph 5: Scatterplot of latency and age for the divided attention task



3.7 Hypothesis Six

The vigilance task was used to assess the ability to maintain attention during the presentation of a high number of non-target stimuli, thus requiring internal maintenance of attention. Table 3 shows the mean response latencies for gene carriers and non-carriers, and Table 5 shows the means adapted for covariation with age. The differences between means do not seem large.

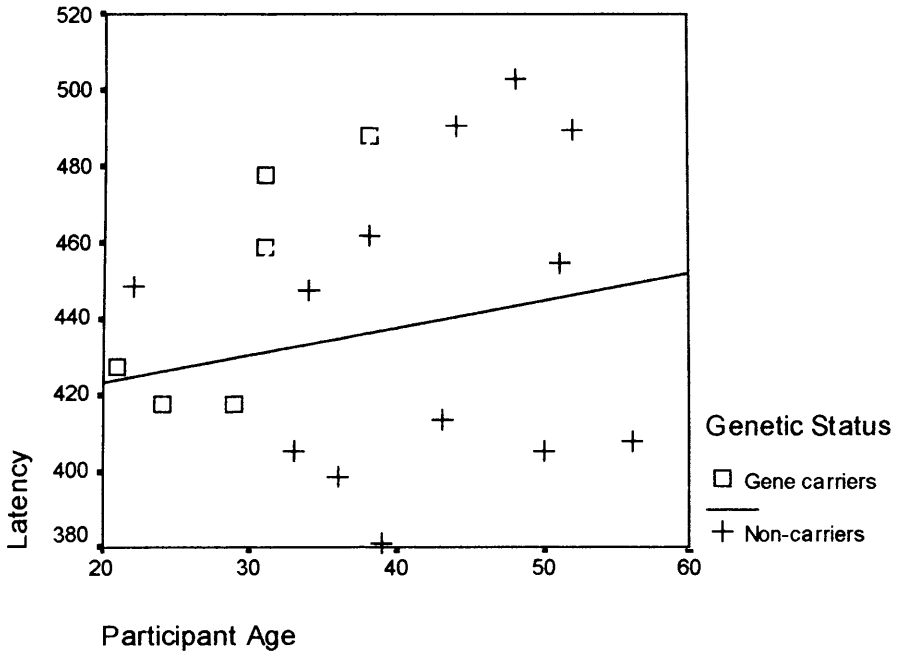
Analysis of covariance did not show a significant effect of age on response latency [F(1) = 2.576, P = 0.127] or error rate [F(1) = 0.417, P = 0.528]. With age removed as a covariate, there was no significant difference between the gene positive and gene negative groups for latency [F(1) = 0.087, P = 0.772] and error rate [F(1) = 2.086, P = 0.168].

Graph 6 shows the relationship between age and latency on the vigilance task for each group. There does not seem to be any relationship between these variables.

There is no obvious difference between the groups in terms of latency, which is consistent with the test result.

The hypothesis that gene carriers would have poorer performance on a test of vigilance than non-carriers has not been upheld.

Graph 6: Scatterplot of latency and age for the vigilance task

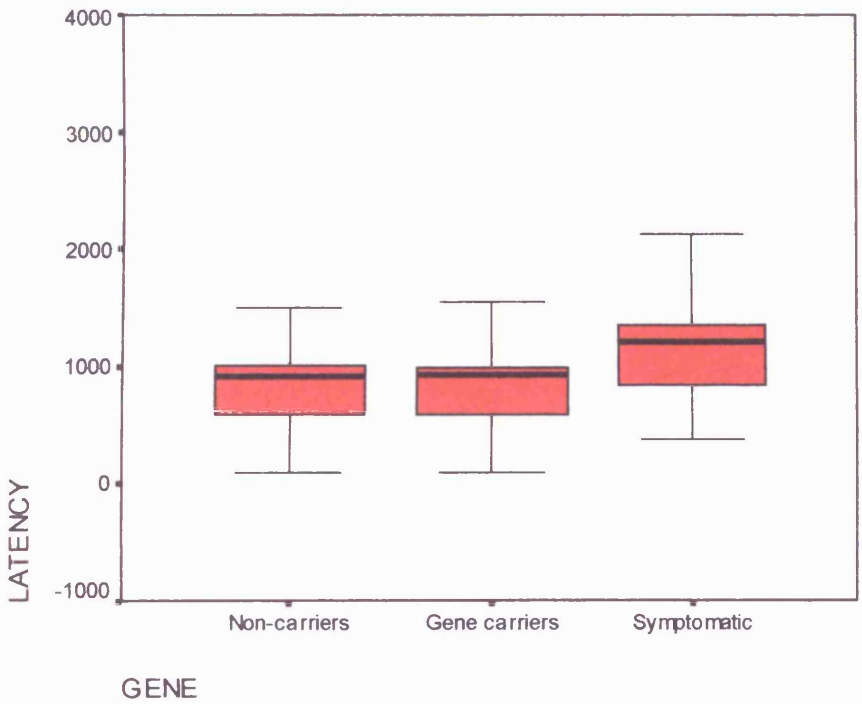


3.8 Symptomatic gene carriers

Since there were only two symptomatic gene carriers it is not reasonable to include their data in the statistical analyses. It does however seem useful to examine their performance on the test battery since it may indicate the nature of attentional problems in symptomatic HD patients, and indicate whether the tests used were sensitive to any changes. However, these results must be treated with caution since the symptomatic gene carriers were on the whole considerably older than other participants.

