

THE COGNITIVE AND PERSONALITY PROFILES OF INDIVIDUALS WHO
REQUEST PREDICTIVE TESTING FOR HUNTINGTON'S DISEASE

Marilyn Doreen Lucas

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DECLARATION

I, Marilyn Lucas declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Marilyn Lucas

18th day of December 1998

To my family

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS THESIS

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ABSTRACT

Huntington's disease (HD), first described in 1872, is a progressive, debilitating, and ultimately fatal, neuropsychiatric genetic disorder. The discovery of a polymorphic DNA marker in 1983 closely localised HD to the short arm of chromosome 4, and the breakthrough finding of the specific gene responsible in 1993, mapped within a small segment of 4p16.3, led to the establishment of predictive testing programmes from the mid 1980's. Several psychological investigations arose from these programmes including whether or not cognitive impairment was present presymptomatically in those at risk for HD, and whether those who requested testing were a self selected group. To date, the results of the neuropsychological studies have been conflicting and inconclusive. Methodological limitations and the stressfulness of predictive testing have probably contributed to the differing findings. The present study addressed the methodological flaws of previous studies and specifically controlled for the psychological experience of being at risk for a life threatening disease. To this end, 26 individuals at risk, but presymptomatic, for HD were recruited from the Johannesburg Predictive Testing Programme. Subjects were administered a battery of psychological tests prior to molecular analysis. A carefully chosen control group, matched for age, sex, and education, and a group of individuals experiencing a life threatening illness (without CNS involvement) were administered the same battery of psychological tests. Molecular analysis confirmed 11 of the at risk were positive for the gene (HD+ group), and 15 negative (HD- group). Four way analysis of variance was conducted using the Bonferroni comparison of variances to detect group differences between the groups. The results indicated that stress negatively impacted upon the test performance of the HD- and stress group but not the HD+ group. The HD+ group showed mild impairment for declarative memory function. It was concluded that cognitive impairment was present prior to a clinical diagnosis of HD. A further outcome of the present study indicated that those who request predictive testing are self selected with regard to personality style and their goals in life. These findings have far reaching consequences for current and future predictive testing programmes in general.

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INTRODUCTION

Huntington's disease (HD), first described over 100 years ago (Huntington, 1872), is a progressive neuropsychiatric disorder conspicuous for its presentation of chorea, personality and behavioural change, and generalised intellectual deterioration (Brandt, 1991; Bruyn, 1968). The disorder has a pattern of Mendelian autosomal gene dominance with full penetrance. With a prevalence rate of approximately 1 in 10,000, the average age of onset is in the late 30's and early 40's for those positive for the gene. Neuropathological findings point to an early involvement of the striatal structures, particularly the putamen and caudate nuclei, with extension to cortical structures, especially the frontal, temporal and parietal lobes, in the later stages of the disease (Hayden, 1981).

Chapter one of this thesis will give an overview of the epidemiological, neuropathological and clinical presentation of the disease. Emphasis will be given to the cognitive impairment associated with HD as this forms the focus of the present study. Cognitive impairment is

usually associated with a frontal lobe-like dysfunction and has been correlated with structural and functional dysfunction of the subcortical structures. This topic will also be discussed in this first chapter.

HD is a disease with devastating consequences, causing distress and misery to sufferers and their families alike (Tyler, 1996). Searching for a means by which the disorder could be predicted either before onset of symptoms or at the earliest possible stage has been a major goal of much of HD research (Lanto et al., 1990; Slater & Roth, 1969). Underlying this search was the assumption that the gene phenotype would be expressed before the onset of clear signs and symptoms (Hayden, 1981). This concept is known as the continuity hypothesis and implies that signs of a disorder are present before the onset of the disorder, perhaps even from birth.

The emphasis of Chapter two will initially centre on early clinical efforts to identify a predictor of HD in those at risk prior to symptom onset. The early attempts to identify specific first signs of cognitive impairment will be discussed. Without knowing which gene was involved in this disorder, however, this search proved generally

unsuccessful (Paulson, 1979). After the discovery of a marker for HD, and then the gene, located at 4p16.3 in the IT15 transcript, researchers continued to search for the initial indicators of HD, again including a search for the earliest cognitive changes.

Surprisingly, clarification of the initial symptoms of HD was not readily forthcoming in spite of knowledge of the responsible gene. Instead the results of such search were confusing and conflicting. Chapter two continues with a detailed discussion of this research and suggested reasons for its failure to identify the onset of cognitive impairment in HD are given. The chapter concludes with the working hypotheses of the present study which encapsulate the main consideration of this thesis: that the disease process in HD is discontinuous, and specifically, that neuropsychological impairment is not present in those at risk for HD prior to symptom onset.

It is suggested that the inability to resolve this issue to date is, in part at least, due to the methodological limitations of previous studies and non-neurological factors influencing test performance. The present study expands upon the methodological limitations of previous

studies. In addition, non-neurological factors in predictive testing that could influence cognitive performance such as the stressfulness of being at risk for a life threatening disease are controlled for.

In Chapter three the methodology of the present study is given. Four groups of subjects were used: those found positive for HD after molecular analysis (the HD+ group), those found negative for HD after molecular analysis (the HD- group), normal volunteers (control group), and a group of individuals also at risk for a life threatening disease (the stress group). The psychological test results of four groups were compared by means of one way analysis of variance.

The results of the statistical analyses are presented in Chapter four. Several differences were identified between all four groups on the psychological tests administered. Chapter five presents a discussion of the results within the framework of the information given in Chapters one and two. The results indicated that not all the postulated null hypotheses in the present study could be upheld. The implications of this are discussed and recommendations for further study are given. Concluding remarks are presented

in Chapter 6, including a warning against a recent suggestion for the abandonment of predictive testing programmes for genetic disorders.

Chapter One

1.0 HUNTINGTON'S DISEASE: THE DISORDER

Huntington's disease (HD) is a progressive, debilitating, and ultimately fatal, neuropsychiatric disorder, which has been part of neurological nosology for more than 100 years. Marked by chorea, personality and behavioural change, and generalised intellectual deterioration (Adams, Victor & Ropper, 1997; Brandt, 1991; Bruyn, 1968; Barbeau, Chase & Paulson, 1973), it was first accurately described by George Huntington in 1872, a country medical practitioner born in East Hampton, New York (DeJong, 1973). Calling the disease 'Hereditary Chorea', he published a careful and detailed account of the disorder based on the patient records of his father and grandfather in their practice in Long Island (Huntington, 1872)¹.

The disorder has a pattern of Mendelian autosomal gene dominance with full penetrance (Adams et al., 1997). As such every child of an affected parent has a 50% risk of

¹See Hayden, 1981, and selected chapters from *Advances in Neurology* (Barbeau, Chase & Paulson, 1973), for a more detailed account of the history of HD.

inheriting the disorder regardless of the sex of the child². Further, an affected parent of either sex can transmit the gene. This premise may, however, only hold for adult onset; in the child onset variant of HD the parent is four times more likely to be the father (Myrianthopoulos, 1973 but cf. Wallace, 1979). There is also a suggestion that anticipation (the tendency for a disease to manifest at an earlier age with each generation) occurs more through male transmission of the disorder (Wallace, 1979).

1.1 The epidemiology of Huntington's disease

The disease probably originated in North Western Europe, which presumably accounts for its greater prevalence in races with a strong European influence and its lessor appearance in Asian (Nakashima et al., 1996; Narabayashi, 1973), African, and American Black peoples (Hayden, 1981). The advent of HD in South Africa (SA) can be traced back to one of the first free burghers of the Cape of Good Hope,

² From recent findings it seems that only approximately 40% of those at-risk actually possess the defective gene (Gusella, MacDonald, Ambrose & Duyao, 1993). The reason for this is unclear.

who arrived at the Cape in 1658 from Holland aboard the Dordrecht (Hayden, Hopkins, Macrae & Beighton, 1980).

The reporting of prevalence figures for HD has varied with time. Myrianthopoulos, in 1973, documented an estimated frequency of 4 to 5 affected individuals per population million. Hayden (1981) recorded the prevalence of HD internationally as 30 to 70 per million and Gusella et al. (1983) reported similar figures of 5-10 in 100,000. More recent epidemiological studies have estimated the prevalence to be 1 in 10,000 in those of European origin (Harper, 1996a). The latest figures show increased prevalence but this may only be reflecting greater awareness of the disorder in more recent years or more efficient techniques in data collection.

In SA the prevalence is slightly lower than European figures for those of caucasian or mixed ancestry (approximately 22 per million or 1 in 45,000; Hayden, MacGregor & Beighton, 1980), and it is considered extremely rare amongst the African Black population (Glass & Saffer, 1979; Scrimgeour, 1982). A prevalence rate of approximately 0.1 per million in the South African Black population has been cited by Hayden, MacGregor et al.

(1980). This figure probably underestimates the occurrence of HD in Black populations as more cases continue to be reported in Africa (Samuels & Gelfand, 1978; Scrimgeour, 1982; Scrimgeour & Pfumojena, 1992; Scrimgeour & Simpson, 1992).

Age of onset is difficult to pinpoint because of the insidiousness of the disorder, but typically it is in the fourth or fifth decades of life (Adams et al., 1997; Brandt, 1991; Harper, 1996b; The Huntington's Disease Collaborative Research Group, 1993). However, onset in childhood can occur (Farrer & Conneally, 1987), and incidence of onset has been reported as early as the first year of life (Pleydell, 1954) to as late as the eighth decade of life (Lyon, 1962). Onset in childhood probably accounts for 1 to 5% of cases (Goodman, Hall, Terango, Perrine & Roberts, 1966). The course of the disease is, on average, between 10-20 years (Hayden, 1981; The Huntington's Disease Collaborative Research Group, 1993), with little clinical difference between the sexes (Harper, 1996b). Its progression is relentless until death ensues (Adams et al., 1997).

In SA, age of onset appears to be younger than in European settings (Hayden, 1981), with the disease commencing during the third decade of life. Climate may be a contributing factor to this anomaly. It has been reported that the first signs of HD appear at an earlier age in several hot climates including SA, Australia and parts of North America (Brackenridge, 1974). Increased susceptibility to infection in hot climates has been suggested to explain this phenomenon (Brackenridge, 1974). In spite of an earlier age of onset, the duration of the disease appears slightly longer in SA than in European countries and consequently age of death in SA is similar to that seen internationally (Hayden, 1981).

Environmental factors not only affect time of disease onset but appear to play a role in disease presentation. Oepen (1973), in a single case study, recorded one pair of monozygotic twin sisters, who both developed HD at an early age but differed in clinical symptoms both in terms of neurological presentation and psychiatric profile. He suggested these differences could be due to the influence of environmental factors perhaps dating from early embryonic life. Nevertheless, the impact of environmental

3

factors upon the disease are thought to play only a minimal role in the disease phenotype (Harper, 1996b).

The severity and initial presentation of symptoms may be influenced by age of onset. Juvenile HD often manifests with more severe symptoms and a more rapid course of deterioration (The Huntington's Disease Collaborative Research Group, 1993; Young, Shoulson *et al.*, 1986). In general, the disease is usually more severe when onset is before 40 years of age and when emotional disturbance precedes chorea and intellectual loss (Chandler, Reed & DeJong 1960). Late onset, defined as development of symptoms after the age of 60 years, presents with relatively mild disabling symptoms of predominantly motor disturbance (Britton, Uitti, Ahlskog, Robinson, Kremer & Hayden, 1995; James, Houlihan, Snell, Cheadle & Harper, 1994).

1.2 The neuropathology of Huntington's disease

The pathogenesis of HD is presently unknown, but a distinctive pattern of neuropathology in HD has been recognised since the early 20th century (Alzheimer, 1911 in Forno & Jose, 1973; Jelgersma, 1908 in Harper, 1996b).

Invariably there is a selective premature loss of neurones and gliosis in the caudate nucleus and putamen and, to a lesser extent, the claustrum and globus pallidus (Fahn, Mishkin & Hoffman, 1973; Hayden, 1981; The Huntington's Disease Collaborative Research Group, 1993; Klintworth, 1973; Mann, Oliver & Snowden, 1993; Starkstein et al., 1988). There is evidence to suggest that the putamen is the earliest structure to be involved (Harris et al., 1992, but cf. Young, Penney, et al., 1986). Changes in the caudate typically progress ventrally and laterally from the dorsal medial areas (Vonsattel, Meyers, Stevens, Ferrante, Bird & Richardson, 1985). Brain stem structures have also been implicated, especially in Black patients (Zweig, Kovén, Hedreen, Maestri, Kazazian & Folstein, 1989). Age of disease onset may be related to rate of basal ganglia atrophy (Aylward et al., 1997).

The characteristic pattern of early pathology is of fibrillary astrocytosis and neuronal loss (Hedreen & Folstein, 1995, which commences in the dorsal aspect of the putamen and medial paraventricular portions of the caudate nucleus (Adams et al, 1997). It is currently believed that oxidative stress may be causal or at least contributory in neurodegenerative disorders, including HD, resulting from

excessive activation of glutamate-gated ion channels (Peyser et al., 1995). Gamma-aminobutyric acid neurones that innervate the external globus pallidus and substantia nigra pars reticulata are lost initially. Loss to the internal globus pallidus only occurs late in the disorder (Penney & Young, 1986). Gross neuropathological findings in advanced HD reveal cerebral atrophy predominantly in the anterior cerebral areas (Mann et al., 1993), and particularly the frontal lobe areas (Klintworth, 1973; Vonsattel et al., 1985). More recently, significant loss of neurones in the posterior cortical regions, and the angular gyrus in particular, has been reported (Macdonald, Halliday, Trent, McCusker, 1997).

Neuroradiological imaging techniques have supported the clinical morphological findings. An early computed axial tomography (CT) study demonstrated atrophy of the basal nuclei and cerebral cortex (Neophytides, Di Chiro, Barron & Chase, 1979). CT imaging at the onset of neurological signs has revealed atrophy of the caudate nucleus, putamen & globus pallidus (Bamford, Caine, Kido, Plassche & Shoulson, 1989; Lenti & Bianchini, 1993; Sharma, Savy, Britton, Taylor, Howick & Patton, 1996) as well as the frontal, temporal, and parietal cortical areas with more

white matter than grey matter being lost (Aylward et al., 1998; Barbosa, Haddad, Bacheschi & Scaff, 1996). Atrophy of the caudate has even been detected on CT prior to symptom onset (Cala, Black, Collins, Ellison & Zubrick, 1990).

Magnetic Resonance Imaging (MRI) techniques reveal greatest reductions in striatal structures (Brandt, Bylsma, Aylward, Rothlind & Gow, 1995; Starkstein, Brandt, Bylsma, Peyser, Folstein & Folstein, 1992) with detectable abnormalities in the orbitofrontal and inferior mesial temporal lobe structures as the disease progresses (Aylward et al., 1998; Jernigan, Salmon, Butters & Hesselink, 1991).

Disturbances in the metabolism of several neurotransmitters have been postulated but not clearly understood (Adams et al., 1997; Klawans, Goetz & Perlik, 1980). The movement disorder has been attributed to heightened sensitivity of dopamine receptors in the striatum (Klawans, Paulson & Barbeau, 1970; Weeks, Piccini, Harding & Brooks, 1996). Measurement of the striatal binding of D_1 and D_2 dopamine receptors using positron emission tomography (PET) has shown that early symptomatic HD subjects have reduced dopamine receptor binding. A negative correlation between

dopamine D₂ receptor binding and duration of symptoms has been reported (Pogarell, Tatsch, Ott, Schwarz & Oertel, 1996). In those presymptomatic but genetically loaded for HD, a variable pattern is shown: not all those at risk show reduced binding.

Lower metabolism in the caudate and putamen than matched controls has been detected in HD patients using positron emission tomography (PET) (Berent et al., 1988; Mayberg, Starkstein, Peyser, Brandt, Dannals & Folstein, 1992). Lower cerebral metabolic ratios have been reported in those considered at high risk for HD. The left frontal cortex, right caudate, and bilateral insula were especially implicated (Lanto, Riege, Mazziotta, Pahl & Phelps, 1990). The findings from Proton Magnetic Resonance Spectroscopy show disturbed cerebral energy metabolism in the frontal region of both affected patients and those at risk (Harms, Meierkord, Timm, Pfeiffer & Ludolph, 1997).

A similar pattern of involvement is seen in reduced regional blood flow using single photon emission tomography. Reductions in flow were observed in the caudate (Reid, Besson, Best, Sharp, Gemmell & Smith, 1988), lentiform nuclei, frontal and parietal areas (Hasselbalch

et al., 1992). See Brandt (1991) for a further discussion of cerebral blood flow and metabolism in HD.

Morphological studies have been combined with cognitive abilities. Caudate atrophy as measured on CT scan has been correlated with the cognitive impairment in multiple tracking abilities and shifting set (Starkstein et al., 1988). Memory impairment has been correlated with caudate and frontal atrophy as measured on MRI (Starkstein et al., 1992). Similarly, reduced metabolism measured on PET has been correlated with verbal learning and memory (Berent et al., 1988).

In summary, regardless of the medium of analysis, neuropathological findings all point to early involvement of the striatal structures, particularly the putamen and caudate nuclei, with extension to cortical structures, especially the frontal, temporal and parietal lobes, in the later stages of the disease. Cognitive impairment of the type usually associated with frontal lobe impairment has been correlated with structural and functional dysfunction of the subcortical structures.

1.3 The clinical presentation of Huntington's disease

The initial onset appears to favour neurological symptoms as the most prevalent, with psychiatric symptoms following (Di Maio, Squitieri, Napolitano, Campanella, Trofatter & Conneally, 1993a; Hayden, 1981). According to Hayden neurological symptoms occur as the initial symptom, on average, 46% of the time, and psychiatric symptoms 36% of the time. However, the onset of this disease is gradual and a mixed presentation of neurological and psychiatric symptoms is common (Brackenridge, 1973; Pflanz, Besson, Ebmeier & Simpson, 1991).

1.3.1 Neurological symptomatology

The earliest noticeable neurological signs of the disease are usually movements of the hands and face initially presenting as restlessness, random jerks, and twitches (Adams, et al., 1997; Paulson, 1979). In the early stages of the disease sufferers often attempt to disguise these movements by incorporating them into voluntary actions such as rearranging their hair (Slater & Roth, 1969). Chorea is the most frequent motor abnormality and apparent in some 90% of affected individuals (Hayden, 1981), but is not the

only abnormal motor symptom to present during the disease (Quarrell & Harper, 1996). Hypertonicity and slowed oculomotor responses occur in the early stages (Young, Penney *et al.*, 1986), and other motor abnormalities such as dystonia, rigidity, bradykinesia and decreased movement develop as the disease progresses (Quarrell & Harper, 1996). The neurological signs of dysarthria, dysphagia, disturbance of gaze, gait, epilepsy, incontinence, and cerebellar signs also develop during the progression of the disorder (Quarrell & Harper, 1996; Hayden, 1981).

1.3.2 Psychiatric symptomatology

Huntington (1872) noted that sufferers of the hereditary chorea, as he referred to HD, had a tendency to insanity. The most frequent early psychiatric symptoms include personality changes, loss of interest, nervousness, irritability, agitation, labile affect, and depression (Caine, Hunt, Weingartner & Ebert, 1978; Di Maio *et al.*, 1993a; Pflanz *et al.*, 1991; Shiwach, 1994). Occasionally there is paranoia, or a schizophreniform psychosis may manifest either before the choreiform movements (Hayden, 1981; Lovestone, Hodgson, Sham, Differ & Levy, 1996; Shiwach, 1994; Wilson & Garron, 1979), or during the

disease (Lovestone et al., 1996). Personality changes tend to fall into two types: an exaggeration, or a reversal, of premorbid personality style (Hayden, 1981).

Psychiatric symptoms are thought to be aetiologically related to the disease process itself (Jensen, Sørensen, Fenger & Bolwig, 1993) because of the rich neural connections between caudate and limbic system (Peyser & Folstein, 1990), although a secondary effect because of living in a disordered family environment has been suggested (Folstein, 1991). However, receiving a positive diagnosis for HD in those with early neurological evidence of HD does not appear to increase psychiatric symptoms (Jankovic, Beach & Ashizawa, 1995).

As well as psychiatric illness, there is significant risk in HD of suicide (Farrer, 1986; Harris & Barraclough, 1994). Huntington (1872) himself had commented that there was a tendency to suicide in HD. In an early study in Michigan of HD, suicide accounted for 7.8% of deaths in noninstitutionalised males and 6.4% of deaths in females (Chandler et al., 1960). More recently, the profile of an HD patient with the highest risk for suicide is reported to be a childless, unmarried male, with a family history of

suicide (Lipe, Schultz & Bird, 1993). In SA, suicide in HD sufferers is approximately 2200 times more common than the general population (Hayden, MacGregor *et al.*, 1980).

There is little evidence to suggest psychiatric morbidity in nonbiological family members (Shiwach & Norbury, 1994). In those at risk for HD the evidence is equivocal. Several studies find no greater incidence of psychiatric illness in those at risk than the normal population (Jensen *et al.*, 1993; Watt & Sellar, 1993), but other researchers disagree, finding a greater psychiatric morbidity for affective disorders in those at risk and the biological family members of those at risk (Baxter *et al.*, 1992; Di Maio, Squitieri, Napolitano, Campanella, Trofatter & Conneally, 1993b; Shiwach & Norbury, 1994; Wong, Chang, Yu, Chan & Chan, 1994; and see also Kessler, 1987a, 1987b for discussion of this issue). However, presymptomatic psychiatric symptoms are probably related to the stress of being at risk for a life threatening illness and are not generally considered early indicators of the disorder (Shiwach, 1994; Shiwach & Norbury, 1994).

Intellectual deterioration also presents early in HD (Klawans *et al.*, 1980). As this topic is an important

aspect of the present study and will be discussed in more detail in the next section.

1.4 The cognitive impairment associated with Huntington's disease

Dementia is one of the triad of distinguishing features of HD (Adams *et al.*, 1997) and some degree of cognitive impairment is present without exception (Caine & Fisher, 1985). Cognitive changes occur early in the progression of this disease (Klawans *et al.*, 1980), and are probably the major cause of disability, rather than the choreic movements, in the initial stages of HD (Mayeux, Stern, Herman, Greenbaum & Fahn, 1986; Rothlind, Bylsma, Peyser, Folstein & Brandt, 1993).

In spite of early awareness of a dementing process in HD, scientific interest in the character of the cognitive decline in this illness only began in earnest some thirty years ago. The first detailed neuropsychological evaluation of HD was described in 1974 by Boll, Heaton and Reitan. A broad range of neuropsychological impairment was reported by these researchers. Several comprehensive reviews have been produced since then (e.g. Brandt, 1991;

Caine & Fisher, 1985; Caine et al., 1978), and a plethora of literature on the subject has arisen, but many controversies regarding the nature of the specific deficits of HD have been raised and continue to be debated.

1.4.1 The typology of Huntington's dementia

Perhaps the major area of debate in HD concerns the aetiology of the dementia. Caine et al. (1978) had suggested that Huntington's dementia resembled the 'frontal lobe syndrome' described by Luria (1973). A suggestion which had previously been put forward by Benson and Geschwind (1975). In more recent times the pattern of cognitive impairment in HD has been equated with subcortical dementia to the extent that the dementia of HD has become the paradigm for subcortical dementia studies.

The reported cognitive impairments associated with frontal lobe dementia are dominated by deficits of executive skills (poor planning and purposive action, perseveration, ineffective performance, and inability to organise cognitive activities temporally; Lezak, 1995), impairments of verbal and design fluency, memory deficits characterised by poor free recall but good recognition of novel

information, and generally well preserved visuospatial skills (Baldwin & Förstl, 1993; Cummings, 1993; Lezak, 1995; Miller *et al.*, 1991; Neary, Snowden, Northen, & Goulding, 1988). Changes in mood and affect in frontal lobe dementia include a progressive breakdown in social conduct and/or insidious change in personality with altered behaviour ranging from disinhibition, in the early stages, to extreme apathy, as the disorder progresses (Miller *et al.*, 1991; The Lund & Manchester Groups, 1994; Neary, Snowden, & Mann, 1993).

A distinct profile of cognitive disturbances, associated with damage to subcortical structures, has been described by Albert, Feldman and Willis (1974), Cummings (1986), Cummings and Benson (1984), and McHugh and Folstein (1975)³. This profile includes slowing of cognition (bradyphrenia), difficulties with new learning and memory disturbances (particularly for spontaneous recall of

³There is strong evidence to suggest that a differential pattern of impairment can be distinguished on neuropsychological grounds between subcortical and cortical categories of dementia (e.g. Brandt, Folstein & Folstein, 1988; Pillon, Dubois, Ploska, Agid, 1991; Salmon, Kwo-on-Yuen, Heindel, Butters & Thal, 1989) in spite of this concept being periodically challenged (Brown & Marsden, 1988; Whitehouse, 1986).

material), and some difficulty with complex intellectual tasks (e.g. impaired ability to manipulate acquired knowledge, and difficulties with strategy generation and problem solving). In addition, visuospatial difficulties and changes in mood and affect have also been documented (Cummings, 1986; Fedio, Cox, Neophytides, Canal-Frederick & Chase, 1979; Hodges, Salmon & Butters, 1990; Mendez, Adams, & Lewandowski, 1989).

There is considerable overlap between the description of the symptoms of subcortical dementia and frontal lobe dementia presented above, in spite of evidence to suggest that subcortical and cortical dementias can be distinguished on neuropsychological grounds (e.g. Brandt et al., 1988; Pillon et al., 1991; Salmon et al., 1989). An explanation for this apparent paradox can be derived from purported parallel organization of functionally segregated circuits linking basal nuclei and cortex (DeLong & Georgopoulos, 1979).

The basal nuclei have extensive input and output projections to the cerebral cortex (DeLong & Georgopoulos, 1979), and to the grey matter of the frontal cortex in particular. These complex pathways receive output from

five different frontal regions - the motor, oculomotor, prefrontal, orbitofrontal and cingulate areas - from which projections are sent to the striatum (caudate nuclei, putamen and ventral striatum), pallidum and substantia nigra, and specific thalamic nuclei, before returning to the cortical structures of origin, thereby forming a 'closed' loop system (Alexander, DeLong, & Strick, 1986; Cummings, 1993; Cummings & Benson, 1990; DeLong, Georgopoulos, Crutcher, Mitchell, Richardson & Alexander, 1984; Nauta & Domesick, 1984).

Three of these circuits have, according to Cummings (1993), distinct neurobehavioural syndromes all of which can be differentially affected depending on the site of their pathological involvement. The dorsolateral prefrontal syndrome comprises deficits of executive function and motor programming; the orbitofrontal syndrome focuses upon changes in personality; and the anterior cingulate (medial frontal) syndrome is reflected in lack of motivation and in failure to inhibit inappropriate responses. The 'closed' loop concept infers that deficits associated with damage to the prefrontal areas are recapitulated in the connected subcortical areas, including the caudate nuclei (Cummings, 1993). Thus, the attribution of HD dementia to both

cortical and subcortical aetiologies can be explained on the basis of a common frontal corticostriatal system.

This suggestion has been supported by neuroimaging (Bäckman, Robins-Wahlin, Lundin, Ginovart & Farde, 1997). Correlating PET and MRI measurements with cognitive task performance, these researchers found that the overall pattern of cognitive impairment in HD correlated with multiple sites in the frontostriatal circuitry.

1.4.2 General intelligence in Huntington's dementia

Assessment of intelligence has been repeatedly explored in HD and the Wechsler Adult Intelligence Scale (WAIS) has been used widely in the assessment of general intelligence in individuals with Huntington's dementia, particularly in early studies (Brandt, 1991). Findings have been varied. Goodman *et al.* (1966); Aminoff, Marshall, Smith, and Wyke (1975); Butters, Sax, Montgomery & Tarlow (1978); and Caine *et al.* (1978) mentioned no prominent pattern of decline in the intelligence quotient (IQ), but Oscar-Berman, Sax and Opoliner (1973); Boll *et al.* (1974); McHugh and Folstein (1975) and Norton (1975) reported generalised decline.

Norton (1975) found differences between the HD group and a group of mixed brain damaged subjects and suggested that the generalised intellectual impairment in HD was similar to that of general brain damage. Aminoff et al. (1975) suggested that the abnormalities on the WAIS merely resembled that of normal individuals of advanced age. These latter researchers presumably were suggesting that, by the use of the term 'advanced age', the WAIS presentation was nevertheless abnormal for the HD group who were probably from a younger age group.

Other researchers also reported a general decline for all three of the IQ scales (verbal IQ [VIQ], performance IQ [PIQ] and full IQ [FIQ] scales, Butters et al., 1978; Butters, Albert & Sax, 1979), with the greatest decline occurring in PIQ scores (Butters et al., 1978; Wilson & Garron, 1979). The Picture Arrangement and Digit Symbol subtests of the WAIS appear to be the most vulnerable to early symptoms of Huntington's dementia (Butters et al., 1978, 1979; Caine et al., 1978; Josiassen, Currey, Roemer, DeBease & Mancall, 1982).

Although intellectual abilities fall within the normal range in the early stages of the illness (Caine et al.,

1978), and deteriorate as the disease progresses (Butters et al., 1978; Josiassen et al., 1982), the measuring of general intelligence has proved to be a poor predictor of precise neuropsychological deficit in HD (Brandt, 1991). It should be noted however, as pointed out by Caine et al. (1978) and Josiassen et al. (1982), that instruments such as the WAIS are primarily a measure of IQ and are not specifically designed to detect or localise brain dysfunction.

1.4.3 Learning and memory in Huntington's dementia

From the early studies of cognitive impairment in HD it became clear that a memory deficit formed one of the core areas of deterioration (Boll et al., 1974; Butters et al., 1978, Caine et al., 1978, but cf. Slater & Roth, 1969 who stated that "memory...surprisingly well retained"). It was even suggested that the impairment in new learning which presents as a memory deficit may have been present years prior to the onset of the choreic movements (Butters et al., 1978, 1979).

Theoretical approaches to memory systems suggest that several functional, or descriptive, divisions exist (i.e.

procedural and declarative, or implicit and explicit, episodic and semantic, anterograde and retrograde; Gabrieli, 1998; Heindel, Butters & Salmon, 1988). However, it should be noted that empirical support for the presence of these divisions has not been fully established and can be contradictory and confusing (Randolph, 1991). Nevertheless, these terms are frequently used in current literature and a similar approach has been adopted in the present study. A detailed evaluation of the memory and learning difficulties in HD will now be presented.

1.4.3.1 Episodic memory

The nature of episodic, explicit, or anterograde⁴ memory impairment in HD has been described as an impairment of short term memory⁵ with difficulties in learning new

⁴Terms which are essentially interchangeable in meaning and refer to a subtype of declarative memory. Declarative memory refers to memory for facts. Episodic memory describes past events in an individual's life with particular temporal and/or spatial contexts that are available to conscious recollection (Butters, Granholm, Salmon, Grant & Wolfe, 1987; Kolb & Whishaw, 1995; Squire, 1987).

⁵The use of the term 'short term memory' strictly refers to the retainment and recall of information over a period of time of about 90 seconds. However, the term has come to mean memory for a time period of minutes, hours (Parkin & Leng, 1993). It is in this latter sense that the term has been used here.

material and a loss of information with time (Butters et al., 1978, 1979). From early research with HD patients it was suggested that the memory impairment may be due to a failure of ability to elaborate or analyse information at the encoding process stage which lead to impaired free recall (Lyle & Gottesman, 1977). It was assumed that the impaired encoding of information would lead to reduced remembering even with cues or memory prompts (e.g. Weingartner, Caine & Ebert, 1979). This view has not been generally supported in later research⁶. The current hypothesis is that the most prominent memory difficulty is of retrieval (Butters, Salmon, Heindel & Granholm, 1988; Butters, Wolfe, Granholm & Martone, 1986; Butters Wolfe, Martone, Granholm & Cermak, 1985; Heindel, Salmon & Butters, 1990; Martone, Butters, Payne, Becker & Sax, 1984), although it has been suggested that encoding is not intact (Brandt, Corwin & Krafft, 1992; Massman, Delis, Butters, Levin & Salmon, 1990).

There are several possible reasons for the discrepancy. In the early stages of the disease, poor performance on memory

⁶Interestingly, a more recent MRI study has reported volume loss in the mesial temporal lobe structures (Jernigan et al., 1991) which would add support to Weingartner et al's (1979) early suggestion.

tests may be due to slowed cognitive processing rather than memory impairment itself (Huber & Paulson, 1987). The described inability to initiate a proactive strategic search for the retrieval of stored information has also been frequently suggested as the mechanism underlying the memory deficit (Boll et al., 1974; Butters et al., 1985; Lundervold, Reinvang & Lundervold, 1994). Further, individuals with HD tend not to use learning strategies such as active rehearsal to encode the information (Massman et al., 1990; Weingartner et al., 1979), thus, a combination of poor encoding and poor retrieval may underlie the memory impairment.

