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**DISTINGUISHING HUNTINGTON'S DEMENTIA FROM
ALZHEIMER'S DEMENTIA IN CLINICAL TRIAL BATTERIES**

by

DENISE WALKER, B.A.

. . . thesis submitted to
the Faculty of Graduate Studies and Research
in partial fulfilment of
the requirements for the degree of

**Master of Arts
Department of Psychology**

Carleton University

Ottawa, Ontario

07 December 1992

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ALZHEIMER'S DEMENTIA IN CLINICAL TRIAL BATTERIES

submitted by Denise Walker, B.A.
in partial fulfilment of the requirements for
the degree of Master of Arts

Thesis Supervisor

Chair, Department of _____

Carleton University

21 December 1992

ABSTRACT

This study examined the performance of Alzheimer's patients (AD), a cortical dementia, and Huntington's patients (HD), a subcortical dementia, on traditional psychometric measures and clinical trial batteries. Traditional psychometric measures could clearly distinguish between AD and Normal Control subjects (NC). Traditional measures could also distinguish, to some degree, HD from NC. There was, however, a failure of these tests to differentiate HD from AD. Two of the three clinical trial batteries used (Alzheimer's Disease Assessment Scale and Cognitive Drug Research Battery) could distinguish AD from NC, but not HD from either NC or AD. The third clinical trial battery, the newly developed Repeatable Battery for the Assessment of Dementia, could distinguish the three groups from each other, suggesting that only this test is adequately sampling cognitive domains impaired in both AD and HD. The other tests included in this study appear biased towards domains associated with cortical involvement.

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INTRODUCTION

The concept of dementia has been an evolving concept, changing its definition to suit the conditions inherent in a society at that particular time. The term dementia is taken from the Latin term "dementatus", which literally translates to the state of being out of one's mind (Mahendra, 1987; Weiner, 1991), and for many centuries the diagnosis was given to persons with behavioral and psychiatric syndromes (Mahendra, 1987). Today, however, dementia as a diagnosis is limited to persons exhibiting intellectual deficits, being defined as an unusual, acquired loss of intellectual functioning beyond the decline in intellect associated with normal aging, and not associated with conditions in which functioning was not normal to begin with, such as mental retardation (Joynt & Shoulson, 1985; Mahendra, 1987). The intellectual deficits required for a diagnosis of dementia are global, with impairment occurring in the areas of memory, general intellect, and personality functioning (Mahendra, 1987). As well, these deficits must occur when the patient is fully conscious. The requirements for a diagnosis rule out syndromes in which only one area of intellect is impaired, such as focal neurological syndromes (Joynt & Shoulson, 1985; Mohr et al, 1991).

Although dementia was once thought of as a disease in itself, it is now known to be a symptom of many disorders

which have varied etiologies and pathologies. At present, there are over 60 different disorders known which cause dementia, including Alzheimer's Disease, Huntington's Disease, Parkinson's Disease, Progressive Supranuclear Palsy, head injury, tumors, AIDS, drug toxicity, vitamin deficiency, subdural haematoma, metabolic disturbances, and chemical substance abuse to name but a few (Patterson & Whitehouse, 1990, Mohr et al, 1991). The dementia symptomatology exhibited in these disorders is not identical. However, in disorders which affect similar areas of the brain, the dementia characteristics tend to be alike. This has resulted in a diagnostic classification system which groups the disorders causing dementia according to the principal area of pathology occurring in the disease process. The system breaks the dementias into two groups: localized dementias, which are further broken down into disorders affecting primarily cortical, subcortical, and axial structures, and mixed dementias which consist of disorders affecting more than one of the three localized areas (Joynt & Shoulson, 1985). The majority of dementias can be classified into the cortical and subcortical dichotomy, and it is these two areas that this study will focus on.

Alzheimer's Disease

Dementias classified as "cortical dementias" are so named due to the area in the brain predominantly affected and the subsequent neurological deficits exhibited by patients afflicted with these disorders. The areas of cognitive impairment generally observed include language (aphasia), skilled movement (apraxia) and higher order perception (agnosia), which are found affected in Alzheimer's disease, Pick's disease, and Angular Gyrus syndrome (Joynt & Shoulson, 1985). Although the progression rate or order of deficits shown in these disorders is not exactly the same, a characteristic pattern of deficits does occur, resulting in a common classification.

The principal disorder classified as a cortical dementia is Alzheimer's disease, which accounts for over half of all dementia cases (Katzman, 1986; Mohr et al, 1991). This neurodegenerative disorder has its principal pathology in the cerebral cortex, however other subcortical structures are also affected, resulting in a wide array of cognitive and behavioral deficits.

The pattern of pathology observed in Alzheimer's disease primarily involves atrophy of the cerebral cortex, the loss of neurons in both the cortex and subcortical nuclei, and the presence of neurofibrillary tangles and neuritic plaques (Katzman, 1986). In particular, the cerebral cortex suffers a diffuse generalized atrophy, with an average weight of approximately 1,000 grams reflecting a

9% loss as compared to age-matched controls (Perl, 1986). The areas principally affected include the parietotemporal association cortices, with the primary motor, somatosensory, and visual cortices remaining relatively intact (Katzman, 1986; Mohr et al, 1991). The cortical mantle is thinned and a loss of white matter occurs, resulting in the enlargement of the lateral ventricles (Mahendra, 1987).

Neurons which are affected in the disease process consist of those with a cross-sectional area of greater than $90 \mu\text{m}^2$. In this particular population, approximately 40 to 60 percent are destroyed (Katzman, 1986). Some of the small neurons, those with areas of 40 to $90 \mu\text{m}^2$, are compromised, however the amount does not reach significance. The glial cells, which have an area of less than $40 \mu\text{m}^2$, are not affected (Katzman, 1986).

The cell loss in the cerebral cortex results in a substantial decline, with cell population loss of more than 50 percent and as much as 70 percent of neurons located in deep cortical layers (Mahendra, 1987). This loss occurs predominantly in the frontal and parietotemporal cortex. However a substantial loss of cortical neurons may also be found in the healthy brains of older persons. Therefore the precise relationship between cell loss and disease manifestation is unclear and does not appear to correlate completely (Price, 1984). A further analysis of neurons in the cortex shows that the number of dendritic spines is

reduced, with a concomitant reduction in dendritic branching (Mahendra, 1987; Price, 1984). Significant cell loss also occurs in the hippocampus, amygdala, entorhinal cortex, locus coeruleus, thalamus, and the basal forebrain structures of the medial septum, diagonal band of Broca, and the nucleus basalis of Meynert (Price, 1984; Katzman, 1986; Xuereb et al, 1991).

The neurofibrillary tangles and neuritic plaques found in Alzheimer's disease are not distributed randomly throughout the brain, but, like cell loss, are restricted to certain regions with other areas remaining largely unaffected. The neurofibrillary tangles are found in the cell body of neurons and consist of paired helical filaments which are wound around each other in a pattern resembling a double helix (Price, 1984; Katzman, 1986). These tangles also appear in normal healthy elderly individuals, but are generally restricted to the anterior olfactory nucleus, the anterior hippocampal gyrus, and, as age increases, the CA1 field of the hippocampus, amygdala, and neocortex. However, in healthy individuals the last two areas show very few affected cells, and the cells bearing these tangles in the other three areas show substantially fewer numbers than observed in Alzheimer's patients (Price, 1991). In mildly demented Alzheimer's patients, neurofibrillary tangles occur in much higher concentrations in the same areas as found in nondemented control subjects. In mildly demented

individuals, tangles also occur in small numbers in other areas of the amygdala, and in the substantia innominata, including the nucleus basalis of Meynert (Price, 1991). In moderate to severely demented Alzheimer's patients, tangles increase substantially in number in the same areas as found in the mildly demented patients, and the distribution of tangles in the neocortex spreads dramatically (Mahendra, 1987; Price, 1991). In the cortex in particular, it is believed that tangles occur predominantly in the long pyramidal cells which are involved in corticocortical projections from primary and secondary sensory regions to higher level association areas, and projections back to the sensory areas (Hof et al, 1991).

Neuritic plaques consist of degenerating nerve terminals clustered together, and contain a core of amyloid protein (Katzman, 1986). These can also be found in healthy nondemented elderly persons, but usually are quite limited in number (Mahendra, 1987). In mildly demented Alzheimer's patients, plaques may be found in fairly high numbers spread throughout the cortex, and may occur in some subcortical structures including the basal ganglia, amygdala, subiculum, presubiculum, and hippocampus (Rogers & Morrison, 1985). However, these plaques tend to be of a more immature type than those observed in severely demented patients (Price et al, 1991). In the latter cases, while distribution is

similar, they tend to be a more mature version, suggesting that plaques change as the disease progresses (Price, 1991).

The transmitter system cited as being the most consistently and severely affected in Alzheimer's disease is the cholinergic system (Price, 1984; Mohr et al, 1991). The damage to this system is believed to be directly related to the memory and cognitive deficits observed in this disorder (Mohr et al, 1991). Studies examining this system have found substantial decrements in the synthesizing enzyme choline acetyltransferase (ChAT) in frontal, temporal, and parietal areas of the cortex, as well as in the hippocampus (Reinikainen et al, 1990; Price, 1984). This corresponds with the selective cholinergic cell loss occurring in the nucleus basalis of Meynert, which provides a large cholinergic projection system to the hippocampus and cerebral cortex (Price, 1984; Mohr et al, 1991). Although there is a loss of presynaptic muscarinic receptor sites in more severe cases of Alzheimer's disease, the postsynaptic sites appear to be preserved (Reinikainen et al, 1990; Mohr et al, 1991).

Deficits have also been reported in the monoaminergic transmitter systems. In particular, the locus coeruleus, the principal source of noradrenergic innervation of the prefrontal cortex, evidences major cell loss. As there is a major pathway projecting from the locus coeruleus to the cerebral cortex, this results in a loss of noradrenergic

markers in the cortex (Price, 1984). Reductions of norepinephrine have also been reported in the hippocampus and striatum (Reinikainen et al, 1990). Although there is little empirical evidence of cell loss in the substantia nigra, the dopaminergic end metabolite (homovanillic acid) concentrations are putatively decreased in the basal ganglia (Gottfries, 1990). Some studies have reported a loss of dopaminergic concentration in the cortex and hippocampus (Reinikainen et al, 1990), while other studies have not found a significant decrease (Gottfries, 1990).

The serotonergic system is also affected in Alzheimer's disease, and is suggested as being affected early on in the disease process (Cross, 1990). Reported loss of serotonin and its end metabolite (5-hydroxyindoleacetic acid) occur in the temporal cortex and hippocampus in particular, and to a lesser degree in the frontal cortex (Cross, 1990; Reinikainen et al, 1990). As well, 5-HT₁ and 5-HT₂ serotonin receptors are reduced in the temporal cortex, with a reduction also found in the frontal cortex and cingulate gyrus (Cross, 1990; Mohr et al, 1991).

The effect of Alzheimer's disease on neuropeptides has also been studied, and again alterations have been found. In particular, somatostatin, corticotropin-releasing factor, and alpha-melanocyte-stimulating hormone have been found reduced in all areas of the cerebral cortex (Husain & Nemeroff, 1990; Leake et al, 1991). As well, vasopressin

has been reported to be decreased in the hippocampus, neurotensin decreased in the amygdala and septum, and beta-endorphin slightly decreased in the cerebral cortex (Husain & Nemeroff, 1990).

In positron emission tomography studies in Alzheimer's disease, a dysfunction in glucose metabolism has been found, particularly in the association cortices (Nyback et al, 1991; Rapoport et al, 1991). Metabolism in the primary motor and sensory cortices were, however, not affected. This parallels the principal cortical areas of cell loss reported previously.

The precise etiology of the widespread damage to the brain observed in Alzheimer's disease has not yet been identified. However, there are a number of theories as to cause, with increasing research efforts being focused on this aspect of the disorder. One of the hypotheses involves an environmental toxin as precipitating the degenerative chain of events (Price, 1984; Edwards, 1990). Two other neurodegenerative disorders have animal models which are related to environmental factors. The first involved the seed of a plant which caused a condition in Macaque monkeys resembling the amyotrophic lateral sclerosis-Parkinson-dementia observed among a group of people in Guam. The second included an MPTP product which results in a Parkinsonian-like disorder in animals. These two models support the hypothesis that environmental toxins can

contribute to neurodegeneration and possibly result in a neurodegenerative disorder such as Alzheimer's disease (Edwards, 1990). A hypothesis for a slow virus-like infection causing Alzheimer's disease has been postulated as well. In the case of other neurodegenerative disorders, such as Creutzfeldt Jacob disease and Kuru, infectious etiologies have been confirmed (Edwards, 1990).