Graph 7 shows the range of response latency scores for gene carriers, non-carriers and symptomatic gene carriers (groups 1,2 and 3 respectively) on the alertness task. The range for the symptomatic participants is noticeably higher. This is reflected in the means and ranges given in Table 3. Both symptomatic gene carriers have higher mean, minimum and maximum response latencies.

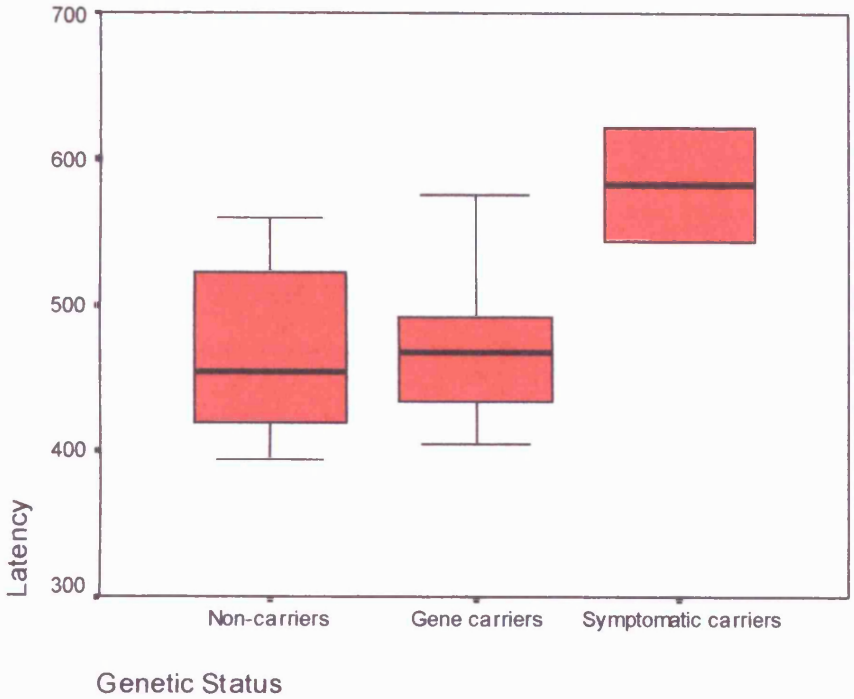
<u>Graph 7:</u> Boxplot of latency for each group on the alertness task



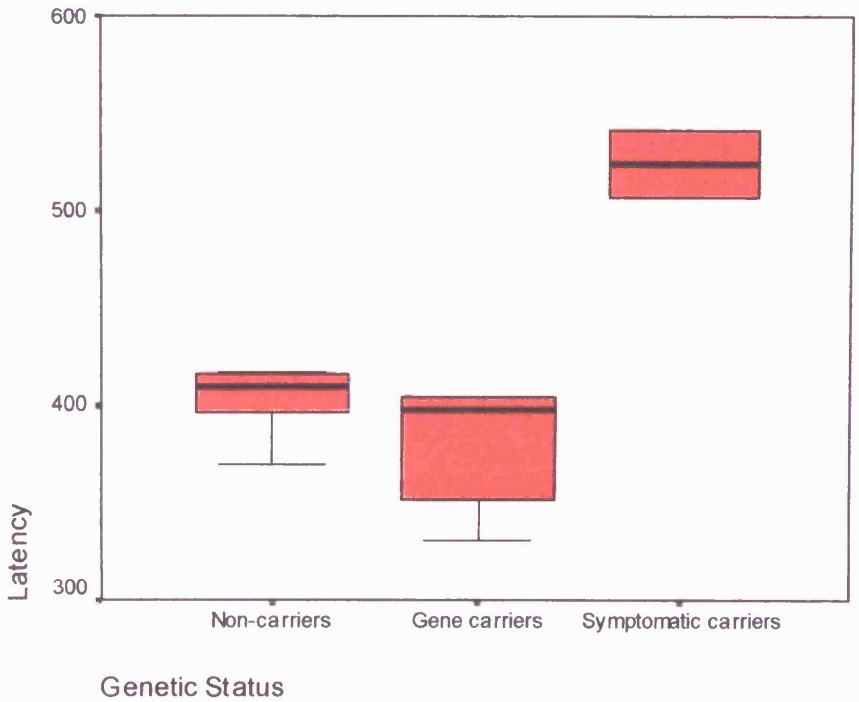
Graph 8 shows the same information for the response flexibility task. There is a trend in this data for longer response latencies by symptomatic gene carriers. This can also be seen in the means and ranges shown in Table 3.