In addition to the primary impairment in episodic memory, subtle error making tendencies related to this type of memory impairment have been documented. A tendency to make omission⁷ errors rather than prior item errors⁸ has been reported (Butters et al., 1979). This may not be a stable phenomenon as Granholm and Butters (1988) found that Huntington's subjects made more prior list intrusion errors than controls but did not differ for omission errors. HD

⁷Leaving out information previously given.

⁸Information given prior to the present information that is irrelevant to the present information.

subjects also make proactive interference⁹, intrusion and perseveration errors (Lange, Sahakian, Quinn, Marsden & Robbins, 1995), but produce less of these errors than alcoholic Korsakoff patients (Butters et al., 1986; 1987; 1988; Rich, Campodonico, Rothlind, Pylsma & Brandt, 1997) or patients with Alzheimer's disease (DAT) (Butters et al., 1988; Kramer, Delis, Blusewicz, Brandt, Ober & Strauss, 1988). HD subjects make less extra list errors¹⁰ (Granholm & Butters, 1988) but will make more false positive errors¹¹ than subjects with DAT (Butters et al., 1986). This latter finding has been challenged more recently by Brandt et al. (1992), who found DAT patients more prone to false positive errors than the HD subjects.

Savings scores¹² in HD are superior to DAT but not as high as in normal controls (Tröster et al., 1993). Rate of forgetting is relatively intact in HD, once learned, information decays at a relatively normal rate (Martone,

⁹A similar concept to prior-item errors.

¹⁰Words generated by the subject at a recall trial that had not been previously presented at any time during the learning trials.

¹¹The tendency to adopt a liberal response bias when uncertain about distractor words.

¹²Percentage of recently learned information retained over time.

Butters & Trauner, 1986; Tröster et al., 1993). Brandt et al. (1995) have also found a dissociation between memory for contrived facts and source of these facts. HD subjects could remember the information presented to them but made errors in knowing where they learned the information. In the later stages of the disease, differentiation between what has been recently learned and what must be retrieved becomes compromised (Kramer, Levin, Brandt & Delis, 1989).

It has been suggested that the basal nuclei play a primary role in episodic memory function. Support for this hypothesis comes from the use of neuroimaging. Impaired performance on various neuropsychological tests of memory has been correlated with atrophy of the basal nuclei (e.g. Bamford et al., 1989; Bamford, Caine, Kido, Cox & Shoulson, 1995; Brandt et al., 1995; Hasselbalch et al., 1992) but not with frontal atrophy (Starkstein et al., 1992). Further, the severity of the motor impairment, in relation to basal nuclei neuronal loss, was reported to be a good indicator of memory decline (Brandt, Strauss, Larus, Jensen, Folstein & Folstein, 1984).

Pillon, Deweer, Michon, Malapani and Agid (1994) found a comparable pattern of explicit memory deficit in three

prototypical subcortical dementias (Progressive Supranuclear Palsy, Parkinson's disease, and HD) which differed from that found in DAT and suggested that striatofrontal dysfunction could be the common denominator in the subcortical dementias where a retrieval deficit underlies dysfunctional memory processing.

Many of the subtle episodic memory impairments noted in HD also occur with frontal lobe impairment (Brandt et al., 1995; Lange et al., 1995). Pillon, Deweer, Agid and Dubois (1993) found a positive relationship between impaired memory performance and impaired executive function scores in subjects with HD, and suggested that both areas of impairment had frontal lobe dysfunction as a common aetiology. Moreover, the episodic memory impairment in HD is thought to be typical of impaired executive functioning: reasonable encoding but poor free recall with good recognition skills for declarative learning (Pillon et al., 1993).

Whether or not episodic memory impairment in HD is directly related to loss of neurones in the striatum, or frontal lobe areas, or a disconnection between the two areas is unresolved at this stage. Nevertheless, the hypothesis

that the underlying anatomical substrate for the retrieval difficulty appears to be related to the degeneration of the neostriatum and the neostriatal-frontal cortex interconnections (Salmon et al., 1989) is generally supported.

1.4.3.2 Semantic memory

Semantic memory deficits¹³ have been generally measured through the use of word fluency or word generation tests. When administered to HD subjects, it was found that they produced fewer words on a verbal fluency task than a control group (Butters et al., 1978, 1979, 1988), an alcoholic Korsakoff group (Butters et al., 1986), and a group with DAT (Rosser & Hodges, 1994; Tröster, Salmon, McCullough & Butters, 1989), but made less perseverative responses than DAT or Korsakoff patients (Butters, Albert, Sax, Miliotis, Nagode & Sterste, 1983).

In HD the deficit is initially mild (Brandt et al., 1992) with the degree of semantic memory impairment related to the severity of the dementia (Tröster et al., 1989). It

¹³A subdivision of declarative memory, semantic memory refers to knowledge of the world: facts, concepts and vocabulary (Squires, 1987).

has been suggested that, in the initial stages at least, a semantic memory deficit is due to impaired speed in the analysis of information and is only due to memory disturbance later in the disease process (Huber & Paulson, 1987). The nature of this later memory impairment seems one of retrieval rather than loss of information (Butters et al., 1988).

1.4.3.3 Procedural memory

There is also support for the proposal that those with HD are impaired for procedural or implicit¹⁴ memory even when patients obvious motor impairment is taken into account (e.g. Heindel et al., 1988; Knopman & Nissen, 1991; Martone et al., 1984). This suggestion has been challenged in more recent research by Sprengelmeyer, Canavan, Lange & Hömberg (1995). Procedural impairment may be more prevalent in subcortical disorders such as Parkinson's disease rather than HD (Sprengelmeyer, Canavan et al., 1995); or only

¹⁴Also known as procedural or motor skill learning, it is memory for skills and other cognitive operations learned unintentionally or unconsciously (Kolb & Whishaw, 1995; Squires, 1987 but cf. Bedford, 1997 for a discussion refuting implicit learning as a specific category of memory).

present in more advanced states of HD (Butters et al., 1985; Saint-Cyr, Taylor & Lang, 1988).

The reason for the differing views may relate to the specific category of procedural testing: motor skills learning or visual and auditory priming¹⁵. The basal nuclei may be more involved in motor skill learning (impaired in HD) than verbal priming (relatively spared in HD), which appears to rely more on the relatively intact cortical function of semantic memory (Heindel et al., 1988). An alternative suggestion is that the procedural memory deficit in HD is secondary to initiation difficulties (Butters et al., 1988). In HD, false positive errors occur in implicit learning as they do in explicit learning (Bylsma, Rebok & Brandt, 1991), suggesting the presence of a similar underlying process such as initiation difficulties.

¹⁵Priming involves giving a subject part of a picture or word and later asking them to say "the first thing you can think of". There is usually a greater than chance occurrence that the word produced will be related to the picture or word-stem (Heindel et al., 1990).

1.4.3.4 Retrograde memory

A retrograde¹⁶ memory deficit has also been reported in HD. Boll et al. (1974) described retrograde memory impairment for visuospatial memory, measured by map reading in which details of known areas were lost but the major outlines of countries retained. Unlike the amnesic syndrome typical of Korsakoff's disease, retrograde amnesia in HD does not show a temporal gradient (Butters et al., 1979). Instead, HD sufferers are equally impaired for the recall of events regardless of when the event took place in time (Martone et al., 1984). It has been suggested that this finding supports the theory of a declarative retrieval impairment rather than an encoding difficulty in HD (Brandt & Butters, 1986).

1.4.3.5 Summary of memory impairment in Huntington's dementia

In summary, HD patients appear to find all active stages of episodic memory processing difficult (Lundervold et al., 1994), but the predominant memory deficit is probably that

¹⁶This term refers to past episodic memories (Squire, 1987).

of retrieval of new learned information rather than encoding. Initiation and perseveration difficulties may explain impaired recall especially in the early stages of the disorder. Semantic memory skills are relatively intact, especially in the early stages of the disorder (Podoll, Caspary, Lange & Noth, 1988). Such skills can be utilised for the storage of information but may not be available to instigate search strategies for the retrieval of this information (Brandt & Butters, 1986; Martone et al., 1984). Semantic memory skills may facilitate one type of procedural memory - priming, but motor skills learning appears to be impaired. A confounding factor to this type of procedural learning task is the presence of primary motor deficits in basal nuclei disorders. Thus, motor impairment, stage of illness, and confounding variables such as poor task initiation may account for the unresolved findings in this area of research.

1.4.4 Visuospatial impairment in Huntington's dementia

Many studies of early cognitive decline in HD reported a variety of visuospatial difficulties including copy of designs (Hodges et al., 1990), disorders of visuospatial judgement, perceptuomotor integration, and egocentric

orientation (Bamford et al., 1989; Brouwers, Cox, Martin, Chase & Fedio, 1984; Bylsma, Brandt & Strauss, 1992; Fedio et al., 1979; Goldberg, Berman, Mohr & Weinberger, 1990; Hayward, Zubrick & Hall, 1985; Josiassen, Currey & Mancall, 1983; Moses, Golden, Berger & Wisniewski, 1981).

Confrontational naming errors in HD have been attributed to impaired visual analysis rather than anomia (Hodges, Salmon & Butters, 1991). Reported impairment in facial identity and facial affect has also been attributed to visual processing difficulties (Jacobs, Shuren, Heilman, 1995).

It has always been unclear whether the visuospatial impairment was directly related to neuronal loss in the subcortical structures or secondary to a frontal lobe planning deficit (see Lezak, 1995 pp.235-6 for example). A recent study may offer an answer to this problem. Filoteo et al. (1995) found that a sample of HD patients showed visuoperceptual difficulties on a task which required little memory, problem solving or complex motor responses, supporting the idea that the impairment is primarily visuospatial in HD and not related to frontal lobe function. Further support of this finding, from Gómez-Tortosa, del Barrio, Barroso and García Ruiz (1996),

found that early visuoperceptual impairment in HD was probably due to complex visual processing deficits rather than ocular scanning, visual attention or visuoconstructive impairment.

1.4.5 Difficulties with attention in Huntington's dementia

It is not possible to give a description of attention in a single definition (van Zomeren & Brouwer 1994). A working categorisation of attention, however, can be derived from the findings of clinical research. A typology of attention would include the subtypes of focused attention, divided attention, and sustained attention (van Zomeren & Brouwer, 1994).

Early difficulties with attention and concentration in HD have been widely reported (Mendez, 1994; Orsini, Fragassi, Chiacchio, Falanga, Cocchiaro & Grossi, 1987). Scores on subtests of attention differentiate HD subjects from DAT subjects when sensitive screening batteries are used (Randolph, Tierney, Mohr & Chase, 1998). Even at a rudimentary level, impairment in initiation/perseveration measures on dementia screening instruments such as the Mini Mental Status Examination and the Mattis Dementia Rating

Scale can be successfully used to differentiate HD patients from DAT patients (Brandt et al., 1988; Paulsen et al., 1995).

Nevertheless, there are few studies that have specifically investigated attention, in spite of extensive assessments of cognitive function (Georgiou, Bradshaw, Phillips & Chiu, 1997). Yet, it is possible that attentional disturbances underlie many of the 'higher' cognitive deficits associated with this disorder (Filoteo et al., 1995; Sprengelmeyer, Lange & Hömberg, 1995), especially in the early stages.

Much measure of attention and concentration has relied upon selected subtests of the WAIS. The most consistent finding was poor performance on the Digit Span and Digit Symbol subtests (Catona, Lazzarine & McCormack, 1985; Josiassen et al., 1982; Kosky, 1981). These subtests are, however, complex and attention forms one of several skills needed to successfully complete the task requirements.

Bamford et al. (1989) described impairment on a task of divided attention early in the course of HD. Support for this suggestion comes from Georgiou et al. (1997) who found that HD subjects appeared to have considerable difficulty

in allocating attentional resources between expected and unexpected events. Filoteo et al. (1995), however, found ability to shift attention in a task of divided attention to be intact, as did Sprengelmeyer, Lange et al. (1995). This discrepancy may be explained on the basis that passive attention is probably intact in early HD along with the ability to disengage from stimuli, but patients are impaired when attentional tasks require self generation abilities involving active engagement or unexpected shifting of attention (Georgiou, Bradshaw, Phillips & Chiu, 1996; Sprengelmeyer, Lange et al., 1995). Attention appeared further compromised in advanced HD (Butters et al., 1978) although these researchers did not specifically detail the attentional impairment.

The caudate nucleus, in concert with the frontostriatal system, is thought to play a role in focused attention (Passingham, 1993). Evaluation of the bicaudate ratio measured on CT scan showed a correlation between caudal atrophy and performance of neuropsychological tests of attention (Starkstein et al., 1988).

1.4.6 Executive function in Huntington's dementia

Impaired executive function is considered to reflect frontal lobe dysfunction (Fuster, 1989; Lange et al., 1995; Lezak, 1995) and has been widely described in HD (Brandt, 1991). The early study of Boll et al. (1974) reported impairment in problems solving, but perhaps the best phenomenological description of executive impairment is the study of Caine et al. (1978). They described difficulties of volition as a lack of spontaneity to initiate activities; poor organization, planning and sequential arrangement of information, and ineffective ability to deal with large amounts of information.

More formal neuropsychological studies of HD using tests purported to measure frontal lobe dysfunction have been conducted with a wide range of executive impairment reported including difficulties with shifting response set and self monitoring (Lange et al., 1995; Lawrence, Sahakian, Hodges, Rosser, Lange & Robbins, 1996). Difficulties in word generation (Tröster et al., 1989), poor maze performance (Fedio et al., 1979), loss of cognitive flexibility, changing set, and perseveration

(Josiassen et al., 1983; Starkstein et al., 1988) have been described.

Brandt (1991) has suggested that the fundamental deficit underlying executive neuropsychological impairment in HD is one of temporal coding. Fuster (1989) has suggested that a superordinate function of the prefrontal lobes is the formation of "temporal structures of behaviour" (p.158; see Fuster, 1989 for a detailed discussion of this hypothesis). On this basis of this relationship, it would seem that many of the executive deficits of HD are synonymous with frontal lobe impairment.

1.4.7 Language impairment in Huntington's dementia

Difficulties with language are not usually considered part of the constellation of HD deficits until very late in the disorder and language abilities have been reported to be normal in early stage patients (Lundervold & Reinvang, 1991; Podoll et al., 1988). However, less obvious linguistic deficits may exist in addition to the more obvious motor speech impairments (Brandt, 1991). For example, subtle naming difficulties have been reported (Hodges et al., 1991), as have difficulties in both

discrimination of affective and propositional prosody (Speedie, Brake, Folstein, Bowers & Heilman, 1990), reduced verbal fluency (Butters et al., 1986), disrupted syntactic organisation, and reduced language complexity (Illes, 1989).

1.4.8 Concluding remarks about cognitive impairment in Huntington's dementia

In summary, it appears that early cognitive decline in HD comprises impairment in new learning and memory, visuospatial dysfunction, and attentional difficulties. Impairment in these functions can be considered 'markers' for early diagnosis of the disease (Lundervold & Reinvang, 1991). As the disease progresses problem solving, organisation and planning abilities, concept formation, and general intelligence become compromised.

Cognitive symptoms of HD appear congruent with both subcortical dementia and frontal lobe dementia, however, congruency between the two dementia typologies is not complete. For example, behaviour and insight into one's dementia may differ between the two types. Caine et al. (1978) found that patients with HD had insight into their

dementia, which was also reported by Aminoff et al. (1975). Lack of insight is a hallmark of frontal lobe dementia (Neary, 1994a). Behavioural withdrawal with apathy are all cited as early symptoms of HD (Mendez, 1994), but patients with frontal lobe dementia tend to have behavioural changes associated with inappropriate and disinhibited conduct (Neary et al., 1993).

The degree to which subcortical deficits share the frontal lobe type dysfunction appears to be dependent upon the stage of the illness and amount of involvement, at a subcortical level, of the purported frontosubcortical circuits (Lange et al., 1995). This would, perhaps, explain why confusion exists regarding the aetiology of cognitive impairment in HD and the comments of researchers such Brandt and Butters (1986), Neary (1994b), Robbins et al. (1994) that frontal impairment as a consequence of subcortical involvement differs both in specific nature and severity from primary frontal lobe damage or other dementias and amnesic syndromes.

Cognitive changes in the later stages of HD dementia are more reminiscent of cortical impairment congruent with the neuronal loss occurring in areas outside of the

subcortical/frontal areas (Mann et al., 1993; Spargo, Overall & Lantos, 1993), eventually leading to a nonfocal generalised impairment (Butters et al., 1978). This sequence would concur with the morphological studies that show the progression of HD from subcortical areas to cortical areas.

Chapter Two

2.0 THE PREDICTION OF HUNTINGTON'S DISEASE PRIOR TO SYMPTOM ONSET

HD is a genetically determined progressive neuropsychiatric dementing disorder with devastating consequences, causing distress and misery to sufferers and their families alike (Tyler, 1996). Consequently, there has always been a strong need to find a means by which the disorder could be predicted either before onset of symptoms or at the earliest possible stage (Slater & Roth, 1969). To find such a predictor of HD has been a major goal of virtually all HD research (Harper, Soldan & Tyler, 1996; Lanto et al., 1990). This topic will be discussed in this chapter.

Virtually every aspect of HD has been examined in an attempt to find a definitive way of predicting who would develop the symptoms of HD prior to their onset. Underlying this search was the assumption that the gene phenotype would be expressed before the onset of clear signs and symptoms (Hayden, 1981). This concept is known as the continuity hypothesis and implies that signs of a

disorder are present before the onset of the disorder, perhaps even from birth.

The continuity/discontinuity debate for late onset illnesses is not new (see Gowers, 1902), nor is it limited to HD. For example, a proportion of schizophrenic patients are reported to show signs of social abnormalities during childhood before the onset of schizophrenic symptoms (Castle, Wessely & Murray, 1993), and there is neuroradiological evidence that brain abnormalities also exist in schizophrenia prior to symptom onset (O'Callaghan, Larkin, Redmond, Stack, Ennis & Waddington, 1988; Waddington, O'Callaghan & Larkin, 1988; Weinberger, 1988).

Historically, several reasons for justification of the continuity hypothesis for HD, had been offered. Goodman et al. (1966; Goodman, Ashkenazi, Adam & Greenfield, 1973) reported that mothers of children at risk were good judges of which of their offspring would develop HD. Also, they suggested that organic brain dysfunction can be detected in a suspected sufferer before the symptoms manifest by means of personality assessment. Furthermore, Lyle & Gottesman (1977) found that deterioration in intellectual abilities could occur in those at risk for HD many years before the

onset of clinical choreic symptoms, exacerbating just prior to symptom onset. Finally, the continuity model has also been put forward to explain the considerable intersubject variability on predictive neuropsychological testing, to be discussed in more detail below.

2.1 Early approaches to prediction of Huntington's disease

Perhaps the earliest approach to prediction and control was to suggest eradication of the HD gene through reduction of progeny by means of sterilization for those with chorea (Davenport & Muncey, 1916 cited in Hayden, 1981). This approach was obviously untenable because of strong negative ethical and emotional connotations, and impractical as often the progeny have been born by the time the disease presents.

In spite of this early awareness of disease control, little systematic research was conducted into the exploration of early predictors of HD until the 1960's. A driving force behind modern research has been Marjorie Guthrie, Woody Guthrie's¹⁷ widow, who founded a commission to combat HD

¹⁷Woody Guthrie was a famous American folk singer of the 1930's who had HD.

and the Wexler family¹⁸ who also became involved in the search for the cause of H.D (see Pollen, 1993).

Three approaches have been commonly used in this area of research: clinical evaluation involving psychological testing and assessment of abnormal muscle movements; biochemical research; and genetic studies emphasising linkage, which now include chromosomal studies (Goodman et al., 1973). The early cognitive and behavioural changes of the disease were often targeted for investigation (Palm, 1973) and these will be explored in some length as this has a direct bearing on the present study. The other areas are beyond the scope of the present study but see Klawans et al. (1980) for a discussion of these categories.

Historically, investigations of early cognitive changes relied upon two strategies; cross sectional comparison and longitudinal analysis.

¹⁸In particular, Nancy Wexler, herself at risk for H.D., has worked with the Venezuelan families who provided the large kindred necessary for the isolation of the gene responsible for HD.

2.1.1 Cross sectional studies

The cross sectional approach involved making comparisons between all potentially at risk individuals with either controls who were not at risk, and/or patients with a firm diagnosis of HD. An example of this approach is that of Baro (1973) who used neuropsychological tests to differentiate between a control group and a group of at risk individuals. No clear differences between groups were found. Wexler (1979) utilised a similar approach using an extensive battery of neuropsychological tests but again found no meaningful differences between groups. She did, however, find a subgroup of at risk subjects who scored lower than matched controls on the Paired Associate task of the Wechsler Memory Scale.

Fedio et al. (1979), in another early cross sectional study, did find selective cognitive differences between the at risk group and normal controls. The at risk group performed significantly worse than controls on tests of perceptual and spatial judgement (the Mosaic Comparisons, Money's Road Map Test of Directional Sense, and the Stylus Maze Test). A later study by Hayward et al. (1985) corroborated Fedio et al's (1979) findings.

Conflicting results have continued to be reported in cross sectional studies. For example, Josiassen et al. (1982) found significantly increased variability on two subtests of the WAIS, the Digit Span and Picture Arrangement subtests, but Strauss & Brandt (1986), using the same test, did not demonstrate any group differences. Visuomotor assessment (Oepen, Mohr, Willmes & Thoden, 1985; Petajan, Jarcho & Thurman, 1979) identified a subgroup whose performance was similar to that of HD patients, but Johnson, McSorley, Brandt & Strauss (1987), found no differences on California Verbal Learning Test between those at risk and controls.

A more recent study of at risk subjects on a task of word learning identified a subgroup of subjects who presented with low metabolism in the anterior cerebral regions, areas found sensitive to hypometabolism in HD (Lanto et al., 1990). This subgroup made significantly more false positive responses than the remaining at risk group or the controls group. This type of response is found present in already diagnosed HD subjects (Butters et al., 1986). One subject from Lanto's subgroup subsequently developed clinical symptoms of HD so it is possible that members of

the subgroup did more poorly on neuropsychological testing because they were perisymptomatic¹⁹.

Cognitive symptomatology has been reported as early as childhood and adolescence in several groups at risk for HD (Catona et al., 1985; Kosky, 1981). In Catona et al.'s study, the at risk group performed worse than the control group on the Digit Span and Coding subtests of the Wechsler Intelligence Scale for Children-Revised (WAIS-R), and it was suggested that these tests may be useful in assessing memory function in children at risk. However, the at risk group performed better than controls on three other subtests of the same scale, making the authors suggestion appear to be somewhat arbitrary. Further, the at risk group comprised individuals of both primary and secondary at risk status (having a grandparent with symptomatic HD only), some of whom would probably develop HD and some who would not.

Other attempts of finding early indicators other than neuropsychological studies have been undertaken and include the study of 'soft signs' (Young, Shoulson et al., 1986);

¹⁹The average time period from clinical suspicion to diagnosis is about four and a half years (Young, 1996).

anomalies of conjugate ocular movements, fine finger and tongue control (Petit & Milbled, 1973); fine motor control (Petajan et al., 1979); muscle tremor (Myers & Falek, 1979); and abnormal muscle tone (Baro, 1973). Again, no clear or reliable predictors were elicited (Klawans et al., 1980).

In summary, the results from cross sectional studies were inconsistent. Several studies reported no differences between at risk and control subjects (e.g. Baro, 1973; Strauss & Brandt, 1986). Other studies reported a subgroup of at risk subjects who performance was significantly different from the controls, "or similar to confirmed HD patients (e.g. Fedio et al., 1979; Lanto et al., 1990; Wexler, 1979). While still other studies found the entire at risk group to perform worse than the control group (e.g. Catona et al., 1985; Fedio et al., 1979).

The reason for these differing results can be summed up by Fedio and colleagues "...every at risk group contains both escapees and individuals who may or may not be manifesting subclinical features of Huntington's disease" (p.253), and there was no way of knowing in the study group, who belongs

to which group. This criticism holds for all cross sectional studies.

2.1.2 Longitudinal studies

Longitudinal analysis involved the testing of all at risk individuals on a chosen measure before clinical symptomatology was present and then repeating the analysis in those who later manifested the disease (e.g. Lyle & Quast, 1976; Lyle & Gottesman, 1977; Palm, 1973). This was done in the hope that, retrospectively, analysis of the original data would uncover early signs which could be then used prospectively.

For example, in one study (Palm, 1973) the Wechsler-Bellevue Individual Intelligence Scale, The Minnesota Multiphasic Personality Inventory and the Rorschach Ink Blot Test were administered to a group of at risk individuals. The retest findings 20 years later failed to reveal any differences in IQ between those at risk and the national average. A major flaw in this study may have been due to sampling error: at a 20 year follow up only one member of the test group had developed clinical symptoms. Nevertheless, the results concur with a more recent cross

sectional study using an updated test of intellectual function (WAIS) which failed to differentiate between symptomatic HD subjects and at risk subjects when using both discriminant analysis and cluster analysis (Strauss & Brandt, 1986).

Another retrospective study carried out by Lyle & Quast (1976) reinterpreted protocols of the Bender Motor Gestalt Test performed by at risk individuals some 20 years earlier. Even with the knowledge of who of these pretested individuals had subsequently developed HD, reanalysis of the drawings still did not reveal any reliable predictors.

Lyle & Gottesman (1977) assessed at 15 to 20 year follow up a previously tested group of HD offspring. They had been administered the Shipley-Hartford Retreat Scale, the Bender Visual Motor Gestalt Test and three subtests of the WAIS, used to estimate full IQ. An evaluation was conducted by Lyle and Gottesman between those who were clinically symptomatic at time of original testing, those who developed HD clinically soon after the original testing, those who developed symptoms much later, and those who remained clinically free at time of second testing. Differences were found between those who later developed HD

and those who were symptom free at the time of retesting. From their results of progressively lower tests scores over groups, they suggested a gradual erosion of intellectual abilities rather than sudden onset began around the time of evident motor symptomatology.

Although the abovementioned study presented some interesting findings, which on first perusal seem conclusive, there are some problems. It is not possible to be completely sure that the symptom free group 15 years later were genetically free of HD as age of disease onset can occur as delayed as the late 70's (James et al., 1994). Further, no control groups were used with subjects free of any association with HD. Consequently, the symptom free group were under the threat of HD at both testings and this could have impacted upon their test performance. This last point is an issue which will be raised again in the studies concerned with predictive testing.

A more recently reported longitudinal prospective study by Cala et al. (1990) of 45 subjects who were at risk for HD but asymptomatic at the onset of the study, showed that over the course of 13 years, five subjects became symptomatic. Retrospective analysis showed that only one

of these five subjects had abnormal neuropsychological test results at the time of first assessment. Discriminant analysis of the subsequently five symptomatic subjects only categorised the test results of four of the five subjects as being at risk for HD. Even with a prospective longitudinal study, the results were not completely conclusive.

In general, as with the cross sectional approach, the longitudinal method proved to be unreliable (Lyle & Quast, 1976; Palm, 1973). Neither of the longitudinal or cross sectional approaches provided specific and reliable indicators for the prediction of HD (Klawans et al., 1980), or the answer to the continuity/discontinuity debate. It appeared that without knowing which gene was involved in this disorder, early prediction was very difficult and diagnosis remained one of clinical judgement (Paulson, 1979). This changed in 1983 when a marker for the gene was found.

2.2 The finding of a marker for the gene

In 1983 a polymorphic DNA marker for HD was identified, closely localising HD to the short arm of chromosome 4,

(Gusella et al.). This marker, termed a restriction fragment length polymorphism, made available DNA predictive testing. This was a completely new phenomenon in medicine (Evers-Kiebooms, Swerts, Cassiman & Van Den Berghe, 1989) and offered a novel approach to predictive testing and allowed up to a 95% accuracy in prediction for at risk individuals, depending on the marker used (Beilby, Chin, Porter, Walpole & Goldblatt, 1994). Possible HD sufferers were no longer reliant upon dubious sampling procedures or temporal analysis to assess their risk status.

The procedure, however, was not always straight forward. The test did not identify the gene itself but was dependant upon linkage analysis. Thus, blood samples were required from at least two affected family members, preferably from two generations, in which a clear segregation of the marker was possible (Adams et al., 1997; Beilby et al., 1994; Gusella et al., 1983).

In spite of the obvious advantages of recombinant DNA technology, it was not always feasible to carry out accurate genetic predictor testing as unsuitable family structures, lack of living affected relatives, poor marker separation, or uncooperative relations reduced the accuracy

of the testing. It was found that only 40% of the at risk population had sufficient information for successful linkage testing (Kessler, 1987b). These problems were resolved with the discovery of the gene itself, mapped within a gene in a small segment of 4p16.3, by The Huntington's Disease Collaborative Research Group (1993).

2.3 The huntingtin gene

It is now known that HD is due to mutation in a single gene. This gene that codes for a functionally unknown protein, now named 'huntingtin', is located at 4p16.3 in the IT15 transcript and contains expanded and unstable polymorphic trinucleotide cytosine-adenine-guanine (CAG) repeats (Beilby et al., 1994; MacMillan et al., 1993)²⁰. All individuals have this stretch of CAG repeats, which is crucial for normal development (Nasir, Goldberg & Hayden, 1996). Persons with fewer than 32 copies are not at risk for HD but those with 38 or more are highly likely to manifest HD (Beilby et al., 1994). What happens in the intermediate range between 32 and 38 repeats is not certain (Hersch, Jones, Koroschetz & Quaid, 1994), although it now

²⁰See Harper and Shaw (1996) for the history of the search for the gene.

appears that those with repeats of less than 35 are not at risk for HD (Furtado, Suchowersky, Rewcastle, Graham, Klimek & Garber, 1996) but those between 36-39 may have reduced penetrance. This group, and their offspring, are still at risk to develop HD, because of modifying factors which influence disease expression (Harper & Shaw, 1996; Xuereb, MacMillan, Snell, Davies & Harper, 1996).

The use of a polymerase chain reaction based test to discover the number of CAG repeats meant that complicated linkage testing and other family members was no longer required. It was now possible to directly analyse an individual's DNA alone (Beilby et al., 1994; Gusella et al., 1993; Hersch et al., 1994).

The discovery of a genetic marker for HD, and later the gene, simplified the search for early indicators of HD, and provided the means by which HD could be identified presymptomatically. More broadly, this discovery in HD has offered the unique chance, because of the late presentation, full gene penetrance, and fairly circumscribed early neuropathology, to study the ontogenesis of decline in a neurological disorder from the earliest presentations of symptoms till conclusion (Brandt,

1991). One consequence of this breakthrough was the introduction of predictive testing programmes.

2.4 Predictive testing programmes

HD was the first neuropsychiatric disorder for which testing programmes were available (Farmer & Owen, 1996), and has become the model for other neurogenetic predictive testing programmes (Rosenberg & Iannaccone, 1995).

Deontological concerns regarding predictive testing had been raised before a predictive marker had been found. Myrianthopoulos (1973) warned that any predictive testing for HD should be used with "extreme caution in selected cases only, after extensive preparation and counselling, and then always under medical and psychiatric supervision..." (p.157). Similar concerns were raised by Goodman et al. (1973) and the provision of mass screening programmes was condemned by Husquinet, Franck and Vranckx (1973) because of the possible risks involved when an individual receives a positive diagnosis. They expressed concerns of subsequent depression and suicide. These fears have been raised again with the advent of formalised

testing programmes (Gusella et al., 1993; Kessler, 1987a; 1987b; Kessler, Field, Worth, Mosbarger, 1987).

2.4.1 International predictive programmes

The establishment of predictive testing programmes began internationally in the mid 1980's (Brandt, 1991). In general, all predictive programmes comprised in depth assessment for neurological, psychiatric, and psychological status, including personality testing and cognitive evaluation. The initial aim of the programmes was to afford individuals with familial risk for HD the opportunity to clarify their position in regard to the disease in a structured and supportively caring environment before the onset of symptoms; assess the ego strength of the individual; identify those at risk for negative consequences such as psychological distress or psychiatric disorder; educate, and determine the demand for predictive testing (Fox, Bloch, Fahy & Hayden, 1989; Kessler, 1994). For example, The Johns Hopkins University School of Medicine's programme, one of the first in America, designed their predictive programme to determine the psychiatric, psychological and social consequences of informing people of their HD status; whether pretest characteristics could

predict how someone would adapt to their HD status; and whether it was possible through education and therapy to mitigate morbid outcomes (Brandt, 1991).