Trace metals, such as aluminum, have also been suggested as containing a toxic element, possibly contributing to the pathogenesis of Alzheimer's disease. Aluminum has been found in some studies in a higher concentration in Alzheimer's disease, and aluminum is detected in neurofibrillary tangles (Price, 1984; Edwards, 1990). However, evidence for aluminum toxicity as being causally related to Alzheimer's disease remains largely circumstantial with several factors arguing against this hypothesis. One factor not supporting an aluminum hypothesis is the fact that exposure to aluminum is relatively uniform across the population. Also, there is a failure of aluminum to cause Alzheimer-like neurofibrillary tangles when injected into the brains of animals (Price, 1984; Edwards, 1990).

Genetic factors have been cited as being responsible for a certain subset of Alzheimer's disease. This is supported by the fact that all Down's syndrome patients, upon reaching a certain age, develop Alzheimer's-type

pathology in the brain, suggesting that chromosome 21 may contribute (Bradley, 1990). As well, a subpopulation of Alzheimer's patients with early-onset of the disease, transmit the disorder in an autosomal dominant fashion (Edwards, 1990). The gene activating this particular degeneration has been located on the long arm of chromosome 21. However it has not been determined whether this group represents a specific separate population or if these results can be generalized to all Alzheimer's patients (Edwards, 1990; Bradley, 1990).

A clinical diagnosis of Alzheimer's disease can be made if certain characteristic symptoms are present. However the diagnosis can only be confirmed histopathologically at autopsy (Mahendra, 1987). Prior to 1980, a diagnosis of this disorder was established based on exclusionary criteria only, with support for the diagnosis coming from the ruling out of other disorders which could cause dementia. In 1980, the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (American Psychiatric Association, 1980), changed the 'exclusionary-only' criteria to one of a combined exclusionary/inclusionary criteria (Cummings, 1990). In this set of criteria, other disorders were excluded as before, but a requirement of certain deficits in cognitive behaviour was added. This increased the accuracy of diagnosis, and with further refinements in the clinical characteristics required, the present day accuracy of

diagnosis, when also utilizing the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease (McKhann et al, 1984), is approximately 85% (Cummings, 1990). However, a definitive diagnosis of Alzheimer's disease still requires a histopathological confirmation.

Clinically, Alzheimer's disease is characterized by an insidious onset with a gradual progressive deterioration in intellectual, behavioral, and social functioning culminating in death, generally due to aspiration pneumonia or urinary tract infection, on average approximately 10 years after the onset of symptoms (Reisberg, 1983; Mahendra, 1987; Chui, 1989).

One of the earliest affected systems in most patients with Alzheimer's disease involves memory (Joynt & Shoulson, 1985; Cummings, 1990). The disruption to this system is widespread, affecting almost all areas of memory. Investigators have found increasing impairments in both short and long term (Mahendra, 1987; Cummings, 1990), verbal (Nebes, 1989; Cummings, 1990) and visuospatial memory (Mahendra, 1987; Chui, 1989; Cummings, 1990). Patients show deficient functioning in the learning of new information, and, as the disease progresses, also in the recall of remote personal and public event information (Corkin, 1985; Cummings, 1990). The recall of remote personal memories,

however, tend to show a temporal gradient, with a better recall of events occurring in earlier years (Cummings, 1990). Also, memory devices, which aid in the memory of older nondemented persons, such as introducing a recognition task as opposed to recall task, priming, supplying semantic connections or cueing, generally do not result in an increase in performance for Alzheimer's patients (Cummings, 1990).

Other cognitive areas which exhibit an impairment early in the disease process with increasing deficits as the disease progresses include language functions such as word list generation and confrontation naming, although speech is usually preserved early on (Reisberg, 1983; Mahendra, 1987; Cummings, 1990), and calculation abilities (Cummings, 1990). As the disorder progresses, dysfunction in the areas of abstraction, judgement, and visuospatial skills also occur (Cummings, 1990).

Changes in mood or behaviour accompany the intellectual deficits in Alzheimer's disease. Depression is relatively common in the early stages of this disorder (Mahendra, 1987). As the intellectual impairments increase, anxiety tends to also increase. Denial may play a role in individual patients. Flattening of affect or apathetic state is a common concomitant of the disease process (Mahendra, 1987). In some patients, at approximately mid-stage of the disorder, psychiatric disturbances may be

observed, with delusions, hallucinations, and paranoia occurring (Reisberg, 1983; Joynt & Shoulson, 1985; Cummings, 1990). In the terminal stages of the disorder, patients take on a relatively passive role, and the ability to speak or walk is lost (Reisberg, 1983; Cummings, 1990).

In terminal phases, praxic disorders and frontal release signs, such as the grasp or suck reflex, may be present (Joynt & Shoulson, 1985; Cummings, 1990). Some patients may also suffer from grand mal seizures, which can occur at any time during the disorder, and myoclonus, which generally occurs during the latter stages (Cummings, 1990).

Treatment of Alzheimer's disease has mainly focused on the replacement of neurotransmitters, as this type of therapy has had success in other disorders, such as Parkinson's disease (Mohr et al, 1991). As acetylcholine has been found to be the system most affected, drug treatment has focused on this area. In general, attempts to stimulate post-synaptic receptors, increase levels of cholinergic precursors, increase acetylcholine release, and inhibit synaptic degradation have not met with much success (Leonard, 1990; Mohr et al, 1991; Cooper, 1991).

While attenuation of cognitive symptoms has met with little success to date, emotional and behavioral problems have repeatedly been treated more successfully. While noradrenergic and serotonergic therapies have not shown cognitive improvement, some antidepressants, specifically a

serotonin uptake inhibitor, have diminished the emotional problems exhibited by some patients (Leonard, 1990; Cooper, 1991). Therapy aimed at peptide systems has also not had positive results (Growdon, in press).

Therapies which are presently being studied for cognitive improvement in Alzheimer's disease include a class of drugs called "nootropics", which exert their effect by stimulating the metabolic activity of the neurons (Leonard, 1990; Cooper, 1991). Little success to date though has been reported (Claus et al, 1991). Monoamine oxidase (MAO) inhibition is another area currently being investigated, as blocking this enzyme would enable a neurotransmitter to remain in the synaptic cleft longer with a better ability to excite postsynaptic receptors. One MAO-B inhibitor, deprenyl, has shown moderate success treating mood and motor symptoms in Parkinson's patients (Birkmayer et al, 1982). Treatment of Alzheimer's patients with compounds like deprenyl have shown modest success (Tariot et al, 1987). Other stronger MAO-B inhibitors, such as lazabemide, are just now coming to clinical trial. Putative neuroprotective efforts of this class of compounds remain highly speculative. However, this therapeutic route may well have considerable therapeutic potential.

Huntington's Disease

The syndrome of subcortical dementia consists of bradyphrenia (cognitive slowing), memory abnormalities, breakdown of intellectual functions, and changes in mood and personality. Although there may be a limited verbal output, afflicted patients rarely exhibit the defining features observed in the cortical dementias of aphasia, agnosia or apraxia (Cummings, 1990; Mohr et al, 1991). The pathology contributing to this complex syndrome involves axial structures of the rostral brain stem, thalamus, basal ganglia, and the frontal lobe projections of subcortical structures. Although there are numerous diseases with diverse etiologies which exhibit this subcortical syndrome, such as degenerative extrapyramidal syndromes, subcortical infarctions, multiple sclerosis, AIDS, Basal Ganglia disease other than Huntington's disease, thalamic degenerative disorders, subcortical trauma, inflammatory processes, and neoplasms, these diseases are grouped together due to the overlap in neuropathology and the common pattern of neuropsychological dysfunction (Cummings, 1990).

Huntington's disease is a principal example of a subcortical dementia. The main pathology observed in this disorder occurs in the neostriatum, with a volume loss of approximately 60% (Bruyn et al, 1979; De La Monte et al, 1988). In particular, it is the small Golgi type II neurons, which outnumber the larger neurons found in the

caudate nucleus and putamen, that are preferentially destroyed and lead to a marked depletion of this cell population in Huntington's disease.

More specifically within the neostriatum, there occurs a progressive degeneration of the caudate nucleus and putamen with cell death beginning in the paraventricular portion of the caudate nucleus and the dorsal putamen, and spreading ventrally and laterally (Vonsattel et al, 1985; Young et al, 1986; Brandt, 1991). Support for this comes from both cell counting techniques (Vonsattel, 1985) and PET scan examination of metabolism (Young, 1986). Examination of basal ganglia metabolism indicated that in early cases of Huntington's disease there is greater disruption of caudate metabolism than in the putamen, suggesting that the disorder originates in the caudate nucleus and spreads to involve the putamen (Young et al, 1986). The globus pallidus neurons appear relatively spared, with atrophic changes being contributed to the degeneration of fibre connections as opposed to death of nerve cell bodies. The nucleus accumbens also appears relatively intact (Vonsattel et al, 1985; Roos et al, 1985).

Within the neostriatum various changes in neurotransmitter function and receptor sites occurs. Significant reductions in the transmitters acetylcholine and gamma-aminobutyric acid (GABA), as well as their precursors choline acetyltransferase (ChAT) and glutamic acid

decarboxylase (GAD) have been reported (Bruyn et al, 1979). Reductions in the neuropeptide substance P have also been observed (Bruyn et al, 1979). The losses observed in these neurotransmitters are believed to be a direct result of population loss, as opposed to disease processes directly affecting transmitter function through mechanisms such as synthesis or storage (Bruyn et al, 1979).

The receptor alterations occurring in this area also reflect the nerve cell loss, with a decrease in receptor density found principally for muscarinic cholinergic, GABAergic, as well as receptor sites binding to benzodiazepine, and neuropeptides such as cholecystokinin, and dopaminergic receptors (Weiner & Lang, 1989; Folstein, 1990). It is also suggested that a type II benzodiazepine-binding receptor, which decreases in number, is located presynaptically, leading to the conclusion that receptor losses in Huntington's disease occurs on both the pre- and postsynaptic sides (Whitehouse et al, 1985). Within the neocortex, decreases in dopaminergic, cholecystokinin, and muscarinic cholinergic receptors has been found (Whitehouse et al, 1985). Also reported is an increase in benzodiazepine receptor density in the cortex, substantia nigra, and cerebellum which the authors suggest as possibly being caused by denervation supersensitivity due to GABAergic neuronal loss. GABA related receptors are also apparently increased in the cortex, which may be a

functionally adaptive response to the loss of GABAergic neurons (Whitehouse et al, 1985). The investigators suggest that receptor alterations throughout the brain may be due to a number of different processes, including the reflection of a loss of particular populations of neurons, accompanying gliosis, adaptive responses to the disease process, or directly due to the disease process (Whitehouse et al, 1985).

The neostriatum, although exhibiting the most cell loss, is not the only area of the brain to be affected in Huntington's disease. There is an overall reduction of brain weight of up to 30% resulting from atrophy in the cerebral cortex, white matter, hippocampus, amygdala, thalamus, and striatum (Bruyn et al, 1979; De La Monte et al, 1988; Jernigan et al, 1991). The cerebral cortex shows an areal reduction of up to 20-30%, with an accompanying decrease in the thickness of the cortical ribbon (De La Monte et al, 1988). The changes to the cerebral cortex occur in a graded fashion, with a higher deterioration found in the brains of patients with increasing severity of the disease (De La Monte et al, 1988). Upon examination of the cortex with magnetic resonance imaging (MRI), significant cortical volume reductions are found, however restricted to specific regions (Jernigan et al, 1991). The affected areas putatively involve the inferior cortical surfaces with reduced volume noted in mesial temporal, orbitofrontal, and

temporo-occipital areas. Superior regions, including the dorsolateral frontal, mesial frontal, and parietal cortices, appear to remain relatively intact (Jernigan et al, 1991). In other areas, interneurons in the thalamus were found to be reduced by 50%, widespread loss of hypothalamic neurons occurs, a moderate loss (up to 30%) of Golgi II neurons occurs in the subthalamic nucleus, and mild-to-moderate cell damage is reportedly present in the substantia nigra. The cerebellum is also widely affected, according to an earlier report, with mild to near complete loss of Purkinje cells with accompanying gliosis of cortex and dentate, severe damage to the brainstem, and gliosis of the spinal cord (Bruyn et al, 1979).