Graph 9 illustrates the same relationship for the response inhibition task. Again it can be observed that symptomatic gene carriers have noticeably longer reponse latencies than other participants. This is also evident from the data shown in Table 3.

Graph 8: **Boxplot of latency for each group on the response flexibility task**



Graph 9: **Boxplot of latency for each group on the response inhibition task**



This pattern can also be seen in the results for inter-modal integration, divided attention and vigilance tasks (Table 3). Data is not available for both symptomatic participants on all tasks since there were occasions when symptomatic participants did not respond (indicated by 0) or desisted early in the task due to extreme difficulty. This was endorsed as it was potentially distressing for participants if they were pressured to continue.

Symptomatic gene carriers also exhibited considerably higher error scores on certain tasks (Table 4). On the response flexibility task both symptomatic gene carriers scored remarkably high numbers of errors, whilst on response inhibition, divided attention and vigilance tasks the number of errors is still noticeably higher than for other participants. Overall, symptomatic gene carriers exhibited considerably poorer performance on all tasks than either presymptomatic gene carriers or non-carriers.

4 Discussion

The study of presymptomatic cognitive changes in HD has gained new interest since the development of a reliable genetic indicator, but is still a relatively small area and has yet to provide conclusive results.

The present study utilised a test battery that specified one area of potential changes, i.e. attention, which had previously been found to be affected in symptomatic HD patients. This battery allowed the investigation of six hypotheses about the precise nature of deficits of attention. The study compared presymptomatic HD gene carriers with people at-risk who were confirmed not to carry the gene. The performance of these two groups was then compared in terms of response latency and error on six tasks, each of which was designed to test a sub-function of attention, and related to one of the hypotheses.

The findings of this study will be addressed in relation to each hypothesis and the data from symptomatic participants on the same tasks will be discussed. The implications of these findings will also be considered. A reflection on the strengths and limitations of the study will follow.

4.1 Explanation of the results

4.1.1 Hypothesis One

From the data given in Table 3 and Table 5 it can be seen that there does not appear to be any significant difference between presymptomatic gene carriers and non-carriers in externally cued alertness. The finding that there were no significant differences on externally cued alertness (even when results were covaried for age) is consistent with hypothesis one. This is an important finding because alertness is a requirement for the completion of other tasks, and is vital to everyday functioning.

Symptomatic gene carriers were notably slower on this task, but did not score more errors. Given the disparity in age and the small sample size, this result should be interpreted with caution. The difference observed may indicate that this test is sensitive to onset of HD or to the normal effects of ageing, or might be the result of differences between individuals. Normative data for this task is not available so it is not possible to make further comparisons, but HD patients have previously been found to be impaired on this task (Sprengelmeyer et al, 1995).

4.1.2 Hypothesis Two

Hypothesis two proposed that gene carriers would show impairments on a task requiring attentional set shifting. Gene carriers were found to be significantly slower than non-carriers on this task when the effect of age was taken into account. This result seems to support hypothesis two and implies that the presence of the gene for HD might well have a detrimental effect on this ability. Given the limitations of this study, this result should be treated cautiously. If impairments in attentional set shifting are present they might be expected to cause difficulties in everyday functioning since this is an important ability.

The performance of symptomatic gene carriers on this task was perceptibly slower and very clearly more prone to errors than that of other participants (Tables 3 and 4). Again the same cautions about interpretation of these results apply, however it might be argued that whilst older participants might be expected to be slower they would not necessarily score so many errors. If this assumption is accepted then this results goes some way to confirming the finding of other studies (e.g. Lawrence et al, 1998) that HD patients are impaired in their ability to shift attentional set.

4.1.3 Hypothesis Three

Hypothesis three proposed that the ability to integrate information from different sensory modalities would be impaired in presymptomatic gene carriers. Response

latencies for presymptomatic gene carriers were significantly slower than for non-carriers when the effect of age was taken into account. This finding supports the veracity of hypothesis three. It might be argued that impairments in this area could be related to attentional set shifting since there is an element of switching attention between two stimuli, but this is not necessarily proven. Problems with the ability to integrate information from different sensory modes might have a significant effect on an individual's functioning

Symptomatic gene carriers were unable to complete this task. Qualitative observation during testing would suggest that they found the task too difficult to complete since one participant desisted after the first 8-9 trials commenting that the task was "too hard". The second participant attempted the task but was unable to monitor both stimuli and consequently did not respond to any trials, commenting that the difficulty lay in monitoring two things at once.

4.1.4 Hypothesis Four

Hypothesis four related to the ability to inhibit unwanted responses and posited that presymptomatic gene carriers would have poorer performance than non-carriers in this respect. No significant differences were found, although the difference in latency scores approached significance. It would not be advisable to make any assumptions from this result.