In addition, programmes offered genetic and social counselling, including role playing for test outcome. Prior to the instigation of these programmes, little attention had been paid to genetic counselling for HD sufferers and their families (Martindale, 1987), in spite of the early ethical concerns.

Members of all programmes have been urged to follow the guidelines set out for molecular genetics testing recommended by the International Huntington Association and revised by the World Federation of Neurology Research Group on Huntington's Chorea (see Benjamin et al., 1994 and Guidelines for the molecular genetics predictive test in Huntington's disease, 1994).

First reports of these programmes were published by Hayden, Hewitt, Stoessl, Clark, Ammann and Martin (1987) and Meissen et al. (1988). Since then a multitude of reports from widely dispersed countries have been published.

2.4.2 South African predictive testing programmes

A South African programme commenced in 1991, under the auspices of The University of the Witwatersrand, involving a collaboration between the Departments of Human Genetics, Psychiatry and Neurology²¹. The programme set up in SA was based on guidelines used in Manchester, England at Department of Psychiatry and Medical Genetics, St Mary's Hospital (Craufurd & Tyler, 1992).

The Johannesburg team comprises a genetic counsellor, psychiatrist, neurologist, psychologist, molecular geneticist, and medical geneticist. The protocol consists of seven appointments. Each applicant is interviewed initially by the genetic counsellor before making two visits to the psychologist. With the results of these visits, the psychiatrist and then neurologist see the client. When all reports are at hand, the genetic counsellor interviews the client again and a blood sample is collected. At the final interview, the results are

²¹A similar programme has subsequently been established in Cape Town, which follows international guidelines but does not include a full psychological evaluation (Dr Alan Bryer, 1996, personal communication). A programme is also available in QwaZulu/Natal (Dr Schlebusch, 1996, personal communication).

given (Kromberg et al., 1997). The programme has now been operational for some seven years at the time of writing.

The author has been the psychologist involved with the Johannesburg programme since a few months after its inception, and consequently has had access to almost every patient who wished to participate in the programme. There have been two components to the psychologist's role in this programme: first, to assess the ego strength of the individual and identify psychological distress or psychiatric disorder in those at risk, and second, to assess the cognitive status of each applicant.

With the discovery of a definitive means to identify HD carriers presymptomatically, it seemed now possible to answer the question of when does the onset of the disease occur, and, more pertinent to the present study, is there cognitive impairment present in those at risk for HD prior to symptom onset?

Studies of various clinical aspects of HD have been generated out of the predictive testing programmes, many of which have directly or indirectly addressed these questions. Research related to various aspects of these

questions will be discussed in the next section. As the use of neuropsychological studies to answer these questions forms the main core of the present study, these will be discussed in depth, but other aspects such as neurological and psychiatric evaluations that also form part of predictive testing programmes will be included.

2.5 Neuropsychological assessment of at risk individuals since the advent of molecular analysis

The majority of presymptomatic neuropsychological studies published since the discovery of a genetic marker and gene for HD have centred on discovering whether or not cognitive impairment is present before clinical onset of HD. The typical procedure used is the administration of a battery of psychological tests, prior to blood sampling, to asymptomatic at risk individuals who come forward for predictive testing.

After the blood results are made available, the group mean test scores of those at risk who were found positive for HD (AR+, or HD+ group) are compared to those found negative for HD (AR-, or HD- group). Significant group differences are considered indicative of cognitive differences between

the two groups. Significantly lower scores in the HD+ group would suggest that cognitive impairment is present preclinically in those at risk for HD.

The studies discussed below represent, to the best of the writer's knowledge, all the mainstream literature available on neuropsychological evaluation of at risk subjects. This amounts to a total of 17 papers in 2 languages. These will be briefly summarised and then criticised.

2.5.1 Cross sectional presymptomatic neuropsychological studies

The first study of this nature published was that by Jason *et al.* (1988). They reported cognitive impairment in marker positive at risk individuals but not in marker negative at risk persons. More specifically, they found neuropsychological deficits for visuospatial skills (visuospatial memory skills especially) and frontal lobe functioning in the marker positive subjects.

Strauss and Brandt (1990) carried out similar testing to that of Jason *et al.* (1988) but were unable to confirm the existence of such differences. In their criticism of Jason

et al's findings, Strauss and Braiddt noted that Jason and colleagues sample size had been small with a high degree of relationship between the subjects. They warned that if the kindred subjects had not been equally distributed between the two groups (marker positive and marker negative), but clustered into one group, then the differences found on the tests may reflect familial genetic influences rather than HD symptoms. Also, a large battery of tests was administered, with multiple statistical comparisons, increasing the risk of a type I error. Further, parametric statistics had been used and the statistical differences had been small; nonparametric analysis would have been more appropriate in the small sample size.

A later study from the same Johns Hopkins group (Bylsma et al., 1992) designed to specifically measure personal and extrapersonal spatial orientation in HD included at risk individuals. The results did not elicit test differences between the marker positive and marker negative groups. In addition, no intergroup differences were found between the at risk group and normal volunteers, nor between the within group analysis comparing positive, negative or unknown DNA marker groups. They had used a different sample to the

first study carried out by Strauss and Brandt (1990), but found the same outcome.

The positive findings of Jason et al. (1988) were supported by Diamond et al. (1992). However, closer analysis of their results indicated that only one test (Paired Associate Learning of the WMS) showed significant group differences between marker positive and marker negative groups. Similar criticisms as given above for Jason et al.'s study can be applied to the study by Diamond et al. (1992). Sample size was small and a large battery of tests were administered.

A brief assessment of memory functioning in a presymptomatic group of patients was carried out by Rothlind, Brandt, Zee, Codori & Folstein (1993) but no differences between groups testing positive or negative for HD were found on a test of verbal learning.

Rosenberg, Sørensen and Christensen (1995) found inferior performance on tests of attention, learning and planning in their HD carrier group when compared to the noncarriers. They concluded that cognitive impairment was present before clinical manifestations of the disease.

Using a different statistical approach from previous studies, and a battery of tests measuring sensorimotor function, psychomotor speed and efficiency, and memory, Lundervold & Reinvang (1995) found that all their at risk positive subjects showed a degree of impaired functioning but so did four of the at risk negative group. Impaired functioning was judged present when a scaled T score fell below the fifth percentile of the normal range.

In the largest study to date in terms of sample size, Foroud et al. (1995) found intellectual deficits present in those found positive for HD prior to symptom onset. Unfortunately, only six subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) were used and no custom designed psychological tests to assess neuropsychological function were administered. The subtests Picture Arrangement and Digit Symbol showed impaired scores in the positive group, findings similar as those previously found impaired in subjects who were tested in the early stages of H.D (Butters et al., 1978; Caine et al., 1978).

Blackmore, Simpson, and Crawford (1995) found only one test to be significantly different between at risk individuals found positive and those found negative for HD. This

difference was paradoxical, however, as the AR+ group performed better on the Corsi Supraspan task than the AR- group. The general trend was for the AR- group scores to be lower than the AR+, but these differences did not reach significance. Blackmore et al. (1995) expressed the view that minimal deficits did exist but that current measures of assessment are not sufficiently sensitive to isolate them.

A more recent study of intelligence in at risk subjects (de Boo et al., 1997b) found no group differences using the same test as Foroud et al. (1995). The sample size was smaller than that of Foroud et al. (1995), but all subtests of the WAIS-R intelligence test were used (Foroud et al., 1995, had only used six subtests). Their research did uncover a statistical difference, however, in their at risk group between VIQ and PIQ. The IQ scores for both at risk were within the normal range and high normal range respectively but the VIQ was significantly lower than PIQ. This finding cannot be explained on the basis of the typical early HD pattern of cognitive impairment on intelligence tests. Usually performance tasks are more susceptible to early decline in HD (Butters et al., 1978; Caine et al., 1978; Foroud et al., 1995). De Boo et al

(1997b) proposed that psychosocial reasons could explain this discrepancy.

Two Spanish studies by Gómez-Tortosa and colleagues (Gómez-Tortosa et al., 1996; Gómez-Tortosa, del Barrio Alba, Sánchez Pernaute, Benítez, Barroso & García Yébenes, 1997) reported no difference between presymptomatic carriers and noncarriers of HD. Gómez-Tortosa et al. (1996) conducted a detailed investigation of visual processing in those with a diagnosis of HD and those at risk. The latter group underwent molecular analysis after neuropsychological evaluation. No differences were reported between the presymptomatic carriers and the noncarriers. Apart from the Hooper test (a test of visuoperceptive function), none of the subjects in stage 1 of HD differed from the noncarriers either.

2.5.2 Longitudinal presymptomatic neuropsychological studies

The majority of the neuropsychological studies are cross sectional, however, a few longitudinal studies have been conducted. A four year longitudinal study of those at risk at two year assessment intervals found no group differences

between those positive for HD and those negative (Giordani et al., 1995). A similar finding was found in another two year study carried out by Campodonico, Codori and Brandt (1996). Both groups of researchers concluded from these studies that there was no indication that genetic predisposition to HD produced greater impairment than seen in those at risk but not predisposed to HD. Interpretation of the results of both these studies is restricted by the short follow up time span.

In summary, the neuropsychological studies presented in the above sections reveal mixed findings. In regard to cognitive impairment in those at risk for HD, several studies find support for presymptomatic cognitive impairment (e.g. Diamond et al., 1992; Foroud et al., 1995; Jason et al., 1988; Rosenberg et al., 1995), while other studies do not (e.g. Giordani et al., 1995; Gómez-Tortosa et al., 1996; Rothlind, Brandt et al., 1993; Strauss & Brandt, 1990).

2.6 The influence of CAG repeats in Huntington's disease

Since the utilisation of recombinant DNA technology and the discovery that the gene for HD contains expanded and

unstable CAG repeats, the significance of the number of repeats has become evident. It has been shown that longer trinucleotide repeat length is associated with a faster rate of deterioration, increased symptom instability, and greater pathological severity (Aylward et al., 1997; Brandt, Bylsma, Gross, Stine, Ranen & Ross, 1996; Furtado et al., 1996; Penney Vonsattel, MacDonald, Gusella, & Myers, 1997; Zappacosta et al., 1996).

A correlation between age of onset and number of CAG repeats has also been reported (Claes et al., 1995; The Huntington's Disease Collaborative Research Group, 1993; Illarioshkin et al., 1994; James et al., 1994). Increased length of CAG repeats is associated with a younger onset of the disorder but the correlation is not linear and age of disease onset cannot be predicted from the size of triplet repeat (Stine, Pleasant, Franz, Abbott, Folstein & Ross, 1993). Paternal transmission is also associated with earlier age of onset and with the sporadic cases of HD, which are probably due to expansion of repeats from the intermediate range of 32-35 into the affected range of 36+ (Harper, 1996c).

Length of trinucleotide repeat has been connected to greater neuropathological changes in the striatum, even when age at death and disease duration have been controlled for (Furtado et al., 1996; Illarionov et al., 1994), and ratio of percent loss in striatal D₂ receptor binding (Antonini, Leenders, Eidelberg, 1998).

However, there does not appear to be a relationship between number of CAG repeats and psychiatric illness (Weigell-Weber, Schmid & Spiegel, 1996; Zappacosta et al., 1996), type of symptom at onset (neurological, psychiatric or cognitive) or mode of progression (Claes et al., 1995; Zappacosta et al., 1996).

2.7 The relationship between cognitive impairment and CAG repeats

Few researchers have studied the relationship between cognition and number of CAG repeats. Foroud et al. (1995) had reported an inverse relationship between scores on subtests of the WAIS-R and number of CAG repeats in asymptomatic, but positive individuals. A later study of cognitive function using at risk subjects was concerned with relationships between cognition, age, clinical onset,

disease progression and genetic analyses (Jason, Suchowersky et al., 1997). A relationship was reported between number of CAG repeats, age of disease onset, and cognitive decline. They suggested that a high number of repeats may produce cognitive impairment well before clinical onset.

A similar conclusion was reached in another recent study (Hahn-Barma et al., 1998). HD+ subjects were compared to the subsequently noncarrier group on a range of neuropsychological tests. Significant group differences were found. The researchers then correlated test performance in the HD+ group with number of CAG repeats and found a significant correlation between repeat numbers and impaired performance on tests of executive function and memory. It was suggested that the greater heterogeneity in test performance found in gene carriers was related to the variability of CAG repeats at an individual level.

2.8 The relationship between cognitive impairment and motor functioning in those at risk

Of some interest has been whether or not subtle neurological impairment exists in those at risk. This is

a challenging task to investigate as presence of movement disorder is a diagnostic criterion for the disease. Another major complication with this issue has been determining the presence of significant motor dysfunction as often healthy individuals can present with neurological dysfunction reminiscent of early HD. Deciding on the moment of onset of the disorder is also difficult to establish because of its insidious and variable onset (Brandt, 1991; Scholz & Berlemann, 1987).

Nevertheless subtle impairment has been described in those at risk when compared to matched controls. For example, motor changes have been noted during the neurological examination (Siemers et al., 1996). Slowing of rapid voluntary motor movements (Heftner, Hömberg, Lange & Freund, 1987); slowed oral motor movements (Coleman, Anderson & Lovrien, 1990); deficits in initiation, spatial representation of movement, and use of information given in advance in order to prepare for the correct movement responses (Bradshaw et al., 1992) have been reported. Subtle involuntary movements, however, are not reliable indicators of incipient disease (de Boo, Tibben, Hermans, Maat & Roos, 1998).

Neurological evaluation, either quantitatively or qualitatively, has been included in the majority of the predictive testing neuropsychological literature, but only a few studies have correlated motor symptoms and neuropsychological findings. Rothlind, Brandt et al. (1993) specifically correlated oculomotor control and verbal memory but found both functions intact in those who were positive for the HD gene but nonsymptomatic. De Boo et al. (1997a) found that motor changes preceded cognitive changes in a longitudinal study of at risk subjects. In their study AR+ and AR- groups, initially free of cognitive differences, were followed up two years later. Six of the AR+ group were found symptomatic on neurological evaluation. Yet, when evaluated neuropsychologically, no cognitive differences were found between the three groups (AR-, AR+, and AR+ symptomatic). However, the symptomatic group performed less well than the other two groups on motor tasks.

2.9 The relationship between cognitive impairment and psychiatric illness in those at risk

The majority of predictive testing programmes incorporate a psychiatric evaluation. Many studies report no

differences in psychiatric symptomatology between those who are subsequently diagnosed AR+ and those found to be negative for the gene (Evers-Kiebooms, Decruyenaere, Fryns & Demyttenaere, 1997; Shiwach & Norbury, 1994; Wiggins et al., 1992), but isolated instances of traumatic sequelae upon receiving an increased risk of HD have been reported (Bloch, Fahy, Fox & Hayden, 1989; Lam et al., 1988; Mlynik-Szmid, 1997). Baxter et al. (1992) found the AR+ group to score higher on the anger/hostility subscale of the Profile of Mood States questionnaire, but neither the AR+ or the AR- group differed on the depression subscale. Adverse reactions by those who received an unexpected lowered risk, as well as 'survivor guilt' by this group have been documented (Huggins et al., 1992; Tibben, Duivenvoorden et al., 1993; Wiggins et al., 1992).

Some, but not all, researchers of the neuropsychological studies have included psychiatric rating scales in their test battery (e.g. Strauss & Brandt, 1988; Diamond et al., 1992). The primary use of these questionnaires has been as a screening aid, probably because the symptoms of early onset of HD can present as a psychiatric disorder. The most popular measuring instruments have been the Symptom Checklist-90 items revised, the Profile of Mood States and

Beck's Depression and Hopelessness scales. No differences between the AR groups were found in any of the studies and neither was there any suggestion of psychiatric illness.

2.10 Neuropathological studies of those at risk for Huntington's disease

Support for a discontinuity model comes from a SPECT study of metabolic changes in the frontal lobes of controls and asymptomatic gene carriers. The pattern of metabolic activity between the two groups was similar (Harms et al., 1997). Results from physiological studies also support this finding. Reduced dopamine receptor binding is seen in early symptomatic HD patients but not necessarily so in those who are asymptomatic, indicating that, in terms of dopamine receptor efficiency at least, the presymptomatic brains of HD individuals can be intact (Guttman, Thomson, Hussey, Wilson & Houle, 1996). However, the above is challenged by the findings of Hayden, Hewitt et al. (1987) and by Aylward, Brandt, Codori, Mangus, Barta & Harris (1994) who describe changes in caudate metabolism and reduced basal nuclei volume in asymptomatic gene carriers.

In spite of the discovery of a definitive predictor for HD, a definitive outcome with regard to the continuity/discontinuity hypothesis has remained unanswered in spite of a variety of different approaches to addressing the question. More specific to the present study, it is still unclear whether or not cognitive impairment precedes an unequivocal clinical diagnosis. It would appear that the body of literature on neuropsychological testing of those at risk for HD is growing but the question "when does cognitive impairment begin in HD?" remains unanswered. Part of the reason for this failure may lie in methodological constraints in the neuropsychological studies.

2.11 Small sample sizes and large test batteries in presymptomatic neuropsychological studies.

Views canvassed prior to the availability of predictive testing suggested that, should a testing procedure become available, many of those at risk would be interested in establishing their HD status presymptomatically (Evers-Kiebooms et al., 1989; Kessler, 1987b; Kessler et al., 1987). However, the actual response to the availability of a test has been mixed (van der Steenstraten, Tibben, Roos,

van de Kamp & Niermeijer, 1994). Generally, far fewer than expected requests for predictive testing have been made (Brandt et al., 1989; Craufurd, Dodge, Kerzin-Storarr & Harris, 1989, Meissen et al., 1988; Quaid, Brandt, Faden, & Folstein, 1989; Tyler, Ball et al., 1992; Williamson, 1992). For example, in Manchester only 16% (Craufurd et al., 1989) and in South Wales only 9% (Tyler, Morris, Lazarou, Meredith, Myring & Harper, 1992) of the at risk population entered a predictive testing programme. It would seem that when confronted with the opportunity of finding out HD status, most of those at risk choose not to do so.

This had meant that the size of samples for research purposes are generally small, particularly in the early research data published. For example, the first study reported (Jason et al., 1988) had only a sample size of 10. With the exception of the study by Foroud et al. 1995 in which only six subtests of the WAIS were used, the size of all other studies averaged 40 subjects (range 10-91). This is particularly problematic when the typical procedure in these studies has been to administer a large battery of psychometric tests, increasing the risk of Type I errors (Foroud et al., 1995; Jason et al., 1988). Several studies

attempted to overcome this risk by dramatically increasing the value of α (Blackmore et al., 1995; Foroud et al., 1995). Although this does decrease the risk of a Type I error, it creates other difficulties as it increases the risk of a type II error. This is a limitation which is probably inherent in all neuropsychological research of this nature but must be borne in mind when interpreting results.

2.12 Age of participants in neuropsychological studies

Linked to the question whether or not cognitive impairment presents before the onset of clear signs and symptoms, is the knowledge that intellectual deterioration is an early symptom of HD (Klawans et al., 1980). As HD is considered a disease of adult onset with age of onset averaging in the late 30's or early 40's years, the age of the subjects in the various neuropsychological studies may influence whether or not cognitive impairment in the at risk group is reported.

In general, the ages of those at risk ranged from 26.2 years in the study by Giordani et al. (1995), to 41.1 years of age in the study by Foroud et al. (1995), with the mean

ages of most subjects being in the early 30's (e.g. Hahn-Barma et al., 1998; Lundervold et al., 1995; Rosenberg et al., 1995; Strauss & Brandt, 1990).

All neuropsychological studies report no significant differences between the average age of the HD+ and HD- groups. It is possible, however, that the mean age of subjects in the studies may be contributing to whether or not significant differences are found between HD+ and HD- subjects. When the mean ages of the subjects of the abovementioned studies were grouped according to whether significant differences between the HD+ and HD- groups were averaged, the mean age for studies who did not report differences was approximately 31 years of age, and for those studies where a difference was described, the mean age was approximately 34 years of age.

As only those who volunteer for predictive testing participate in the neuropsychological studies, age of subjects is not amenable to methodological manipulation. Nevertheless, age as a possible reason for differing findings between the HD+ and HD- groups must also be considered when interpreting results.

2.13 The type of control groups used in the neuropsychological studies

The general rule has been for researchers to use the AR-group as the control group (Blackmore et al., 1995; Campodonico et al., 1996; de Boo et al., 1997b; Diamond et al., 1992; Foroud et al., 1995; Gómez-Tortosa et al., 1996, 1997; Hahn-Barma et al., 1998; Jason et al., 1988; Jason, Suchowersky et al., 1997; Rosenberg et al., 1995; Rothlind, Brandt et al., 1993). These studies have compared the AR+ group with the AR- group blind to the molecular blood results. Although the HD- group would appear to be the most appropriate control group against which the test performance of the HD+ subjects could be compared, using this group alone may have led to a restricted interpretation of the results, especially in the presence of small sample sizes.

Participating in a predictive testing programme for a genetic disorder, the results of which have the potential to radically change and limit one's lifestyle and life itself, cannot be a benign process. At the very least, it is understandable that those who do request testing experience intrusive thoughts, rumination, and

introspection during the predictive testing process: about the programme itself, or the consequences of the testing. Such psychological factors are known to negatively influence cognitive processing (Wells & Matthews, 1994).

Although both the HD+ and HD- subjects come from families vulnerable to dysfunction and educational disruption, and are exposed to the same testing procedure, the interaction between varying levels of stress, either on an individual basis, or group basis, and the disease itself may variably impact and interact with test performance. Thus, the inconsistent results of research between positive and negative presymptomatic individuals could be influenced by functional factors. There is little literature on this topic in regard to participants in testing programmes.

Although the general trend has been to use the HD- group as the control group, normal volunteer control groups have been used in some studies. Strauss and Brandt (1990), who found no group differences between AR+ and AR- groups, did use normal volunteers as a control group, matched for age, education, and gender with the AR group. They compared the at risk group with the control group prior to genetic marker results, and reported three significant differences

between the at risk group and controls. The at risk group's performance was inferior on the WAIS-R Vocabulary test, the Standardized Road-Map Test of Directional Sense, and a nonstandardised memory test.

A suggestion for this study may have been to compare the AR+ and the AR- individually with the control group after molecular analysis in order to ascertain which specific group was contributing to these three significant differences. It is not possible to say whether it was the at risk status, or subsequent molecular status that contributed to the test differences.

Lundervold and Reinvang (1995) used a wide range of control groups: already diagnosed HD subjects, nondemented patients with a recent diagnosis of idiopathic Parkinson's Disease, and patients with dermatological disease without known involvement of the central nervous system (CNS). In spite of this wide range of control subjects, all such subjects were potentially unwell, and none comprised normal control volunteers. Neither did these researchers explain why they found four subjects of their subsequently AR- negative group to show a significant degree of impaired functioning.

The study conducted to date which appears to have the most appropriate control group is that of Giordani et al. (1995). They compared AR+, AR-, symptomatic subjects, and normal controls on a wide range of neuropsychological tests. Significant differences were reported on most tests between the symptomatic and control groups, and between the AR+ and control groups. In both cases, those subjects who already presented with Huntington's disease were more impaired than the controls and the AR+ subjects. When comparing the AR+ to controls, there was a significant difference on full scale IQ and the Picture Completion subtest of the WAIS-R, with the AR+ group performing worse than the control group.

Only one test difference was noted between the AR+ and the AR- groups (Tactual Performance Location), with the performance of the AR- being inferior to that of the AR+ group. Of interest is the finding that the AR- also performed significantly worse on the WAIS-R Arithmetic subscale, Paired Associates subtest of the WMS, Tactual Performance Time per Block, and Stroop Color/Word when compared to controls. Reasons for these unexpected findings were discussed but not explored further by the researchers.

It would appear that none of the studies to date, with the exception of Giordani and colleagues, have undertaken a post molecular comparison of the AR+ and AR- groups with a volunteer control group.

2.14 Anomalies in test performance in neuropsychological studies

Several studies have reported test findings incongruent with the working hypothesis that the AR+ group would always produce an inferior performance to the AR- group. As noted above, Giordani et al. (1995) found that the AR+ group performed better than the AR- group on a test of Tactual Performance Location and the AR- group performed significantly worse than the controls on the WAIS-R Arithmetic subscale, Paired Associates subtest of the WMS, Tactual Performance Time per Block, and Stroop Color/Word.

A similar trend had been recorded by Strauss and Brandt (1990). Although no significant differences were found between the AR+ and AR- groups by these researchers, their results are interesting in that they found the AR+ group to perform better than the AR- group on the Standardized Road-Map Test of Directional Sense. Blackmore et al. (1995)

also reported a similar paradoxical finding for the Corsi Supraspan test. Neither research groups commented further on this trend.

Lundervold & Reinvang (1995) found that all their AR+ subjects showed a degree of impaired functioning but so did four of the AR- group. They attributed this finding to the possibility that some of the subjects who had been allocated to the AR+ group on the basis of a genetic marker result, may have been misallocated. Some of these subjects had been assigned an estimated risk of 10-50%.

De Boo et al. (1997b) found that the VIQ was lower than PIQ, in their at risk group when compared to normal controls, a pattern that could not be explained on the basis of early HD. The typical presentation is decline in PIQ scores before VIQ scores (Butters et al., 1978; Wilson & Garron, 1979). They proposed that psychosocial reasons could explain this discrepancy but did not explore this hypothesis further.

The majority of the few research groups that have attempted to explain these anomalies in their research findings have raised the question of nongenetic issues influencing test

results (Bylsma et al., 1992; de Boo et al., 1997b; Giordani et al., 1995; Rosenberg et al., 1995). These issues will be discussed in next section.

2.15 Education, IQ, and socioeconomic status of those who request predictive testing

Giordani and colleagues put forward several suggestions for the poor performance of the AR group when compared to the control group. Firstly, on reanalysis of their data, education differences across their groups were identified: they found that the mean level of education for the AR-group was two years below that of the AR+ and control group - a difference that reached significance. In addition, they had used controls from an intellectual community of students. They suggested that using university students as controls was possibly inappropriate since their IQ may be heightened when compared to the experimental groups, regardless of equal levels of education across groups. More so as students are 'test wise' and more familiar with testing situations.

Perusal of the other predictive neuropsychological research revealed that education has not played a major role in

influencing the outcome of the research. Not all studies recorded whether or not education levels were similar across research groups (e.g. Foroud et al., 1995; Gómez-Tortosa et al., 1996; Jason et al., 1988), however, in studies that did, no significant differences in levels of education were reported between the AR+ and AR- groups. In the studies where education levels were recorded, both differences (e.g. Diamond et al., 1992) and no differences between AR+ and AR- groups (e.g. Blackmore et al., 1995; de Boo et al., 1997b; Strauss and Brandt, 1990; Rothlind, Brandt et al., 1993) were reported. Thus, education may have played a role in the study of Giordani and colleagues, but is not the reason for the discrepancies in the rest of the at risk neuropsychological research.

De Boo et al. (1997b) in response to the comments in Giordani's study, underscored that a control group from a socioeconomically similar population to that of the at risk subjects rather than students should be used.

The general trend implied from predictive testing research is that those who request molecular analysis come from the higher socioeconomic groups (Kessler, 1987b; Tyler, Morris et al., 1992). Such individuals are usually employed in

white collar occupations and have a higher level of education than the general population (Bloch et al., 1989; Codori, Hanson & Brandt, 1994; Tibben, Frets et al., 1993). Socioeconomic status was specifically noted in one predictive testing programme (but not a neuropsychological study; Tyler, Ball et al., 1992), the participants of which largely came from the higher socioeconomic groups. Socioeconomic status has not been mentioned in neuropsychological studies apart from a comment by Blackmore et al. (1995) that participants in their study were from a middle class background.

2.16 The stress of being at risk as a nongenetic factor in neuropsychological test performance

Giordani et al.'s (1995) raised the suggestion that variability in predictive neuropsychological testing was influenced by stress which could be responsible for the poorer scores in at risk groups. As a life threatening disorder, HD has wide personal and social ramifications, and as such, the process of finding out whether one has the gene or not, is likely to be extremely anxiety provoking (Baum, Friedman & Zakowski, 1997). It is now widely recognised that not knowing one's risk status for a life

threatening disease is stressful (Baum et al., 1997; Blackmore et al., 1995), and that anxiety and stress can negatively impact upon cognitive functioning (Everly & Horton, 1989; Hindmarch, 1998; Pillon et al., 1991). HD is no exception. It is possible that the neuropsychological impairments reported by some researchers merely reflect the distress of being at risk for a life threatening disease and the decision process of applying for predictive testing rather than more sombre reasons of HD symptomatology.

This suggestion, put forward by Giordani et al. (1995), has been raised in other neuropsychological studies. Rosenberg et al. (1995) had mentioned stress as an influencing factor in predictive testing. In their study, the AR- group performed below standardised norms on tests of concentration, which Rosenberg and colleagues put down to stress, related to the testing situation. The notion was not pursued however.

Similarly, De Boo et al. (1997b) proposed that psychosocial stressors could explain why they found a higher PIQ score in relation to VIQ in their at risk group. This IQ profile is not typical of HD which presents with the greatest decline in PIQ scores (Butters et al., 1978; Wilson &

Garron, 1979). It was suggested that individuals in homes where someone has HD may result in an environment which discourages academic training. In turn this could lead to educational underachievement and lack of ambition, which could lead to a lower VIQ score as the content of verbal subtests is strongly education dependent (De Boo et al., 1997b).

Only one presymptomatic neuropsychological study to date has purposively attempted to control for the stress of being at risk for HD (Bylsma et al., 1992). They tested HD patients, spouses of HD patients, at risk subjects, and normal volunteer controls. They used healthy community volunteers to control for the ... "potentially deleterious effect of knowing that one may develop an incurable, ultimately fatal disease." (pp.114-115). Using merely two specialised tests of spatial cognition, they only compared the at risk group to the volunteers and found no difference between the two groups. They presumably assumed from this result that the at risk group were cognitively intact, so did not compare the AR+ and AR- groups individually with this control group. Thus, masked differences which could have been identified if each of the AR group had been

compared individually with the volunteer control group were not controlled for.

2.16.1 The impact of stress on cognition

Although stress can negatively impact upon cognitive functioning (Everly & Horton, 1989; Pillon et al., 1991), the precise nature and impact of life event stress on cognition is not a well researched area. Much of this work has been carried out in the field of post traumatic stress disorder (PTSD), which has among its diagnostic criteria difficulties with concentration and memory (DSM-IV, 1994). Impairments reported in combat veterans with PTSD suggest mild attention, concentration, and memory difficulties, deficits in concept formation, problem solving, and use of feedback in decision making (Barrett, Green, Morris, Giles & Croft, 1996; Bremner et al., 1993; Dalton, Pederson & Ryan, 1989; Everly & Horton, 1989; Sillanpaa, Agar, Milner, Podany, Alexrod & Brown, 1997). Similar impairments present in those at risk for HD (e.g. Diamond et al., 1992; Rosenberg et al., 1995).

Reports of cognitive impairment in other disorders for which a limited life expectancy is a constant threat have

also been described. Cancer sufferers, for example, frequently report symptoms of inattention, inability to concentrate, and memory problems (Blackmore, 1989; Cull, Hay, Love, Mackie, Smets & Stewart, 1996).

Everly & Horton (1989) suggested that high intensity neural stimulation leads to hypersensitivity within the limbic circuitry causing widespread psychological disturbance. In support of this Elliott & Sahakian (1995) have reported that stress has been found to cause excessive dopamine release in the limbic regions that have projections to the frontal cortex. They suggested that increased dopamine could result in a subjective perception of higher stress levels and poor objective efforts to modulate the elevated stress levels, which, in turn, could result in compromised neuropsychological test performance.

2.16.2 Measuring cognitive impairment associated with stress

Making the assumption that neuropsychological test scores are sacrosanct measures of brain damage is incorrect (Keefe, 1995). Poor test performance does not **only** reflect irreversible structural changes to brain architecture, but

can be attributed to reversible factors such as tiredness and stress (Reitan & Wolfson, 1997), sleep deprivation (Horne, 1993), and the formal testing situation itself (Wells & Matthews, 1994).

For example, in a study by Horne (1988) on the effects of 36 hours of total sleep deprivation on the neuropsychological function of medical staff, impairment was found in word fluency, nonverbal planning, creativity, and originality, which could only be partly overcome with increased subjective effort. In the same study, perseveration was observed in all tests of divergent thinking. Functioning returned to normal after sleep. Horne (1993) attributed impaired neuropsychological test performance to reversible prefrontal cortical dysfunction secondary to lack of sleep.