Although cortical changes do occur in this disease, cortical metabolism appears to remain relatively normal (Weinberger et al, 1988). In a study of the cerebral blood flow in Huntington's patients it was found that an actual increase in metabolism occurred in the prefrontal area, as compared to control values, when measured during behaviour considered indicative of frontal lobe functioning (Weinberger et al, 1988). As the caudate nucleus receives considerable cortical input from the prefrontal area, it is suggested that the increase is due to a compensatory mechanism for the severe caudate atrophy found in Huntington's patients. Correlations were also observed during frontal activity to temporal and parietal metabolism,

which was believed to be secondary to the prefrontal changes, as these areas are connected to the basal ganglia only in a limited way.

Huntington's disease is a genetic disorder, transmitted as an autosomal dominant trait with complete penetrance. The defective gene has been mapped to near the end of the short arm of chromosome 4, but the specific gene causing the disorder has not yet been identified (Folstein, 1990). The specific cause of the destruction of the neurons has not been elucidated either to date, however there are some theories as to possible contributors. A review article by Carter et al (1989) implicated the neurotransmitter glutamate. It is suggested that this amino acid may take on a neurotoxic form, possibly through an overstimulation of the glutamate receptors, or an alteration or aberration in the synaptic transmission cycle. The theory of glutamic neurotoxicity is supported by studies utilizing an analogue of glutamate, kainic acid, which causes lesions similar to those found in the brains of Huntington's patients when injected into the striatum of rats.

A common factor with all neurons involved in this disease is that they have a greater metabolic need based on characteristics such as a larger surface area to volume ratio, a utilization of glucose in the synthesis of neurotransmitter (which include GABA, acetylcholine, and glutamate neurons), and a glutamate input. This commonality

may be a contributing factor to the death of specific neurons, with a possible cerebral metabolic dysfunction making neurons more susceptible to neurotoxicity (Carter et al, 1989).

Clinically, Huntington's disease manifests itself with an insidious onset of choreic movements, cognitive dysfunction, and affective changes (Brandt, 1991). The disease generally presents during adulthood, with the average age of onset being approximately 40 years of age, however it can occur at any age from childhood to late adulthood (Folstein, 1990). In the general population, the disease occurs in between 5 and 7 per 100,000 population; however it is more common in adults with the prevalence in the 40 to 55 age range increasing to 12 per 100,000 (Folstein, 1990). The disease involves a progressive deterioration with death occurring on average approximately 17 years after onset (Folstein, 1990; Brandt, 1991).

The choreic movements observed in Huntington's disease are always present, however they are not necessarily the first signs of the disorder since these may occur after affective and cognitive changes. Movements consist of two different types: involuntary movements which consist of jerky unpredictable movements observed in the face, limbs and trunks of most patients, and voluntary movements dysfunction consisting of the slowing of movements in the eyes and limbs, delay in the ability to initiate movement,

and an overall clumsiness (Folstein et al, 1990). Both the voluntary and involuntary components of the movement disorder worsen as the disease progresses. During the end stages of the disorder the primitive snout, grasp or suck reflexes may occur (Paulson, 1979).

Many Huntington's disease patients experience affective changes of varying severity, which often occur prior to the onset of either choreic or cognitive dysfunction (Folstein et al, 1990). Some of the changes frequently occurring include depression, which can also be bipolar, anxiety and irritability, which can lead to aggression, and delusions (Caine et al, 1978; Folstein et al, 1990). As the disorder progresses, a state of apathy is also very common, with patients exhibiting a decline in the initiation of any activity (Caine et al, 1978; Folstein et al, 1990).

One of the primary features of Huntington's disease is progressive dementia. Although in some patients the motor deficit is initially the primary presenting problem, very few patients with severe motor dysfunction do not also show a concurrent mental deterioration (Paulson, 1979).

Cognitive function, in general, declines during the course of Huntington's disease, as measured by tests such as the Mini Mental State Exam (Folstein et al, 1975), and the Wechsler Adult Intelligence Scale (Wechsler, 1981). However, there are patterns within these tests of specific areas which decline more than others, as well as some areas

which remain relatively intact until the later stages of the illness (Josiassen et al, 1982; Folstein et al, 1990).

In particular, one of the earliest affected areas of cognition is attention and concentration, assessed by tasks such as mental arithmetic, digit-symbol coding, and reaction time (Fedio et al, 1979; Folstein et al, 1990). Other areas affected early in the disease process are the so-called "executive" functions, which include such behaviours as planning, sequencing, and organizing. Testing in this area includes specific tests, such as the Wisconsin Card Sort (Heaton, 1981) and the Trail Making Test (Reitan, 1958), as well as specific tasks such as verbal fluency, maze performance, and postural adjustments, all of which show regular deficits in Huntington's disease (Caine et al, 1978; Folstein et al, 1990; Brandt 1991).

Visuospatial cognition is another primary area affected. However, it appears that extrapersonal spatial perception as well as construction skill may remain relatively intact, whereas spatial judgement related to an internal reference (egocentric spatial perception) is impaired (Brouwers et al, 1984; Brandt, 1991; Mohr et al, 1990). Deficits have also been observed in the Wechsler Adult Intelligence Scale subtests of Object Assembly and Block Design, which purport to measure constructional ability and visuomotor skill (Folstein et al, 1990). As well, deficits are reported in tests which are free of motor

demands, implying that these deficits cannot be attributed to motor difficulty or slowing (Fedio et al, 1979).

Although Huntington's patients do not exhibit a generalized language impairment, as is observed in the cortical dementias, there are impairments in certain areas. Poor performance is found in this population in visual confrontation naming, repetition, and verbal fluency (Folstein et al, 1990; Brandt, 1991).

The cognitive area which has been studied the most in Huntington's disease is memory. Deficits in this area appear early in the course of the illness, however, again it is certain types of memory which are more impaired than others. Huntington's patients show consistent impairment in the areas of free recall of, for example, repeated word lists, suggesting an inability to initiate a retrieval process (Butters et al, 1985; Moss et al, 1986). However, when a recognition paradigm is presented, patients' performance improves to a level closer to that of normal control subjects, suggesting that the information is stored, but cannot be accessed (Butters et al, 1985; Moss et al, 1986). Impairment is also observed in remote memory functioning (Mohr et al, 1991).

At present, there is no effective therapy for Huntington's disease, nor is there any agent which is useful in terms of symptomatic attenuation. Experimental therapeutic attempts have concentrated primarily on

neurotransmitter replacement, as this approach has been fairly successfully in alleviating some of the symptoms of Parkinson's disease (Mohr et al, 1991). Effective reduction of choreic movements has been achieved through dopamine antagonists specifically targeted for reducing dopamine activity on the postsynaptic side (Shoulson, 1979). Amelioration of cognitive deficits, however, has not met with the same success.

Attempts to replace deficient GABA and acetylcholine supplies, which are believed to be involved in the cognitive deficits, have not resulted in positive results. Although some investigators report some marginal success (Perry et al, 1979), other researchers have not been able to show even that (Waszczak et al, 1979).

Other areas currently being examined include definitive intercession at the cellular level, including work with nerve growth factor (Mohr et al, 1991). However, these investigative areas are currently principally in the preclinical stages and clinical trials have yet to take place.

Neurocognitive Domains of Impairment

Memory

One core area of research in the context of cortical and subcortical dementia has been memory, as impairment in this system is suggested to be one of the hallmarks of the

dementing illnesses (Cummings & Benson, 1983; Granholm & Butters, 1988). Memory, though, is not simply a unitary function, but has many different facets which are dependent on various neural systems. It is these facets which are suggested to be affected differently in cortical and subcortical disorders, leading to a differential pattern of memory impairment.

In defining areas of memory, some investigators have suggested two broad categories: declarative memory, which is defined as including specific facts and episodes that occur and are learned in day-to-day experience, and procedural memory, which contains memory for specific learned skills and can only be assessed through performance (Shimamura et al, 1987). Declarative memory is further broken down into semantic memory, which includes knowledge of words and their concepts, meanings, and associations, and episodic memory, which is the autobiographical record of events experienced by an individual (Nebes, 1989).

Episodic Memory: In Alzheimer's disease, severe deficits are found in episodic memory. These have been primarily assessed with tests of recall and recognition. With free recall tasks, Alzheimer's patients show impairments as compared to age-matched normal controls with verbal, spatial, and configurational material, suggesting that impairment is not limited to one type of material (Salmon et al, 1991). When patients at an earlier stage of

the disease were compared to a more advanced group, the spatial and verbal material differentiated between these two groups, with more severe deficits occurring in the advanced group. The authors interpreted these results as suggesting that impairments occur at an early stage in the disease process and progress as the disease advances. When delayed recall was examined in this study, Alzheimer's patients exhibited severe deficits in both mildly and moderately demented groups for verbal material, with highly rapid rates of forgetting for each group (Salmon et al, 1991).

Other studies have replicated these results with both recall and recognition tasks, suggesting that the memory impairment found in Alzheimer's disease is a result of deficient encoding or acquisition (Rosen, 1983; Corkin, 1985; Litvan et al, 1991). Further support for this hypothesis is found in a study in which an Alzheimer's patient group was compared to an age-matched normal control group on rates of forgetting in a picture recognition task. The patient population did not differ from the normal control group on tests of retention given at various times after exposure to the stimulus. The Alzheimer's patients, though, required a longer exposure time to bring them up to the same initial level of learning, suggesting that the encoding process is impaired (Corkin, 1985).

Other studies have also concurred with the finding of a progressive impairment, suggesting that impairments

occurring at very early stages of the disorder and gradually worsening (Rosen, 1983; Morris et al, 1991; Welsh et al, 1991).

Huntington's patients also show deficits in episodic memory. Impairments have been found in this population with free recall paradigms, which some investigators attributed to a deficient encoding process (Buschke, 1973; Weingartner et al, 1979). Upon further examination of this hypothesis, however, it was suggested that encoding processes in Huntington's patients were relatively intact (Beatty & Butters, 1986). This was supported by the finding that Huntington's patients were able to recall more highly imageable words than words with low imagery. This effect was comparable to normal controls, even though the gross number of words recalled was less than normal controls. If encoding was deficient in the patient population, imagery should not make a difference in the number of words recalled. The investigators also examined the amount of proactive interference elicited by the patients and found a normal release from the interference when taxonomic categories were shifted. This release from proactive interference is suggested as being indicative of a normal encoding process (Beatty & Butters, 1986).

Further investigations into the episodic memory impairments observed in Huntington's disease have suggested a deficit in retrieval processes. This hypothesis is

supported by studies which utilize both recall and recognition tasks (Butters et al, 1986; Massman et al, 1990). These studies have found that although free-recall measures result in deficiencies for Huntington's patients, when a recognition task was presented a significant improvement was found. This is interpreted as suggesting that the material is encoded by the Huntington's patients but can not be accessed or retrieved.

One study also examined the development of episodic memory dysfunction in the disease process by examining Huntington's patients with limited functional disability, and thus in a relatively early stage of the disease, versus patients with a more advanced form of the disease (Butters et al, 1986). Both patients groups exhibited a significant functional loss in retrieval ability. The advanced patient group, while exhibiting a slightly poorer performance, did not show a substantial decrement as compared to the earlier stage patients. The investigators suggested, based on these results that substantial impairment in retrieval occurs at an early stage in the disease, with only a moderate worsening as the disease progresses (Butters et al, 1986). However, the dementia levels for these two groups, as assessed by the Mattis Dementia Rating Scale (Mattis, 1976), were not substantially different, with an overlap in scores occurring between the two groups. Thus, perhaps bigger differences in dementia levels may be needed to determine

the further effect of advancing dementia with the disease progression.

Huntington's patients appear to be able to encode only verbal material though. In studies examining material other than in verbal form, Huntington's patients do not show the same intact recognition ability (Moss, 1986; Folstein et al, 1990). With colours, patterns, faces, and spatial positions, patients were just as impaired on recognition tests as other patient populations (Moss, 1986).

It appears from these studies that differences may exist in the impairments in episodic memory observed in Alzheimer's and Huntington's disease. However, to establish whether these differences are due to true cognitive differences, or are merely a reflection of different investigative techniques, studies are needed directly comparing these two populations.