Symptomatic gene carriers scored higher numbers of errors and longer response latencies as can be seen from Tables 3 and 4, and Graph 9. As before this should be interpreted with caution, but is consistent with the suggestion that HD patients make more errors on tasks requiring the inhibition of unwanted responses (Sprengelmeyer et al, 1995).

4.1.5 Hypothesis Five

Hypothesis five posited that presymptomatic gene carriers would produce worse performances on tasks requiring the simultaneous division of attention between two separate tasks in different sensory modes. The results obtained for this test are not significant even allowing for the effect of age. This hypothesis is not upheld.

Data was not produced by one of the symptomatic gene carriers on this task, who reported that it was too difficult. The second symptomatic participant produced more errors than other participants and had a longer mean response latency. The differences were not of a large magnitude and it seems unwise to draw any conclusions from this data.

4.1.6 Hypothesis Six

Hypothesis six propounded that presymptomatic gene carriers would perform significantly worse than non-carriers on a test requiring internally maintained vigilance. The analyses did not confirm this since no significant results were obtained.

The first of the symptomatic gene carriers had desisted on earlier tasks and did not attempt this task due to fatigue. The second of the symptomatic participants committed considerably more errors and had notably longer response latencies on this task, which is consistent with the findings of Sprengelmeyer et al (1995)

4.2 Implications of the study

This study does provide further evidence for the likelihood of cognitive impairment in HD, particularly in attentional set shifting and integration from separate sensory modes. It further confirmed that impairments are unlikely in alertness to externally cued stimuli. This is consistent with findings of previous studies (Sprengelmeyer et al, 1995; Lawrence et al, 1998) and with reports of the

difficulties that people experience later in the disease e.g. perseveration. Eventually these abilities might be examined as an early indicator of onset, although these results will need effective corroboration before this can be employed.

It can be suggested that this area might be of some importance since these skills are essential to many everyday abilities (Zimmermann et al, 1993). Reported difficulties in coping with previously unproblematic tasks (Starkstein et al, 1988) might be attributable to subtle deficits such as these. These abilities may also have implications for other impairments commonly seen in HD patients such as those involving planning, organising and sequencing.

Given that none of the gene carrier participants reported difficulties in everyday functioning, it might be proposed that effects at this stage are so subtle as to be unnoticeable to the individual. However impairments at this stage may indicate later progression, and the detection of changes has other useful implications. For instance, as mentioned earlier, interventions might begin at an earlier point in the disease. Hence, where prophylactic treatment is possible, gene carriers might be protected from some of the effects of the disease.

This study has possible implications for the techniques that might be used in future research. Like Sprengelmeyer et al (1995) and Lawrence et al (1998) this study employed a more specific and customised approach to testing rather than a standard clinical instrument. This seems, practically and intuitively, to be the best option for investigating pre-clinical and probably sub-clinical change. The lack of standardisation is, however, an obvious hindrance to clinical utility.

No evidence of presymptomatic impairment was found in relation to other attentional functions i.e. vigilance and divided attention. This implies that there may be no impairment in these abilities although caution should be exercised given the limitations detailed below. Some evidence, although not significant, was found for impairment in inhibition. This remains inconclusive.

It is seems unlikely that the identification of presymptomatic cognitive indicators of onset will ever be of use to people who have not been tested for the HD gene. Given that genetic testing is a reliable indicator, cognitive testing for early onset would seem to be of most use in identifying when intervention can begin.

4.3 Limitations of the study

The specific limitations of this study will be addressed in relation to specific areas.

4.3.1 Selection and sample size

Participants for this study were self-selecting from within the population of people at-risk in two respects. Firstly they were all people who had chosen to undergo testing for the HD gene. Secondly from within that group the participants were all volunteers. This undermines the ability of this study to generalise to other HD gene carriers. There is also the possibility that there may be another factor at work which compelled the participants to volunteer. For instance, gene carriers who felt that they had undergone some sort of change might be more likely to volunteer for such a study in the hope of either confirming or excluding this as a symptom of onset. No such bias was evident at the time of data collection but this does not exclude the possibility.

Additionally any generalisations would be weakened by the small sample size that was used (presymptomatic gene carriers N = 6). As in previously published work, there was difficulty in reaching and recruiting sufficient numbers of participants due to the relative rarity of HD. Even though two genetics departments assisted in contacting everyone at-risk who was not otherwise excluded and had been tested for HD in a specified period, the sample was still very small. Within the existing literature this is not uncommon and many authors have still made tentative generalisations.

The self-selection of participants has created further difficulties in terms the age of the gene carriers. The average age of this group is in the late twenties, which makes comparisons with the older non-carrier group problematic. Also the young age of these participants increases the gap until likely time of onset of the disease. Information about the number of CAG repeats for each individual is not stored by the genetics services hence time to onset could not be estimated. Since it is as yet unconfirmed whether the course of the disease is continuous or discontinuous, it is unclear if this group could be expected to have undergone the presymptomatic changes that are predicted in both this and previous research. One might argue that the existence of a significant effect in this young group serves to strengthen the argument for the existence of presymptomatic cognitive changes.