2.17 Are those who request testing a self selected group?

Another potential source of influence on psychological test performance, inferred by Giordani et al. (1995), comes from a question raised by other researchers such as Codori et al. (1994), Kessler (1994) and Tyler, Ball et al. (1992). Are those who request predictive testing self selected?

The nature of predictive testing programmes is such that those at risk for the disease volunteer to participate in the programme and are not recruited. Does this mean that these participants differ from the general population in some way, or from those at risk who do not request testing? It must be mentioned that the evidence supports that only a certain group of those at risk do request testing, giving as a reason for this request, the need to alleviate the uncertainty of their HD status. The uncertainty is stressful; so stressful in fact that even finding out that one is going to get this awful disease is preferable to not knowing (Codori & Brandt, 1994; Meissen, Mastromauro, Kiely, McNamara & Myers, 1991).

There has been a plethora of research documenting the outcome of predictive testing programmes, much of which supports the hypothesis that only a certain subgroup of those at risk do request testing. Included in this research are details of matters such as the characteristics and demographic variables of those who request testing, attitudes towards testing, demand for testing, and psychological sequelae to testing (e.g. Codori & Brandt, 1994; Holloway et al., 1994; Tyler, Ball et al., 1992), as well as availability of social support (Fox et al., 1989;

Tibben, Frets et al., 1993), coping abilities (Decruyenaere et al., 1995), and quality of life (Codori, Slavney, Young, Miglioretti & Brandt, 1997).

From this research has come the view that those who come forward for testing are highly motivated (Tyler, Morris et al., 1992), feel able to cope with a positive result (Codori et al., 1994; Tibben, Frets et al., 1993), have high ego strength (Codori et al., 1994; Decruyenaere et al., 1995), are resourceful and psychologically well adjusted (Decruyenaere et al., 1995).

Feeling able to cope with knowing one's HD status appears to be related to good self concept, well developed interpersonal skills, ability to tolerate anxiety, persevere in the face of adversity (Codori et al., 1994), and being more socially extroverted than a general population (Decruyenaere et al., 1995). In a sense those who request testing appear to need a strong degree of control over their future.

2.18 Concluding remarks concerning methodological and nongenetic reasons for conflicting neuropsychological test performance

There are several methodological shortcomings that may be contributing to the irresolution of the continuity/discontinuity hypothesis. In particular, small sample sizes, large numbers of independent variables, as well as the differing mean age of subjects in the various studies. Failure to compare the HD+ and HD- groups with a carefully matched control group comprising subjects with no investment in HD may also limit the interpretation of the test results.

Furthermore, failure to control for the psychological impact of being at risk for a life threatening disease and participating in a predictive testing programme to ascertain personal disease risk may be a contributing factor to the inconclusiveness of the present research findings. Finally, the at risk group may be a self selected group and present with a particular personality style and way of dealing with the predictive programme and the disease itself. Consequently, the presence of cognitive impairment in those at risk for HD does not

necessarily imply structural variation within the brain or the onset of HD, but could, in part at least, represent secondary factors associated with an at risk status.

Apart from the small study carried out by Bylsma and colleagues, the suggestions of nongenetic reasons for poor test performance have not been fully investigated to date. As mentioned by Giordani *et al.* (1995), "...future research in AR subjects should include a search for nongenetic factors that might explain the poor functioning in AR subjects...." These issues warrant further consideration before the debate regarding symptom onset in HD can be settled.

2.19 Overall conclusion to Chapters one and two

A literature review of HD, including neuropathology, genetics, and clinical presentation, with special emphasis on neuropsychological presentation has been presented in Chapter one above. With an emphasis on neuropsychological research, Chapter two was devoted to a discussion of early attempts to identify HD preclinically prior to the discovery of molecular analysis and to the discovery of a genetic means to predict who of those at risk will go on to

manifest symptoms of the disease. Attempts to identify HD preclinically on the basis of cognitive functioning with the advantage of molecular analysis and therefore possibly answer the continuity/discontinuity hypothesis were also discussed. Possible reasons for the failure of current research to answer this hypothesis were then presented. Methodological and non-neurological suggestions for the equivocal test results were also put forward in Chapter two.

It is concluded from the above, that methodological restrictions could exist in the majority of neuropsychological studies aimed at assessing whether cognitive impairment is present presymptomatically in HD. It is also concluded that the experience of being at risk for a life threatening disease and participating in a predictive testing programme for that disease may be stressful, which in turn may influence the cognitive performance of those at risk for HD. Further, those who request predictive testing may be a self selected group. None of the studies to date have explored possible non-neurological reasons that could account for the conflicting results in neuropsychological studies.

In the light of the above, the null hypotheses of the present study will now be stated.

2.20 Hypotheses of the present study

The central null hypothesis of the present study is that

Neuropsychological impairment is not present in those at risk for HD prior to symptom onset.

In order to comprehensively investigate this null hypothesis the following more specific hypotheses have been generated:

- 1) In individuals at risk, those subsequently found positive for HD after molecular analysis will not differ in performance from those who are subsequently found negative for HD on a battery of psychological tests.
- 2) In individuals at risk, those subsequently found positive for HD after molecular analysis will not

differ in performance from a matched volunteer control group on a battery of psychological tests.

3) Those subsequently found negative for HD after molecular analysis will not differ in performance from a matched volunteer control group on a battery of psychological tests.

4) The scores from a stress control group will not differ in performance from a matched volunteer control group on a battery of psychological tests.

5) Those subsequently found positive for HD after molecular analysis will not differ in performance from a stress control group on a battery of psychological tests.

6) Those subsequently found negative for HD after molecular analysis will not differ in performance from a stress control group on a battery of psychological tests.

7) Those subsequently found positive for HD will not show a significantly greater incidence of

psychiatric illness than those found negative for HD.

- 8) Those subsequently found positive for HD will not show significantly greater number of neurological signs than those found negative for HD.
- 9) There will no correlation between the neuropsychological scores for those subsequently found positive for HD and neurological signs.
- 10) Those who request predictive testing are not a self selected group and consequently, there will be no differences in a) purpose in life or b) personality style between the at risk group and the matched volunteer control group.

Chapter Three

3.0 METHODOLOGY

The methodology of the present study is discussed below.

3.1 Subjects

3.1.1 Experimental group

By the end of December, 1997, 31 people had requested molecular analysis and completed the Gauteng predictive testing programme for Huntington's disease. Of these, 26 had agreed to take part in the present study and formed the experimental group.

In the light of the discussion previously presented in this thesis in the arena of predictive testing for HD, a normal control group made up of individuals unrelated to the predictive testing programme was included.

3.1.2 Normal volunteer control group

The normal volunteer control group in the present study comprised 26 individuals matched for age, sex, and education with the experimental group. Every endeavour was made to find controls who individually corresponded with each subject according to these variables and the use of university students was avoided. As the employment status of members of the at risk group could be equated with class III and above according to the British Registrar General's Scale (Liberatos, Link & Kelsey, 1988), the volunteer control group were matched accordingly.

Assessment of socioeconomic status usually includes information concerning highest level of education, occupation (usually of household head) and income (Liberatos et al., 1988). Socioeconomic status has been partially controlled for in many neuropsychological studies through the analysis of education. Data concerning participants occupation, or occupation of the breadwinner in the case of a fulltime housewife was also collected. Use of students as normal volunteer controls was limited to two post graduate subjects who, at the time of testing for this study had only just commenced their first day of

training as aspirant psychometrists. They not been exposed to any practical psychometric (or neuropsychological) testing themselves. They were included in the control group because their biographical details corresponded with members of the HD group.

3.1.3 Stress control group

The stress control group comprised 12 subjects who were recruited from the outpatient urology clinic at the Johannesburg Hospital, the Reach for Recovery support group, and from personal referral by friends and colleagues by means of a snowball approach. The choice of subjects for this group had been difficult to make. HD is the only genetic disease with a clear and established predictive testing programme, so comparing the HD groups with another genetic disease group was not possible. Other illnesses that exert a limited life expectancy often have a dementing process as part of the illness constellation (e.g. the Human Immunodeficiency Virus) which would have been inappropriate. Consequently, the subjects chosen were adults in remission from a cancer which had not involved brain structures or CNS, who were not receiving active treatment for their illness, and whose cancer had not

metastasised. This was done in order to exclude any possible test interference by radiation therapy or chemotherapy, or focal site of disease.

The presence of cognitive impairment in cancer patients is somewhat controversial but appears to be related to several distinguishable factors. Higher cognitive dysfunction has been reported as a long term sequelae to childhood cancers where CNS irradiation and intrathecal chemotherapy have been given (Gamis & Nesbit, 1991; Moore, Copeland, Reid & Levy, 1992; Rodgers, Britton, Morris, Kernahan & Craft, 1992), in terminal cancer patients (Pereira, Hanson & Bruera, 1997), in adult bone marrow transplant recipients (Andrykowski, Schmitt, Gregg, Brady, Lamb & Henslee-Downey, 1992), in patients whose cancers have had CNS involvement (Kramer & Moore, 1989; Meyers & Scheibel, 1990), and in patients with paraneoplastic syndrome (Meyers, Byrne & Komaki, 1995).

Certain forms of treatment for cancer have been held responsible for cognitive dysfunction (Meyers, Scheibel & Forman, 1991), but this has been challenged. For example, reports of improvement in cognitive function after treatment have been described (e.g. Bruera, Miller,

McCallion, Macmillan, Krefting & Hanson, 1992; Jason, Pajurkova, Taenzer & Bultz, 1997; Valentine, Meyers, & Talpaz, 1995). Further, there does not appear to be any long term deleterious effects on cognitive functioning with chemotherapy on tumours outside the CNS (Mocre et al., 1992) or with prophylactic intrathecal chemotherapy (Andrykowski et al., 1992).

In the light of the above, the criteria, stated above, for inclusion into this stress group excluded any cancer patients at risk for cognitive impairment as a result of the cancer itself rather than the psychological consequences of having received, and been treated for, a diagnosis of cancer.

The Beck Depression Inventory (1987) was administered as a screening test to rule out depression as a reason for poor test performance. Otherwise suitable individuals were excluded from the study if they scored more than 10 on the Beck Depression Inventory.

This group of subjects proved very difficult to recruit. Consequently, the careful matching of all demographic

variables of this group with the at risk and control group was not possible.

3.2 Psychological tests

A full list of tests administered to the subjects is presented in Table 3.1. These tests were administered to all three groups in the same order of presentation. See Appendix 1 for test order.

Table 3.1 Test Battery (in alphabetical order)

Bicycle Drawing Test
Boston Naming Test
Controlled Oral Word Association Test
Design Fluency Test
Judgement of Line Orientation Test Form V
Millon Multiaxial Clinical Inventory-II
Modified Wisconsin Card Sorting Test
National Adult Reading Test
Purpose in Life Test
Rey Auditory Verbal Learning Test
South African Wechsler Adult Intelligence Scale
Stroop Color/Word Test
Tinkertoy Test
Topographical Orientation
Trail Making Test
Wechsler Memory Scale

3.2.1 Tests of general intellectual function

The South African Wechsler Adult Intelligence Scale (SAWAIS; 1983) was the primary tool used to evaluate intellectual function in the at risk group²².

The National Adult Reading Test (NART) (Nelson & O'Connell, 1978) was used to estimate IQ in the normal control group and stress group due to time constraints. This test takes considerably less time to administer than the SAWAIS.

The Wechsler Memory Scale (WMS) (Wechsler, 1945) can be considered analogous to IQ (Wechsler, 1945). During the development of the test the Memory Quotient (MQ), the scale's total adjusted score, was calculated to correlate with IQ score. However, as memory deterioration is a very early indicator of HD, the test was not used in the present

²²The validity of the SAWAIS as a relevant and accurate measure of IQ has been challenged (see Nell, 1994). However, South African research findings suggest that the NART correlated well with the SAWAIS (Struben & Tredoux, 1989). Further, the NART had been administered to 17 of the at-risk group. The results of which gave an estimate of FIQ as 115 (SD=5.92) with VIQ as 115 (SD=6.44) and PIQ 114 (SD=4.63). The estimated scores on the NART were remarkably similar to those obtained from the SAWAIS.

study as a measure of IQ. Instead it was used for its principal function, as a memory test.

3.2.2 Psychological tests used for neuropsychological assessment

Although all cognitive tests can be subsumed under the umbrella term of psychological tests, many have become intrinsically associated with the specialised psychological field of neuropsychology. Thus, the term 'neuropsychological test' is used to convey psychological tests commonly used by neuropsychologists.

The neuropsychological test battery in the present study was chosen to isolate purported deficits associated with damage to the basal ganglia/cerebral prefrontal lobe structures. This was done for two reasons. Firstly, an analogous approach has been used by most of the researchers in similar studies, and secondly, in the early stages of the disease these are the anatomical structures primarily involved. It seems reasonable to presume that the first presentation of any cognitive impairment in an individual at risk for HD would reflect difficulties in tests considered capable of isolating functions of the

subcortical/cortical prefrontal loops. Further, using a relatively large test battery (>10 tests) is more likely to detect subtle impairment in asymptomatic subjects than smaller batteries (White, Heaton & Monsch, 1995).

The neuropsychological test battery chosen for the South African programme utilised a design similar to that of Jason *et al.* (1988) and Strauss & Brandt (1990). These studies had already been published at the time of onset of the South African Programme. The specific tests used aim to test deficits known to be vulnerable to the early onset of HD. For example, Butters *et al.* (1978) have noted that, at early diagnosis, patients already had memory difficulties and reduced verbal fluency. Caine *et al.* (1978) described difficulties associated with frontal lobe pathology in early HD.

Not all varieties of memory impairments were measured because of two reasons. Firstly, time constraints limited the size of the battery. Secondly, the literature suggests that episodic declarative memory impairment is seen at early onset of HD. Thus, this memory type was tested most extensively in the battery.

Lezak (1995) has been used as the main source of test function identification.

Wechsler Memory Scale (WMS) (Wechsler, 1945)

A well known test used to rapidly assess various aspects of memory function including immediate memory, declarative memory (both episodic and semantic memory), remote memory, verbal and nonverbal (spatial) memory, and working memory.

This test has been extensively used in HD research (e.g. Diamond et al., 1992; Giordani et al., 1995; Jason et al., 1988; Pillon et al., 1994). Because of its wide use, and because of time constraints, the original form was used rather than the updated WMS-II form.

The Rey Complex Figure (RCF) (Rey, 1941)

The RCF is a familiar neuropsychological test of visuospatial skills, nonverbal learning and recall, as well as planning and organisational skills. It has been used in HD research to measure all these abilities (Brouwers et al., 1984; Jason et al., 1988; Sprengelmeyer, Canavan et al., 1995).

The subject is presented with the figure and required to accurately copy it. After a delay and without the stimulus figure, the subject is asked to draw the figure again. The copy trial measures visuospatial, planning and organisational skills, while the delayed trial measures implicit learning (Kolb & Whishaw, 1995). The scoring adopted in the present study is the approach set out by Rey-Osterreith (see Lezak, 1995). Elements of the drawing, their positional accuracy, and strategy of drawing style were all scored.

Key Auditory Verbal Learning Test (RAVLT) (Rey, 1964)

At a later point in the study it was thought that the memory tests utilised were not sufficient to measure both free recall and recognition of new learning information and the RAVLT was administered from patient no 8 onwards. This is a well known test of declarative verbal memory abilities.

This test requires the subject to listen to a list of simple, english words read at the rate of one word per second. After which, he/she is required to call out, in any order, remembered words. This procedure is repeated



for a further four times, each time it is anticipated that more words will be remembered. An interference trial of 15 different words are then read out and recall of these words requested. The subject is then asked to recall the first list. Finally, the test requires the subject to identify the 15 words from the first list from a bank of 50 words. This bank includes words from both lists, as well as semantically and phonemically similar words.

In the present study scores from trial 1 and trial 5, the interference trial, trial 6 and the recognition trial were used for statistical analysis. In addition, the number of extra list errors (words not included in the list) and repetitions (words previously generated in a given trial) made were also scored.

This test is similar to the California Auditory Verbal Learning Test both of which are extensively used in HD research (e.g. Diamond et al., 1992, Lundervold et al., 1994; Pillon et al., 1993).

The Stroop Color (sic)/Word Test (Golden, 1978)

A test of attention and mental tracking (Lezak, 1995). There are three separate forms to this test, each comprising 100 items. The first requires the subject to read the words RED, BLUE, GREEN, in a randomly presented order. The second form requires the naming of coloured crosses (XXXX). The final form requires the naming of the colour in which the name of a colour is printed. The actual colour of printing and the written word are incongruent (e.g. the word BLUE is printed in red and the correct answer is the response 'red'). This third form requires inhibition of the more automatic word reading response and selective production of the colour naming response. The Stroop has been frequently used in HD research (e.g. Brandt et al., 1995; Giordani et al., 1995; Starkstein et al., 1992; Strauss & Brandt, 1990). This test is considered a sensitive indicator of cognitive dysfunction in HD (Wexler, 1979).

Trail Making Test (Reitan, 1958)

A timed test of visual scanning, conceptual, visuomotor tracking and divided attention (Lezak, 1995). The test has

two parts: Trail A requires the subject to connect consecutively numbered circles and Trail B requires the subject to alternate between consecutively numbered and lettered circles (i.e. 1 - A - 2 - B - 3 - C etc.).

This test is well established and used frequently in HD research (Bamford et al., 1989, 1995; Diamond et al., 1992; Giordani et al., 1995)

The Tinkertoy Test (Lezak, 1982)

A test of executive function requiring the subject to initiate, plan and carry out a complex task in an unstructured environment. The test, adapted from a child's constructional toy, requires the individual "...make whatever you wish..." in ten minutes with 50 predetermined pieces. This test has not been used on a HD population to date but has been used as a test of executive function in closed head injury (Bayless, Varney & Roberts, 1989). It was used in the present study as a novel way to assess purported frontal lobe functioning.

Wisconsin Card Sorting Test (WCST) (Berg, 1948)

The modified version of administration was used of the Wisconsin Card Sorting Test (MWCST; Nelson, 1976). A test used primarily to assess concept formation and reasoning, and ability to shift set (Lezak, 1995). This test is frequently used to measure frontal lobe dysfunction (Drewe, 1974), although the use of this test to identify frontal lobe dysfunction has come into debate in recent years (Anderson, Damasio, Dallas Jones, & Tranel, 1991). Nevertheless, it continues to be well cited in HD literature (Blackmore et al., 1995; Diamond et al., 1992; Paulsen, Salmon, Monsch, Butters, Swenson & Bondi, 1995; Pillon et al., 1994; Rothlind, Brandt et al., 1993; Starkstein et al., 1992). In general, those with HD perform more poorly on this test than controls.

Free drawing test - Bicycle

Free drawing taps mechanical reasoning and visuographic function. This task required the subject to draw, freehand, a bicycle. The scoring paradigm used was that provided by Lezak (1995). Individuals with frontal lobe

damage reportedly fail to draw an adequate bicycle (Messerli, Seron & Tissot, 1979 cited in Lezak, 1995).

Topographical orientation

A nonstandardised test based on the Test of Geographic Orientation (Benton, Levin & Van Allen, 1974) but designed for SA use. The subject is required to name the cities identified by eight points on a map of SA. As far as can be established, this test has not been used in HD research to date but was used in the present study as a variation on the visuospatial tests used. Visuospatial impairment is considered an early presenting feature of cognitive decline in HD (Fedio et al., 1979; Josiassen et al., 1983), and impaired map reading has been specifically described in those with HD (Boll et al., 1974).

Judgement of Line Orientation Test Form V (Benton, Hamsher, Varney & Spreen, 1983)

A task originally developed to compare hemispheric specialisation in identification of slope of lines. Results of the initial studies revealed a marked impairment for this visuospatial task in patients with right

hemisphere lesions (Benton, Hannay & Varney, 1975). The subject is required to identify two target lines presented on one page from a multiple choice card of 11 lines presented in different directional orientations presented on a different page. This task was included in the neuropsychological battery because of its sensitivity to visuospatial impairment. It was used by Blackmore et al. (1995) in their study of presymptomatic at risk subjects.

Design Fluency Test (Jones-Gotman & Milner, 1977)

This is a nonverbal version of Thurstone's Word Fluency Test (a test similar to the COWAT). The task aims to measure spontaneous output of nonfamiliar drawings. The methodology used in the present study was the same as that described by Jones-Gotman & Milner (1977). The individual is required to generate as many different designs as possible in four minutes using 4 lines. Two examples are given. This test is not as well used in HD research as its verbal counterpart, but was used in one of the first neuropsychological evaluations of predictive testing (Jason et al., 1988).

Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1989)

The COWAT, a test of semantic retrieval and generative naming, has three timed trials. Each trial requires the subject to rapidly generate words within a time limit of 60 seconds. The letters F A S are the initials of choice for each respective trial in the present study. Two rules must be adhered to: no words beginning with a proper noun can be used, nor can the same stem have different suffixes added (e.g. happy, happier, happily).

This test is considered a sensitive indicator of brain dysfunction, especially when due to frontal lobe lesions (Benton, 1968). It has been found that HD patients perform poorly on this task (Hodges *et al.*, 1990; Rosser & Hodges, 1989).

The Boston Naming Test (Kaplan, Goodglass, Weintraub & Segal, 1983)

A test of object naming requiring the subject to spontaneously name 60 pictures of high and low frequency. This test has been used in two ways in the HD literature:

either as a test of basic intelligence (Pillon et al., 1991), or to investigate naming abilities in HD patients (Hodges et al., 1991).

Earlier studies reported naming skills to be intact in HD (Butters et al., 1978). However, deficits due to visually based errors have been reported on this ~~Boston~~ Naming Test (Hodges et al., 1991).

3.2.3 Test formulation according to cognitive function

The above section gave each test individually with its main use. In this section, the various functions assessed by this battery are presented. However, it is emphasised that neuropsychological tests are multifactorial in function and that the information presented below is a guideline only to the dominant function of each test.

Attention (including sustained, focused, and divided attention)

Attention abilities were measured using the Digit Span forward and Mental Control subtests of the WMS, the first two forms of the Stroop test, and the Trail Making A test.

Divided attention skills were measured by means of the Digit Span backward of the WMS, the Trail Making B test, and the last form of the Stroop Test.

Memory

Memory was tested by means of the Logical Memory, Spatial Reproduction and Paired Associate subtests of the WMS, RCF recall, and RAVLT.

Executive function

Planning and organisation skills were measured by means of the drawing approach used for the RCF and the Tinkertoy Test.

Shifting set was measured by means of the MWCST, Trail Making B test, and last form of the Stroop test.

Conceptual reasoning

Conceptual reasoning was measured by means of the free drawing test and the MWCST.

Language skills

Word generation was tested using the COWAT and object naming by means of the Boston Naming Test.

Visuospatial skills

Visuospatial skills were measured by the Judgement of Line Orientation test, RCF, topographical orientation, and free drawing task. Spatial design generation was measured by means of the Design Fluency test.

3.2.4 Assessment of self selectedness

A broad range of rating scales has been used to analyse whether or not those who request testing are a self selected group, but two areas of research have not been extensively covered by other researchers. These are the personality profile of those who request testing and their sense of purpose in life. To assess both these aspects of self selection the following instruments were used.

The Millon Clinical Multiaxial Inventory-II (MCMI-II)
(1987)

The MCMI-II (1987) is primarily for use in a clinical population. The normative data for this personality scale was based on persons who had psychological symptoms, or were engaged in psychotherapy or psychodiagnostic assessment. It was used in the present study as the subjects of this study were undergoing psychological and psychiatric assessment as part of the predictive testing process.

Nonetheless, it has been used on a normal population several times (e.g. Craig & Olson, 1992; Munley, Bains, Bloem, Busby & Pendziszewski, 1995), and Choca, Shanley & Van Denburg (1992) suggested that as long as cognisance is taken of the original population of standardisation on this test, there is nothing intrinsically wrong with using it on a nonpsychiatric population. Its good correlation with the 16 PF, a test of normal trait personality scales further suggests that its use on the normal population may be justified (Craig & Olson, 1992)²³.

²³For example, when compared to the 16PF, the Narcissism scale of the MCMI correlates positively with Independent, Dominant, and Venturesome scales; the

The MCMI-II has three subscales: personality style scales, severe personality scales, and clinical symptom scales. By personality style Millon (Choca et al., 1992) means the "psychological essence of the person...the 'enduring pattern' of perceiving, relating to, and thinking about the environment and oneself" (p.5). Millon & Everly (1985) conceived the more severe personality scales as syndromal elaborations of the, milder, personality style scales, differing in intensity, frequency and chronicity of symptom presentation. The remaining clinical scales measure symptoms that are superimposed upon the personality style and which lead to a DSM-III-R diagnosis (Choca et al., 1992).

A more recent edition of the MCMI has been produced, the MCMI-III, developed to correlate with the DSM-IV, the latest version of the manual. However, at the commencement of this study, the DSM-III-R was the most current diagnostic manual available to the psychiatrist, and consequently the MCMI-II was the obvious choice. In order to maintain

Compulsive scale correlates moderately with Emotionally Controlled, Conscientious and Self-disciplined scales; and the Histrionic corresponds with Extroversion, Venturesome, Enthusiastic, Independent, and Dominant scales (Craig & Olson, 1992).

uniformity in the present study, the use of the MCMI-II has continued.

The Purpose in Life Test (PIL) (Crumbaugh & Maholick, 1969b)

The PIL was constructed from a logotherapeutic orientation as an attitude scale to measure Frankl's basic concept of 'existential vacuum' (Crumbaugh & Maholick, 1964). The scale was based on a hypothesis that an individual can and will give a reasonably reliable assessment of his true feelings regarding purpose in life from conscious considerations (Crumbaugh & Maholick, 1969a).

There are three sections to this questionnaire. Part A of the PIL test can be objectively scored as it uses a linear scale and this part is most generally used in research because of its objective scoring system (Crumbaugh & Maholick, 1969a). Part B utilises an open ended statement style, and Part C requests the candidate to write a paragraph describing aims, ambitions, and goals in life. Part A is used in the present study, because it lends itself to quantitative analysis. Sections of Part B and

Part C have been subjected to limited content analysis.

3.3 Procedure

3.3.1 Experimental group

Testing took place over two days at the Johannesburg Hospital for the experimental group. Details of age, sex, education, marital status, index parent, and number of siblings were obtained at the first interview, along with the reasons for requesting predictive testing. When the programme commenced, reasons for requesting testing were largely unknown and the compilation of a formal questionnaire was therefore difficult. Consequently, reasons were elicited at the initial interview by means of open ended questioning. Item analysis of this information was undertaken after the interview in order to cluster the reasons into separate categories.

The administration of the MCMI-II, the PIL test, and SAWAIS was also carried out during the first interview. The remaining neuropsychological tests were administered at the second interview, and the same test order was used throughout.

In order to objectively establish the presence or otherwise of any cognitive or behavioural differences between the AR+ and AR- groups, such individuals underwent the above mentioned interviews before undergoing the DNA testing procedure. Thus, the status of each individual in terms of HD was not known. The blood samples were only drawn for laboratory testing at the end of the programme. This part of the study was, therefore, blind and prospective. Apportionment to HD group was carried out after the results of molecular analysis had been established.

The psychiatric and neurological status of the experimental group was gained from the reports received from the psychiatrist and neurologist. The psychiatrist used a semistructured clinical interview to evaluate patients. See Appendix 2 for this format. The neurologist evaluated each patient clinically and commented upon a full neurological examination in his report. See Appendix 3 for specific neurological signs assessed and Appendix 4 for a table setting out each subject's individual neurological profile.

3.3.2 Normal volunteer control group

Only one interview was required for the volunteer control group. Subjects were tested either at the hospital or in their homes, depending upon the personal convenience of the volunteer. Information regarding age, sex, occupation, education, and marital status was collected. Subjects were excluded if there was a history of learning disorders neurological and/or psychiatric illnesses.

The test battery administered to the control group comprised the MCMI-II, the PIL, and all neuropsychological tests. The NART was given to establish FIQ as the administration of the full SAWAIS was considered to be too time consuming and demanding upon the good will of the control group. In addition to using the NART to estimate IQ in the control group, however, two subtests of the SAWAIS, the Information and Block Design subtests, were also administered. This was done as a backup measure of IQ as subtests of a standardised intelligence scale give a reasonable extrapolation of FIQ (Randolph, Mohr & Chase, 1993). The neuropsychological tests were administered in one session in keeping with the procedure followed for the

at risk subjects. They were asked to fill in the MCMI-II and PIL separately.

3.3.3 Stress control group

Subjects were tested at the Johannesburg clinics and in their home. Information regarding age, sex, occupation, education, and marital status was collected as well as details concerning their illness. The same battery as given to the normal volunteer control group was used.

In order to avoid tester bias, the psychologist who administered the battery of tests to the HD group did not administer the tests to either of the control groups. This administration was carried out by an experienced registered psychometrist who had been initially trained by the writer to administer and score the battery of tests used in the present study. The neuropsychological tests of the present study are generally open to objective scoring but inter-rater discrepancies in scores can occur. In order to avoid this, the tests were first scored by the psychometrist and then, independently, scored by the writer. Any discrepancies in scores were discussed together by both

parties and the score to the satisfaction of both was used²⁴.

Ethics Committee approval for this study was given in 1993 (Protocol 930344, see Appendix 5).

3.4 Scoring of data

The biographical data could be objectively scored.

The PIL required the totalling of scores presented in Section A of the task on a Likert Scale ranging from 1 to 7. A score of 1 represented the least agreement with the given statement; a score of 7 represented the most agreement.

The MCMI-II was scored using a computer programme supplied for that purpose. There are four anchor points to interpreting the base rate scores. A score of 35 is considered the median point for a nonpsychiatric population, while a psychiatric populations median score is 60. A score greater than 75 on any of the subscales is considered indicative of a definite presence of that

²⁴In reality, very few discrepancies were found.

particular characteristic and a score of 85 or greater is an indication of the most predominant characteristic of the individual (Choca et al., 1992).

The SAWAIS was scored according to the manual provided (1983).

The scoring for the WMS came from the manual provided (1945).

All the neuropsychological tests could be scored objectively according to norm tables. Scoring for these tests was usually based on speed and/or accuracy. Where applicable, the author checked the psychometrist's scoring on the neuropsychological tests. As all the tests can be scored objectively and quantitatively, few discrepancies in tests were found, and the few that were noted were due to calculation errors rather than scoring differences.

3.5 The research design

This study adopted a nonexperimental design. The dependent variables being the status of the subjects in regard to HD. The at risk group of 26 subjects, after molecular analysis,

were assigned to two groups according to their risk status for HD. The HD+ group comprised those whose results of molecular analysis were positive for the disorder, and the HD- group comprised those subjects who were not positive for HD. The remaining other two dependent variables comprised the normal volunteer control group (referred to in future as the control group), and the group who had also experienced being at risk for a life threatening disorder (referred to in future as the stress group). Group comparisons were undertaken between the abovementioned four groups.

The independent variables included biographical data (e.g. age, sex, education, sex of index parent), neurological signs, reasons for requesting testing, purpose in life test findings, personality dimensions, intellectual quotient, and neuropsychological test results. Data included nominal, interval, and ratio variables.

3.6 Statistical analysis

There were 105 independent variables in the present study. Such a large number of variables increases the risk of type I errors (Jason et al., 1988). This has been a problem for

the majority of neuropsychological studies. To overcome this problem several researchers have increased the value of α dramatically (Blackmore et al., 1995; Foroud et al., 1995). Doing this, however, increases the risk of a type II error.

In the present study Pearson's product correlations were performed on all the data in order to reduce the number of variables as an attempt to reduce the risk of type I error but not unduly increase the risk of type II errors. As a further measure against type I errors, a correlation of .7 and more was used to identify areas of overlap in variables.

Comparison of the HD groups individually with a control group was also adopted, in part, as an attempt to reduce type II errors. The small sample size may have masked actual test differences between the HD groups and by individually comparing each group to a carefully matched control group subtle group differences should be elicited.

One-way analyses of variance were conducted because of the relatively small group sizes on the data measured by interval and ratio scales. Bonferroni pairwise comparisons

of means were performed to identify significant group differences and identify the pattern of differing group means. A significance level was set at <0.05 for all comparisons. In the case of unequal variances, measured by Bartlett's test of equal variances ($p < 0.05$), Kruskal-Willis analyses were conducted.

To investigate whether or not neurological signs in total or individually contributed to poor test performances on those tests which showed significant group differences between the HD- and HD+ groups, two-sample T tests were conducted.

Pearson's chi-square was undertaken on nominal data where possible, but if the cell did not have the expected values, two-tailed Fisher exact tests were carried out.