A number of studies have compared Alzheimer's with Huntington's disease in tests of episodic memory, with results effectively discriminating the two populations. These investigators have found that Alzheimer's and Huntington's patients are not significantly different from each other for general recall of verbal information, but are significantly impaired as compared to normal controls. However, on recognition tasks the Huntington's patients' performance approaches the level of the normal controls, whereas the Alzheimer's patients remain significantly

impaired (Moss et al, 1986; Granholm & Butters, 1988). One study also compared the performance of Alzheimer's and Huntington's patients with tests of recall and recognition in a spatial condition and a colour, pattern, and facial condition. There were no significant differences between the two groups, suggesting that with Huntington's patients only verbal material is encoded and therefore able to be accessed in a recognition paradigm (Moss et al, 1986).

Not all investigators have been able to show this dissociation though. One study administered the Rey Auditory Verbal Learning Test (AVLT) (Rey, 1964), a test of verbal recall and recognition, to Alzheimer's and Huntington's patients (Shimamura et al, 1987). Both patient groups exhibited significant impairment from control groups on tests of recall and recognition. The Huntington's patients, however, performed only slightly better than the Alzheimer's patients on both tests. The difficulty in interpreting these results though, lies in the fact that the patient groups were not matched for overall dementia level. Another study used the California Verbal Learning Test (Delis et al, 1987) which is similar to the AVLT in using verbal recall and recognition tasks, but consists of sixteen words from four semantic categories. Only Huntington's patient scoring above 24 on the Folstein Mini Mental State Exam (Folstein, 1975) had a better performance than Alzheimer's patients on a verbal recognition test, with

patients scoring below 24 performing as poorly as Alzheimer's patients (Kramer et al, 1988).

Another area which has been cited as supporting the distinction in episodic memory between Huntington's and Alzheimer's patients has been in the domain of retrograde amnesia (Beatty et al, 1988; Salmon et al, 1991).

Huntington's patients are repeatedly equally impaired in remembering public events from all periods of time, whereas Alzheimer's patients evidently display a temporal gradient with greater recall for events which happened further in the past (Beatty et al, 1988; Salmon et al, 1991). The authors suggest that this provides further support for the hypothesis that Alzheimer's patients have trouble encoding events which becomes progressively worse as the disease progresses. Huntington's patients, on the other hand, are assumed to have a relatively intact encoding process prior to the disease process and thus the retrograde amnesia shown is indicative of a deficient retrieval process.

Semantic Memory: Semantic memory has generally been assessed through tests of category membership, object naming, and verbal fluency (Podoll et al, 1988; Troster et al, 1989; Hodges et al, 1990). With Alzheimer's disease, severe deficits have been found in tests of verbal fluency and object naming, with impairments increasing as the disease progresses (Brown & Marsden, 1988; Nebes, 1989; Litvan et al, 1991; Salmon et al, 1991). In the early

stages of the disorder, though, some studies have not found deficient naming ability (Bayles & Tomoeda, 1983). Thus, this aspect of semantic memory impairment may not occur until the later stages of the disorder.

Huntington's patients have also exhibited deficient functional ability in some tests of semantic memory, while other areas have not shown consistent results. On tests of verbal fluency, patients evidently exhibit significant impairment which appears early in the illness (Folstein et al, 1990). However, with picture naming, some studies have found fairly normal results (Butters et al, 1978) while others have found deficits (Smith et al, 1988). The deficits in picture naming though, while impaired as compared to normal controls, were not of the magnitude observed in Alzheimer's patients, suggesting that this area may remain at least partially intact (Smith et al, 1988).

A number of studies have directly compared the performance of Alzheimer's and Huntington's patients on tests of semantic memory, but the results have not been consistent. On tests of verbal fluency, category fluency, and vocabulary, mildly demented Huntington's and Alzheimer's patients both showed decrements as compared to normal controls, with Huntington's patients performing slightly worse than Alzheimer's patients (Troster et al, 1989; Hodges et al, 1990). The authors suggested that these results may indicate a possible common deficit in retrieval ability

between the two groups (Troster et al, 1989). However, another study found, when comparing mildly demented Alzheimer's and Huntington's patients on category and letter fluency tests, that Huntington's patients were impaired on both tests while Alzheimer's patients were impaired only on the category test (Butters et al, 1987). The Alzheimer's patients in this study also appeared more susceptible to proactive interference and, in the letter fluency test, made more perseverative errors. These results were interpreted as suggesting that Huntington's patients exhibit impairment due to a general retrieval deficit which makes them unable to effectively and systematically search their memory stores. This is consistent with the results found in the episodic memory studies. Alzheimer's patients, on the other hand, are suggested as having a possible reduction in the number of exemplars which comprise a specific category. With fewer words available to be accessed for a specific category, patients would not be able to generate as many words. This may be due to a breakdown in the hierarchical organization of semantic memory (Salmon et al, 1991).

Although differences in the impairments of semantic memory between Huntington's and Alzheimer's patients has been proposed, the number of studies examining these deficits has been limited. To further investigate the differences between the two disorders, more studies are needed which directly compare the two populations.

Procedural Memory: This domain of memory is suggested as being independent of conscious awareness and is accessible to testing only through performance. It is examined through tests of skill learning and verbal priming. Studies examining procedural memory in Alzheimer's and Huntington's patients have found a double dissociation in the performance of the two groups on different tasks.

On tests of skill learning, Huntington's patients have been found to be impaired, not showing normal rates of learning. The performance of Huntington's patients versus normal controls on a mirror reading task was examined (Butters, 1984). A decrease in the time required to read the reflected words was suggested as evidence of learning this particular skill. While normal control subjects exhibited this decrease, Huntington's patients did not. The patients, however, did recognize words that were repeatedly shown. As well, in a recognition task in which subjects had to choose which words were or were not shown in the mirror reading trial, Huntington's patients did not perform significantly worse than normal controls. The authors suggested that Huntington's patients were impaired in their ability to acquire a skill, but retained their ability to encode verbal material (Butters, 1984). Huntington's patients have also been found to be deficient in their ability to learn a stylus maze, even when provided with substantial practice (Folstein et al, 1990). This is

suggested as further evidence of impaired procedural memory processing in Huntington's disease. However, one study has not found this to be completely true (Brandt, 1991). The investigator suggests that only some aspects of maze learning are impaired, while other aspects may remain intact. This is shown by the Huntington's patients' ability to learn specific individual maze routes at a rate not different from normal controls. The difficulty in this area lies in an inability of these patients to generalize their skills across mazes, and a failure to exhibit superior performances on mazes which have predictable routes. The author suggests that this supports a hypothesis of possible separate entities within procedural memory (Brandt, 1991).

When Alzheimer's and Huntington's patients are directly compared on tests of skill learning, the results support a distinction between the two groups. On pursuit rotor tasks, in which subjects had to maintain contact with a disk on a rotating turntable, Alzheimer's patients show normal acquisition rates while Huntington's patients exhibit impaired performance (Heindel et al, 1989; Salmon et al, 1991). It was also found that the deficit on this task with the Huntington's patients was significantly correlated with the degree of dementia, suggesting that impairment increases as the disease progresses. By adjusting the speed of the task, all subjects were equated at the beginning of the test. With Huntington's patients, therefore, deficient

functioning could not be attributed solely to the accompanying motor disorder.

With verbal priming tasks, the opposite pattern appears between Alzheimer's and Huntington's patients. In stem completion tasks subjects are shown a list of words. They are asked to rate on a scale of one to ten how much they like the word. The patients are then shown the first three letters of words (word stems) and are asked to complete the word stem with the first word that comes into their minds. The word stem list is comprised of the previously rated words and other words which were not on the word-rating list (Shimamura et al, 1987). Studies using this task have found Alzheimer's patients to be severely impaired, completing significantly fewer words from the word stems with words they were previously shown. Huntington's patients, on the other hand, exhibit intact word stem completion (Shimamura et al, 1987; Salmon et al, 1991).

A different priming task has shown the same results. With lexical priming subjects are shown pairs of semantically related words which, as in the stem completion task, they rate on how much they like the words. The subjects are then asked to "free associate" to the first word of the word pair they were previously shown. With this task, again Alzheimer's patients do not give the second word of the word pair above baseline guessing rates. Huntington's patients, though, do not differ from normal

controls on the number of correct word pairs given (Heindel et al, 1989; Salmon et al, 1991). The investigators suggest from these results that with Alzheimer's patients there is a possible breakdown in semantic memory which manifests itself even in the seemingly "automatic" processing task of priming (Salmon et al, 1991). Alternatively, it is suggested that there may be an inability with Alzheimer's patients to adequately activate the representations which are stored in lexical memory (Shimamura et al, 1987). Huntington's patients, though, appear to retain their priming ability and thus perhaps retain certain abilities integral to both procedural and semantic memory.

Although the exact mechanisms behind the impairments have not been clarified, it does appear that both Huntington's and Alzheimer's patients are consistently compromised on different aspects of procedural memory. Huntington's patients are impaired in their ability to acquire skills and generalize their learned skill across different situations, whereas their priming ability remains intact. Alzheimer's patients exhibit deficient priming capabilities while retaining the ability to learn a skill. Further studies are needed in this area though, to further define the parameters of these deficits, and attempt to relate the impairments to damaged areas in the brain.

Visuospatial Functioning

Another area which has been examined in both cortical and subcortical dementia has been visuospatial functioning. The studies, however, have not been as numerous as in the memory domain, leading to a wide array of testing techniques and limited possibilities for inter-study comparisons.

In general, studies have found deficient functioning in visuospatial ability in both Alzheimer's and Huntington's disease, but there appears to be some areas which can be differentiated. With Alzheimer's disease, impairments have occurred in tests of construction, such as the Block Design in the WAIS, and drawing tasks (Salmon et al, 1991). The investigators also suggest these deficits increase progressively as the disease progresses. Functioning has also shown deterioration on tests of line orientation, with Alzheimer's patients exhibiting significantly more and significantly different types of errors from normal control subjects (Ska et al, 1990).

Huntington's patients have been found to be impaired on some of the same tests as Alzheimer's patients. With the WAIS subtests of Block Design and Object Assembly deficits are noted early in the illness (Brown & Marsden, 1988; Folstein et al, 1990). Other visuospatial tasks, such as the Rey Osterieth Complex Figure, also exhibit subnormal performance (Brandt, 1991). Although these disabilities could be attributed to motor dysfunction in Huntington's

disease, dysfunction is also detected on tasks which are not dependent on motor skills, such as the Mosaic Comparisons test (Folstein et al, 1990). This suggests that visuospatial impairments are not related to motor impairments in this disorder.

In comparing the two disorders on a variety of visuospatial functions one study found differential decrements (Brouwers et al, 1984). This study used the Road Map test, a complex figure, Mosaic Comparisons, and a stylus maze test. Alzheimer's patients were impaired on the complex figure, Mosaic Comparisons, and stylus maze test, while showing normal ability on the Road Map test. Huntington's patients exhibited deficiencies only on the Mosaic Comparisons tests. The authors suggested that Alzheimer's patients were impaired on spatial functioning related to extrapersonal perception, while egocentric spatial ability remains intact. Huntington's patients exhibited the opposite pattern, showing deficits with egocentric spatial ability while retaining extrapersonal perceptual abilities (Brouwers et al, 1984).

Although this study suggested that Alzheimer's and Huntington's patients exhibit differential visuospatial impairment patterns, some of the results have not been replicated. One study suggests that Huntington's patients show a loss of ability on tests of constructional and drawing ability. According to the previous study (Brouwers

et al, 1984) this is an extrapersonal perceptual function and should be intact in Huntington's disease. Perhaps it depends on the dementia level of the subjects, or the complexity of the constructional figure, as to whether impairments are observed. More investigations are necessary to determine the nature and extent of the impairments in these two disorders.

Executive Function

Executive functioning is suggested as being dependent on the frontal lobes. This cognitive domain involves 'higher-order' processing, such as planning and organization, behavioral regulation, and mental flexibility (Folstein et al, 1990). As the pathological process in Huntington's disease affects primarily the basal ganglia, which has substantial connections to and from the frontal cortex, it is expected that these patients would exhibit impairments in executive functioning (Brandt, 1991).