There is also the possibility of error that is not systematic but occurs by chance. The sample used in this study might by chance be less impaired or display a different pattern of impairment from other carriers. Given that there is some variation in the symptomatic presentation of the disease it seems likely that individuals will also vary in terms of any presymptomatic changes.

Other studies have had no strict criteria for identification of motor symptoms therefore group membership in terms of symptoms has been unreliable. Participants might have been excluded here who would not have been elsewhere. Thus the reliability of comparison of results across studies is not assured.

4.3.2 Measures and data collection

The development of tests is often problematic. As previously discussed existing tools for assessment are believed to be inadequate for this task. The tests used herein seem more suited and have been used previously for a similar purpose, but their reliability and validity have not been extensively tested. Re-testing of the same individuals might therefore produce different results, even without considering whether the ability being measured is stable over time excepting the effects of age or pathological involvement.

Questions might be asked about whether the tests used achieve the level of specificity desired. As discussed earlier (Section 1.10) attention is a multidimensional system of related but semi-independent processes. Thus the measurement of one sub-function may depend on the exercise of another. The organisation of attentional functions seems to be hierarchical since, for instance, attentional set-shifting includes the ability to direct and maintain attention and may be dependant on 'level of activation', all of which are involved in alertness and vigilance tasks. It has already been argued that other studies have an inherent weakness in their lack of consideration of underlying skills involved in the completion of standard tests.

Given that no impairments were found on tests of alertness and vigilance, but were found on attentional set shifting, one might argue that this indicates a more specific dysfunction.

A further issue that might contribute to an underestimate of differences between carriers and non-carriers is the level of difficulty of tests. As mentioned earlier some clinical tools suffer ceiling effects when used to measure subtle changes, and it might be the case that the methods used herein did not sufficiently tax the abilities being tested and were, therefore, not sensitive enough. It might be argued however that an assessment which is any more sensitive, by virtue of difficulty or any other factor, would be prone to so much natural variation between individuals that it would be unable to discriminate between groups. Changes within or between individuals that are particularly small will likely be indistinguishable from normal variations.

As noted in the introduction, previous studies have found that the difficulty of tests is not a sufficient explanation on its' own for the differences found between gene carriers and non-carriers. It seems reasonable to suppose that a pathological impairment will at some point be evident as a quantitative difference from the natural variation. This raises the question of, if changes do occur in

presymptomatic gene carriers, can they be measured? If they cannot be measured then this raises the possibility that they are of such a small magnitude that they are not worth investigating. One would argue that as indicators of later progression of the disease, and signs of onset, they are worthy of study.

A final consideration about the tests used is one of length. The various tests are not of equal length. Zimmermann et al (1993) and Sprengelmeyer et al (1995) did use tests of similar length to the ones used in this study. Longer tests may or may not have produced different results and test length seems in some ways to be a similar issue to test difficulty. The test used are intended to be long enough to provide workable and useful data but short enough that volunteer participants will complete them and not be too bored or distressed by the experience.

4.3.3 Analysis

Given the small size of the sample the meaningfulness and generalisation of any results must be treated carefully. Also the effect of this on the analysis must be considered. The groups were of different sizes and the data did not seem normally distributed, but the use of parametric tests was preferred. The data was scrutinised graphically to examine whether it appeared consistent with the results of the analysis. There was no evidence here to suggest that this data could not be treated as it was. The results should still, perhaps, be treated tentatively until such time as they can be reproduced reliably.

Two other possible sources of variance were mental health (i.e. anxiety/depression) and family membership. Neither of these factors were considered in the analysis. To exclude participants because of either of these issues would have reduced the sample to an unacceptable size, and neither occurred to such an extent that a covariate analysis seemed implicated.

4.3.4 Time and resource constraints

This study was conducted in a very short period of time, with very few resources and with an academic deadline to meet. These restrictions have had three main effects. Firstly the recruitment of participants has been more limited than would be ideal, given more time a larger group could have been recruited both through the services already involved and perhaps by widening the geographical area. This would facilitate better age matching. Secondly, a pilot study could have been conducted, which might have led to a more focussed approach e.g. in-depth examination of attentional set shifting. Thirdly, although the comparison of people at-risk with the wider population may not be ideal, it would be useful to collect standardisation data for the test battery, in order that a sense of the reliability of the tests could be obtained.

4.3.5 General difficulties in researching this area

The study of presymptomatic impairment in HD raises concerns other than those already mentioned. One important concern, ethically, is that people who are going to develop Huntington's disease may view the testing procedure as a form of diagnosis, and mistakenly attach significance to their performance. This can also lead to a degree of anxiety about testing. Although every effort was made to put participants at ease and to inform them that testing would not involve diagnosis some anxiety was unavoidable. Methodologically this might also have been of some importance since high anxiety could effect performance.