Chapter Four

4.0 RESULTS

The results of the Pearson's product correlations performed on the 105 independent variables in the present study indicated that the data could be grouped into several categories with minimal intercorrelations between these groups. Accordingly several independent categories were identified: biographical data (including age, sex, years of education, and sex of index parent), reasons for requesting testing, personality subscales of the MCMI-II, neurological signs, IQ test scores, and neuropsychological test scores were clustered into separate groups. It can be reasonably assumed that the various groups of data are measuring different constructs and the results of the present study, therefore, are discussed below with this in mind.

4.1 Demographic findings

As mentioned in the Methods section, from the commencement of the programme in 1991 until the end of the present study in December, 1997, 31 individuals requested testing, of

which 26 were available, and agreed, to participate in the present study.

Molecular analysis, undertaken at the end of the predictive programme, revealed that 11 of the at risk subject group received a positive result implying they would develop HD at a later stage, and 15 received a negative result.

4.1.1 Familial details of the at risk group

The 26 participants of the predictive testing programme in the present study derived from 22 different families. There were four pairs of siblings in the study. Two sets of siblings were also first cousins. All other participants were from unrelated families. Of all those related to each other, three subjects were subsequently found positive for HD and five found negative. No significant difference was found between the HD+ and HD- groups and number of sanguinity relationships using the Fisher exact probability test ($p=0.2463$). However, three pairs of siblings were both negative for HD, and in one pair, one sibling was negative but the other was positive for HD.

The index parent was known to all subjects. For eight subjects, it was their mother who had HD, and 18 subjects had a father with HD. There was no significant difference between molecular analysis results and index parent. See Table 4.1 for results.

Table 4.1 Relationship between HD status and sex of index parent

	HD+	HD-
Male Index Parent	7	11
Female Index Parent	4	4

No significant differences were found using the Fisher exact probability test ($p=0.6828$). Thus, the sex of the index parent did not predispose subjects to a positive or negative HD status.

As the sex of the index parent may influence age of disease onset, which may have indirectly influenced the point in time when the subject applied for predictive testing, two-sample T test for group differences was used to investigate whether there was a relationship between age of the subjects found positive for HD and the sex of index parent. See Table 4.2 for results.

Table 4.2 Relationship between mean ages of HD+ subjects and sex of index parent

Sex of Index Parent	HD+ group Mean age (SD)	P value
Male	34.14 (8.28)	
Female	30.25 (6.65)	0.4448

No difference was found in group mean age for those found positive for HD between those whose father was the index parent and those whose mother was the index parent ($p > 0.05$). Thus, sex of parent did not indicate an earlier age of presentation to the predictive testing programme.

Seventeen participants were married, two divorced and seven unmarried. Of the married and divorced subjects, 14 had children, with an average of two children per family.

4.1.2 Ages of all groups

The mean ages and range of ages for the HD+ group, the HD-, the control group and stress group are given in Table 4.3.

Table 4.3 Mean age, standard deviations, and age ranges for all groups

HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
32.73 (7.60)	32.87 (8.98)	32.77 (8.53)	45.25 (11.80)	0.0045
23-46	22-52	22-52	25-58	

Using one-way analysis of variances with four groups (HD+, HD-, control group, and stress group) there was no significant age differences between the HD+, HD- , and control group, but the mean age for the stress group was older than any of the other groups and this reached significance when compared to the other groups ($p < 0.005$).

4.1.3 Race of all groups

All participants in all groups were caucasian²⁵.

4.1.4 Distribution of sexes of all groups

There was an uneven distribution of sexes in the at risk group with more women than men applying to the programme.

²⁵Although only White participants requested testing, there is some evidence that the clinical presentation of the disease differs between races (Zweig et al., 1989).

The nature of the matching paradigms for the volunteer control group meant a similar sex distribution in the controls to that of the at risk group. Similarly, the stress group comprised more women than men. See Table 4.4 for actual distribution rates.

Table 4.4 Distribution of sexes for all groups

Group	Female	Male
HD+ (N=11)	7 (64%)	4 (36%)
HD- (N=15)	8 (53%)	7 (47%)
Control (N=26)	15 (58%)	11 (42%)
Stress (N=12)	9 (75%)	3 (25%)

No significant difference was found between the male:female ratio for all groups using Pearson's chi square ($p=0.6800$), although two cells had lower than expected numbers.

4.1.5 Highest level of education of all groups

The average years of education for all the groups is given in Table 4.5.

Table 4.5 Mean years of education, standard deviations, and range of years for all groups

HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
13.46 (2.54)	13.40 (1.59)	13.39 (1.75)	13.58 (1.73)	0.3554
10-18	11-15	11-17	12-17	

Using one-way analysis of variance for four groups, no significant difference in years of education was found between the HD+ and H.D- groups, the control group and stress group ($p > 0.05$).

4.1.6 Socioeconomic status of all groups

The employment status of members of the at risk group was equal to class III and above according to the British Registrar General's Scale (Liberatos et al., 1988), indicating that the subjects had professional, management and skilled worker status. As far as possible, the control group were matched accordingly, with limited use of students in the volunteer control group as suggested by De Boo et al. (1997b).

4.2 Psychiatric findings

None of the at risk subjects were diagnosed with a current psychiatric disorder according to the DSM-III-R or DSM-IV by the programme psychiatrist and no one was refused testing because of psychiatric reasons. Two subjects, however, both with histories of psychiatric illness, personally delayed their progress through the predictive programme (second and third subjects mentioned below).

Few subjects reported any previous psychiatric problems. One patient had a history of anxiety eight years prior to assessment, which was due to financial difficulties. Another subject had a recent history of major depression, which had been treated. One subject had experienced a prolonged psychotic episode four years prior to testing thought due to cannabis abuse. A further subject had consulted a psychologist about issues surrounding self growth.

Psychiatric illness was an exclusion criterion for the volunteer control group. Consequently, no control group subject had a current or history of psychiatric illness. As the presence of mood disorders is described in life

threatening illnesses (Cull et al., 1996), and as depression can impact upon cognitive abilities, the Beck Depression Inventory was administered to the stress group. A score of 10 and less indicates the normal ups and downs of life. Consequently, a score higher than 10, indicating a potentially more significant mood disturbance than normally experienced, was an exclusion criterion. The stress group mean score on the Beck Depression Inventory was 6.00 (SD 2.63; range 1-10).

4.3 Neurological findings of the at risk group

The neurological evaluation was carried out by the neurologist appointed to predictive testing programme and included special assessment for evidence of involuntary twitches/choreiform movements both resting and under stress, presence of oculomotor dysfunction/abnormal eye movements, diminished saccadic movements, papillary hippus, gaze abnormalities, dysarthria, or abnormal tongue movements, as well as a brief assessment of cognitive status and mood (these two latter functions were assessed in more depth by the psychologist and psychiatrist respectively).

Ten subjects had no neurological signs at all, two of these 10 were later found positive on molecular analysis for HD, and eight were negative. The remaining 16 had one or more neurological signs on examination: four individuals showed mild choreiform movements only detected upon stress, one showed abnormal eye movements, four had slowed saccadic movements, four showed headthrusts, eight had hippus, two displayed abnormal tongue movements and three demonstrated twitches. Presence of dysarthria was not detected in any subject. Informal assessment of mood, and administration of the Mini Mental Status Examination (MMSE) by the neurologist showed eight subjects to be either subjectively labile or anxious, while six subjects lost points on the MMSE.

The neurologist who examined the subjects for the present study did not consider the signs sufficient to make a conclusive diagnosis of HD. He did not exclude any of these applicants from the predictive testing programme on the basis of the neurological examination, or suggest that the DNA analysis be used for diagnostic reasons instead. Consequently, none of the subjects were excluded on neurological grounds from the present study.

In order to ascertain whether or not there was an association between HD status and the presence or absence of the various neurological signs, Fisher exact probability tests were conducted because of the small sample sizes. The probability values for each neurological sign are presented in Table 4.6 below.

Table 4.6 Group differences between the HD+ and HD- groups for each neurological sign

Neurological Sign	HD+ subjects	HD- subjects	P value
Choreiform Movements	4	0	0.0221*
Twitches	0	3	0.2385
Abnormal eye movements	1	0	0.4231
Saccadic movements	3	1	0.2789
Hippus	5	3	0.2183
Headthrusts	3	1	0.2789
Abnormal tongue movements	1	1	1.0000
Score on MMSE	3	3	1.0000
Mood changes	4	4	0.6828

*significant at the 0.05 level

In general, neurological signs were detected in both groups, with three exceptions. Choreiform movements and

abnormal eye movements were only detected in those subsequently found positive for HD, and twitches were only found in those subsequently found negative for HD. The presence of chorea was only elicited when subjects were examined under stress. In all instances, the movements were on the left side. Only the presence of choreiform movements showed a significant difference between the two groups ($p < 0.05$). No subject in the HD- group presented with choreiform movements. When the mean number of neurological signs present in the HD+ and HD- groups were compared using two sample T test, the groups did not significantly differ from each other ($p > 0.05$). See Table 4.7 below.

Table 4.7 Mean number of neurological signs, standard deviations, and range of signs for the HD+ and HD- groups

HD+ group	HD- group	P Value
2.18 (1.66)	1.07 (1.67)	0.1046
0-5	0-6	

4.4 Intellectual function for all groups

Intellectually, the HD at risk group had an IQ in the high average range. Estimated IQ's for the control group and

stress group, using the NART, also fell in the high average range. The FIQ, VIQ, PIQ from the SAWAIS and NART FIQ scores are presented in Table 4.8 below.

Table 4.8 Means and standard deviations for the SAWAIS scores and NART scores for all groups

Group	SAWAIS FIQ	SAWAIS VIQ	SAWAIS PIQ	NART FIQ
HD+ (N=11)	112.17 (12.16)	111.42 (12.46)	112.58 (14.24)	
HD- (N=15)	114.80 (10.38)	112.13 (9.04)	117.33 (13.62)	
Control (N=26)				116.15 (3.80)
Stress (N=12)				118.67 (2.42)

No significant group differences for IQ scores were found ($p=0.1084$) when using Kruskal-Wallis one-way nonparametric analysis of variance for four groups.

The mean scores and standard deviations for the subtests of the SAWAIS for the HD groups were analysed using one way analysis of variance. The results are presented in Table 4.9.

Table 4.9 Mean and standard deviations for the SAWAIS subtests

SAWAIS Subtest	HD+ group (N=11)	HD- group (N=15)	P value
Information	10.36 (1.57)	10.70 (0.86)	0.4580
Comprehension	11.86 (1.70)	11.43 (1.72)	0.5330
Arithmetic	9.64 (1.61)	9.73 (1.72)	0.8854
Digit Span	12.46 (1.13)	13.00 (1.51)	0.3242
Similarities	12.00 (2.62)	12.33 (2.06)	0.7192
Picture Completion	11.77 (2.35)	12.03 (2.49)	0.7895
Object Assembly	9.55 (3.26)	10.00 (2.01)	0.6641
Block Design	11.77 (2.65)	12.97 (2.99)	0.3024
Digit Symbol	11.36 (2.30)	11.87 (2.12)	0.7770
Picture Arrangement	11.91 (1.69)	12.30 (1.51)	0.5403

No significant differences were found between the HD groups for any of the subtests of the SAWAIS ($p > 0.05$).

4.5 Neuropsychological test results for all groups

The central aim of the present study was to investigate whether or not neuropsychological impairment could be

detected in those who request predictive testing. In order to reduce Type I errors, a correlational analysis of results for the neuropsychological tests administered to the at risk group, the control group and stress group was undertaken to establish whether or not the same construct was being measured by more than one test. Several tests consistently showed correlations greater than .7 across all groups. Thus, the three trials of the COWAT (F A, and S) were represented by the Adjusted score only. Trial 5 and trial 6 of the RAVLT were represented by trial 5 only. Passage 1 and passage 2 of the Logical Memory subtest of the WMS was represented by the mean of these two passages (as recommended in the standardised scoring system of the test).

A comparison of the at risk group and control group did identify statistically different test performances but this approach does not control for the impact of genetic status. Consequently, this statistical calculation was not included in the present study. Instead a four group one-way analysis of variance approach was used to identify any significant group differences between the HD+ group, the HD- group, the normal volunteer control group, and the stress group. The results of the neuropsychological tests

for the HD+, HD, volunteer control, and stress groups are presented in Tables 4.10 to 4.22.

The Wechsler Memory Scale (WMS) (Wechsler, 1945)

The results of the subtests of the WMS are presented in Table 4.10 below.

Table 4.10 Mean and standard deviation scores for the WMS and subtests

Test	HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
M.Q.	113.27 (13.43)	119.93 (14.77)	125.81 (12.99)	122.67 (11.97)	0.0750
Information	5.55 (0.69)	5.80 (0.41)	5.35 (0.94)	5.17 (1.03)	0.2763
Orientation	5.00	5.00	5.00	5.00	Scores tied
Mental Control	7.82 (1.17)	7.00 (1.56)	8.12 (1.14)	8.08 (1.16)	0.0490*
Logical Memory	10.73 (3.52)	11.47 (2.52)	11.46 (2.94)	8.70 (2.56)	0.0461*
Digit Span					
Forward	7.00 (0.77)	7.33 (0.72)	7.19 (0.85)	6.58 (0.90)	0.1025
Backward	5.45 (0.82)	5.67 (1.05)	5.65 (1.20)	5.25 (1.06)	0.7052
Total	12.46 (1.13)	13.00 (1.51)	12.85 (1.83)	11.83 (1.75)	0.2545
Visual Reproduction	11.09 (1.97)	12.53 (1.68)	12.96 (1.37)	12.04 (1.74)	0.0178**
Associate Learning	15.91 (3.50)	17.40 (2.71)	18.94 (1.95)	17.71 (2.43)	0.0124**

* = significant at the 0.05 level
 ** = significant at the 0.02 level

Using analysis of variance, a significant difference was found on scores for the Logical Memory subtest at the 0.05 level. Significant differences were found for the Associate Learning subtest and Visual Reproduction subtest at to 0.02 level. The pattern of significant score differences will be discussed in section 4.6 below.

The Rey Complex Figure (RCF) (Rey, 1941)

The results of the copy and recall trials of the RCF are presented in Table 4.11 below.

Table 4.11 Mean and standard deviation scores for the RCF

Trial	HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
Copy	34.55 (1.51)	34.94 (1.22)	35.19 (1.06)	33.17 (1.47)	0.0003*
Recall	20.82 (7.45)	22.70 (6.15)	24.31 (6.23)	18.92 (7.96)	0.1294

* = significant at the 0.0005

Using analysis of variance, a highly significant difference was found on the Copy trial of the RCF. A discussion of the specific nature of the group difference is presented below in section 4.6.

The Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964)

The results of the first and fifth learning trials, recall trials, and number of errors and repetitions (perseverations) made during the learning trials of the RAVLT are presented in Table 4.12 below. Lower scores on the number of errors and repetitions made indicates superior performance.

Table 4.12 Mean and standard deviation scores for the RAVLT

Trial	HD+ group (N=08)	HD- group (N=11)	Control group (N=26)	Stress group (N=12)	P value
I	8.63 (2.72)	8.00 (1.41)	7.58 (2.50)	6.42 (1.38)	0.0865
V	13.88 (1.36)	14.09 (1.22)	13.96 (1.28)	13.68 (1.44)	0.8806
VI	11.63 (3.11)	12.64 (1.29)	13.04 (2.44)	11.58 (3.80)	0.4899
B	6.88 (1.36)	6.64 (2.11)	7.15 (3.03)	6.42 (1.78)	0.9856
Repetitions	3.00 (2.98)	2.91 (4.64)	1.12 (1.40)	0.58 (1.44)	0.0269*
Errors	0.75 (1.04)	0.64 (1.43)	0.69 (1.26)	0.75 (1.22)	0.9960
Recognition	14.25 (1.04)	14.46 (0.69)	14.35 (0.89)	13.50 (1.38)	0.0806

* significant at the 0.05 level

There was a significant group difference for the number of repetitions made over the learning trials of the RAVLT. The nature of this difference will be presented in section 4.6 below.

The Stroop Color (sic)/Word Test (Golden, 1978)

The results of the three trials of the Stroop Test are presented in Table 4.13 below.

Table 4.13 Mean and standard deviation scores for the Stroop Test

Trial	HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
Color	71.22 (13.50)	70.53 (13.46)	76.73 (13.73)	72.25 (8.16)	0.4110
Word	107.50 (13.92)	100.00 (19.93)	102.46 (13.48)	105.17 (13.17)	0.6224
Color/ Word	46.09 (8.62)	40.93 (9.99)	48.00 (10.33)	41.42 (7.73)	0.0787

No significant groups differences were found for any of the trials using analysis of variance ($p > 0.05$).

Trail Making Test (Reitan, 1958)

The results of Trails A and B are presented in Table 4.14 below. Lower scores indicate superior performance.

Table 4.14 Mean and standard deviation scores for the Trail Making Test

Trial	HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group N=12)	P value
Trail A	32.77 (10.82)	35.40 (9.61)	27.42 (9.81)	35.08 (9.43)	0.0448*
Trail B	63.55 (17.48)	74.47 (23.49)	59.27 (17.82)	74.67 (17.90)	0.0424*

* significant at the 0.05 level

The results for both Trail A and B showed significant group differences at the 0.05 level using analysis of variance. The nature of the between groups significance is presented below in section 4.6.

The Tinkertoy Test (Lezak, 1982)

The results of the Tinkertoy Test are presented in Table 4.15 below.

Table 4.15 Mean and standard deviation scores for Tinkertoy Test

Tinkertoy Test	HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
Score	9.18 (1.60)	9.33 (1.76)	10.42 (0.95)	8.33 (1.11)	0.0022*

*significant at the 0.005 level

Using analysis of variance a highly significant difference was found between groups for the Tinkertoy test. A discussion of this significance will be presented below in section 4.6.

Modified Wisconsin Card Sorting Test (MWCST) (Nelson, 1976)

The number of categories achieved, errors, and perseverative errors made for the WCST, modified form, are presented in Table 4.16 below. Lower scores on the number of errors and perseverative errors made on this test indicate better performance.

Table 4.16 Mean and standard deviation scores for the MWCST

Trial	HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
Categories achieved	6.00 (0.00)	6.00 (0.00)	5.92 (0.39)	6.00 (0.00)	0.7046
Errors	3.64 (2.42)	3.27 (2.43)	0.04 (0.20)	0.08 (0.29)	0.000*
Perseverations	0.91 (1.38)	0.73 (1.22)	0.69 (2.36)	0.08 (0.29)	0.1789

* = significant at the 0.0000 level

No significant differences were found for categories achieved or number of perseverations made ($p > 0.05$), but a highly significant difference was found on the number of errors made on the MWCST. The nature of this significance will be discussed in section 4.6 below.

Free drawing test - Bicycle

The scores for the free drawing of a bicycle are presented in Table 4.17 below.

Table 4.17 Mean and standard deviation scores for the free drawing test

HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
13.14 (3.02)	13.37 (2.91)	13.60 (3.07)	12.38 (3.73)	0.8224

Using analysis of variance, no significant differences between groups was found ($p > 0.05$).

Topographical orientation

Topical orientation scores for all groups are presented in Table 4.18 below.

Table 4.18 Mean and standard deviation scores for Topographical Orientation

HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
7.64 (0.67)	7.07 (1.75)	7.15 (1.01)	7.17 (1.53)	0.5915

No significant differences between groups was found using analysis of variance ($p > 0.05$).

Judgement of Line Orientation Test Form V (JLOT) (Benton et al., 1983)

The results of the JLOT are presented in Table 4.19 below.

Table 4.19 Mean and standard deviation scores for JLOT

HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
24.46 (5.77)	25.40 (4.97)	27.50 (2.08)	27.67 (2.96)	0.1723

Using analysis of variance, no significant differences between groups was found ($p > 0.05$).

Design Fluency Test (Jones-Gotman & Milner, 1977)

The results of the Design Fluency test are presented in Table 4.20 below.

Table 4.20 Mean and standard deviation scores for Design Fluency test

HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
28.73 (9.56)	28.20 (10.10)	24.19 (8.44)	23.17 (10.99)	0.3126

Using analysis of variance, no significant differences between groups was found ($p>0.05$).

Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1989)

The results of the adjusted scores for the COWAT are presented in Table 4.21 below.

Table 4.21 Mean and standard deviation scores for the COWAT

HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
43.27 (7.68)	41.40 (5.96)	44.08 (8.28)	44.67 (8.65)	0.5146

All three letters of this test (F A S) significantly correlated with each other, consequently, the adjusted score was used for analysis to represent this data. No significant differences between group was found for the COWAT using analysis of variance ($p>0.05$).

The Boston Naming Test (Kaplan et al., 1983)

Scores for the Boston Naming Test are presented in Table 4.22 below.

Table 4.22 Mean and standard deviation scores for the Boston Naming Test

HD+ group (N=11)	HD- group (N=5)	Control group (N=26)	Stress group (N=12)	P value
54.34 (5.35)	55.27 (2.63)	52.96 (4.20)	54.25 (3.57)	0.3463

No significant differences between groups was found using analysis of variance ($p > 0.05$).

4.6 Profile of significant test differences

The results of several tests indicated group differences. Using Bonferroni pairwise comparisons of means, the profile of these significant test differences are presented below.

Mental Control subtest from WMS

Group	Group Differences and Similarities	Means
Stress Group	I	8.15
Control Group	I I	8.12
HD+ Group	I I	7.82
HD- Group	I	7.00

The means of the stress group and the HD- group significantly differed from each other. No other groups comparisons were significant i.e. the control group and the

stress group do not significantly differ from each other, and the HD+ and HD- groups do not significantly differ from each other.

Logical Memory subtest from WMS

Group	Group Differences and Similarities	Means
HD- Group	I	11.47
Control Group	I	11.42
HD+ Group	I I	10.77
Stress Group	I	8.71

The means of the HD- group and the control group significantly differed from the stress group. No other group means significantly differed from each other.

Visual Reproduction subtest from WMS

Group	Group Differences and Similarities	Means
Control Group	I	12.96
HD- Group	I I	12.33
Stress Group	I I	12.04
HD+ Group	I	11.09

The means for the control group and HD+ group significantly differed from each other. No other group means were significantly different.

Paired Associate subtest from WMS

Group	Group Differences and Similarities	Means
Control Group	I	18.94
Stress Group	I I	17.77
HD- Group	I I	17.40
HD+ Group	I	15.91

The means for the control group and HD+ group significantly differed from each other. No other group means were significantly different from each other.

RCF Copy Trial

Group	Group Differences and Similarities	Means
Control Group	I	35.20
HD- Group	I	34.93
HD+ Group	I I	34.55
Stress Group	I	33.17

The mean for the stress group significantly differed from the control group and the HD- group. No other means significantly differed from each other.

Repetitions made on RAVLT

Group	Group Differences and Similarities	Means
Stress Group	I	0.58
Control Group	I	1.12
HD- group	I I	2.91
HD+ group	I	3.00

The stress group and the control group significantly differed from the HD+ group on number of repetitions made during the learning trials of this test. No other significant group differences were found.

Trail A

Group	Group Differences and Similarities	Means
Control Group	I	27.42
HD+ Group	I I	32.73
Stress Group	I	35.08
HD- Group	I	35.40

The means for the stress group and HD- group significantly differed from the control group. No other significant group differences were found.

Trail B

Group	Group Differences and Similarities	Means
Control Group	I	59.27
HD+ Group	I I	63.55
HD- Group	I	74.47
Stress Group	I	74.67

The means for the stress group and HD- group significantly differed from the control group. No other significant group differences were found.

Tinkertoy Test

Group	Group Differences and Similarities	Means
Control Group	I	10.42
HD- Group	I I	9.33
HD+ Group	I I	9.18
Stress Group	I	8.83

The means for the control group and stress group significantly differed from each other. No other significant group differences were found.

Errors made on the MWCST

Group	Group Differences and Similarities	Means
Control Group	I	0.04
Stress Group	I	0.08
HD- Group	I	3.27
HD+ Group	I	3.64

The means of the control group and stress group did not significantly differ from each, but did significantly differ from the HD- and HD+ groups. The means for the HD- and HD+ groups did not significantly differ from each other.

4.7 Summary of neuropsychological test results

The results of the battery of neuropsychological tests administered have been presented in tables 4.10 to 4.22 above. Overall, there were 10 significant group differences.

In seven of these 10 tests the control group's mean score reflected a superior performance over the other three groups. In three tests (the Mental Control subtest of the WMS, the Logical Memory subtest of the WMS, and number of repetitions made on the RAVLT) the control group scores did not significantly differ from the highest score. In the case of the Mental Control subtest of the WMS, the mean score for the control group was only 0.03 below that of the stress group, in the Logical Memory subtest of the WMS, the control group mean score was only 0.05 below that of the HD- group, and in repetitions on the RAVLT, the control

group mean score was only 0.54 below that of the stress group. Thus, on all tests with significant results, the control group either produced the most superior test performance, or did not significantly differ from the group that did produce the best test performance.

The scores for the HD+ group significantly differed from those of the control group on four tests (the Paired Associate subtest of the WMS, on number of repetitions made on the RAVLT, the Visual Reproduction subtest of the WMS, and the errors made on the MWCST).

The scores for the HD- group significantly differed from those of the control group on four tests (Trails A and B, errors made on the MWCST, and Mental Control subtest).

The scores for the stress group significantly differed from those of the control group on five tests (the Logical Memory subtest of the WMS, repetitions made on the RAVLT, RCF Copy Trial, Tinkertoy Test, Trail A and Trail B).

4.8 Reasons for requesting predictive testing

Unlike, Kessler's (1994) experience, most of the participants in the present study were able to clearly articulate their reasons for wanting predictive testing. The reasons for entering into the programme were canvassed during the clinical psychological interview.

Overwhelmingly, the most common reason for undertaking the testing, was to make plans for the future. Item analysis revealed six clear specific groupings in this regard into which all responses could be categorised. These are presented in Table 4.23 below (individual reasons for each participant is given in Appendix 6). In Table 4.24 the between group mean scores for the reasons given are presented.

Table 4.23 Reasons for requesting testing and number of responses for each reason

Specific reason	Responses
1. A need to make long term financial plans and plans for eventual care should the result be positive for HD.	13
2. A wish to know before a future planned marriage, or remarriage.	6
3. A wish to know before starting a family, or having further children.	10
4. A wish to inform one's children of their risk status. Individuals in this category hoped to eliminate the need for their own children to undergo predictive testing by being tested themselves.	6
5. To make career decisions. For example, whether to enter into one's own business, or make major career moves.	6
6. To alleviate the dissonance caused by not knowing one's HD status. For some, the anxiety of not knowing was perceived as worse than receiving a positive HD status. Or, there was a preoccupation with looking for, or worrying about, possible early symptoms, which was proving to be very distressing.	9

Using two group T test, the HD+ group and the HD- group did not significantly differ in the pattern of reasons given ($p>0.05$). See Table 4.24 below.

Table 4.24 Mean scores for reasons given by HD+ and HD- groups

Reason Number	HD+ Group	HD- Group	P Value
1	0.45 (0.52)	0.60 (0.51)	0.4823
2	0.18 (0.40)	0.26 (0.46)	0.6287
3	0.27 (0.47)	0.47 (0.52)	0.3349
4	0.18 (0.41)	0.27 (0.46)	0.6287
5	0.27 (0.47)	0.20 (0.41)	0.6787
6	0.55 (0.52)	0.27 (0.46)	0.1611

4.9 Results of the MCMI-II

In Table 4.25 the results for each subscale of the MCMI-II for the at risk group and control group is presented.

Table 4.25 Base rate mean scores and standard deviations for each subscale of the MCMI-II for the at risk group and control group

Subscale	At risk Group (N=23)	Control group (N=26)	P value
Disclosure	34.44 (24.32)	45.62 (22.56)	0.1017
Desirability	68.04 (17.68)	62.23 (21.97)	0.3170
Debasement	25.35 (20.69)	25.23 (20.63)	0.9843
PERSONALITY SCALES			
Schizoid	51.44 (23.74)	48.50 (26.75)	0.6881
Avoidant	37.09 (25.31)	32.88 (31.15)	0.6097
Dependent	49.70 (27.91)	52.15 (28.92)	0.7641
Histrionic	64.65 (15.90)	64.61 (29.28)	0.2444
Narcissistic	69.30 (17.33)	66.23 (29.26)	0.8901
Antisocial	53.87 (14.97)	59.54 (22.95)	0.1596
Compulsive	73.22 (22.96)	64.69 (14.84)	0.0303*
Passive- Aggressive	37.60 (30.18)	38.92 (30.13)	0.8796

SEVERE PERSONALITY SCALES			
Aggressive/Sadistic	65.30 (16.50)	64.85 (24.64)	0.9402
Self-Defeating	35.96 (25.48)	39.50 (22.83)	0.6100
Schizotypal	46.43 (19.42)	43.50 (17.80)	0.5836
Borderline	38.13 (20.81)	43.46 (18.87)	0.3519
Paranoid	60.87 (12.52)	56.35 (16.87)	0.2973
CLINICAL SCALES			
Anxiety	34.17 (23.97)	27.81 (19.36)	0.3094
Somatoform	50.00 (19.04)	51.92 (16.04)	0.7030
Bipolar: Manic	54.87 (16.49)	48.88 (22.02)	0.2922
Dysthymia	23.96 (20.91)	19.58 (17.37)	0.4273
Alcohol Dependence	25.91 (21.13)	32.69 (24.80)	0.3116
Drug Dependence	43.13 (16.63)	47.04 (23.99)	0.5163
Thought Disorder	33.17 (25.51)	34.96 (26.39)	0.8111
Major Depression	29.13 (28.88)	28.88 (21.35)	0.9697
Delusional Disorder	47.04 (18.46)	45.31 (23.08)	0.7745

* significant at the 0.05 level

Only one significant difference was identified between the at risk group and the control group with regard to mean scores for the subscales of the personality inventory. The at risk group scored higher on the compulsive subscale ($p < 0.05$).

The three highest scores over the base rate over 60 for the personality style subtests in the at risk group were Compulsive, Histrionic, and Narcissistic respectively. The Aggressive/Sadistic severe personality scale was the highest in that category. The means for these four scales were all above the median base rate of 60 but none of the at risk group mean scores on any scale were higher than 75, which is the baseline point for the definite presence of that particular characteristic (Choca et al., 1992). No clinical scale reached the median score of 60.

The three highest group scaled scores for the personality style subtests in the control group were Narcissistic, Compulsive, and Histrionic respectively. The Aggressive/Sadistic severe personality scale was also the highest in that category. The means for these four scales were all above the median base rate of 60 but no at risk group mean score on any scale were higher than 75, which is

the baseline point for the definite presence of that particular characteristic (Choca et al., 1992). No clinical scale reached the median score of 60.

4.10 Results of the Purpose in Life Test

Only part A of the PIL test can be quantified. The results are presented in Table 4.26 below.

Table 4.26 Mean and standard deviation scores for the PIL

HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P value
117.82	118.33	113.08	113.38	
(14.11)	(8.92)	(11.58)	(11.42)	0.4101

No significant differences were found between groups for part A of the PIL test using analysis of variance ($p > 0.05$).

An interpretation of the results presented in this chapter, with cognisance of the findings of the introductory chapters, will be presented in the next chapter.

Chapter Five

5.0 DISCUSSION

Since Huntington first described the neuropsychiatric genetic disorder in 1872 that now carries his name, there has been a search for presymptomatic markers of this disease. Based on a hypothesis of disease continuity, out of this search has come the question of whether or not cognitive impairment is present in those who have inherited the gene for HD but are not yet symptomatic. Although researchers had attempted to answer this question using both cross-sectional and longitudinal analyses of psychological test performance, the results were conflicting and inconclusive, primarily because the genetic status of the subjects at the time of investigation was unknown. The discovery of a genetic marker for HD in 1983 with the potential to identify the genetic status of subjects presymptomatically, implied that this question could finally be answered.

Since the onset of the present study, in excess of 17 journal papers have been published specifically addressing this issue but, in spite of the knowledge regarding an

individual's HD status, the results of these studies have been as inconclusive as the earlier studies. Studies that either support and refute the continuity hypothesis have been reported. Researchers have suggested that factors other than the cognitive decline may be contributing to poor presymptomatic test performance (Gior^y et al., 1995). Further, the typical research methodology used may have raised methodological difficulties, which, in turn, have contributed to the ongoing inconclusiveness of the research findings.

The main aims of the present study were to investigate whether or not cognitive impairment is present in those who request predictive testing for HD but are not yet symptomatic. To do this it was necessary to evaluate the performance of those at risk on a suitable battery of psychological tests. While, at the same time, expanding on previous attempts to answer this question by comparing the HD group performance with that of a carefully matched control group. Further, it was necessary to accommodate and evaluate other suggested, non-neurological, reasons for poor test performance in the at risk group.