Studies have found deficits in Huntington's patients on tests of executive functioning. The Wisconsin Card Sort test is a standard test of executive function, and Huntington's patients exhibit substantial impairment even in mild stages of the disorder (Brown & Marsden, 1988; Folstein et al, 1990; Brandt, 1991). Patients were able to figure out the appropriate response strategy for the initial category, but were then unable to switch to the next

category, with repeated perseverations back to the initial category (Folstein et al, 1990). On other tasks of frontal functioning, Huntington's patients also exhibit decrements. These are manifested by an impairment in maze performance, a decrease in mental flexibility, and a tendency to perseverate, as measured by tests such as the Trail Making test and the Stroop colour-word task (Brown & Marsden, 1988; Folstein et al, 1990).

Alzheimer's disease has not traditionally been associated with executive function deficits. If functional loss does occur, it has generally been to a milder degree and tends to appear later in the disease process than found in subcortical dementias (Litvan et al, 1991). However, a few studies have looked at this area with Alzheimer's patients and have found deficits. One study examined executive abilities in Alzheimer's patients on the Mattis Dementia Rating Scale conceptualization subtest and the Wisconsin Card Sort. The patients were found to be significantly impaired as compared to normal controls, but showed less compromise than patients with Parkinson's disease (another 'subcortical' dementia) (Litvan et al, 1991). Salmon et al (1991) also report Alzheimer's patients as being impaired on tests of executive function which they attribute to an impairment in cognitive flexibility. The results, though, are not consistent, as Brown & Marsden (1988) report other studies which do not find impairments on

the Wisconsin Card Sort. Although these studies with Alzheimer's patients are limited in number, they may be suggestive of a milder degeneration of executive functioning than found in subcortical dementias, occurring more in the middle to later stages of the disorder.

Thus, it appears that both Alzheimer's and Huntington's disease patients may exhibit deficits in executive functioning. However, studies are needed directly comparing these two disorders at varying stages of their respective illnesses on a wide variety of frontal functioning to determine how the two disorders differ.

Attention and Concentration

As with executive functioning, the area of attention and concentration has been examined more closely in Huntington's disease. The few comparative studies available, though, do suggest that deficits exist in both Huntington's and Alzheimer's dementias, however they may be more severe in Huntington's disease.

Traditionally, attention functioning has been assessed through tests of mental arithmetic, digit-symbol coding, and digit and verbal memory span (Folstein et al, 1990; Brandt, 1991). Huntington's patients have shown significant dysfunction on these tests (Orsini et al, 1987; Brandt, 1991). Alzheimer's patients have also been shown to be impaired on tests concentration, such as digit and word

memory span and mental arithmetic, however some studies do not show a severe deficit until later stages of the illness (Reisberg et al, 1985; Brown & Marsden, 1988).

Studies comparing the two disorders on tests of attention have usually done so via more global intelligence or mental status tests. One such investigation compared Huntington's and Alzheimer's patients on the Folstein Mini Mental Status Exam, which includes tests of attention consisting of subtracting serial seven's starting from one hundred (Brandt et al, 1988). Although both patient groups showed deficient performance on this subtest as compared to many other subtest scores, the Alzheimer's patients performed significantly better than the Huntington's patients. This pattern occurred until the last testable stages of dementia. Within the Mini Mental score range of 5 to 9, Huntington's patients could not perform any subtractions, while Alzheimer's patients could perform approximately 15% of the subtractions. At the last testable range of scores, neither population could perform any subtractions. Another study also found that Huntington's patients performed worse than Alzheimer's patients tests of attention, with Huntington's patients showing the most difficulty with a digit span test (Pillon et al, 1991).

From these results, although few in number, it appears that both dementia groups show impairment that progresses concurrently with the disorder. However, deficits in

Alzheimer's disease may not occur until later in the disease process. More studies are needed comparing the two groups on different areas of attention and concentration. As well, studies are needed to determine whether impairments in this area occur in mild stage Alzheimer's patients.

Language

Language disturbances have long been associated with the cortical dementia of Alzheimer's disease (Brown & Marsden, 1988). As well, language disturbances have traditionally been one of the areas used to distinguish cortical from subcortical dementias, as the deficits in the two dementias occur at different stages and in different patterns.

With Alzheimer's disease, some functions of language remain essentially intact. Vocabulary level in most studies has appeared resistant to deterioration (Brown & Marsden, 1988). As well, no grammatic, repetitive, or phonologic disturbances are found until the terminal phases of the illness when all language abilities are lost (Kempler, 1991). There are also no deficits with the motor skills necessary to produce speech until the later stages of the disease (Kempler, 1991). The specific language impairments observed in Alzheimer's disease revolve around word-finding deficits or anomia. This is apparent early in the illness and shows a progressive deterioration as the illness

advances (Kempler, 1991). Anomia is present in formal tests of language such as verbal fluency and confrontation naming, as well as in spontaneous speech (Salmon et al, 1991). Although investigators are unsure as to the cause of the word-finding decrement, it is suggested to be primarily a deficit of verbal processing, as opposed to a difficulty in the perception of objects (Kempler, 1991). It has not been determined though, whether this deficit represents a limitation in verbal processing which is interfering with access, or a deficiency in the actual representations stored in lexical memory (Kempler, 1991). In all probability, the language impairment is not attributable to one particular deficit, but involves deficits from other areas of cognition such as attention and memory.

Huntington's patients show some similar patterns of deficits. In confrontation naming and verbal fluency, these patients exhibit subnormal functioning. However, the deficits are suggested as being attributable to different pathological processes than those occurring in Alzheimer's disease (Brown & Marsden, 1988). With verbal fluency, impairment is believed to be caused by an ineffective retrieval ability, as outlined in the semantic memory section of this paper. Confrontation naming is attributed to a visuoperceptual impairment. This is supported by the fact that errors occurring in naming were predominantly of a visual as opposed to semantic nature, as well as the lack of

word-finding difficulties occurring in the spontaneous speech of Huntington's patients (Podoll et al, 1988). Verbal communication deficits are observed in this population with a decrease in verbal output, deficits in articulation, and impairment in prosody being predominant. This has been attributed to a dysarthric motor disorder caused by chorea as opposed to a specific language impairment (Podoll, 1988). Dysgraphia is also observed in Huntington's patients which is separate from a choreic disorder. This deficit is also not attributed to a language impairment, as similar errors are observed in drawing and copying, suggesting a constructional impairment as the cause (Podoll, 1988). All of the deficits in Huntington's disease occur in a progressively deteriorating fashion.

Thus, with language functions it appears that both Alzheimer's and Huntington's patients are affected, however the patterns of impairment can be differentiated. Alzheimer's patients show a progressive breakdown of semantic and pragmatic capabilities, as exhibited by anomia in spontaneous speech and specific word-finding tasks (Kempler, 1991; Salmon et al, 1991). Huntington's patients, on the other hand, exhibit anomic patterns in certain areas, such as confrontation naming and verbal fluency, and communicative impairments, but these appear to be secondary to other interfering deficits (Podoll, 1988). These

patterns should be able to be differentially detected on specific tests of language.

Global Intellectual Status

Global intelligence, as measured by tests such as the Wechsler Adult Intelligence Test, deteriorate in a progressive fashion in both Alzheimer's and Huntington's disease (Mahendra, 1987; Folstein et al, 1990). The pattern of impairment within the subtests of these tests, however, is not the same, with each disorder exhibiting more deficient functioning in some areas while others remain essentially intact until the later stages of the illness. Dementia levels, as measured by tests such as the Folstein Mini Mental State and the Mattis Dementia Rating Scale, also increase in a progressive fashion for each disorder as the disease progresses (Brandt et al, 1988; Brandt, 1991). Again, though, the subtests within each test are differentially impaired with a distinct pattern appearing for each disorder. Thus, with global tests such as these, patient groups can be matched for overall dementia or intelligence level and directly compared. This also provides an opportunity to observe the progression of the disorders.

Currently Available Instruments

Some investigators have examined specific neuropsychological tests used in assessing mental status in dementing disorders to determine if the differential patterns of deficits, as outlined in the previous sections, can be detected. A pattern of double dissociation was expected, with Alzheimer's patients performing worse than Huntington's patients in some areas, with Huntington's patients performing worse than Alzheimer's patients on other areas.

Alzheimer's and Huntington's patients were compared on the Mini Mental State Exam, which is a brief cognitive test examining the domains of orientation, registration, attention and calculation, recall, and language (Brandt et al, 1988). The two groups were divided into five sections of MMSE scores: 20-24, 15-19, 10-14, 5-9, and 1-4. On this test, the lower the score the greater the deficit. At a range of 20-24 both groups were impaired as compared to controls in the orientation, serial seven's, delayed recall of three items, phrase repeat, and copy design tasks. Within this range, Huntington's patients performed significantly better than Alzheimer's patients on the date portion of the orientation task and the delayed recall of three items, which are tests of episodic memory. The Alzheimer's patients, though, performed significantly better than Huntington's patients on the serial seven's task, a

test of attention and concentration. When patients had an MMSE score of 15-19 the groups were significantly worse than normal controls on more tasks, including orientation, serial seven's, delayed recall, repeat phrase, writing sentence, and copy design. Again a pattern of double dissociation was observed between the two groups, with Huntington's patients more impaired on tests of registering three items, serial seven's, writing a sentence, and copying a design, while Alzheimer's patients exhibited a poorer performance on the date and delayed recall tasks. The greater deficits in this MMSE range occurring in Huntington's patients may be attributable to attention and concentration difficulties (registration of items, serial sevens) as well as motor control decrements (writing, drawing). With Alzheimer's disease, greater memory deficits may have contributed to the poorer performance on the date and delayed recall tasks. This study thus supports the hypothesis that differential patterns of impairment occur in Huntington's and Alzheimer's disorders which can be detected on standardized neuropsychological tests.

Huntington's and Alzheimer's patients were also compared on the Wechsler Memory Scale - Revised (Wechsler, 1981; Troster et al, 1989). With this test a number of scores can be calculated from results obtained on either the five indexes or particular subtests. Subtraction of initial subtest scores from a respective delayed subtest score

results in a "savings score", essentially representing how much is remembered over time. In this study, savings scores were calculated for the Logical Memory and Visual Reproduction tests. Alzheimer's patients obtained significantly lower savings scores than Huntington's patients, which the authors interpreted as evidence of more rapid rates of forgetting. A second measure involved an Attention/Concentration and General Memory Index (difference between the Attention/ Concentration Index and the General Memory Index). Both patient groups had positive index scores, indicating better attention/concentration than general memory scores, but Huntington's patients generally had lower Indices than Alzheimer's patients and, as a result, obtained a significantly less positive ACI-GMI scores. Finally, Huntington's patients also had somewhat lower Visual Memory Indices than Alzheimer's patients. These findings were replicated with mildly demented Alzheimer's and Huntington's patients, again suggesting that differential impairments can be detected (Troster et al, 1989).

Another frequently used test in mental status examination is the Mattis Dementia Rating Scale (DRS). Comparisons of Huntington's and Alzheimer's patients on the DRS again resulted in a double dissociation in the subtest profiles (Salmon et al, 1989). Huntington's patients performed significantly worse than patients with Alzheimer's

disease on the Initiation section, which includes subtests in verbal fluency, verbal repetition, and double alternating movements. Also Huntington's patients in general had a more impaired performance on the Attention section. On the other hand, Alzheimer's patients showed significantly greater deficits on the Memory section than Huntington's patients.

The above studies have shown that there are differential cognitive impairments between the cortical dementia of Alzheimer's disease and the subcortical dementia of Huntington's disease, with these patterns often representing a double dissociation.

While standard neuropsychometric tests can reliably show differences between cortical and subcortical dementia, clinical trials batteries are usually exclusively designed for use with Alzheimer's disease and may therefore not be sensitive to cognitive changes associated with subcortical dementia. In order to establish potential sensitivity regardless of dementia subtype, we undertook a study attempting to replicate the double dissociations found on standard neuropsychometric batteries with clinical trials batteries and their multiple test forms. The standard batteries administered included the Mini Mental State Examination, the Mattis Dementia Rating Scale, and the Wechsler Memory Scale - Revised. The Alzheimer's Disease Assessment Scale (Rosen, 1984), a clinical trials battery used only in Alzheimer's populations, was also administered.

As well, two experimental clinical trials batteries, designed more globally for dementing disorders, were included. The first experimental battery was the Cognitive Drug Research Computerized Assessment System battery, which is comprised of tests of verbal, pictorial, and facial recognition, sustained attention, simple and choice reaction time, and delayed recognition. The second novel battery, the Repeatable Battery for the Assessment of Dementia, is currently under joint development by the (U.S.) National Institute of Health and the (Canadian) Institute of Mental Health Research, and consisted of tests of immediate memory, visuospatial/ constructional ability, language, attention, and delayed recall.