Secondly as HD is genetic and relatively rare, participants recruited in any given area are often from the same pedigree. As mentioned earlier the use of participants from a small number of families, in HD research, has been criticised since it may introduce other genetic factors into the study. It is possible that using genetically related participants will reduce variation in some respects but may also decrease the generalisability of the study. The chances of this are increased by the use of

small samples containing many participants with a common inheritance. To some extent this study did suffer from this problem.

4.4 Strengths of the study

The results of this study will hopefully contribute to the knowledge base in this relatively under researched but rapidly expanding area. It might be predicted that, in the future as in the past, technological innovations will play a crucial role in developing this field, for example in improved scanning and imaging techniques or development of knowledge about the mode of action of the gene.

This study has offered a new approach to investigating the issue of presymptomatic cognitive changes in carriers of the HD gene. Firstly the tests used have never been used with this population before and provide a more detailed picture of the possible nature of deficits in attention. Secondly this study offers innovation in terms of the approach to testing in a more specific and detailed manner rather than using broad batteries of tests. Whilst this does not imply that broad avenues of investigation should be abandoned it does suggest that a more detailed approach to testing might be useful especially if based on the evidence provided by other studies.

The validity of the methods used here seems to have been demonstrated to some extent by the noticeably poorer performance of symptomatic HD patients both in this study and previously (Sprengelmeyer et al, 1995). This seems to suggest that the tests used herein do tap into cognitive changes that occur around onset of the disease.

The argument presented in this thesis has attempted to make specific links between the fields of neuropathology and functional neuroanatomy in relating the pattern of atrophy to predicted dysfunction. It seems from the literature that this is not widely explored, perhaps for good reason given earlier comments about the nature

of brain-behaviour relationship, but again this has been an attempt to view the problem from a different angle.

This study is also one of only a few to use a UK based sample (eg Blackmore et al, 1995; Lawrence et al, 1998).

4.5 Future development of research ideas

Research in this field is likely to develop in the future, and the current study suggests some possibilities.

4.5.1 Primary research questions

A range of possible lines of enquiry have not been addressed herein. For instance effects on verbal fluency, and on eye movements have been found in this group. It is worth noting that the predicted problems with eye movement, i.e. saccadic suppression, would not be expected to have an effect on the performance of participants in this study. Future research might explore more fully the nature of all of these deficits and any possible relationship between them.

It could also be productive to consider other areas in which impairments might occur. These areas might be identified by consideration of the pathology of HD or by exploratory testing. The selection of tests for exploratory testing may continue to be problematic if the arguments presented about lack of specificity and sensitivity are correct. This in itself is worthy of further consideration.

4.5.2 Replication of results

Before any firm conclusions can be drawn about difficulties in attention the results obtained in this study and by Lawrence et al (1998) need to be replicated. The methods employed would perhaps be most useful if they are specific and replicate those used by either of these studies. One would argue that Zimmermann et al's

(1993) ideas are useful for their simplicity and relative clarity, where some of the tests used by Lawrence et al (1998) seem more complicated.

Both replication studies and primary research questions would be strengthened considerably by control of other sources of variation and increased ability to generalise. Hence it would be useful to have larger numbers of participants, of similar ages, and with more than a few pedigrees. Also if information about the number of CAG repeats can be collected, then estimated time to onset can be calculated, and more information could be obtained about the course of cognitive deterioration and possible symptom sequence.

This might be crucial, although reservations about the likelihood of homogeneity across participants remain. Alexander and Crutcher (1990) argue that even within the different circuits in the basal ganglia the functional architecture is essentially parallel. This seems to imply that small differences in neuropathology might be expected to produce different results, and hence individuals may vary widely. This would necessitate an understanding of the constellation of possible effects of the gene before this sort of research could be used clinically.

It is worth noting that, methodologically, the best test of the reliability and validity of this type of research would be the ability to discriminate between gene carriers and non-carriers. Unfortunately the time and resources were not available on this occasion but it would be desirable to conduct neuropsychological testing before people at-risk had been tested for the gene. This would help to eliminate any experimenter bias and the effect of knowledge about test results on participants.

4.5.3 Therapeutic or clinical

The development of this, and other similar research, into clinical practice is liable to take some time. Before such ideas could be used to inform the timing or nature of intervention there will have to be extensive confirmation and replication of the nature of what is currently considered to be presymptomatic cognitive change.

Future studies will also have to consider the rights of the participant to information that might affect their care. If researchers consistently find effects in presymptomatic gene carriers then it could be argued that gene carriers have a right to that information at some point. Careful consideration will be needed to determine how much evidence is needed and how much information can be given to gene carriers and their families.

5 Conclusions

The present study has supported the argument that carriers of the HD gene who are considered to be presymptomatic may experience specific cognitive changes in attentional set-shifting ability and integration of information from different sensory modalities.