In the following discussion the results of the present study will be documented. Biographical details of all four groups will be submitted first. This will be followed by a discussion of the neuropsychological status of the HD+, HD-, and stress groups when compared with a normal volunteer control group. The impact of neurological signs and psychiatric illness on the neuropsychological performance of the HD+ and HD- group will then be analysed. Included in this section will be a discussion of several of the non-neurological factors that may influence research into the neuropsychological profile of those at risk for HD but not yet symptomatic. Finally, the issue of self selection in those who request predictive testing, with the emphasis on personality profiles will be examined.

5.1 Sample size of the at risk group

As discussed in Chapter 2, in general, relatively few individuals have requested predictive testing (Craufurd et al., 1989, Decruyenaere et al., 1995; Quaid et al., 1989; Tyler, Ball et al., 1992; Williamson, 1992). Subjects for the present study could only be canvassed from those who approached the Department of Human Genetics at the University of the Witwatersrand on their own cognisances.

Until the end of 1997, when this study was ended, only 31 persons had requested predictive testing and had completed the programme and received their molecular results. Of this group, 26 could be approached and agreed to participate in this study. The reason for the five exclusions were of a practical nature rather than direct refusal to participate. Two had travelled considerable distance and only had limited time available for the programme, and three had completed the procedures before the author of this study became involved in the programme. Analysis of biographical data of these five gives no reason to suggest that they differed from the research population in any way.

Of the total number of participants in the programme, 15 were positive and 16 negative for HD. Craufurd et al. (1989) have suggested that an equivalence of scores implies that it is unlikely that any of the participants, suspicious of manifesting early symptoms of HD, were using the programme as an alternative, and subjectively less traumatic, way by which their HD status could be established.

In the present study of 26 subjects, less than half of the study sample were positive (n=11). The remaining 15 subjects were given a negative molecular result.

5.2 Familial relationships of the Huntington's disease subjects

Most participants were married (n=17) or, if divorced were contemplating remarriage, or considering marriage for the first time. Most of the married, or previously married, subjects had children. The present group reflects the trend found in international studies: most of those who request testing are in a stable relationship (e.g. Codori & Brandt, 1994; Evers-Kiebooms et al., 1989; Wiggins et al., 1992).

There was a considerable degree of familial concordance in the present study. Of the 26 subjects, there were four pairs of siblings, and two sets of these siblings were first cousins. Thus, 8 subjects had a kinship relationship. Concerns had been raised that a predominance of sanguinity in one HD group may lead to a bias in results (Strauss & Brandt, 1990). Genetic factors (e.g. learning disabilities) other than HD may bias test performance

(Strauss & Brandt, 1990). In the present study subjects with a kinship status were not found predominantly in either of the HD groups. After molecular analysis, three subjects were positive and five subjects were negative for HD. This difference was not significant ($p > 0.05$). However, there was diagnostic concordance (all were HD-) between three sets of siblings which could place a limitation upon the interpretation of the results.

An anticipatory relationship between age of individual at time of disease onset and having a father with HD has been suggested (Wallace, 1979), which could not be directly measured in the present study as the subjects were presumed asymptomatic. However, no correlation was found between outcome of molecular testing and the sex of the affected parent ($p > 0.05$). None of the HD+ group were more likely to have a father as the index parent. Furthermore, in the HD+ group, the mean age for those whose father had HD did not significantly differ from subjects whose mother was the index parent ($p > 0.05$). Although not conclusive, there did not appear to be a reason in the present study to suggest an anticipation effect.

5.3 Age of subjects

The average age for the at risk group in the present study was 32.81 years. When this group was classified according to molecular status, the mean age of the HD+ group was 32.73 years and 32.87 years for the HD- group. Similar to all other published neuropsychological studies, no significant differences were found between the two HD groups ($p > 0.05$).

The age for the at risk group in the present study is similar to the mean age of participants of several other predictive testing programmes (Decruyenaere et al., 1995; Holloway et al., 1994; Tyler, Ball et al., 1992) and neuropsychological studies. For example, the mean age of subjects in the study by Hahn-Barma et al. (1998) was 33.2 years for the HD- group and 33.4 years for the HD+ group. In the study by Rosenberg et al. (1995) the mean ages were 33.6 for noncarriers and 30.2 years for carriers. Strauss & Brandt (1990) reported ages of 30.1 and 32.2 years for their marker-positive and marker-negative groups respectively.

This mean age of around 33 years is also close to the age of disease onset in SA (M=34.93 years, Hayden, 1981), and may reflect an increasing awareness on the part of the at risk individual of their at risk status.

The control group had been carefully matched to the experimental group and their mean age was 32.77 years. No significant difference ($p>0.05$) was found between the HD and control groups.

Because of the difficulty in recruiting a stress group who matched the inclusion criteria, this group could not be carefully matched for age. Their mean age of 45.25 years was statistically significant from the experimental and normal control groups ($p<0.001$).

5.4 Sex distribution of subjects

There was an uneven distribution of sexes in the programme with more women participating than men. A predominance of females in predictive testing programmes is common (e.g. Bloch *et al.*, 1989; Holloway *et al.*, 1994; Meissen *et al.*, 1988; Tibben, Frets *et al.*, 1993; Tyler, Ball *et al.*, 1992; van der Steenstraten *et al.*, 1994) and does not reflect the

disease distribution between the sexes as the disease is autosomal dominant. Instead, it has been suggested that this ratio reflects women's concern for their children or potential children's wellbeing (Jones, 1994; Meissen et al., 1988), or men's greater capacity to deny their feelings (Bloch et al., 1989). This was borne out by the Johannesburg experience, where twice as many women than men gave the reason for participating in the programme as wanting to know their own status as before they had children, or before their children had children (see sections 4.8 and 5.13.2 for discussion of reasons for requesting testing).

The control group subjects were matched on an individual basis and consequently the sex ratio is the same as the experimental group. For the stress group, 9 women and 3 men participated, this ratio was in the same direction as both the experimental and control group and was not significantly different from both these groups ($p > 0.05$).

5.5 Highest level of education of subjects

The at risk group averaged 13.15 years of education with the mean for the HD+ group being 13.46 years and 13.40



years for the HD- group. No significant differences in education were found between the two HD groups ($p > 0.05$), ruling out the possibility that any differences in neuropsychological test results could be attributed to differing levels of education as found by Giordani et al. (1995).

With the exception of three subjects who had been educated in England to 'O' level (equivalent to Grade 11 in SA), all HD subjects had been educated in SA. Half the subjects had some degree of tertiary education, with the remainder having completed matriculation (Grade 12). This finding of above average levels of education is in keeping with international studies of predictive testing programmes (e.g. Brandt et al., 1989; Decruyenaere et al., 1995; Meissen et al., 1988; Quaid et al., 1989; Tibben, Frets et al., 1993; van der Steenstraten et al., 1994; Wiggins et al., 1992), as well as neuropsychological studies (e.g. Bylsma et al., 1992; Diamond et al., 1992; Hahn-Barma et al., 1998). Those who request predictive testing tend to be better educated than the general population.

The control group was matched for years of education with the experimental group and no significant differences

between the HD+, HD- and control group were found ($p>0.05$). Similarly, the mean years of education for the stress group, 13.58 years, did not significantly differ from any of the other groups ($p>0.05$).

5.6 Socioeconomic status of subjects

The general trend implied from predictive testing research suggests that those who request molecular analysis come from the higher socioeconomic groups (Kessler, 1987b; Tyler, Morris, et al., 1992). Individuals are usually employed in white collar occupations and have a higher level of education than the general population (Bloch et al., 1989; Codori et al., 1994; Tibben, Frets et al., 1993). The trend of above average levels of education in those who request predictive testing has already been supported in the present study, and discussed in the previous section.

Socioeconomic status has not been documented in the neuropsychological studies apart from a comment by Blackmore et al. (1995) that participants in their study were from a middle class background. This was true of the present study in which all applicants to the predictive

testing programme were of class III status and above as measured by the British Registrar General's Scale (i.e. class I = professional; II = intermediate; III = skilled, manual and nonmanual). Such a finding adds to the concept that those who request testing are a self selected group.

In the present study, in accordance with the suggestion put forward by Giordani et al. (1995), the use of 'test-wise' students as volunteer controls was avoided. In general, the occupations of the control group were of similar class to that of the experimental group.

5.7 Race of subjects

The at risk group were all of caucasian origin. This does not reflect the ethnic distribution of SA or of the disease. In the Cape Town study (Greenberg, Beatty, Soltau & Bryer, 1996), several of the participants of that predictive testing programme came from mixed ethnic backgrounds reflecting the race distribution of that city. The race of participants in international studies has not been described so comparisons cannot be made, but in the present study, the dominance of White subjects is probably

related to self selectedness of the group. All subjects in the control group and stress group were caucasian.

5.8 Subjects' Intelligence Quotient

The SAWAIS, was administered to the at risk group at the first interview as part of the general psychological assessment. The findings indicate that this group had an above average IQ, which fell into the 'high intelligent' classification. The IQ scores for the HD+ and HD- were not significantly different from each other ($p>0.05$). When each subtest of the SAWAIS was analysed no subtest showed significant differences across the HD groups ($p>0.05$).

The Picture Arrangement and Digit Symbol subtests of the WAIS appear to be the most vulnerable to early symptoms of Huntington's dementia (Butters et al., 1978, 1979; Caine et al., 1978; Josiassen et al., 1982) and have also been reported significantly impaired in an HD+ at risk group who requested predictive testing (Foroud et al., 1995). As mentioned above, neither the Picture Arrangement or Digit Symbol subtest of the SAWAIS manifested this pattern of impairment in the present study.

Measurement of IQ in those who request predictive testing is usually limited to the neuropsychological studies. The measurement of IQ has formed either part of, or been the entire purpose of several such studies (de Boo et al., 1997b; Diamond et al., 1992; Foroud et al., 1995; Jason, Suchowersky et al., 1997; Lundervold & Reinvang, 1995). In all these specific studies the AR- group was used as the control group. Some researchers find differences in IQ between the at risk groups (e.g. Foroud et al., 1995; Lundervold & Reinvang, 1995) while others do not (e.g. de Boo et al., 1997b; Diamond et al., 1992). The results of the present study concur with the latter researchers in this matter.

The SAWAIS is time consuming to administer. Consequently, an abbreviated form of IQ assessment was administered to the normal volunteer control group and the stress group. The test chosen for this was the NART (Nelson & O'Connell, 1978). A comparison of IQ test results indicated that no significant differences were found between the SAWAIS scores and the NART scores ($p > 0.05$). As mentioned before, there is support for test equivalence between the NART and SAWAIS (Struben & Tredoux, 1989). As a further measure, however, two subtests from the SAWAIS (Information and

Block Design subtests) were administered to the control groups (see Appendix 7 for scores). No group differences were found ($p > 0.05$) between the HD+, HD-, normal controls, and stress group for either subtest.

No significant differences in IQ in the groups complied with the recommendation of Giordani et al. (1995) who had implied in their study that the IQ of the control group should be matched to that of the HD group. The nonsignificant between group IQ scores in the present study, however, was an *apriori* factor. It had not been the explicit intention of the present study to match the control group and experimental group on IQ as it could be argued that, by matching the at risk group and control group on intellectual skills, early decline in the HD+ group could be camouflaged. Nevertheless it was a preferred starting point for the present study. The careful analysis of deterioration in skills of executive function, attention and memory, considered the earliest indicators of cognitive decline in HD (Caine et al., 1978), could be carried out in the knowledge that IQ was constant.

In summary, the at risk group recruited from the Johannesburg predictive testing programme share a similar

biographical profile to those of international programmes. Age, the male/female ratio, education, and socioeconomic status of the South African group closely concur with other studies. Highest level of education achieved by this group, as well as IQ and socioeconomic status, however, are not representative of the general population and support the suggestion of Codori *et al.* (1994) and Kessler (1994) that those who request predictive testing are a self selected group.

To incorporate the suggestions put forward by Giordani *et al.* (1995), regarding the matching of the HD group and control group, the normal volunteer control group was matched with the at risk group according to age, sex, socioeconomic status, and education. Although not the original purpose of the matching criteria, IQ was not significantly different between any of the groups either. This extremely careful matching was done in order to reduce any potentially extraneous variables that could account for any cognitive differences between the groups. In addition, cognisance was taken of other criticisms of previous neuropsychological studies. In order to reduce type I errors, correlational analyses of all the variables in the present study were carried out. Thirteen

neuropsychological tests were identified as markers to evaluate functions typically found to be compromised early in the disease process of HD. Comparing the HD groups individually with the control group could also be considered an attempt to reduce Type II errors.

5.9 Neuropsychological test performance

5.9.1 Group differences

The group differences between the HD+, HD-, control, and stress groups, in the present study, were analysed using parametric one-way analysis of variance or Kruskal-Wallis one-way nonparametric analysis of variance for four groups, depending upon the equality of variances as measured by Bartlett's test of equal variances.

The HD+ and HD- group did not differ significantly from each other on any cognitive measure, and, consequently, the first hypothesis of the present study was upheld. This finding concurs with several research findings in presymptomatic testing (Blackmore et al., 1995; Bylsma et al., 1992; Campodonico et al., 1996; de Boo et al., 1997b; Giordani et al., 1995; Gómez-Tortosa et al., 1996, 1997;

Rothlind, Brandt et al., 1993; Strauss & Brandt, 1990) and suggests that no cognitive impairment is present in those at risk for HD prior to clinical symptom onset.

However, if the stressfulness of the testing experience had differentially affected the two HD groups, the unavoidable small sample size and use of a relatively large battery of tests may have masked significant test differences between the HD groups. Individual comparison between the HD+, HD-, control and stress groups did reveal several group differences, albeit of modest significance.

First, the control group scores were generally superior when compared to those of the at risk groups and significant differences were elicited. The HD+ group significantly differed from the normal volunteer group on four tests, as did the scores of the HD- group. Second, the performance of the stress group was also generally inferior to that of the volunteer control group. Their mean scores were significantly below the control group on five tests. Their raw score performance, however, was superior to that of the normal volunteer control group on two tests but the score difference was not significant.

In regard to specific test differences, the scores for the HD- group were significantly inferior to that of the control group on the Mental Control subtest of the WMS, number of errors made on the MWCST, and Trails A and B. The HD+ group scores significantly differed from the control group on the Visual Reproduction subtest of the WMS, the Paired Associate subtest of the WMS, the number of repetitions made over the first five trials of the RAVLT, and the number of errors made on the MWCST. The stress group differed significantly from the control group on the Logical Memory subtest of the WMS, Copy trial of the RCF, Trails A & B, and the Tinkertoy test.

Unlike the studies that reported test anomalies (e.g. Blackmore et al., 1995; Giordani et al., 1995; Lundervold & Reinvang, 1995; Strauss & Brandt, 1990), the HD+ group did not show a significantly superior test performance than that of the HD- group or the normal volunteer control group on any of the tests.

The three experimental groups (HD+, HD-, and stress groups) presented with both differences and similarities in test profile when compared to the control group. The HD- and stress groups scores for the trials A & B, while

significantly different from the control group, did not differ significantly from each other. The HD+ and HD- groups differed significantly from the control group on number of errors made on the WCST, but their scores did not differ from each other on this test. Consequently, the only test for which the HD- group showed selective inferior performance from the control group was for Mental Control subtest of WMS. The stress group differed selectively on the Logical Memory subtest of the WMS, Copy trial of the RCF, and the Tinkertoy test. The HD+ group's particular differences were for the Visual Reproduction and Paired Associate subtests of the WMS and number of repeated words on the RAVLT (see Table 5.1).

Table 5.1 Test similarities and differences between groups when compared to the control group

	HD- Group	HD+ Group	Stress Group
Tests with overlapping scores	Trail A Trail B Errors on MWCST	Errors on MWCST	Trail A Trail B
Tests of selective to one group	Mental control subtest of WMS	Visual Reproduction subtest Associate Pairs subtest Repetitions on RAVLT	Logical Memory subtest Copy trial of RCF Tinkertoy Test

By comparing the test scores of the four groups with each other certain information comes to light. The HD+, HD- and stress groups show variable patterns of impaired test scores with a degree of overlap when compared to a carefully matched control group. In part, the experimental groups share commonalities of dysfunction but each group shows its own idiosyncratic pattern of impairment.

By adopting an approach of comparing the experimental groups to the control group and to each other, it has been possible to separate out test scores that are unique to each group.

5.9.2 Functional implications of group differences

As discussed in the methodology section of this thesis, neuropsychological tests are multifaceted and rarely measure only one function. However, over time, tests have become associated with specific categories of function and have been considered to be dominant measures of those functions. In the spirit of this working approach, the tests found to exhibit significant group differences have been categorised according to the current accepted functional bias.

It must be stressed, however, that the following functional implications are, at best, tentative. Several alternative explanations, based on the limitations of the present study, for group differences exist that preclude making a more definitive interpretation of the score profiles mentioned in section 5.9.1 above. For example, the unavoidable small sample size and relatively large test battery in the present study does reduce the statistical power of group comparisons.

Additionally, the presence of consanguinity in the study of Jason et al., (1988) had been raised as a criticism by

Strauss and Brandt (1990). Although in the present study the overall number of sanguinity relationships (sibling and cousinships) was not clustered into one HD group, only one subject in any sibling relationship was positive for HD. The remaining siblings were negative for HD. This presentation lessens the potential bias of familial learning disabilities contributing to the HD+ cognitive impairment, but, conversely, could afford familial cognitive strengths on the HD- group.

Further, four subjects had neurological features specific to the HD+ group only. Although they were considered by the neurologist to be candidates for the predictive testing programme, and hence were included in the present study, the presence of choreiform movements, albeit detected unilaterally under stress, may be construed as being perisymptomatic. This may have had the potential to negatively influence the significance of some neuropsychological test results.

Finally, the stress group did differ from the control group in several dimensions. The two groups were not matched for age, or stage of illness knowledge, or illness type. These factors could well influence test results. In the light of

these limitations, however, a conditional discussion of the functional implications of the test results is given.

In the HD- group, attentional resources appeared to be compromised, especially for the more cognitively demanding tests of executive attention. This is a sophisticated skill that has limited capacity and is extremely sensitive and vulnerable to external conditions (Lezak, 1995; van Zomeren & Brouwer, 1994). It is understandable that, under the pressure of investigating one's HD status, an individual undergoing predictive testing would present with reduced attentional capacity. Particularly as immediate mood is a stronger predictor of test deficit than underlying dispositions to anxiety (Wells & Matthews, 1994). Thus, cognitive impairment present in the HD- group could be explained on the basis of the presenting stressful situation. Poor test performance on tests of attention is secondary to the stressfulness of the predictive testing situation. This group did not present with any other cognitive impairment.

The stress group also appeared to be an attentional disadvantage. It can be hypothesised that the reasons given for reduced attentional capacity in the HD- group can

apply to the stress group as well. This group live under the threat of limited life expectancy as do those at risk for HD prior to receiving a negative molecular analysis result and the issue of whether both groups gave impaired performances because of the awareness of their limited life span cannot be dismissed. However, the stress group had further deficits in declarative memory and executive function (Logical Memory subtest of WMS, Copy trial of RCF, Tinkertoy test).

The inferior group performance by the stress group on the Logical Memory subtest was found due to one subject whose scores were particularly low. When this score was removed no significant group differences were found ($p=0.128$, using one way analysis of variance for four groups).

The copy trial of the RCF is considered a measure of visuospatial perception, visuospatial organisation and motor functioning (Spreeen & Strauss, 1998). The Tinkertoy test is considered a measure of purposive behaviour, a component of executive function (Lezak, 1995; Spreeen & Strauss, 1998). These two tests presented with stronger statistical effects than the attention measures. There are several possible explanations as to why the stress group

showed deficits in these functions. One possibility is the age difference between the stress group and the control group.

Stress group subjects were older than the other groups, and age can negatively impact upon cognitive test performance. In the present study, using Spearman rank correlation because of the small sample size, there was no relationship between increased age and score for the Copy trial of the RCF ($r_s = -0.0823$, $p > 0.05$), or for the Tinkertoy test ($r_s = -0.1641$, $p > 0.05$). It would appear that advanced age in the stress group does not explain the executive dysfunction.

Alternative explanations to be considered must include their disease process. Though subjects were carefully screened regarding the extent of their cancer and the type of treatment they had received and their current mood, there was no measure of degree of situational stress. It is possible that the subjects in this group were more worried about their condition because they had already received their diagnosis and this had negatively impacted upon the cognitively demanding executive function test. Or their illness may have had greater systemic effect than originally thought, and this impacted negatively upon

executive function²⁶. For example, in a sample of patients with small cell lung cancer, memory deficits, executive dysfunction, and impaired motor coordination have been reported prior to treatment, which did improve after treatment (Meyers et al., 1995). Similarly in a study of adult candidates for bone marrow transplants for a malignant disease, memory was the most impaired neuropsychological function but attention was the least likely cognitive function to be impaired (Andrykowski et al., 1992).

Attentional impairment was not found in the HD+ group. Instead, selective deficits were found on two subtests of the WMS: the Paired Associate subtest and the Verbal Reproduction subtest. The Paired Associate subtest of the WMS is considered a measure of episodic declarative verbal memory, with reasonable correlation to everyday memory performance (Loring & Papanicolaou, 1987). The Visual Reproduction subtest was developed to measure spatial memory function but is primarily a test of visual-

²⁶RCF Copy performance was found impaired on a group of South African subjects who, defined with high levels of stress, improved performance after micronutrient intervention (Bosch, 1999). The impairment was attributed to carelessness.

perceptual-motor ability and secondly a test of spatial memory (Loring & Papanicolaou, 1987).

In addition, this group had increased numbers of repeated words (perseverations) made on the RAVLT learning trial. This usually represents impaired self monitoring skills as the subject is often unaware of making them. It has been suggested that the deficit is the inability to distinguish between what words have been said and what is still to be recalled (Sandson & Albert, 1984).

Impairment of both spatial memory and higher visuospatial skills, along with verbal memory, have been reported in symptomatic HD subjects, free of more general cognitive deterioration (Bamford et al., 1995; Butters et al., 1978; Josiassen et al., 1983; Lawrence et al., 1996; Lundervold & Reinvang, 1991; Moses et al., 1981).

The Paired Associate learning subtest has been specifically cited as a sensitive subtest of memory impairment in early HD (Butters et al., 1978). Item analysis of this test was undertaken to clarify the nature of the memory impairment found. The HD+ group produced an inferior performance on both the 'easy' and 'hard' pairs of the test, although

neither were individually statistically different from the control group ($p > 0.05$). This finding supports the view that early verbal memory deficits in HD, at least at a presymptomatic stage, are the result of a poor initiation of systematic search strategies for information (Butters et al., 1985, 1986, 1988; Massman et al., 1990). This is in contradiction to the view that early memory deficits in HD are due to passive learning strategies (Huber & Paulson, 1987; Lundervold et al., 1994) which would lead to an inferior performance on the 'hard' pairs only.

The Visual Reproduction subtest has also been previously described as impaired early in HD (Pillon et al., 1991). Item analysis of the HD+ group's Visual Reproduction test highlighted visuospatial difficulties, missing details, or confabulation tendencies in all the subjects ($n=11$). In a similar analysis of the HD- group ($n=15$), subjects only lost points because of missing details. Visuospatial impairment and confabulation was not found in the control group either.

Why did the HD+ group show impairment on the Visual Reproduction subtest but not RCF Copy or recall? The RCF is also a visuospatial memory task, and more complex than

the Visual Reproduction subtest. The tasks differ, however, in that the RCF requires a copy trial with the figure visible while the Visual Reproduction subtest relies on visual appraisal only. Gómez-Tortosa et al. (1996) has attributed early visuoperceptive impairment in HD to visual processing deficits rather than visuoconstructive deficits. Interestingly, in the present study, the lowest score on the Visual Reproduction subtest (7/14) was held by the only subject to have oculomotor dysfunction. This subject was also from the HD+ group.

The memory impairment found in the HD+ group is congruent with the predictive neuropsychological investigations that reported differences between the HD+ and HD groups. For example, visual recall (measured using the Visual Reproduction subtest of WMS) was inferior in the HD+ group in the study conducted by Jason et al. (1988). Diamond et al. (1992) found in their study, a significant inferior performance by the HD+ group on the Paired Associate Learning of the WMS. Visual memory (measured by Ruth Andersen's Visual Gestalts test) was found impaired in the study by Rosenberg et al. (1995), and verbal memory impairment (measured using the California Verbal Learning Test) was reported by Lundervold & Reinvang (1995).

However, these studies did not report the memory impairment as an isolated phenomenon, other deficits as well as memory deficits were also described.

Number of repetitions or perseverations made on learning trials of auditory verbal learning tests has also been mentioned in studies of early cognitive decline in HD (Lange et al., 1995; Lundervold et al., 1994 but cf. Butters et al., 1988 who report that HD patients do not make more perservations than a matched control group) and in the predictive testing studies. In Blackmore et al's (1995) study, no repetition differences were found between the HD+ and HD- group, but in the study by Hahn-Barma et al. (1998), an above average number of repetitions was found.

In the present study, repetition scores correlated highly with number of errors made on the MWCST in the HD group ($r=0.8692$, $p<0.005$) but this correlation was not seen in the control group ($r=0.0669$, $p>0.05$). It would seem that a shared underlying process explained both the repetition deficits and MWCST errors made in the HD groups. Horne (1993) had found reversible perseveration errors in his sleep deprived subjects. Thus, it would appear that the

self monitoring deficit found in the HD+ group may have been more related to the testing situation than HD itself. More so, as inspection of the raw data showed that the mean repetition score for the HD- group, while not significantly different from the control group, was merely 0.09 repetitions lower than the HD+ group.

It is interesting that the HD+ group did not present with the same degree of the attentional impairment found in the other groups. Is it possible that accompanying the cognitive changes was less concern about the possibility of inheriting HD (Tyler, Ball et al., 1992)?

Zappacosta et al. (1996) have speculated that disease denial in early HD may be a true anosognosia associated with damage to the corticolimbic structures. It has been noted that those with frontal lobe damage show impaired self awareness of memory deficits (Jurado, Junqué, Vendrell, Treserras & Grafman, 1998). It was not possible to verify this issue in the present study but it is worthy of note in the light of the purported anatomical structures involved in early HD and the finding that HD patients have reduced subjective awareness for their movements (Snowden, Craufurd, Griffiths & Neary, 1988).

In summary, by comparing the scores of the HD groups individually with a control group and stress group an attempt has been made to eliminate the impact on cognition of the stressfulness of being at risk for a life threatening disorder and being part of a predictive testing programme. Furthermore, these comparisons were also made in an attempt to reduce the possibility that subtle differences between the HD+ and HD- group were being masked by the reduced statistical power of small group comparisons. The results of these manipulations in the present study lay foundations for further investigation into the hypothesis that, in those positive for HD, an impairment of declarative memory is the earliest identifiable cognitive deficit. This finding is consistent both with predictive testing studies that do report differences between the AR+ and AR- groups, and the studies of early impairment in symptomatic HD.

From the above discussion, it becomes apparent that hypotheses two to six of the present study could not be upheld. Significant cognitive differences were found between the control group and the HD+, HD- and stress groups. Further, differences were found between the stress group and the HD+ and HD- groups.

As in several other programmes, the participants in the Johannesburg predictive testing programme were not psychiatrically or neurologically screened prior to neuropsychological evaluation (e.g. de Boo et al., 1997b; Lundervold & Reinvang, 1995). As both psychiatric and neurological signs present early in HD, the impact of these results on cognitive impairment in the at risk groups must be considered.

5.10 Psychiatric illness and its implications

In the present study there was little evidence that cognitive impairment could be attributed to the presence of psychiatric disorder as attendant illness was ruled out by the programme psychiatrist. Only two subjects had received prior psychiatric intervention and psychotropic medication. The subject who had a prolonged episode of psychosis with subsequent depression several years prior to the predictive assessment, had responded to appropriate medication. He was found positive for HD on molecular analysis. The other subject had been treated for major depression with unknown HD status cited on Axis IV as a stressor but was well at the time of assessment. She was found negative for HD.

Psychosis can present before neurological features of HD (Di Maio et al., 1993a; Hayden, 1981; Lovestone et al., 1996; Shiwach, 1994; Wilson & Garron, 1979), and could suggest the incipient presence of early symptomatology. In the abovementioned positive subject, considerable time (four years) had elapsed between the psychotic episode (associated at that stage with substance abuse) and application for predictive testing, that the psychiatrist attributed the psychosis to cannabis abuse rather than HD. Situational anxiety had been noted by the programme's resident neurologist in six subjects during his examination, but these six were equally distributed between the two HD groups.

Overall psychiatric symptomatology was evenly distributed between the HD+ and HD- groups. Thus, hypothesis seven, those who are subsequently found positive for HD will not show a significantly greater incidence of psychiatric illness than those found negative for HD, could not be refuted. It would appear that there is little reason to suspect the cognitive impairment found in the HD+ group was due to current psychiatric illness. A finding supported by the results of the MCMI-II in which none of the clinical

scales for either the at risk or control groups were elevated.

5.11 Neurological evidence and its implications

In the present study 16 subjects had one or more neurological signs on examination but none of these subjects were subsequently excluded from the programme by the neurologist. Signs were present in both those subsequently found negative for HD as well as those later found to be positive for the gene. Collectively, more signs were present in the HD+ group, but the between group difference was not significant ($p > 0.05$). Thus, hypothesis eight of this study, that those subsequently found positive for HD will not show a significantly greater number of neurological signs than those found negative for HD, could not be refuted.

A range of mild neurological signs have been reported in the subjects of other neuropsychological studies. In several studies signs were observed but considered to be within normal limits (Bylsma et al., 1992; Diamond et al., 1992; Giordani et al., 1995; Strauss & Brandt, 1990). The

presence of neurological signs in study participants did not predict the differences between the HD- and HD+ groups.

When comparisons were made between the HD groups of the present study for each of the neurological signs, however, one sign, choreiform movements, was significantly exclusive to the HD+ group ($p < 0.05$). Chorea is a well known early sign of HD (Siemers et al., 1996; Young, Shoulson et al., 1986). Only subtle movements were found in four subjects, which were only elicited when subjects were examined under stress, and only found on the left side. A similar unilateral observation had been documented by Oepen et al. (1985) in their study of visuomotor function in offspring of HD patients. They attributed it to callosal dyspraxia.

Exclusion of these four subjects from the present study could have been considered, but the design of the present study was such that absolute knowledge of HD status was only accepted on the basis of the blood analysis results. Removing these subjects would have been contrary to the study design. Instead they were included in the study, and their neurological status acknowledged and discussed (see also section 5.12).

5.12 The relationship between neurological signs and cognitive impairment

In order to examine whether neurological signs correlated with inferior performance on the Paired Associate or Visual Reproduction subtests, Spearman rank correlations were carried out. No significant correlations were found ($p > 0.05$). Choreiform movements did not correlate with either memory test, and thus, hypothesis nine of the present study could not be refuted. This apparent dissociation between motor and cognitive impairment found in the HD+ group could be postulated on the basis of the purported segregated circuits linking basal nuclei to cortex (Alexander et al., 1986). Evidence is accumulating to support the suggestion that HD deficits disrupt the processing associated with different corticostriatal loops (Lawrence, Sakakian & Robbins, 1998). This suggestion, however, must be seen as speculative as hard evidence for the existence of these loops remains outstanding.

The nature of the visual reproduction impairment (a combination of memory and visuospatial deficit dependent to some extent on the ability to acquire and manipulate novel information; Loring & Papanicolaou, 1987) can best be

explained on the basis of dysfunction of the dorsolateral loop (governing the manipulation of new information and spatial memory) along with the input it receives from the parietal cortex (governing visuospatial function; Lawrence et al., 1996). The dorsolateral prefrontal circuit may have two distinct basal nuclei-thalamocortical circuits that selectively influence separate prefrontal areas. The 'closed' loop of the dorsolateral prefrontal cortex receives projections from the parietal cortex and arcuate premotor area. It projects to the dorsolateral head of the caudate nucleus and rostrocaudal areas of the tail of the caudate. Rostral portions of the caudate nucleus project to the dorsomedial globus pallidus and rostra portions of the substantia nigra.