METHOD

Subjects

A total of 45 subjects consented to participate in this study: 15 Alzheimer's patients (4 women, 11 men), 15 Huntington's patients (8 women, 7 men), and 15 normal controls (10 women, 5 men) (see Appendix I for patient characteristics). Alzheimer's patients were diagnosed by a neurologist as having probable Alzheimer's disease according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association

(NINCDS-ADRDA) (McKhann et al, 1984) and the Diagnostic and Statistical Manual of Mental Disorders - Revised (DSM-III-R) (American Psychiatric Association, 1987) (see Appendix II). All participants were free of centrally active medication for at least four weeks prior to study entry and, at the time of the study, were not involved in any other research experiments.

Huntington's patients were evaluated by a neurologist and fulfilled the clinical criteria for Huntington's disease developed by Folstein et al (1989), which included the presence of involuntary choreiform movements, a positive family history for the disorder, and the presence of dementia. One patient did not evidence any choreic movements at the time of study entry; however, in the face of marked neuropsychological deficits and a positive family history she was deemed admissible to this study by the attending neurologist. The patients participating in the study were free of any centrally acting medication for at least four weeks prior to study entry. However, those requiring rescue medication (eg. Haloperidol) for acute symptom management on a PRN basis, were allowed to continue with the study.

Control subjects were either spouses of Alzheimer patients or volunteers, and did not have a history of any neurological disorder. None were presently on any centrally

acting medication. This group was matched to Alzheimer's and Huntington's patients on years of education, and matched with Alzheimer's patients on age.

Huntington's and Alzheimer's patients were matched for dementia level as measured by the Folstein Mini Mental State Exam (see Table 1).

Table 1. Demographic and Psychometric Characteristics of Subject Groups: Mean (Standard Deviation)

Group	Age (Years)	Years of Education	Mini Mental State Score
Alzheimer's (n=15)	68.40 (5.99)	12.87 (3.07)	24.00 (2.85)
Huntington's (n=15)	44.67* (13.40)	11.47 (2.60)	25.23 (3.47)
Normal Control (n=15)	67.13 (6.23)	12.33 (2.92)	--

* Mean significantly different from other two groups at $p < .001$

The distribution of women and men in the three groups did not differ significantly ($\chi^2 = 4.98$, $p > .05$). Alzheimer's patients were matched for age with normal control subjects to ensure that no age-related deficits contributed to potential differences between the two groups. As Huntington's disease can occur at an earlier age than Alzheimer's disease, the groups could not be matched for age ($t = 6.26$, $p < .001$). As expected, the normal control

subjects were also significantly older than Huntington's patients ($t = 5.88$, $p < .001$).

All subjects provided informed consent and were advised of all potential risks and benefits (see Appendix III).

Procedure

Subjects were tested over two sessions lasting from 60 to 90 minutes each. Sessions were generally separated by one week, making the study one week long in total. In the first session patients were given the Wechsler Memory Scale - Revised (Wechsler, 1981), the Alzheimer's Disease Assessment Scale (Rosen et al, 1984), a battery currently in wide use in clinical trials of antidementia compounds, and the Folstein Mini Mental State Exam. The second session included three tests, the first being the Mattis Dementia Rating Scale (Mattis, 1976), a more indepth mental status assessment than the Mini Mental State Exam which includes detailed examination of the areas of attention/concentration, initiation/perseveration, constructional skills, conceptualization, and memory. The second test was a novel clinical trial battery which is currently under joint development by the (U.S.) National Institute of Health and the (Canadian) Institute of Mental Health Research (NIH/IMHR). This test consisted of subtests in the areas of immediate memory, visuospatial/constructional ability, language, attention, and delayed recall (a further

description of subtest components can be found in Appendix IV). The third test consisted of a computer-administered clinical trial battery which is being increasingly used in clinical trials of cognitive enhancers. This set of tests, the Cognitive Drug Research Clinical Trial Battery, consists of tasks of immediate verbal recognition, simple and choice reaction time, digit vigilance, memory scanning, and delayed verbal, pictorial, and facial recognition (a further description of these subtests can be found in Appendix V).

Statistics

The obtained data for each test were evaluated with a multivariate analysis of variance (MANOVA) technique of repeated measures profile analysis. This technique produces three main measures: a test of "levels", a test of "parallelism", and a test of "flatness". The test of levels asks if the groups being tested produce different scores on combined subtests. For example, do Normal Control subjects, on average, score higher across subtests on the Mattis Dementia Rating Scale than Alzheimer's patients. The test of parallelism examines the interaction across the subtests between the three groups. An example of the question asked with this test is whether Alzheimer's patients and Huntington's patients score the same across the subtests on the Wechsler Memory Scale - Revised; do they both score high on the Visual Memory subtest and Delayed Memory subtest

while scoring low on the Verbal Memory and Attention/Concentration subtest. The test of flatness explores the responses of subjects across all of the subtests, independent of groups, asking whether the scores are similar. For example, on the Alzheimer's Disease Assessment Scale, do the three groups combined have the same average mean on each subtest. This last test is usually only examined if the profiles of the groups are parallel, ie. a nonsignificant parallelism test is found.

Once the multivariate analyses were completed and significant results were obtained, univariate tests were performed. Each test battery was examined separately. Within each battery, group means on each subtest were compared, with three T-tests being conducted. On each subtest, group means for Alzheimer's patients were contrasted with Normal Control subjects, means for Huntington's patients were compared with Normal Control subjects, and means for Alzheimer's patients were contrasted with Huntington's patients. As this resulted in a large number of t-tests being performed for each test battery, the alpha level for each t-test was adjusted. An alpha level of 0.05 was divided by the number of comparisons performed on each test battery, with this adjusted alpha level becoming the level required to infer significance. As an example, the Folstein Mini Mental State Exam included five subtests. Three comparisons were performed on each subtest, for a

total of fifteen comparisons. If a per comparison alpha level of .0033 is established as a required significance level, an overall alpha level of .05 for all comparisons is not exceeded for each test battery.

If significant multivariate analyses were obtained, and thus significant differences on the subtests were produced by group membership, a discriminant function analysis was performed. This analysis attempts to create a combination(s) of subtests (called discriminant functions) which can be used to predict group membership. The discriminant functions themselves can also be examined as they consist of a set of subtests which separate groups from each other. This may shed further light on the ability of the test batteries to differentiate groups.

RESULTS

Traditional Psychometric Tests

Wechsler Memory Scale - Revised

The Wechsler Memory Scale - Revised consists of four indices, including Attention/Concentration, Visual Memory, Verbal Memory, and Delayed Memory indices (see Table 2 for standardized group means on indices). The first multivariate test, the test of levels, compared the group means on combined indices. This analysis was significant ($F(2,36) = 17.56, p = .000$), showing that the three groups

differed reliably on their combined index scores. The test of parallelism was also significant (using Wilks' criterion $F(6, 68) = 2.33, p = .042, \text{Eta Squared} = .312$), indicating that the groups produce different profiles across the indices (see Figure 1). As the profiles were significantly different, the test of flatness was not examined.

To determine which indices were contributing to the differential profiles, univariate t-tests were examined (see Table 3 for t-test results). As 12 comparisons were performed (four indices with three comparisons per index), an alpha level of .0042 was required for a particular comparison to be considered significant. At this alpha level, seven comparisons were significant. Comparing Alzheimer's patients with Normal Control subjects, Verbal Memory, Visual Memory, and Delayed Recall indices were significantly different, indicating that Alzheimer's patients perform worse on these indices. Huntington's patients showed significantly worse means than Normal Controls on all four indices (Verbal Memory, Visual Memory, Attention/Concentration, and Delayed Recall). No comparisons between Alzheimer's patients and Huntington's patients were significantly different.

The discriminant function analysis was explored as an aid to the significant MANOVA results. With the two functions included a significant relationship between the groups and predictors was achieved ($\text{Chi square}(14) = 34.52$,

$p = .0017$), accounting for 85% of the between-group variance. With the first function removed, the second function was also highly significant ($\text{Chi square}(3) = 11.89$, $p = .008$) suggesting that this function also provides relevant information for the separation of groups.

The first function included all four indices, with R^2 values of .86 on Verbal Memory, .83 on Visual Memory, .74 on Delayed Memory, and .56 on Attention/Concentration. This function separated Alzheimer's patients from Normal Control subjects, with Huntington's patients situated between the two groups. The second function discriminated between Alzheimer's patients and Huntington's patients, with Normal Control subjects in the middle of the two groups. This function consisted predominantly of the Attention/Concentration index.

The discriminant functions correctly classified 74% of the subjects in this study. Within each group, 77% of Alzheimer's patients, 69% of Huntington's patients, and 77% of Normal Control subjects were classified accurately.

Table 2. Wechsler Memory Scale - Revised Index Group
Characteristics: Mean, Expressed as Z-score
(Standard Deviation)

	Attention/ Concentra	Visual Memory	Verbal Memory	Delayed Memory
Alzheimer (n=13)	0.14 (.760)	-0.32 (.808)	-0.63 (.601)	-0.71 (.845)
Huntington (n=13)	-0.68 (.926)	-0.56 (.842)	-0.31 (.657)	-0.27 (.653)
Control (n=13)	0.66 (.858)	0.91 (.674)	0.93 (.944)	0.87 (.992)

Table 3. Wechsler Memory Scale - Revised Index Paired
Comparisons: T value (p value)

	Attention/ Concentra	Visual Memory	Verbal Memory	Delayed Memory
AD v HD	2.47 (.021)	0.75 (.463)	1.30 (.204)	1.49 (.150)
AD v NC	1.65 (.113)	4.21* (.000)	5.03* (.000)	4.36* (.000)
HD v NC	3.84* (.001)	4.92* (.000)	3.89* (.001)	3.45* (.002)

* Significant $p < .0042$

Figure 1. Wechsler Memory Scale - Revised. The standardized means and standard errors are presented for AD (Alzheimer's patients, O), HD (Huntington's patients, Δ) and NC (Normal Control subjects, $\square$) across indices. The battery indices include Attention/Construction, Visual Memory, Verbal Memory, and Delayed Memory. For t-test paired comparisons on each index, "a" denotes significance ($p < .0042$) between Alzheimer's patients and Normal Controls, "b" denotes significance between Huntington's patients and Normal Controls, and "c" denotes significance between Alzheimer's patients and Huntington's patients.

Mattis Dementia Rating Scale

The Mattis Dementia Rating Scale is a widely used dementia assessment test, consisting of Construction, Initiation/ Perseveration, Conceptualization, Attention, and Memory subtests (see Table 4 for group subtest means). The MANOVA results exhibited a significant test of levels ($F(42,2) = 8.25, p = .001$), indicating that the three groups are different on their combined subtest scores. As well, a significant test of parallelism occurred (using Wilks' Lambda $F(8,78) = 3.07, p = .005$, Eta square = .42) (see Figure 2). This suggests that the groups can be differentiated on their subtest profile. With the significant parallelism test, the test of flatness was not examined.

To determine where the differences in profiles occurred, the univariate t-tests were inspected (see Table 5 for t-test results). As fifteen comparisons were made (five subtests with three comparisons per subtest), an alpha level of .0033 was set to ensure an experimentwise alpha level of .05 was not surpassed.

With Alzheimer's patients and Normal Control subjects, means on the Initiation/Perseveration and Memory subtests were significantly different, with Alzheimer's patients exhibiting impaired performance. The Construction and Memory subtests showed significant differences between Huntington's patients and Normal Control subjects, with

Huntington's patients having lower scores. No comparisons between Alzheimer's patients and Huntington's patients exceeded the required alpha level.

To further aid in the interpretation of the MANOVA results, the discriminant analysis was examined. The two functions combined accounted for 69% of the between-group variance and was highly significant ($\text{Chi Square}(10) = 41.56$, $p = .000$). The second function by itself was also significant ($\text{Chi square}(4) = 14.37$, $p = .006$) suggesting that both functions individually contribute to the separation of groups. The first function separated the two patient groups from the Normal Control subjects, consisting mainly of the Memory ($R^2 = .73$), Attention ($R^2 = .495$), and Initiation/Perseveration ($R^2 = .49$) subtests. The second function consisted primarily of the Memory subtest and differentiated the Alzheimer's patients from the Huntington's patients ($R^2 = .485$). Normal Control subjects, on this function, were situated between the two patient groups.