Additionally this study has found that a focused approach to testing cognitive functions in this population can yield significant and interesting results. Specifically this study suggests that the tests of attention used here may be useful for further exploration.

Future research may follow this more focused approach, and confirmation and replication of results is needed. A broad exploration of this area is not however ruled out, given the potential variation between individuals. It would be valuable if future studies could avoid the problems that this study has suffered, for instance in terms of sample size, and reproduce the same results.

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7 APPENDIX 1 – PARTICIPANT CONSENT FORM

Clinical Psychology Department, Rehabiltation Services Directorate
Sandringham Suite, Windsor House, Troon Way Business Centre
Humberstone Lane, Leicester LE4 9HA

Participant Consent Form

"An investigation into the effects of the Huntington's disease gene on specific cognitive functions."

Principal Investigator: Steve Margison BA(Hons) Clinical Psychologist in Training

I hereby consent to take part in the above named study.

Signature
(participant).....Date.....

Name (block capitals).....

I have explained the above study to the participant and he/she has indicated his/her willingness to take part.

Signature
(researcher).....Date.....

Name (block capitals) .....

8 APPENDIX 2 – PARTICIPANT INVITE AND INFORMATION SHEET

Clinical Psychology Department
Rehabiltation Services Directorate
Sandringham Suite
Windsor House
Troon Way Business Centre
Humberstone Lane
Leicester LE4 9HA

Dear Sir/Madam

"An investigation into the effects of the Huntington's disease gene on specific cognitive functions."

You are invited to volunteer to take part in a research project which will study whether people who carry the gene for Huntington's Disease experience any specific effects on cognitive functions i.e. thinking and processing information. Volunteers will be asked to take part in a selection of tests which will take approximately two hours, and which can be performed at volunteer's homes. These tests are not intrusive and will not require any samples (e.g. blood, urine) to be taken. The tests are not a prediction of onset of the disease.

All information, including the identity of participants, will be treated with the utmost confidentiality. No information will be passed to other agencies or individuals, and any data used in publications will be anonymous. This letter has been sent to you via the Clinical Genetics Service who performed your screening test, they have not passed any information to us.

We urgently require volunteers who have either a positive or a negative result of the test for the Huntington's Disease gene.

Further details can be found on the enclosed information sheet.

If you wish to volunteer, or would like more information please contact me at 0116-225-6845 or use the tear off slip provided on the information sheet.

Yours faithfully,

Steve Margison

Participant Information Leaflet

"An investigation into the effects of the Huntington's disease gene on specific cognitive functions."

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. If you have concerns about Huntington's disease you may contact Dr Heather Dipple, Consultant, Huntington's Disease Service, on 01509-674-582.

Consumers for Ethics in Research (CERES) publish a leaflet entitled "Medical Research and You". This leaflet gives more information about medical research and looks at some questions you may want to ask. A copy may be obtained from CERES, PO Box 1365, London, N16 0BW.

Thank you for reading this.

1. What is the purpose of the study ?

The purpose of this study is to investigate the effects of the Huntington's Disease gene on certain specific abilities. The study hopes to identify these effects and ways of measuring them accurately.

2. Why have I been chosen?

This invitation is being sent to people who have been tested, by the clinical genetics service, for the Huntington's Disease gene. You have been chosen because you have been tested for the Huntington's gene. Volunteers are needed with both positive and negative results of this test. Even if you have discovered that you do not have the gene, but come from a family at risk of Huntington's, we would be interested to hear from you.

3. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of future treatment you receive.

4. What will happen to me if I take part and what will I have to do ?

The tests used in this study will take approximately 2 hours to complete. You will be asked to do a number of tasks which are:

Read a list of words.
Some paper and pencil tasks that ask you to find certain symbols on a printed page.
A computer based task that involves responding to images on the screen by pushing a button.
Look at and answer questions about a series of photographs.

You will also be asked to submit to a brief and simple neurological test, and to provide some basic background information e.g. age, education. These tests can all be done in your own home and you will only have to do them once.

5. What are the possible disadvantages and risks of taking part?

This study does not involve any procedure which will place participants at risk. If during the study we discover anything that indicates that a participant is becoming ill they will be informed of this and advised to contact their GP or the Huntington's Disease Service.

Medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

6. What are the possible benefits of this study?

As this is an early study in this area you will not gain any personal benefit from taking part. The information we get from this study may help us in the future to provide people with Huntington's Disease with better treatment.

There will be no payment for taking part. The study is expected to take one year to complete.

7. Will information obtained in the study be confidential ?

All information gathered during this study will be confidential. No personal infomation or identifying details will be passed to third parties. The researcher will not have access to information about you other than that which you give us, for example, how to contact you. The genetic status of individuals will not be revealed. All data will be stored securely and in accordance with the Data Protection Act of 1984.

Participants who feel that being seen at home would be difficult may be seen at another location.