The role of the dorsolateral prefrontal cortex is considered to be related to executive functioning, included in this nomenclature is flexibility of thought and ability to shift set, verbal and design fluency, organisational strategies for learning tasks (and hence the retrieval of declarative memory), constructional strategies for copying complex designs, and it also plays a role in spatial memory

(Cummings, 1993; Fuster, 1989)²⁷. While the anatomy underlying reduced initiation for the implementation of learning strategies on verbal memory tests has not been established, a relationship with the dorsolateral loop seems the most plausible. Particularly as, when using factor analysis, Starkstein *et al.* (1992) found that verbal and visuospatial memory loaded on the same factor that correlated with bicaudate ratio atrophy²⁸.

The motor circuit links the supplementary motor area to the putamen, ventrolateral two thirds of the internal and external segments of the globus pallidus, and the caudolateral portions of the substantia nigra. Projections extend from the internal pallidal segment to the ventrolateral nucleus of the thalamus and onto the supplementary motor area. Connections to the caudate nucleus are indirect, but the caudate does send projections to the dorsomedial areas of the globus pallidus and rostral portions of the substantia nigra. The choreiform movements

²⁷Barkley (1997; Chapters 5-7) speculates that even the executive functions may be dissociable from each other, albeit interactive and interreliant upon one other.

²⁸Distance between the maximal indentations of the head of the caudate nucleus on the frontal horns, divided by the inner table diameter at the same level, as measured by MRI (Starkstein *et al.*, 1992).

reported in the HD+ group may be related to the motor loop, which, because of its primary connection to the putamen only has an indirect connection with the caudate (and therefore only indirect connection with the prefrontal loops; Starkstein et al., 1988). Some preliminary support for this suggestion comes from the paper cited in the Addendum (Campodonico et al., 1998). Campodonico et al., reported that reduced putamen volume correlated with degree of motor abnormality as measured by the Quantified Neurological Exam whereas only reduced caudate size was associated with scores on the Hopkins Verbal Learning Test.

The relative dissociation between the loops may explain why some studies cite motor signs as the first indicator of HD and others suggest that cognitive impairment is the first presentation of the disease. Symptom onset is dependent upon which of the five frontal-subcortical circuits are involved at an preclinical stage. The deficits described in the present study are probably related to changes in the dorsolateral loop and motor loop (Cummings, 1993). It must be reiterated, however, that the existence of these loops is currently speculative.

Anatomical changes in the putamen and caudate occur early in HD (Fahn et al., 1973; Hayden, 1981; Harris et al., 1992; The Huntington's Disease Collaborative Research Group, 1993; Klintworth, 1973; Mann et al., 1993; Starkstein et al., 1988), and have been reported in those nonsymptomatic but at risk for HD (Aylward et al., 1994), but it is thought that structural change lags behind clinical symptoms (Sax et al., 1996; Vonsattel et al., 1985).

Biochemical changes probably precede structural changes, with reduced energy metabolism particularly affecting the caudate and putamen structures (Augood, Faull & Emson, 1997; Mazziotta et al., 1987; Reid et al., 1988; Weeks et al., 1996; Young, Penney et al., 1986). Thus, metabolic changes may be a more sensitive indicator of early disease than structural changes ((Weeks et al., 1996; Young, Penney et al., 1986). Unfortunately, no neuroimaging studies were carried out in the present study to corroborate this hypothesis.

When the effects of the distress associated with being at risk for a life threatening disease and the predictive testing process are accounted for, cognitive impairment

remains detectable in those positive for HD. The nature of impairment is different from that found in those who live under the threat of premature death and those found negative for HD. The question of self selection in candidates for predictive testing programmes remains to be discussed.

5.13 The self selection question

There is preliminary evidence of self selection from the biographical data collected in the present study. Subjects IQ, socioeconomic status, and highest level of education are above average. In addition, more women request testing than men. Similar findings are prevalent in most predictive testing studies.

5.13.1 Purpose in life

Does living under the threat of HD influence the meaning one places upon life and future plans one makes? There is some evidence that those at risk for HD may not actively plan for their future because of the possibility of developing HD (Huggins et al., 1992; Kessler, 1994). It is not clear whether or not those who request testing part of

this group. Bloch et al. (1989) found their group of at risk subjects to have above average scores on a life satisfaction scale but lower than average scores for a reason for living scale.

The main proponent of a theory of purpose in life was Victor Frankl who developed a theory of Logotherapy based on three assumptions: freedom of will, the will to meaning, and the meaning of life (Frankl, 1969)²⁹. According to

²⁹By the term 'freedom of will' Frankl refers to man's ability or '...freedom to take a stand on whatever conditions might confront him' (p.16, 1969). Frankl acknowledged that man does not have complete free will and is, to some extent, bound by the circumstances he finds himself in. However, man is free to react to these circumstances or detach himself from them.

The second assumption 'the will to meaning' refers to '...the basic striving of man to find and fulfil meaning and purpose [in life]' (p.35, 1969). Frankl did not believe man is a homeostatic creature but that he or she needs the tension that comes out of the search for meaning and purpose to life.

By the phrase 'meaning of life' Frankl referred not to a universal meaning but only unique meanings for individual situations which can have commonality for all humans and, thus, can be called values. The merit of values is relative and it is up to humans to accept or reject, values on moral, ethical or common standards, applying these to the individual merit of each situation. Frankl believed in free will and that man has a choice regarding interpretation and acceptance or otherwise of values. Furthermore, he feels that man has a responsibility to find the right answer to a question and has the capacity to do this through his human condition of having a conscience. Frankl did not doubt there is a meaning in every situation, but he emphasised that it is the job of the individual to

Frankl (1984) humans seek to find meaning and purpose to human existence and failure to do this leads to an existential vacuum, where individuals are caught up in a feeling of aimlessness and emptiness.

The results of part A of the PIL questionnaire administered to the HD group indicated that, in spite of possible potential limitations placed upon both quality and quantity of life by the disease, this group did not differ from the control group for purpose and meaning of life ($p>0.05$). Thus, hypothesis ten (part a), that no differences will be found for purpose in life between the at risk group and control group, could not be refuted. Only one subject in the at risk group reflected lack of life purpose with a score of 90 (26th percentile)³⁰. This score suggests lack of clear meaning in life and possible psychiatric illness. Although not significantly different, the scores for the control group and stress group on this test were lower despite the outlier discussed above.

find that meaning.

³⁰According to Crumbaugh (1966), low scores on the PIL correlate with the depression scale on the Minnesota Multiphasic Personality Inventory. Interestingly, the only low score was from a subject with a history of psychiatric disturbance, and who later proved to be positive for the Huntingtin gene.

Sections B and C of the PIL questionnaire comprise open ended questions. Selective item analysis of these questions on attitudes to life, death, illness and suffering, and suicide indicated that the majority of at risk candidates were not apprehensive of death and saw it as a natural part of the life cycle. Five, however, did express a fear of dying. Most responses inferred that death was final but four subjects described a religious theme of life after death. The response to illness and suffering was mixed. The most prevalent theme, in 14 responses, was of sadness or abhorrence for infirmity and suffering. However, several responses saw illness in a more positive and challenging light.

In answer to the question "To me life is..." there was always a positive response. Adjectives such as "great", "precious", "sacred", "good", "special", "wonderful", and "valuable" were used. Being faced with a life threatening disease may lead to a heightened awareness of the value of personal life. A possible 'Pollyanna effect' may have been occurring as well, perhaps as a denial technique (Bloch et al., 1989; DudokdeWit et al., 1997; Mlynik-Szmíd, 1997). It has been found that the applicants tried to create a positive picture of themselves to the examiners in spite of

a defensive attitude to psychometric testing (Decruyenaere et al., 1995).

One of the reasons for the elaborate testing for the predictive programme is to evaluate every candidate for suicide risk. A question in the PIL addresses this issue. The responses were very varied. The open ended question "The thought of suicide is..." brought nine replies in the first person. Mainly these were denial of personal suicidal intentions, but one answer acknowledged that it had crossed his mind in the past. The general theme was of rejection of the concept as an answer to a problem. Individuals asked this type of question in other programmes have not excluded suicide as a rational response to the onset of a disease as dreadful as HD (Bloch et al., 1989).

In Part C, a brief synopsis of ambitions and goals in life was requested. The focus was negative in only one subject where a theme of self doubt prevailed. For the remainder, themes of secure family life, further education and careers dominated. Other themes included friendships, self development, happiness, travel and financial security. These responses could be related to the reasons for

requesting predictive testing, which is discussed in the next section.

The high mean score on the PIL for the HD group is congruent with successful business personnel and professionals of high motivation (Crumbaugh, 1968), and sets this group apart from the average individual. It would appear that this group suffer none of Frankl's lack of meaning and purpose in life. Instead, the uncertainty of not knowing their HD status may leave many of this group feeling unable to go forward to achieve their goals, and consistent with this hypothesis could be the risk of falling into Frankl's 'existential vacuum'. Nevertheless, it is difficult to know to what extent the subjects were influenced to respond to these questions in a way that they thought congruent with the therapist's expectations. This concern has been raised by other predictive testing programmes (e.g. Bloch et al., 1989).

5.13.2 Reasons for requesting testing

A question raised early by predictive testing researchers was why do those at risk want testing. Views canvassed prior to the availability of predictive testing suggested

that, should a testing procedure become available, many of those at risk would be interested in establishing their HD status presymptomatically (Kessler, 1987b; Kessler et al., 1987). Reasons cited for wanting to know included resolution of fears of mental and physical instability, possible later financial difficulties, issues concerning social stigmata, loss of dignity and inability to care for themselves or their families, and the guilt of possibly passing on the gene to their children (Evers-Kiebooms et al., 1989; Hayden, Ehrlich, Parker & Ferera, 1980).

Those who completed predictive testing give similar reasons. These included either wanting to begin a family or have more children; wanting to inform existing children of their risk status; the reduction of anxiety caused by not knowing one's own status; to make financial and residential plans for the future if positive; whether to marry; or make changes in employment status (Bloch et al., 1989; Codori et al., 1994; Decruyenaere et al., 1995; Evers-Kiebooms et al., 1989; Meissen et al., 1988, 1991; Tibben, Frets et al., 1993; Tyler, Ball et al., 1992; van der Steenstraten et al., 1994). Generally, the reasons given for knowing HD status centre around issues aimed at reducing anxiety and uncertainty (Meissen et al., 1991).

Overwhelmingly, the most common reason given by those in the Johannesburg programme for undertaking the testing, was to make plans for the future. Making long term financial plans and planning a family were the most commonly given concrete reasons. No differences were found between the HD+ and HD- group with regard to the reasons given suggesting that reasoning skills at least in the HD+ group were unimpaired. These reasons are similar to those cited by other research groups and appear consistent across the various international testing programmes.

These reasons may seem logical and practical but have been criticised as being merely "fantasies and wishes" by Kessler (1994, p.164). He feels that, apart from those who wish to make reproductive plans, most applicants for predictive testing have made few concrete steps to achieve these reasons. Kessler (1994) stresses that this observation merely confirms how difficult it must be to prepare for an unfavourable result. A view endorsed in an article written by one at risk participant after undergoing predictive testing (Hayes, 1992).

5.13.3 The personality style of those who request testing

Historically, several researchers have suggested that a personality style specific to HD exists. Boll et al. (1974), using the Minnesota Multiphasic Personality Inventory (MMPI), described those with a diagnosis of HD as showing a particular profile of depression and dissatisfaction with life situations, preoccupation with multiple somatic complaints, confusion and communication difficulties and social isolation. Palm (1973) reported personality characteristics of rebelliousness for social and ethical codes, the presence of a relatively low or high activity drive, and preference to avoid immediate problems rather than face them. Wallace & Parker (1973) studied premorbid personality styles in HD and reported a personality style of impulsiveness and instability sufficient to diagnose HD premorbidly.

Not all researchers have supported a 'prechoreic' personality presentation (e.g. Lyle & Gottesman, 1977). It has been proposed that these symptoms are probably seen in all who experience decline in adaptive abilities due to brain damage (Boll et al., 1974; Norton, 1975). In fact, both Boll et al. (1974) and Goodman et al. (1966) equated

the personality dysfunction of HD to that associated typically with 'chronic brain syndromes'.

The most common personality changes seen after brain disease are emotional dulling, disinhibition, diminution of anxiety, emotional blandness or mild euphoria, and decreased social sensitivity (Lezak, 1995). Depression is the most common psychiatric symptom from brain injury and disease, either as a reaction to the losses associated with the damage, or directly due to the localisation of the damage (Lezak, 1995).

Only a few of the studies describing the applicants for predictive testing programmes have considered their personality profile. Decruyenaere and colleagues (1995; 1996) administered the Minnesota Multiphasic Personality Inventory (MMPI) to those undergoing predictive testing. Their results indicated that their subjects showed strong positive characteristics such as higher ego strength and social extroversion, and had more positive coping strategies available to them. Men had more hysterical characteristics and women lower scores on scales of depression, psychopathic deviation, psychasthenia and schizophrenia than a Dutch and Flemish norm group. Bloch

et al. (1989) suggested that those who request testing are more resourceful than the population at large.

The personality profile of those requesting predictive testing, described by Decruyenaere and colleagues, is very different from that put forward either by Palm (1973) or Wallace and Parker (1973), and cannot easily be attributed to preclinical disease.

In the present study, only one significant difference was found between the at risk group and the normal control group for any of the scales of the MCMI-II. The at risk group score for the compulsive subscale was significantly higher than that of the control group ($p < 0.05$). Thus, hypothesis ten (part b), that no differences in personality style will be found between the at risk group and control group, could not be upheld.

None of the scores reached a score suggestive of a predominant characteristic of pathological significance (score > 75). However, several of the scales were relatively elevated (i.e. score > 60) indicating a robust presence of that characteristic. For example, the desirability subscale score in both groups suggested that

all participants had a high regard for authority, respecting societal rules. They wanted to present themselves in a good light and appear confident, gregarious, cooperative, efficient, and well organised (Choca et al., 1992). A finding that would support the suggestion that subjects are keen to present themselves positively to members of the predictive testing teams (Decruyenaere et al., 1995).

Further, the base rate scores for the histrionic, narcissistic and compulsive personality scales were also greater than 60 in both the control and at risk groups. Based on Millon's Biosocial Learning Theory (Millon & Everly, 1985), the narcissism scale draws upon Millon's 'Passive-independent' personality pattern. In healthy individuals, this reflects high self esteem, outgoing affect and interpersonal style. The compulsive scale taps Millon's 'Passive-ambivalent' style, which reflects conscientious, disciplined and perfectionist traits, a cautious interpersonal style, and sombre affect in healthy individuals. While the histrionic scale, reflecting Millon's 'Active-dependent' style, describes a more outgoing interpersonal style with strong sociability and

needs for positive regard (Choca et al., 1992; Millon & Everly, 1985).

Relatively elevated scores on these three particular personality scales are found in nonpathological subjects used as controls in other studies (Craig & Olson, 1992; Wexler, Kahn, Cahn, van Praag & Asnis, 1990). Instead of suggesting dysfunction, Wexler et al. (1990) suggests that relatively high scores on these scales point to positive self image (narcissistic scale); conformity and ability to be organised (compulsive scale); and sociability (histrionic scale).

These three scales compare well to several scales on the 16 PF, a personality test of normal personality traits. The narcissism scale on the MCMI-II correlates positively with the independent, dominant, and venturesome scales on the 16 PF; the compulsive scale correlates moderately with the emotionally controlled, conscientious and self disciplined scales; and the histrionic scale corresponds with the extroversion, venturesome, enthusiastic, independent, and dominant scales (Craig & Olson, 1992).

The scores of two of the more severe personality scales, the paranoid scale and aggressive/sadistic scale, were also greater than 60. The aggressive/sadistic scale reflects a strong need for dependence and competitiveness, while the paranoid scale (only elevated in the at risk group) is a more pronounced syndromal variant of the compulsive personality style. None of the clinical scales were in the range of a psychiatric population suggesting that both the at risk and control groups were psychiatrically well.

The normal scoring procedure for the MCMI-II is to identify, in chronological order, the three highest scores on a personality scale (Choca et al., 1992). When adopting this procedure, the at risk and control groups in the present study have considerable overlap in elevated scores. They share the same three highest scales but the chronological order differs. This suggests that subtly different personality profiles between the HD group and the control group exist. For the at risk group the compulsive trait scored highest with narcissistic trait and histrionic traits next. For the control group, the narcissistic trait was highest with compulsive and histrionic next.

The significantly stronger presence of compulsive traits found in the at risk group reflects a more disciplined and perfectionistic person who wishes to both obtain and maintain good control of the environment. These traits reflect individuals in need of control, a group who emphasise conformity and organisation. They are field independent people, relying on their own feelings and judgements than those of others. Such a profile is congruent with the suggestion that a primary source of stress for those at risk is lack of control (Meissen et al., 1991).

The control group personality style was dominated by outgoing, charming individuals who enjoy attention. They are friendly and helpful, liking praise and novelty, having a positive self image, and a strong degree of sociability (Wexler et al., 1990). A profile more in keeping with those who would be prepared to volunteer for a research project that took up several hours of their time.

The profile gained from the present study presented above is in contradiction to that put forward by Wallace & Parker (1973) who studied premorbid personality styles in HD and reported a personality style of impulsiveness and

instability. Neither do these results entirely support Baxter et al's (1992) findings of raised scores for anger/hostility on the Profile of Mood States self rating scale. Instead the above results concur more with Decruyenaere and colleagues (1995) findings. They noted that those who request testing do not differ significantly from the general population in terms of psychological symptomatology and may even have more positive characteristics such as higher ego strength.

Those tested through the Johannesburg Predictive Testing programme indeed appear essentially no different from a sample of the general population. The at risk group, however, showed subtle personality differences which may point to a self selection process occurring for predictive testing programmes.

5.13.4 Conclusions regarding the question of self selection

The question raised by several researchers is whether or not those who do proceed with predictive testing are self selected and, if they are, what is the nature of this self selection (Codori et al., 1994; Kessler, 1994; Tyler, Ball

et al., 1992)? Furthermore, what are the implications of self selection?

The present study has identified several factors that support a self selection process in the Johannesburg predictive testing programme. The average applicant is more likely to be female, in her 30's and facing the imminent onset of the disease. She is well educated and comes from a middle class background. She is self disciplined, perfectionistic, and somewhat rigid in outlook, preferring to know where she stands rather than let indecision rule her. She expects to be able to cope with a positive test result. She has clear cut, albeit unfulfilled, reasons for wanting to be tested, which revolve around future life planning, and has a strong sense of personal life values and goals. There is little evidence for subtle clinical indications of the disease, although mild forgetfulness may be reported in those who carry the gene.

This profile differs from that of those who avoid predictive testing (Codori et al., 1994). These individuals perceive themselves less able to cope with an unfavourable test result and express fears that an adverse

result would have far reaching negative effects on themselves and their families, especially as once the result is known, it is not possible to 'undo' the knowledge (Codori et al., 1994; Evers-Kiebooms et al., 1989; Quaid & Morris, 1993; Tyler, Morris et al., 1992; van der Steenstraten et al., 1994). While for some, there is no point to testing since there is no cure at present (Evers-Kiebooms et al., 1989; Quaid & Morris, 1993).

5.14 Failure to uphold all the null hypotheses

Although the first and the latter four hypotheses of the present study could not be rejected (albeit hypothesis nine only partially), none of hypotheses two to six (all related to group neuropsychological status) could be upheld. Consequently, the continuity model with the assumption that the gene phenotype is expressed before the onset of clear signs and symptoms could not be refuted. On various tests of neuropsychological function, the HD+, HD- and stress group differed from the control group and from each other. In the HD+ group reduced cognitive performance on tests of memory function were found and the presence of the early cognitive deterioration associated with HD could not be discounted.

The continuity hypothesis implies that signs of a disorder are present before the onset of the disorder, perhaps even from birth (Penney et al., 1997). The results of the present study were unable to delineate the exact point of disease onset. Several suggestions for further research in this regard can be made.

The mean age of subjects in this study was 33 years suggesting that many of the group could have been in a perisymptomatic phase of the disease. This was unavoidable in the light of the recruitment process for the Johannesburg predictive testing programme. Unfortunately there is no way to estimate cross-sectionally at what point the subjects were in their disease course.

Although more longitudinal studies are required in this regard, a recent neuropsychological study has attempted to overcome this dilemma. Hahn-Barma et al. (1998) divided their HD+ group into two groups: those with impairment on the Paired Associate subtest of the WMS and those with normal scores for this test. The first group displayed cognitive impairment congruent with early HD, while the second group did not differ from the HD- group. However, as no normal volunteer control group was used in this

study, the cognitive well being of the HD- group was not evaluated. This study deserves replication with the inclusion of a normal volunteer control group.

Age of disease onset in the index parent has also been used to estimate the course point of the offspring. This is a crude method since there is considerable variability in the onset of the disease in general, and only a rough similarity between parent and child can be estimated. This information was not available in the present study. Nevertheless, this data should be collated in future neuropsychological studies.

Size of sample and battery used is a prevalent limitation of all the relevant studies to date, reducing the power of all findings. Time constraints limited the number of subjects available to the present study, but the test battery size was modified to control for this weakness. Hopefully the results of larger sample sizes will be reported with the passage of time with the inclusion of relevant control groups.

HD is the result of a gene mutation located at 4p16.3 in the IT15 transcript which contains expanded and unstable

polymorphic trinucleotide CAG repeats (Beilby et al., 1994). The number of CAG expansions appear to play a role in the expressed phenotype of this illness.

Several of the more recent studies have suggested that there is a relationship between CAG repeats and neuropathological changes in the striatum (Aylward et al., 1997; Furtado et al., 1996; Penney et al., 1997), and neuropsychological test performance (Jason, Suchowersky et al., 1997). The nature of this relationship is not well understood. It has been suggested that those individuals with higher repeats may have cognitive impairment prior to clinical onset or that they may have greater impairment (Jason, Suchowersky et al., 1997).

A relationship between CAG repeats and cognitive deterioration has been only recently documented (Hahn-Barma et al., 1998; Jason, Suchowersky et al., 1997). Unfortunately the actual number of CAG repeats for the subjects of the present study were unavailable. The use of CAG repeats predictively to estimate onset of illness has been discouraged (Gusella et al., 1993; Stine et al., 1993). Nevertheless, it would appear that number of CAG

repeats may be of considerable importance for research purposes and needs to be available for future studies.

Similarly, a relationship between cognitive impairment and neuroimaging in those at risk has been found by several (e.g. Aylward et al., 1994) but not all researchers (Guttman et al., 1996). Unfortunately a contribution to this debate could not be made by the present study as neuroimaging was not included in the Johannesburg predictive testing programme. Neuroimaging is typically not routinely used in predictive programmes, but, in the light of biochemical changes preceding structural changes to the basal nuclei, functional neuroimaging has the potential to add clarification in future studies.

The occurrence of cognitive dysfunction before definitive clinical features in HD was proposed from the results of the present study but establishing the precise onset of HD was not possible. However, it appears from the literature that initial presymptomatic changes in function are probably biochemical (Hayden et al., 1987). Neurochemical dysfunction in the basal nuclei, selectively affecting the purported frontal circuits may be the precursor to disease onset. Conclusions to draw from this include suggesting

further impetus to biochemical research in order to discover the protein which is expressed by the huntingtin gene, and the function of that protein.

Chapter Six

6.0 CONCLUSION

The main aim of the present study was to identify whether or not those individuals who requested predictive testing for HD had measurable cognitive impairment prior to onset of clinical symptoms. Previous research in this area had been conflicting and the question remained unresolved. The results of the present study support the hypothesis that no differences exist presymptomatically between those positive for the Huntington gene, and those negative.

It was suggested that methodological restrictions and nongenetic reasons for cognitive impairment could be confounding the test results. In an attempt to deal with these issues several augmentations were implemented to the basic research design generally used by researchers. Like other studies, those at risk for HD were assigned to the experimental groups on the basis of their results from molecular analysis (the HD+ and HD- groups). In the present study, however, the results of the neuropsychological test scores of these two experimental groups were then compared to a carefully matched normal

volunteer control group. In addition, in an attempt to control for the nongenetic (stress) factors potentially influencing cognitive performance, the neuropsychological test battery was administered to a group of individuals in a similar life threatening situation as that of the at risk group.

Group comparisons were made, and significant cognitive impairment, detectable using neuropsychological assessment, was found in the HD+ group, HD- group and stress group when compared to a carefully matched normal volunteer group. The two HD groups shared significantly lower tests scores on one test when individually compared to the control group, possibly suggesting shared dysfunction, but both groups displayed distinct patterns of cognitive impairment as well. Tentative interpretation of these results introduced the possibility that attentional deficits were dominant in the HD- and stress group but not in the HD+ group. The selectively predominant cognitive impairment of this latter group was in visual and verbal memory.

The pattern of impairment found in the HD- and stress groups offered tentative support for the hypothesis put forward by several researchers (Bylsma et al., 1992; de Boo

et al., 1997b; Giordani et al., 1995; Rosenberg et al., 1995) that nongenetic issues may influence the cognitive status of individuals at risk for HD but not yet symptomatic. The functional implications of these particular tests point to anxiety regarding the stressfulness of the situation surrounding a life threatening disorder and the predictive testing scenario.

Nevertheless, when these nongenetic issues were adjusted for, measurable cognitive dysfunction remained in the HD+ group in the form of impairment on tests of episodic declarative memory. There is wide support from studies of early cognitive impairment in HD and other presymptomatic studies that this particular type of memory impairment is one of the earliest indicators of Huntington's dementia. As this memory impairment was specific to the HD+ group and not present in the HD- or stress groups, the presence of cognitive impairment prior to the clinical onset of HD could not be disputed.

There was little evidence of psychiatric illness but subtle indications of choreiform movements were found in four of the HD+ group. Of all the movement disorders present in HD, chorea is considered an very early sign on disease

onset (Siemers et al., 1996; Young, Shoulson et al., 1986). These movements however, did not correlate with the cognitive symptoms. Suggesting that in the early stages of this disease the onset of the clinical features associated with HD can occur separately. A finding which replicates the findings of both de Boo et al. (1998) and Rothlind, Brandt et al. (1993) and gives a degree of support to the theory of functionally segregated circuits linking basal nuclei and cortex (Alexander et al., 1986; Cummings, 1993).

The hypothesis that those who request predictive testing are self selected was supported in the present study. The biographical characteristics of the at risk group differed from the general population in terms of socioeconomic status. Further, the trend in personality style for this group was to have a strong need for control over their lives.

In general, the outcome of the Johannesburg predictive testing programme has been positive. A finding congruent with predictive programmes in general (Brandt et al., 1989; Codori et al., 1994). This has led to the suggestion that the time consuming, involved, and costly pretesting programmes should be abandoned in favour of a generally

available blood test now that direct testing can take place (Codori et al., 1994). Not everyone agrees with the above, and it has been stressed that the counselling protocols should continue (European Community Huntington's Disease Collaborative Study Group, 1993; Hersch et al., 1994; The Huntington's Disease Collaborative Research Group, 1993; Lam et al., 1988; Rosser, Huson & Norbury, 1994; Simpson, Harding et al., 1993). Ethical issues have been raised against a freely available test (European Community Huntington's Disease Collaborative Study Group, 1993; Harper, 1995).

Little is really understood about the psychological reaction to molecular testing. On a short term basis it appears that a result, either of increased risk or decreased risk, is better than uncertainty (Tibben, Duivenvoorden et al., 1993; Wiggins et al., 1992). Understandably, those found to be negative for HD generally experience increased psychological wellbeing (Wiggins et al., 1992), but interestingly, increased wellbeing is also reported in those who are given an increased risk for HD (Wiggins et al., 1992). Of Wiggins et al.'s decreased risk group, 10% had serious difficulties coping with their new status. Issues of 'survivor' guilt are raised (Codori &

Brandt, 1994), and not all of life's difficulties are resolved by the removal of the genetic risk (Reynolds *et al.*, 1994). Denial is a commonly used defence mechanism in those at risk for HD, even after testing, and the long term psychological outcome may be less positive than the present short term findings of wellbeing (DudokdeWit *et al.*, 1997; Kessler, 1987b; Tibben, Duivenvoorden *et al.*, 1993).

Furthermore, mild cognitive impairment may be present in those who request predictive testing before other indications of HD are observed. Admittedly, the impaired scores for visual and verbal memory in the present study were of statistical rather than functional consequence. All those positive for HD in the present study were performing normally in their every day life and appeared to have asymptomatic neuropsychological impairment. None of the group means for the Visual Reproduction and Paired Associate tests fell outside the standardised group norms, but some individual scores did. The undetected presence of cognitive impairment could lead to the making of inappropriate or wrong decisions (Lanto *et al.*, 1990).

The results of the present study caution against abandonment of testing programmes. Like other researchers,

the results of this study suggest that only a self selected group come forward for testing (Codori et al., 1994; Tibben, Frets et al., 1993), and cognitive impairment may be present in this group at the time of molecular analysis. If no cautionary programme for predictive testing is in place, it might lead to those reluctant to be tested or ill prepared for the results being coerced into testing with traumatic consequences (Codori et al., 1994; Kessler, 1994). Alternatively, there is the possible misuse of information by outside agencies such as insurance companies (Brandt et al., 1989. Individuals have the right not to know of their risk status (Decruyenaere, Evers-Kiebooms & Van den Berghe, 1993). This last proviso needs to be emphasised with the increased awareness of the power of molecular genetics. As predictive testing becomes available for a wide variety of neurological and psychiatric illnesses it will be even more important to carefully monitor and support those who choose to define their lives in terms of their risk status.

6.1 Addendum

The results of a very recent published study (Campodonico et al., September, 1998) add support to the findings above. In a group of symptom free but mutation positive subjects, Campodonico and colleagues correlated neuropsychological test scores and the results of a quantified neurological examination, with caudate, putamen and globus pallidus measures, using MRI. Their results indicated that verbal learning varied as a function of caudate size, while motor abnormality varied with size of putamen. Their results support several findings of the present study. First, that cognitive impairment is present presymptomatically in those genetically positive for H.D. Second, that cognitive impairment and motor impairment can coexist but are not necessarily correlated with each other. Finally, Campodonico's study was able to provide evidence from neuroimaging to justify these findings.

7.0 APPENDICES

Appendix 1 Test battery

The neuropsychological tests were administered in the following order:

Wechsler Memory scale, form 1

Complex Figure of Rey - Copy
- immediate recall

Boston Naming test

Controlled Oral Word Association Test

National Adult Reading Test - Table 2 -

Rey Auditory Verbal Learning Test

Complex Figure of Rey - Delayed recall

Topographical orientation

Judgement of Line Orientation Test Form V

Design Fluency test - fixed design sub-test

Free Drawing test - bicycle (Lezak's scoring)

Stroop color/word test - word
- color
- color/word

Modified Wisconsin Card Sorting Test

Trail Making A and B

Tinkertoy Test

Appendix 2 Format of psychiatric interview

Information gained from the Psychiatrist's reports

Patient Name

Motivation:

Psychiatric History:

Family History:

Occupational History:

Relationships:

Attitude to suicide:

Postulated response to testing positive:

Cognitive functions:

Personality:

Conclusion:

Appendix 3 Format of neurological assessment

The neurological examination conducted included special assessment for the following:

Evidence of involuntary twitches/choreiform movements

At rest
Under stress

Headthrusts

Oculomotor dysfunction

Presence of abnormal eye movements
Presence of diminished saccadic movements
Presence of papillary hippus
Presence of gaze abnormalities

Dysarthria

Presence of abnormal tongue movements

Cognitive status

Any subjective report of cognitive status

Brief objective assessment of cognitive status, using Mini Mental Status Examination

Mood

Informal subjective assessment

Appendix 4 At risk subject's individual neurological status

The individual results of the neurological examination are presented in Table A.1.

Key to Table A.1

- Sign 1 - choreiform movements, at rest and under stress
- Sign 2 - involuntary twitches/tremor
- Sign 3 - presence of abnormal eye movements/oculomotor dysfunction
- Sign 4 - diminished saccadic movements
- Sign 5 - presence of papillary hippus
- Sign 6 - presence of head thrusts
- Sign 7 - presence of abnormal tongue movements
- Sign 8 - loss of points on MMSE
- Sign 9 - mood changes reported or observed

Table A.1 Neurological findings for each at risk subject

Subj. No. & HD status	Sign 1	Sign 2	Sign 3	Sign 4	Sign 5	Sign 6	Sign 7	Sign 8	Sign 9
04+	-	-	-	-	-	-	-	+	+
05-	-	-	-	-	-	-	-	-	-
06-	-	-	-	-	-	-	-	-	-
07+	+	-	+	-	-	-	-	+	-
08+	+	-	-	-	+	+	-	-	-
09-	-	-	-	-	-	-	-	-	-
10+	-	-	-	-	-	-	-	-	-
11+	+	-	-	+	-	+	+	-	-
12-	-	-	-	-	-	-	-	-	-
13-	-	-	-	-	+	-	-	-	-
14-	-	-	-	-	+	-	-	+	+
15+	-	-	-	-	-	-	-	-	-
16+	-	-	-	+	+	-	-	-	-
17-	-	-	-	-	-	-	-	-	-
18-	-	+	-	-	+	-	-	-	-
19+	-	-	-	-	-	-	-	-	-
20-	-	-	-	-	-	-	-	-	-
21-	-	-	-	-	-	-	-	-	+
22+	-	-	-	-	+	-	-	-	+
23-	-	-	-	-	-	-	-	+	-
24-	-	+	-	+	-	+	+	+	+
25-	-	+	-	-	-	-	-	-	+
26+	+	-	-	+	+	+	-	-	+
27-	-	-	-	-	-	-	-	-	-
29-	-	-	-	-	-	-	-	-	-
30+	-	-	-	-	+	-	-	+	+

Appendix 5 Ethics clearance certificate

Appendix 6 Subjects individual reasons for requesting testing

In Table A.2 presented below, each subject's individual reasons for requesting testing are given.