The classification for this test showed fairly high rates, with an overall percent correctly classified of 75.6. However, the two patient groups only had 60% for Alzheimer's patients and 67% for Huntington's patients classified accurately. Normal Control subjects were all classified in their respective group.

Table 4. Mattis Dementia Rating Scale Subtest Group Characteristics: Mean, Expressed as Z-score (Standard Deviation)

	Construct	Initiat	Attent	Conceptual	Memory
Alzheimer (n=15)	-0.56 (.918)	-0.13 (.564)	-0.22 (.845)	-0.23 (1.14)	-0.73 (1.07)
Huntington (n=15)	-0.55 (1.08)	-0.49 (1.42)	-0.31 (1.31)	0.12 (1.06)	-0.05 (.879)
Control (n=15)	0.61 (.620)	0.62 (.353)	0.53 (.519)	0.14 (.787)	0.77 (.206)

Table 5. Mattis Dementia Rating Scale Subtest Paired Comparisons: T value (p value)

	Construct	Initiat	Attent	Conceptual	Memory
AD v HD	1.36 (.185)	0.92 (.364)	0.24 (.809)	0.88 (.385)	1.89 (.069)
AD v NC	2.33 (.027)	4.31* (.000)	2.93 (.007)	1.04 (.306)	5.33* (.000)
HD v NC	3.62* (.001)	2.92 (.007)	2.34 (.027)	0.00 (.958)	3.53* (.001)

* Significant $p < .0033$

Figure 2. Mattis Dementia Rating Scale. The standardized means and standard errors are presented for AD (Alzheimer's patients, O), HD (Huntington's patients, Δ) and NC (Normal Control subjects, $\square$) across subtests. The battery subtests include Construction, Initiation/Perseveration, Attention, Conceptualization, and Memory. For t-test paired comparisons on each subtest, "a" denotes significance ($p < .0033$) between Alzheimer's patients and Normal Controls, "b" denotes significance between Huntington's patients and Normal Controls, and "c" denotes significance between Alzheimer's patients and Huntington's patients.

Folstein Mini Mental Status Exam

Similar to the Mattis Dementia Rating Scale, this is a dementia status exam used globally with dementing disorders and consists of five subtests, including Orientation, Immediate Recall, Attention/Calculation, Recall, and Language (see Table 6 for group subtest means). This test showed a significant levels test ($F(40,2) = 12.49$, $p = .000$), indicating that the groups differed on their combined subtest mean scores. The test of parallelism was also significant ($F(8,74) = 2.53$, $p = .017$, Eta squared = .38). This revealed that the groups produced different profiles across the subtests (see Figure 3). The test for flatness was not investigated as a significant parallelism test resulted.

To determine where the differences between groups occurred, the univariate t-tests were analyzed (see Table 7 for group t-tests). With fifteen comparisons, an per comparison alpha level of .0033 was set (five subtests with three comparisons per subtest) to control for an inflated Type I error rate.

Only two t-tests exceeded the adjusted alpha level. On the Recall subtest, both Alzheimer's patients and Huntington's patients performed significantly poorer than Normal Controls. On the Orientation subtest, the comparison between Alzheimer's patients and Normal Control subjects approached significance ($p = .004$), however with the

adjusted alpha level required to control the Type I error rate, this comparison was not deemed significant.

The discriminant function analysis was examined as multivariate analyses were significant. With two discriminant functions, a significant relationship between the groups and predictor variables was obtained ($\text{Chi square}(10) = 34.57, p = .0001$), accounting for 80% of the between-group variance. However, when the second discriminant function was analyzed separately, it was not significant ($\text{Chi square}(4) = 8.55, p = .07$) suggesting that no new information was being added by this second function.

The first function discriminated between the two patient groups and Normal Control subjects, consisting mainly of the Recall test. As the second function was not adding any additional information, it was not examined.

The classification from the functions resulted in a 72% correct classification rate. Within each group, 67% of Alzheimer's patients were correctly classified, 69% of Huntington's patients were accurately classified, and 80% of Normal Control subjects were classified correctly.

Table 6. Folstein Mini Mental State Exam Subtest Group Characteristics: Mean, Expressed as Z-score (Standard Deviation)

	Immed Recall	Language	Attent	Recall	Orient
Alzheimer (n=15)	0.13 (--)	-0.20 (.971)	-0.29 (.952)	-0.58 (.746)	-0.60 (1.22)
Huntington (n=13)	-0.38 (1.85)	-0.32 (1.32)	-0.23 (1.29)	-0.38 (.809)	0.18 (.889)
Control (n=15)	0.13 (--)	0.51 (.392)	0.49 (.528)	0.90 (.746)	0.44 (.441)

Table 7. Folstein Mini Mental State Exam Subtest Paired Comparisons: T value (p value)

	Immed Recall	Language	Attent	Recall	Orient
AD v HD	1.08 (.291)	0.28 (.776)	0.14 (.881)	0.69 (.499)	1.92 (.066)
AD v NC	-- --	2.62 (.014)	2.78 (.010)	5.42* (.000)	3.12 (.004)
HD v NC	1.08 (.291)	2.33 (.028)	1.98 (.059)	4.33* (.000)	1.00 (.326)

* Significant $p < .0033$

Figure 3. Folstein Mini Mental State Exam. The standardized means and standard errors are presented for AD (Alzheimer's patients, O), HD (Huntington's patients, Δ) and NC (Normal Control subjects, $\square$) across subtests. The battery subtests include Immediate Recall, Language, Attention/Calculation, Recall, and Orientation. For t-test paired comparisons on each subtest, "a" denotes significance ($p < .0033$) between Alzheimer's patients and Normal Controls, "b" denotes significance between Huntington's patients and Normal Controls, and "c" denotes significance between Alzheimer's patients and Huntington's patients.

Clinical Trial Batteries

Repeatable Battery for the Assessment of Dementia

The Repeatable Battery for the Assessment of Dementia is made up of five subtests: Immediate Memory, Visuospatial/Construction, Language, Attention, and Delayed Recall. As the delayed memory subtest includes a verbal recognition task, this task was analyzed as a separate dependent variable. This separation was deemed justifiable due to the abundance of studies showing Huntington's patients' significantly better performance on recognition paradigms as opposed to free recall paradigms (Butters et al, 1985; Butters et al, 1986; Moss et al, 1986). This meant six dependent variables were analyzed for this test (see Table 8 for group subtest standardized means). The test of levels for this battery was significant ($F = 14.30$, $p = .000$), showing that the groups were significantly different when scores were averaged across all subtests. When the profiles for each group were examined, significant results were also obtained (using Wilks' criterion $F(10,74) = 3.50$, $p = .001$, Eta squared = .54), thus the three groups did not exhibit parallel profiles across the tests (see Figure 4). As the groups were not parallel, the test of flatness was not of interest in this analysis.

To evaluate the different profiles shown by the groups, univariate t-tests were examined (see Table 9 for results). An alpha level of .0027 (alpha level of .05 divided by 18

comparisons (6 subtests with three comparisons per subtests)) for each t-test was set to ensure an experimentwise error rate of 5% was not exceeded. Comparisons between Alzheimer's patients and Normal Control subjects resulted in five of the six subtests being significantly different, indicating that Alzheimer's patients perform poorer on Attention, Language, Recognition, Immediate Memory, and Delayed Memory subtests. Huntington's patients also showed evidence of impairment on three subtests when compared to Normal Controls, suggesting that these patients can be differentiated from Controls by lower scores on Attention, Immediate Memory, and Delayed Recall subtests. The only comparison between Alzheimer's patients and Huntington's patients which reached significance occurred on the Delayed Recall subtest. On this task, Alzheimer's patients score lower than Huntington's patients.

As MANOVA analyses were significant, discriminant function analysis was performed. As there were three groups of subjects, two discriminant functions were calculated. With both functions included, there was a highly significant relationship between the groups and predictors, with a Chi square ($df = 12$) of 56.08 ($p = .000$). With the first discriminant function removed, the second function also resulted in a significant relation ($\text{Chi square}(5) = 13.64$, $p = .02$, accounting for 17% of the between-group variance),

suggesting that this second function can also be interpreted.

The first function was primarily a measure of the Delayed Recall ($R^2 = .89$) and Immediate Memory ($R^2 = .63$) subtests, with these two subtests separating the Alzheimer's patients from the Normal Control subjects. The Alzheimer's patients show poorer performance on these two subtests than Normal Controls (see Table 8 for group values on subtests). Huntington's patients on this function were situated between the Alzheimer's patients and Control subjects. The second function was essentially a measure of the Attention subtest ($R^2 = .37$), and served to separate Huntington's patients from both Alzheimer's patients and Normal Control subjects. Huntington's patients, on this subtest, perform poorer than Alzheimer's patients and Normal Control subjects. With these two functions, 84% of the patients were correctly classified.

Table 8. Repeatable Battery for the Assessment of Dementia
Subtest Group Characteristics: Mean, Expressed as
Z-scores (Standard Deviation)

	Visuo/ Const	Attent	Lang	Recog	Immed Memory	Delay Recall
Alzheimer (n=15)	-0.04 (.937)	-0.26 (.897)	-0.44 (.942)	-0.65 (.816)	-0.74 (.739)	-0.99 (.605)
Huntington (n=15)	-0.24 (1.26)	-0.58 (.868)	-1.57 (1.13)	0.08 (1.15)	-0.08 (.922)	0.13 (.733)
Control (n=14)	0.30 (.686)	0.88 (.574)	0.65 (.428)	0.66 (.406)	0.88 (.565)	0.91 (.561)

Table 9. Repeatable Battery for the Assessment of Dementia
Subtest Paired Comparisons: T value (p value)

	Visuo/ Const	Attent	Lang	Recog	Immed Memory	Delay Recall
AD v HD	0.49 (.036)	0.96 (.344)	0.76 (.456)	2.03 (.053)	2.20 (.036)	4.55* (.000)
AD v NC	1.13 (.270)	4.06* (.000)	3.95* (.000)	5.42* (.000)	6.61* (.000)	8.74* (.000)
HD v NC	1.43 (.165)	5.29* (.000)	2.50 (.019)	1.78 (.086)	3.32* (.003)	3.20* (.003)

* Groups significantly different $p < .0033$

Figure 4. Repeatable Battery for the Assessment of Dementia. The standardized means and standard errors are presented for AD (Alzheimer's patients, ○), HD (Huntington's patients, △) and NC (Normal Control subjects, □) across subtests. The battery subtests include Visuospatial/Construction, Attention, Language, Recognition, Immediate Memory, and Delayed Recall. For t-test paired comparisons on each subtest, "a" denotes significance ($p < .0028$) between Alzheimer's patients and Normal Controls, "b" denotes significance between Huntington's patients and Normal Controls, and "c" denotes significance between Alzheimer's patients and Huntington's patients.

Cognitive Drug Research Computerized Assessment Battery

This test contained eight subtests, including Immediate Word Recognition, Simple Reaction Time, Choice Reaction Time, Memory Scanning, Digit Vigilance, Delayed Word Recognition, Delayed Picture Recognition, and Delayed Face Recognition (see Table 10 for group subtest standardized means). The groups showed significant F values on the test for levels ($F(40,2) = 8.52, p = .001$) indicating that the three groups had different averages when all of the tests were combined. The test for parallelism was also significant (using Wilks' Lambda $F(14,68) = 2.66, p = .004$, Eta square = .58) showing that the three groups have different profiles across the subtests (see Figure 5). As the test for parallelism was significant, the test for flatness was not examined.

To evaluate which subtests were contributing to the differences between the groups, univariate t-tests were examined (see Table 11 for t-test results). As 24 comparisons were performed (eight subtests with three comparisons per subtest), an alpha level of .0021 was required for a comparison to be considered significant. This ensured that an experimentwise error rate of 5% was not exceeded.

With this calculated alpha level, only three subtests showed significant results. Alzheimer's patients were differentiated from Normal Control subjects on Immediate

Word Recognition, Delayed Word Recognition, and Delayed Face Recognition. No subtests differentiated Huntington's patients from Normal Control subjects, or Huntington's patients from Alzheimer's patients.