8. What will happen to the data and results obtained in the study?

Data collected will be made anonymous and stored by the researcher for statistical analysis. The results of the study will be published in an academic journal within

18 months of the end of the study. Any information used in publications will be anonymous, results will not be fed back to individuals.

It is hoped that this study will help us to understand what, if any, effects the Huntington's gene has on certain specific abilities.

9. Indemnity

This study is indemnified by Leicestershire and Rutland Healthcare NHS Trust. If you have any complaints you should contact them at:

Leicestershire and Rutland Healthcare NHS Trust
George Hine House
Gipsy Lane
Leicester
LE5 0TD
tel:- 0116-225-6000

10. What should I do if I want to volunteer?

If you wish to volunteer please complete the tear off slip and return it in the reply paid envelope provided. You will be contacted by us within one week of receiving your details.

11. Who is organising and funding this research?

Principle Investigator: Steve Margison BA(Hons) Clinical Psychologist in Training

This study is being conducted in collaboration with and is funded, for costs only, by Leicester University.

12. Contact for further information.

You can contact Steve Margison at:
Rehabilitation Psychology, Sandringham
Suite, Windsor Building, Troon Way Business Park,
Humberstone Lane, Leicester, LE5.
Telephone 0116-225- 6825.

Thank you for reading this information sheet and for taking part in this study.

9 APPENDIX 3 – FAMILIAL RELATIONSHIPS BETWEEN PARTICIPANTS

Some participants were members of the same family. Their relationships were as follows:

Relationships	Gene
sister : sister	no : no
father : daughter	no : no
mother : son 1 : son 2	yes : no : yes
brother : brother	no : no
sister: sister	yes : no
sister : sister	yes : yes
mother : son	yes : no

10 APPENDIX 4 – INSTRUCTIONS GIVEN TO PARTICIPANTS FOR COMPLETION OF TESTS OF ATTENTION

Participants were asked after each set of instructions if they understood what was required.

Alertness

"In this test you will see a cross in the middle of the screen. Every time you see the cross press the button as quickly as you can. Sometimes you will hear a tone just before the cross appears. The gap between the tone and the cross appearing is not always the same."

Response Flexibility

"This test is split into three parts, I will tell you about each one separately. For the first part of the test you will see a letter X and a number 7 appear and disappear on the screen at the same time but on opposite sides. Sometimes during the test they will change sides. This happens in a random order. Your task is to push the button that corresponds to the side that you see the letter X, either left or right (indicate buttons to be used, left and right)".

After this is finished.

"In the second part of the test you will see the same things on the screen, but this time your task is to push the button that is on the same side as the number 7."

After this is finished.

"In the last part of this test you will see the same things on the screen again. This time your task is to alternate between the letter and the number. Begin by pushing the button that is on the same side as the letter. Then the next time you see the number and letter push the button that is on the same side as the number. Keep changing back and forth between the two for the whole test. If you lose track of where you are then start again with the next letter that you see, and begin again as you did before."

Response Inhibition

"In this test you will see a symbol that looks like a letter r. Whenever you see this push the button (indicate which button to push). Occasionally you will see the same symbol but it will be backwards, facing the other way. When you see this don't push the button. There are not as many of the opposite facing symbols so you will need to watch carefully for them".

Inter-modal Integration

"In this test you will see something on the screen and hear something and have to match them. On the screen will be an arrow that will point up or down, just after this you will hear a high or low pitched tone. If a high tone and an up arrow appear together then push the button (indicate which button). If a low tone and a down arrow appear together push the same button. If any other combination appears don't do anything. Before you start you will hear some high a low pitched tone so that you know what to expect."

Before the presentation of the main block of trials participants were presented with a sample of high and low tones each of which was accompanied by the relevant label, "High tone" or "Low tone", on the screen.

Divided Attention

"In this test you will be asked to do two things at the same time. You will see two letters appear next to each other in the middle of the screen, these will a combination of X's and Y's. If you see two of the same letter, that's XX or YY, push this button (indicate which button). There also will be a combination of high and low pitched tones, which will sound in pairs just after the letters appear on the screen. If you hear two the same, that's high/high or low/low, then push this button (indicate which button)."

Vigilance

"This is the last task. In this test you will see X's appear on the screen, sometimes there will be one and sometimes two. They will appear to either side of the middle, so that when there are two there will be one on each side. When you see two X's push the button as quickly as you can. There will be a lot of times when you don't have to do anything, so the task is to keep paying attention even if you are not doing anything."

11 APPENDIX 5 – GUIDE TO PROCEDURE

Complete Consent Form

Assign Participant Number

Interview topics
Age and date of birth
Age leaving school
Occupation
Handedness
Alcohol consumption
Medication and drug use
Medical history: illness or injury esp. neurological
Noticed any difficulty in coping with things (more than usual)
Sight
Hearing
Genetic Status
Mental Health

Note ethnic origin

UHDRS – motor scale
NART
HADS

Order of Tests of Attention
Alertness
Inhibition
Flexibility
Inter-modal
Divided
Vigilance