Table A.2 Each subject's reasons for requesting predictive testing

Programme subject no. and sex	Reason 1	Reason 2	Reason 3	Reason 4	Reason 5	Reason 6
04-Female	+					
05-Female	+		+			
06-Female	+		+		+	
07-Female						+
08-Male						+
09-Female	+					+
10-Male	+	+			+	
11-Male	+		+		+	
12-Male	+	+				
13-Male	+					
14-Female				+		+
15-Female	+			+		
16-Female				+		
17-Female		+			+	+
18-Male			+		+	
19-Female			+			+
20-Female				+		
21-Male	+	+	+			
22-Female		+	+		+	+
23-Male	+		+			
24-Female				+		
25-Male	+			+		+
26-Male						+
27-Male		+	+			
29-Female	+		+			
30-Female	+					+

Key to reasons

1. A need to make long term financial plans and plans for eventual care should the result be positive for H.D.
2. A wish to know before a future planned marriage, or remarriage.
3. A wish to know before starting a family, or having further children.
4. To inform one's children of their risk status. Individuals in this category hoped to eliminate the need for their own children to undergo predictive testing by being tested themselves.
5. To make career decisions. For example, whether to enter into one's own business, or make major career moves.
6. To alleviate the dissonance caused by not knowing one's HD status. For some, the anxiety of not knowing was perceived as worse than receiving a positive HD status. Or, there was a preoccupation with looking for, or worrying about, possible early symptoms, which was proving to be very distressing.

Appendix 7 Scores for the Information and Block Design subtests of the SAWAIS

The Information subtest and Block Design subtest of the SAWAIS were administered to all four groups as a control measure for estimating equivalence across all groups for IQ. No significant group differences were found for either test ($p > 0.05$).

Table A.3 Mean and standard deviation scores for two subtests of the SAWAIS

Test	HD+ group (N=11)	HD- group (N=15)	Control group (N=26)	Stress group (N=12)	P Value
Information	10.36 (1.57)	10.70 (0.86)	10.65 (1.38)	10.67 (1.63)	0.9219
Block Design	11.77 (2.65)	12.97 (2.99)	12.39 (2.78)	13.38 (1.84)	0.4772

8.0 REFERENCES³¹

Adams, R., Victor, M. & Ropper, A.H. (1997). Principles of Neurology. (6th ed.). New York: McGraw-Hill.

Albert, M.L., Feldman, R.G. & Willis, A.L. (1974). The 'subcortical dementia' of progressive supranuclear palsy. Journal of Neurology, Neurosurgery, and Psychiatry, 37, 121-130.

Alexander, G.E., DeLong, M.R. & Strick, P.L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neuroscience, 9, 357-381.

Aminoff, M.J., Marshall, J., Smith, E.M. & Wyke, M.A. (1975). Pattern of intellectual impairment in Huntington's chorea. Psychological Medicine, 5, 169-172.

Anderson, S.W., Damasio, H., Dallas Jones, R. & Tranel, D. (1991). Wisconsin card sorting test performance as a measure of frontal lobe damage. Journal of Clinical and Experimental Neuropsychology, 13, 909-922.

Andrykowski, M.A., Schmitt, F.A., Gregg, M.E., Brady, M.J., Lamb, D.G. & Henslee-Downey, P.J. (1992). Neuropsychologic impairment in adult bone marrow transplant candidates. Cancer, 70, 2288-2297.

Antonini, A., Leenders, K.L. & Eidelberg, D. (1998). [¹¹C] Raclopride-PET studies of the Huntington's disease rate of progression: relevance of the trinucleotide repeat length. Annals of Neurology, 43, 253-255.

Augood, S.J., Faull, R.L.M. & Emson, P.C. (1997). Dopamine D₁ and D₂ receptor gene expression in the striatum in Huntington's disease. Annals of Neurology, 42, 215-221.

³¹The referencing system of the American Psychological Association has been used.

Aylward, E.H., Anderson, N.B., Bylsma, F.W., Wagster, M.V., Barta, P.E., Sherr, M., Feeney, J., Davis, A., Rosenblatt, A., Pearlson, G.D. & Ross, C.A. (1998). Frontal lobe volume in patients with Huntington's disease. Neurology, 50, 252-258.

Aylward, E.H., Brandt, J., Codori, A.M., Mangus, R.S., Barta, P.E. & Harris, G.J. (1994). Reduced basal ganglia volume associated with the gene for Huntington's disease in asymptomatic at-risk persons. Neurology, 44, 823-828.

Aylward, E.H., Li, Q., Stine, O.C., Raney, N., Sherr, M., Barta, P.E., Bylsma, F.W., Pearlson, G.D. & Ross, C.A. (1997). Longitudinal change in basal ganglia volume in patients with Huntington's disease. Neurology, 48, 394-399.

Bäckman, L., Robins-Wahlin, T.-B., Lundin, A., Ginovart, N. & Farde, L. (1997). Cognitive deficits in Huntington's disease are predicted by dopaminergic PET markers and brain volumes. Brain, 120, 2207-2217.

Baldwin, B. & Förstl, H. (1993). 'Picks's disease' - 101 years on. Still there, but in need of reform. British Journal of Psychiatry, 163, 100-104.

Bamford, K.A., Caine, E.D., Kido, D.K., Cox, C. & Shoulson, I. (1995). A prospective evaluation of cognitive decline in early Huntington's disease: functional and radiographic correlates. Neurology, 45, 1867-1873.

Bamford, K.A., Caine, E.D., Kido, D.K., Plassche, W.M., Shoulson, I. (1989). Clinical-pathologic correlation in Huntington's disease: a neuropsychological and computed tomography study. Neurology, 39, 796-801.

Barbeau, A., Chase, T.N. & Paulson, G.W. (Eds) (1973). Advances in Neurology (Vol. 1). New York: Raven Press.

Barbosa, E.R., Haddad, M.S., Bacheschi, L.A. & Scaff, M. (1996, June). Magnetic resonance imaging (MRI) of the brain in Huntington's disease. Paper presented at the Fourth International Congress of Movement Disorders, Vienna, Austria.

Barkley, R.A. (1997). ADHD and the nature of self-control. New York: Guildford Press.

Baro, F. (1973). A neuropsychological approach to early detection of Huntington's chorea. In A. Barbeau, T.N. Chase & G.W. Paulson (Eds), Advances in Neurology (Vol. 1, pp. 329-338). New York: Raven Press.

Barrett, D.H., Green, M.L., Morris, R., Giles, W.H. & Croft, J.B. (1996). Cognitive functioning and posttraumatic stress disorder. The American Journal of Psychiatry, 153, 1492-1494.

Baum, A., Friedman, A.L. & Zakowski, S.G. (1997). Stress and genetic testing for disease risk. Health Psychology, 16, 8-19.

Baxter, L.R., Mazziotta, J.C., Pahl, J.J., Grafton, S.T., St. George-Hyslop, P., Haines, J.L., Gusella, J.F., Szuba, M.P., Selin, C.E., Guze, B.H. & Phelps, M.E. (1992). Psychiatric, genetic, and positron emission tomographic evaluation of persons at risk for Huntington's disease. Archives of General Psychiatry, 49, 148-154.

Bayless, J.D., Varney, N.R. & Roberts, R.J. (1989). Tinker Toy Test performance and vocational outcome in patients with closed-head injuries. Journal of Clinical and Experimental Neuropsychology, 11, 913-917.

Beck, A.T. (1987). Beck Depression Inventory. San Antonio, TX: The Psychological Corporation.

Bedford, F.L. (1997). False categories in cognition: the not-the-liver fallacy. Cognition, 64, 231-248.

Beilby, J., Chin, C.Y., Porter, I., Walpole, I.R. & Goldblatt, J. (1994). Improving diagnosis of Huntington's disease by analysis of an intragenic trinucleotide repeat expansion. The Medical Journal of Australia, 161, 356-360.

Benjamin, C.M., Adam, S., Wiggins, S., Theilmann, J.L., Copley, T.T., Bloch, M., Squitieri, F., McKellin, W., Cox, S., Brown, S.A., Kremer, H.P.H., Burgess, M., Meshino, W., Summers, A., Macgregor, D., Buchanan, J., Greenberg, C., Carson, N., Ives, E., Frecker, M., Welch, J.P., Fuller, A., Rosenblatt, D., Miller, S., Dufrasne, S., Roy, M., Andermann, E., Prevost, C., Khalifa, M., Girard, K., Taylor, S., Hunter, A., Goldsmith, C., Whelan, D., Eisenberg, D., Soltan, H., Kane, J., Shokeir, M.H.K., Gibson, A., Cardwell, S., Bamforth, S., Grover, S., Suchowersky, O., Klimek, M., Garber, T., Gardner, H.A.,

MacLeod, P. & Hayden, M.R. (1994). Proceed with care: direct predictive testing for Huntington disease. American Journal of Human Genetics, 55, 606-617.

Benson, D.F. & Geschwind, N. (1975). Psychiatric conditions associated with focal lesions of the central nervous system. In S. Arieti (Ed.), American Handbook of Psychiatry, (2nd ed.) (Vol. 4) (pp. 208-243). New York: Basic Books.

Benton, A.L. (1968). Differential behavioural effects in frontal lobe disease. Neuropsychologia, 6, 53-60.

Benton, A.L. & Hamsher, K. de S. (1989). Multilingual Aphasia Examination, Iowa City: AJA Associates.

Benton, A.L., Hamsher, K., Varney, N.R. & Spreen, O. (1983). Judgment of Line Orientation, Form V. Contributions of neuropsychological assessment. Oxford University Press.

Benton, A., Hannay, H.J. & Varney, N.R. (1975). Visual perception of line direction in patients with unilateral brain disease. Neurology, 25, 907-910.

Benton, A.L., Levin, H.S. & Van Allen, M.W. (1974). Geographic orientation in patients with unilateral cerebral disease. Neuropsychologia, 12, 183-191.

Berent, S., Giordani, B., Lehtinen, S., Markel, D., Penney, J.B., Buchtel, H.A., Starosta-Rubinstein, S., Hichwa, R. & Young, A.B. (1988). Positron emission tomographic scan investigations of Huntington's disease: cerebral metabolic correlates of cognitive function. Annals of Neurology, 23, 541-546.

Berg, E.A. (1948). A simple objective test for measuring flexibility in thinking. Journal of General Psychology, 39, 15-22.

Blackmore, C. (1989). Altered images. Nursing Times, 85, 36-39.

Blackmore, L., Simpson, S.A. & Crawford, J.R. (1995). Cognitive performance in UK sample of presymptomatic people carrying the gene for Huntington's disease. Journal of Medical Genetics, 32, 358-362.

Bloch, M., Fahy, M., Fox, S. & Hayden, M.R. (1989). Predictive testing for Huntington disease: II. demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates. American Journal of Medical Genetics, 32, 217-224.

Boll, T.J., Heaton, R. & Reitan, R.M. (1974). Neuropsychological and emotional correlates of Huntington's chorea. The Journal of Nervous and Mental Disease, 158, 61-69.

Bosch, B.A. Stress-related aspects of learning and memory functions, with specific reference to the role of micronutrients. Paper presented at the 22nd Annual International Neuropsychological Society Mid-year Conference, Durban, South Africa.

Brackenridge, C.J. (1973). Interrelations between some clinical factors in Huntington's chorea. In A. Barbeau, T.N. Chase & G.W. Paulson (Eds), Advances in Neurology (Vol. 1, pp. 65-73). New York: Raven Press.

Brackenridge, C.J. (1974). Effect of climatic temperature on the age of onset of Huntington's chorea. Journal of Neurology, Neurosurgery, and Psychiatry, 37, 297-301.

Bradshaw, J.L., Phillips, J.G., Dennis, C., Mattingley, J.B., Andrewes, D., Chiu, E., Pierson, J.M. & Bradshaw, J.A. (1992). Initiation and execution of movement sequences in those suffering from and at-risk of developing Huntington's disease. Journal of Clinical and Experimental Neuropsychology, 14, 179-192.

Brandt, J. (1991). Cognitive impairments in Huntington's disease: insights into the neuropsychology of the striatum. In F. Boller & J. Grafman (Eds), Handbook of Neuropsychology (Vol. 5, pp. 241-264). Amsterdam, The Netherlands: Elsevier.

Brandt, J. & Butters, N. (1986). The neuropsychology of Huntington's disease. Trends in Neurosciences, 9, 118-120.

Brandt, J., Bylsma, F.W., Aylward, E.H., Rothlind, J. & Gow, C.A. (1995). Impaired source memory in Huntington's disease and its relation to basal ganglia atrophy. Journal of Clinical and Experimental Neuropsychology, 17, 868-877.

Brandt, J., Bylsma, F.W., Gross, B.A., Stine, O.C., Ranen, N. & Ross, C.A. (1996). Trinucleotide repeat length and clinical progression in Huntington's disease. Neurology, 46, 527-531.

Brandt, J., Corwin, J. & Krafft, L. (1992). Is verbal recognition memory really different in Huntington's and Alzheimer's disease? Journal of Clinical and Experimental Neuropsychology, 14, 773-784.

Brandt, J., Folstein, S.E. & Folstein, M.F. (1988). Differential cognitive impairment in Alzheimer's disease and Huntington's disease. Annals of Neurology, 23, 555-561.

Brandt, J., Quaid, K.A., Folstein, S.E., Garber, P., Maestri, N.E., Abbott, M.H., Slavney, P.R., Franz, M.L., Kasch, L. & Kazazian, H.H. (1989). Presymptomatic diagnosis of delayed-onset disease with linked DNA markers. The experience in Huntington's disease. Journal of the American Medical Association, 261, 3108-3114.

Brandt, J., Strauss, M.E., Larus, J., Jensen, B.A., Folstein, S.E. & Folstein, M.F. (1984). Clinical correlates of dementia and disability in Huntington's disease. Journal of Clinical Neuropsychology, 6, 401-412.

Bremner, J.D., Scott, T.M., Delaney, R.C., Southwick, S.M., Mason, J.W., Johnson, D.R., Innis, R.B., McCarthy, G. & Charney, D.S. (1993). Deficits in short-term memory in posttraumatic stress disorder. The American Journal of Psychiatry, 150, 1015-1019.

Britton, J.W., Uitti, R.J., Ahlskog, J.E., Robinson, R.G., Kremer, B. & Hayden, M.R. (1995). Hereditary late-onset chorea without significant dementia: genetic evidence for substantial phenotypic variation in Huntington's disease. Neurology, 45, 443-447.

Brouwers, P., Cox, C., Martin, A., Chase, T. & Fedio, P. (1984). Differential perceptual-spatial impairment in Huntington's and Alzheimer's dementias. Archives of Neurology, 41, 1073-1076.

Brown, R.G. & Marsden, C.D. (1986). Visuospatial function in Parkinson's disease. Brain, 109, 937-1002.

Bruera, E., Miller, L., McCallion, J., Macmillan, K., Krefting, L. & Hanson, J. (1992). Cognitive failure in

patients with terminal cancer: a prospective study. Journal of Pain Symptom Management, 7, 192-195.

Bruyn, G.W. (1968). Huntington's chorea. Historical, clinical and laboratory synopsis. In P.J. Vinken & G.W. Bruyn (Eds), Handbook of Clinical Neurology (Vol. 6, pp. 298-378). Amsterdam: North Holland Publishing Co.

Butters, N., Albert, M.S. & Sax, D. (1979). Investigations of the memory disorders of patients with Huntington's disease. In T.N. Chase, N.S. Wexler & A. Barbeau (Eds), Advances in Neurology (Vol. 23, pp. 203-213). New York: Raven Press.

Butters, N., Albert, M.S., Sax, D.S., Miliotis, P., Nagode, J. & Sterste, A. (1983). The effect of verbal mediators on the pictorial memory of brain-damaged patients. Neuropsychologia, 21, 307-323.

Butters, N., Granholm, E., Salmon, D.P., Grant, I & Wolfe, J. (1987). Episodic and semantic memory: a comparison of amnesic and demented patients. Journal of Clinical and Experimental Neuropsychology, 9, 479-497.

Butters, N., Salmon, D.P., Heindel, W. & Granholm, E. (1988). Episodic, semantic, and procedural memory: some comparisons of Alzheimer and Huntington's disease patients. In R.D. Terry (Ed.), Aging and the Brain (pp. 63-88). New York: Raven Press.

Butters, N., Sax, D., Montgomery, K. & Tarlow, S. (1978). Comparison of the neuropsychological deficits associated with early and advanced Huntington's Disease. Archives of Neurology, 35, 585-589.

Butters, N., Wolfe, J., Granholm, E. & Martone, M. (1986). An assessment of verbal recall, recognition and fluency abilities in patients with Huntington's disease. Cortex, 22, 11-32.

Butters, N., Wolfe, J., Martone, M., Granholm, E., & Cermak, L.S. (1985). Memory disorders associated with Huntington's disease: verbal recall, verbal recognition and procedural memory. Neuropsychologia, 23, 729-743.

Bylsma, F.W., Brandt, J. & Strauss, M.E. (1992). Personal and extrapersonal orientation in Huntington's disease patients and those at risk. Cortex, 28, 113-122.

Eylsma, F.W., Rebok, G.W. & Brandt, J. (1991). Long-term retention of implicit learning in Huntington's disease. Neuropsychologia, 29, 1213-1221.

Caine, E.D. & Fisher, J.M. (1985). Dementia in Huntington's disease. In J.A.M. Frederiks (Ed.), Handbook of Clinical Neurology, (Vol. 2 (46), pp. 305-310). Amsterdam, The Netherlands: Elsevier.

Caine, E.D., Hunt, R.D., Weingartner, H. & Ebert, M.H. (1978). Huntington's dementia. Archives of General Psychiatry, 35, 377-384.

Cala, L.A., Black, J.L., Collins, D.W.K., Ellison, R.M. & Zubrick, S.A. (1990). Thirteen years longitudinal study of computed tomography, visual electrophysiology and neuropsychological changes in Huntington's Chorea patients and 50% at-risk asymptomatic subjects. In M.J. Eadie & C.M. Lander (Eds), Proceedings of the Australian Association of Neurologists. Clinical and Experimental Neurology, 27, 43-63.

Campodonico, J.R., Aylward, E., Codori, A-M., Young, C., Krafft, L., Magdalinski, M., Ranen, N., Slavney, P.R. & Brandt, J. (1998). When does Huntington's disease begin? Journal of the International Neuropsychological Society, 4, 467-473.

Campodonico, J.R., Codori, A.M. & Brandt, J. (1996). Neuropsychological stability over two years in asymptomatic carriers of the Huntington's disease mutation. Journal of Neurology, Neurosurgery, and Psychiatry, 61, 621-624.

Castle, D.J., Wessely, S. & Murray, R.M. (1993). Sex and schizophrenia: effects of diagnostic stringency, and associations with premorbid variables. British Journal of Psychiatry, 162, 658-664.

Catona, M.C., Lazzarine, A.M. & McCormack, M.K. (1985). A psychometric study of children at-risk for Huntington disease. Clinical Genetics, 28, 307-316.

Chandler, J.H., Reed, T.E. & DeJong, R.N. (1960). Huntington's chorea in Michigan: III. Clinical observations. Neurology, 10, 148-153.

Choca, J.P., Shanley, L.A. & Van Denburg, E. (1992). Interpretive guide to the Millon Clinical Multiaxial

Inventory. Washington, DC: American Psychological Association.

Claes, S., Van Zand, K., Leguis, E., Dom, R., Malfroid, M., Baro, F., Godderis, J. & Cassiman, J-J. (1995). Correlations between triplet repeat expansion and clinical features in Huntington's disease. Archives of Neurology, 52, 749-753.

Codori, A-M. & Brandt, J. (1994). Psychological costs and benefits of predictive testing for Huntington's disease. American Journal of Medical Genetics (Neuropsychiatric Genetics), 54, 174-184.

Codori, A-M., Hanson, R. & Brandt, J. (1994). Self-selection in predictive testing for Huntington's disease. American Journal of Medical Genetics (Neuropsychiatric Genetics), 54, 167-173.

Codori, A-M., Slavney, P.R., Young, C., Miglioretti, D.L. & Brandt, J. (1997). Predictors of psychological adjustment to genetic testing for Huntington's disease. Health Psychology, 16, 36-50.

Coleman, R., Anderson, D & Lovrien, E. (1990). Oral motor dysfunction in individuals at risk of Huntington Disease. American Journal of Medical Genetics, 37, 36-39.

Craig, R.J. & Olson, R.E. (1992). Relationship between MCMI-II scales and normal personality traits. Psychological reports, 71, 699-705.

Craufurd D., Dodge, A., Kerzin-Storarr, L. & Harris, R. (1989). Uptake of presymptomatic predictive testing for Huntington's disease. The Lancet, 2, 603-605.

Craufurd, D. & Tyler, A. (1992). Predictive testing for Huntington's disease: protocol of the UK Huntington's Prediction Consortium. Journal of Medical Genetics, 29, 915-918.

Crumbaugh, J.C. (1968). Cross-validation of purpose-in-life test based on Frankl's concepts. Journal of Individual Psychology, 24, 74-81.

Crumbaugh, J.C. & Maholick, L.T. (1964). An experimental study in existentialism: the psychometric approach to

Frankl's concept of noogenic neurosis. Journal of Clinical Psychology, 10, 200-207.

Crumbaugh, J.C. & Maholick, L.T. (1969a). Manual of instructions for The Purpose in Life test. Munster, Indiana: Psychometric Affiliates.

Crumbaugh, J.C. & Maholick, L.T. (1969b). The Purpose in Life test. Munster, Indiana: Psychometric Affiliates.

Cull, A., Hay, C., Love, S.B., Mackie, M., Smets, C. & Stewart, M. (1996). What do cancer patients mean when they complain of concentration and memory problems? British Journal of Cancer, 74, 1674-1679.

Cummings, J.L. (1986). Subcortical Dementia. Neuropsychology, neuropsychiatry, and pathophysiology. British Journal of Psychiatry, 149, 682-697.

Cummings, J.L. (1993). Frontal-subcortical circuits and human behavior. Archives of Neurology, 50, 873-880.

Cummings, J.L. & Benson, D.F. (1984). Subcortical dementia. Review of an emerging concept. Archives of Neurology, 41, 874-879.

Cummings, J.L. & Benson, D.F. (1990). Subcortical mechanisms and human thought. In J.L. Cummings (Ed.), Subcortical dementia. New York: Oxford University Press.

Dalton, J.E., Pederson, S.L. & Ryan, J.J. (1989). Effects of post-traumatic stress disorder on neuropsychological test performance. International Journal of Clinical Neuropsychology, 11, 121-124.

de Boo, G.M., Tibben, A., Hermans, J., Maat, A. & Roos, R.A. (1998). Subtle involuntary movements are not reliable indicators of incipient Huntington's disease. Movements Disorders, 13, 96-99.

de Boo, G.M., Tibben, A., Lanser, J.B.K., Jennekens-Schinkel, A., Hermans, J., Maat-Kievit, A. & Roos, R.A.C. (1997a). Early cognitive and motor symptoms in identified carriers of the gene for Huntington disease. Archives of Neurology, 54, 1353-1357.

de Boo, G.M., Tibben, A., Lanser, J.B.K., Jennekens-Schinkel, A., Hermans, J., Vegter-van der Vlis, M. & Roos,

R.A.C. (1997b). Intelligence indices in people with a high/low risk for developing Huntington's disease. Journal of Medical Genetics, 34, 564-568.

Decruyenaere, M., Evers-Kiebooms, G., Boogaerts, A., Cassiman, J-J., Cloostermans, T., Demyttenaere, K., Dom, R., Fryns, J-P. & Van den Berghe, H. (1995). Predictive testing for Huntington's disease: risk perception, reasons for testing and psychological profile of test applicants. Genetic Counseling, 6, 1-13.

Decruyenaere, M., Evers-Kiebooms, G. & Van den Berghe, H. (1993). Perception of predictive testing for Huntington's disease by young women: preferring uncertainty to certainty? Journal of Medical Genetics, 30, 557-561.

DeJong, R.N. (1973). The history of Huntington's chorea in the United States of America. In A. Barbeau, T.N. Chase & G.W. Paulson (Eds), Advances in Neurology (Vol. 1, pp. 19-27). New York: Raven Press.

DeLong, M.R. & Georgopoulos, A.P. (1979). Physiology of the basal ganglia - A brief overview. In T.N. Chase, N.S. Wexler & A. Barbeau (Eds), Advances in Neurology (Vol. 23, pp. 137-153). New York: Raven Press.

DeLong, M.R., Georgopoulos, A.P., Crutcher, M.D., Mitchell, S.J., Richardson, R.T. & Alexander, G.E. (1984). Functional organization of the basal ganglia: contributions of single-cell recording studies. In D. Evered & M. O'Connor (Eds), Functions of the basal ganglia (pp. 64-82). London: Pitman.

Diagnostic and statistical manual of mental disorders (4th ed.). Washington, D.C.: American Psychiatric Association.

Diamond, R., White, R.F., Myers, R.H., Mastromauro, C., Koroshetz, W.J., Butters, N., Rothstein, D.M., Moss, M.B. & Vasterling, J. (1992). Evidence of presymptomatic cognitive decline in Huntington's disease. Journal of Clinical and Experimental Neuropsychology, 14, 961-975.

Di Maio, L., Squitieri, F., Napolitano, G., Campanella, G., Trofatter, J.A. & Conneally, P.M. (1993a). Onset symptoms of 510 patients with Huntington's disease. Journal of Medical Genetics, 30, 289-292.

Di Maio, L., Squitieri, F., Napolitano, G., Campanella, G., Trofatter, J.A. & Conneally, P.M. (1993b). Suicide risk in

Huntington's disease. Journal of Medical Genetics, 30, 293-295.

Drewe, E.A. (1974). The effect of type and area of brain lesion on Wisconsin card sorting test performance. Cortex, 10, 159-170.

DudokdeWit, A.C., Tibben, A., Duivenvoorden, H.J., Frets, P.G., Zoetewij, M.W., Losekoot, M., van Haeringen, A., Niermeijer, M.F., Passchier, J. and the other members of the Rotterdam/Leiden Genetics Workgroup. (1997). Psychological distress in applicants for predictive DNA testing for autosomal dominant, heritable, late onset disorders. Journal of Medical Genetics, 34, 382-390.

Elliott, R. & Sahakian, B.J. (1995). The neuropsychology of schizophrenia: relations with clinical and neurobiological dimensions. Psychological Medicine, 25, 581-594.

European Community Huntington's Disease Collaborative Study Group. (1993). Ethical and social issues in presymptomatic testing for Huntington's disease: a European Community collaborative study. Journal of Medical Genetics, 30, 1028-1035.

Everly, G.S. & Horton, A.M. (1989). Neuropsychology of posttraumatic stress disorder: a pilot study. Perceptual and Motor Skills, 68, 807-810.

Evers-Kiebooms, G., Decruyenaere, M., Fryns, J-P. & Demyttenaere, K. (1997). Psychological consequences of presymptomatic testing for Huntington's disease. The Lancet, 349, 808-809.

Evers-Kiebooms, G., Swerts, A., Cassiman, J.J. & Van Den Berghe, H. (1989). The motivation of at-risk individuals and their partners in deciding for or against predictive testing for Huntington's disease. Clinical Genetics, 35, 29-40.

Fahn, S., Mishkin, M.M. & Hoffman, R.R. (1973). Pharmacologic and radiologic investigations in Huntington's Chorea. In A. Barbeau, T.N. Chase & G.W. Paulson (Eds), Advances in Neurology (Vol. 1, pp. 581-597). New York: Raven Press.

Farmer, A. & Owen, M.J. (1996). Genomics: the next psychiatric revolution? British Journal of Psychiatry, 169, 135-138.

Farrer, L.A. (1986). Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. American Journal of Medical Genetics, 24, 305-311.

Farrer, L.A. & Conneally, P.M. (1987). Predictability of phenotype in Huntington's disease. Archives of Neurology, 44, 109-113.

Fedio, P., Cox, C.S., Neophytides, A., Canal-Frederick, G. & Chase, T.N. (1979). Neuropsychological profile of Huntington's disease: patients and those at risk. In T.N. Chase, N.S. Wexler & A Barbeau (Eds), Advances in Neurology (Vol. 23, pp. 239-255). New York: Raven Press.

Filoteo, J.V., Delis, D.C., Roman, M.J., Demadura, T., Ford, E., Butters, N., Salmon, D.P., Paulsen, J., Shults, C.W., Swenson, M. & Swerdlow, N. (1995). Visual attention and perception in patients with Huntington's disease: comparisons with other subcortical and cortical dementias. Journal of Clinical and Experimental Neuropsychology, 17, 654-667.

Folstein, S.E. (1991). The psychopathology of Huntington's disease. Research Publication Association Research Nervous Mental Disease, 69, 181-191.

Forno, L.S. & Jose, C. (1973). Huntington's chorea: a pathological study. In A. Barbeau, T.N. Chase & G.W. Paulson (Eds), Advances in Neurology (Vol. 1, pp. 453-470). New York: Raven Press.

Foroud, T., Siemers, E., Kleindorfer, D., Bill, D.J., Hodes, M.E., Norton, J.A., Conneally, P.M. & Christian, J.C. (1995). Cognitive scores in carriers of Huntington's disease gene compared to noncarriers. Annals of Neurology, 37, 657-664.

Fox, S., Bloch, M., Fahy, M. & Hayden, M.R. (1989). Predictive testing for Huntington disease: I. Description of a pilot project in British Columbia. American Journal of Medical Genetics, 32, 211-216.

Frankl, V.E. (1969). The Will to Meaning. New York: New American Library.

Frankl, V.E. (1984). Man's Search for Meaning. New York: Washington Square Press.

Furtado, S., Suchowersky, O., Rewcastle, B., Graham, L., Klimek, M.L. & Garber, A. (1996). Relationship between trinucleotide repeats and neuropathological changes in Huntington's disease. Annals of Neurology, 39, 132-136.

Fuster, J.M. (1989). The Prefrontal Cortex. (2nd ed.). New York: Raven Press.

Gabrieli, J.D.E. (1998). Cognitive neuroscience of human memory. Annual Review of Psychology, 49, 87-115.

Gamis, A.S. & Nesbit, M.E. (1991). Neuropsychologic (cognitive) disabilities in long-term survivors of childhood cancer. Pediatrician, 18, 11-19.

Georgiou, N., Bradshaw, J.L., Phillips, J.G. & Chiu, E. (1996). The effect of Huntington's disease and Gilles de la Tourette's syndrome on the ability to hold and shift attention. Neuropsychologia, 34, 843-851.

Georgiou, N., Bradshaw, J.L., Phillips, J.G. & Chiu, E. (1997). Effect of directed attention in Huntington's disease. Journal of Clinical and Experimental Neuropsychology, 19, 367-377.

Giordani, B., Berent, S., Boivin, M.J., Penney, J.B., Lehtinen, S., Markel, D.S., Hollingsworth, Z., Butterbaugh, G., Hichwa, R.D., Gusella, J.F. & Young, A.B. (1995). Longitudinal neuropsychological and genetic linkage analysis of persons at risk for Huntington's disease. Archives of Neurology, 52, 59-64.

Glass, J. & Saffer, D.S. (1979). Huntington's chorea in a Black family. South African Medical Journal, 56, 685-688.

Goldberg, T.E., Berman, K.F., Mohr, E. & Weinberger, D.R. (1990). Regional cerebral blood flow and cognitive function in Huntington's disease and schizophrenia. Archives of Neurology, 47, 418-422.

Golden, C.J. (1978). Stroop Color and Word Test. Chicago, Illinois: Stoelting.

Author Lucas M D

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