As a significant multivariate analysis was obtained, a discriminant function analysis was performed. With three groups, two discriminant functions were calculated. The first calculation included the first and second discriminant functions combined and was highly significant, accounting for 88% of the between-group variance (Chi square(16) = 44.79, $p = .000$). The second discriminant function by itself was not significant (Chi square(7) = 7.88, $p = .34$) suggesting that this function is providing no additional information. The first function served to separate Alzheimer's patients from both Huntington's patients and Normal Control subjects, being largely a measure of Delayed Word Recognition ($R^2 = .46$), Delayed Picture Recognition ($R^2 = .43$), and Choice Reaction Time ($R^2 = .34$). This is suggesting that these three tests are able to differentiate Alzheimer's patients from Normal Control Subjects and Huntington's patients, with Alzheimer's patients exhibiting impaired performance. However, none of the actual correlations (R^2) exceeded .50.

Using these discriminant functions, 74% of the patients were correctly classified. Examining each group, 79% of

Alzheimer's patients, 64% of Huntington's patients, and 80% of Normal Control subjects were classified correctly.

Table 10. Cognitive Drug Research Computerized Assessment Battery
Subtest Group Characteristics: Mean, Expressed as Z-scores
(Standard Deviation)

	Simple React Time	Memory Scan	Digit Vigil	Face Recog	Immed Word Recog	Choice React	Delay Word Recog	Delay Pict Recog
AD (n=14)	0.18 (.128)	0.05 (.715)	-0.16 (1.04)	-0.32 (1.08)	-0.48 (1.00)	-0.52 (1.21)	-0.75 (.840)	-0.71 (.891)
HD (n=14)	-0.42 (1.71)	-.174 (1.54)	-0.19 (1.39)	-0.21 (.997)	-0.10 (1.12)	0.40 (.713)	0.16 (1.14)	0.10 (1.19)
NC (n=15)	0.23 (.071)	0.21 (.497)	0.34 (.165)	0.62 (.652)	0.58 (.559)	0.25 (.820)	0.55 (.478)	0.57 (0.29)

Table 11. Cognitive Drug Research Computerized Assessment Battery
Subtest Paired Comparisons: T value (p value)

	Simple React Time	Memory Scan	Digit Vigil	Face Recog	Immed Word Recog	Choice React	Delay Word Recog	Delay Pict Recog
AD v HD	1.32 (.199)	0.49 (.631)	0.00 (.945)	0.26 (.789)	0.93 (.364)	2.46 (.021)	2.41 (.023)	2.04 (.052)
AD v NC	1.23 (.230)	0.71 (.483)	1.38 (.078)	2.85 (.008)	3.54* (.001)	2.03 (.052)	5.16* (.000)	5.28* (.000)
HD v NC	1.47 (.152)	0.91 (.370)	1.48 (.152)	2.68 (.012)	2.12 (.044)	0.52 (.609)	1.21 (.237)	1.50 (.146)

* Means significantly different $p < .0021$

Figure 5. Cognitive Drug Research Computerized Assessment Battery. The standardized means and standard errors are presented for AD (Alzheimer's patients, ○), HD (Huntington's patients, △) and NC (Normal Control subjects, □) across subtests. The battery subtests include Simple Reaction Time (SRT), Memory Scan (MS), Digit Vigilance (DV), Delayed Face Recognition (DFR), Immediate Word Recognition (IWR), Choice Reaction Time (CRT), Delayed Word Recognition (DWR), and Delayed Picture Recognition (DPR). For t-test paired comparisons on each subtest, "a" denotes significance ($p < .0021$) between Alzheimer's patients and Normal Controls, "b" denotes significance between Huntington's patients and Normal Controls, and "c" denotes significance between Alzheimer's patients and Huntington's patients.

Alzheimer's Disease Assessment Scale

The last clinical trial battery used in this study was the Alzheimer's Disease Assessment Scale. This test consists of seven subtests, including Recall, Commands, Naming, Orientation, Recognition, Construction, and Ideation, and has been designed for use primarily with Alzheimer's patients (see Table 12 for group subtest means). The test of levels on this battery was significant ($F(40,2) = 5.7, p = .007$), indicating that the three groups were different on their combined subtest score. On examination of the group profiles across subtests, this was also significant (using Wilks' Lambda $F(12,70) = 2.298, p = .016$), showing that the groups could be differentiated by their subtest profiles (see Figure 6). As the profiles were significantly different, the test for flatness was not examined.

To determine which subtests were contributing to the differential profiles, the univariate t-tests were inspected (see Table 13). With 21 comparisons (seven subtests with three comparisons each), a per comparison alpha level of .0024 was set to ensure an experimentwise error rate of 5% was not exceeded.

Three subtests showed significant differences between Alzheimer's patients and Normal Control subjects. These differences occurred on the Recognition, Recall, and Orientation subtests, with Alzheimer's patients performing

poorer on these tasks. No comparisons between Huntington's patients and Normal Control subjects, or between Huntington's patients and Alzheimer's patients, were significantly different.

To aid in the interpretation of the multivariate analysis, a discriminant function analysis was performed. With both functions included in the analysis, there was a highly significant relationship between the groups and predictors, accounting for 85% of the between-group variance ($\text{Chi square}(14) = 34.516, p = .002$). When the second function was analyzed by itself, it was found to be nonsignificant ($\text{Chi square}(6) = 6.64, p = .356$). Thus, only the first function separated the groups in a meaningful way, with the second function not adding any further information.

The first function separated Alzheimer's patients from Huntington's patients and Normal Control subjects, being largely a measure of the Orientation ($R^2 = .65$) and Recall ($R^2 = .58$) subtests. As the second function did not add any information, it was not interpreted.

Using the functions for prediction, 67% of the subjects were classified correctly. On further examination of this classification, it was noted that 80% of Alzheimer's patients, and 86% of Normal Control subjects were classified correctly. However, only 36% of Huntington's patients were classified correctly. As 33% of the patients would be classified into the Huntington's group by chance alone, this

was not a substantial improvement, suggesting that the test did not isolate this population from the other two groups.

Table 12. Alzheimer's Disease Assessment Scale Subtest Group Characteristics: Mean, Expressed as Z-scores (Standard Deviation)

	Command	Naming	Ideat	Construc	Recog	Recall	Orient
Alzheimer (n=15)	0.31 (--)	-0.00 (.882)	-0.12 (.996)	-0.24 (1.21)	-0.37 (.776)	-0.67 (.734)	-0.71 (1.09)
Huntington (n=14)	-0.42 (1.56)	-0.45 (1.30)	-0.27 (1.37)	-0.21 (1.01)	-0.23 (1.36)	-0.09 (1.03)	0.12 (.934)
Control (n=14)	0.13 (.687)	0.45 (.496)	0.42 (.000)	0.47 (.490)	0.62 (.308)	0.69 (.868)	0.64 (--)

Table 13. Alzheimer's Disease Assessment Scale Subtest Paired Comparisons: T value (p value)

	Command	Naming	Ideat	Construc	Recog	Recall	Orient
AD v HD	1.81 (.081)	1.09 (2.85)	0.35 (.732)	0.10 (.939)	0.33 (.738)	1.74 (.093)	2.19 (.037)
AD v NC	1.03 (.309)	1.69 (.103)	2.02 (.054)	2.03 (.053)	4.46* (.000)	4.55* (.000)	4.62* (.000)
HD v NC	1.20 (.240)	2.42 (.023)	1.88 (.071)	2.26 (.033)	2.29 (.030)	2.16 (.041)	2.09 (.047)

* Significant $p < .0024$

Figure 6. Alzheimer's Disease Assessment Scale. The standardized means and standard errors are presented for AD (Alzheimer's patients, ○), HD (Huntington's patients, Δ) and NC (Normal Control subjects, □) across subtests. The battery subtests include Commands, Naming, Ideation, Construction, Recognition, Recall, and Orientation. For t-test paired comparisons on each subtest, "a" denotes significance ($p < .0024$) between Alzheimer's patients and Normal Controls, "b" denotes significance between Huntington's patients and Normal Controls, and "c" denotes significance between Alzheimer's patients and Huntington's patients.

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DISCUSSION

Studies have shown that Alzheimer's disease and Huntington's disease exhibit distinct patterns of cognitive deficits (Granholm & Butters, 1988; Litvan et al, 1991; Pillon et al, 1991; Salmon et al, 1991). These distinct patterns have been attributed to the differing areas of neuropathology observed in the two dementias. These patterns are detectable with current neuropsychometric assessment techniques, and have shown Alzheimer's patients to be most impaired on tasks involving memory and language skills (Mohr et al, 1991). Huntington's patients, on the other hand, show most pronounced deficits with executive functioning and attentional measures (Brandt, 1991). These differences in impairment patterns may be important in the context of clinical trials, where improvement in response to a particular agent tends to be measured with testing instruments developed for Alzheimer's disease. It is therefore altogether unclear whether assessment of other demented populations can yield meaningful results, since it is conceivable that these instruments may not even reliably differentiate between non-Alzheimer-type dementias and normal controls. Their use in clinical trials in non-Alzheimer-type dementia could therefore be problematic, since these batteries may not in fact be able to measure potential areas of improvement.

This study attempted therefore to determine whether clinical trial batteries could differentiate between normals and demented patients (Alzheimer's patients and Huntington's patients), and whether these would show distinct profiles. Accession criteria were based on a matched global dementia level between the patient groups as measured by the Folstein Mini Mental State Exam. Groups were matched for dementia level to ensure that differences in impairment patterns of cognitive domains could not be attributable to simple differences in dementia severity. Traditional psychometric measures were included as well for comparison purposes to ensure that differentiating between demented populations as well as between demented populations and normals in subject groups of comparable global mental status impairment levels could be demonstrated.

Traditional Psychometric Measures

The Wechsler Memory Scale - Revised reliably differentiated both patient groups from Normal Control subjects. Huntington's patients were significantly impaired compared to Controls on all four indices (Attention/Concentration, Visual Memory, Verbal Memory, and Delayed Memory), confirming the Mini Mental State Exam finding of globally deficient cognitive functioning in the domain of memory. On the other hand, Alzheimer's patients performed more poorly than Controls on the Visual, Verbal, and Delayed Memory indices, while not showing significant differences on

the Attention/Concentration index. This confirms previous findings suggesting Huntington's patients show deficits early in their disorder on tasks involving attention and concentration (Orsini et al, 1987; Brandt, 1991). As well, Huntington's patients have been shown to exhibit difficulties in retrieving material stored in memory even in the early stages of the disorder, perhaps explaining the subnormal performance on the three memory indices (Butters et al, 1986; Massman et al, 1990). With Alzheimer's patients, severe deficits early in the illness on both immediate and delayed recall measures have been well documented; their performance in this study confirmed these assertions once again (Corkin, 1985; Litvan et al, 1991; Salmon et al, 1991). Also, the relative absence of performance deficiencies of Alzheimer's patients on the Attention/ Concentration index further supports the hypothesis that this population may not exhibit impairment in this area until the later stages of the disorder (Reisberg et al, 1985; Brown & Marsden, 1988; Brandt et al, 1988). Discriminant function analysis performed on the Wechsler Memory Scale - Revised further confirmed the ability of the test to detect impairment in Alzheimer's patients. The first function separated Alzheimer's patients from Control subjects, with all four indices accounting for more than 50% of the between-group variance. On this function Huntington's patients were situated between

Alzheimer's patients and Control subjects, suggesting that this function could not separate Huntington's patients from Controls. This suggests that the Wechsler Memory Scale - Revised indeed reliably measures functions impaired in Alzheimer's disease.

Although the results appear to indicate an ability of the Wechsler Memory Scale - Revised to differentiate patient groups from Control subjects, dissociation between Alzheimer's patients and Huntington's patients was restricted to the second discriminant function. This function consisted predominantly of the Attention/Concentration index, with Huntington's patients exhibiting poorer performance than Alzheimer's patients. This suggests that some frontal functioning may be measured with this index. As this test failed to separate the demented groups in any other area though, the Wechsler Memory Scale - Revised may not adequately sample those areas which differentiate these two groups (Shimamura et al, 1987; Salmon et al, 1991).

The two tests of mental status included in this study were the Mattis Dementia Rating Scale and the Folstein Mini Mental State Exam. Patients were matched a priori on the Mini Mental State Exam, resulting in the same level of global cognitive dysfunction for both groups. The performance of the two groups on the Mattis Dementia Rating Scale was also not different, suggesting that the Mini

Mental State Exam is an effective tool at determining cognitive status in a short, concise manner. Within each test, though, differences in the ability to differentiate these groups were evident.

Within the Mini Mental State Exam, both patient groups were significantly more impaired relative to Controls on the Recall subtest, which consisted of recall three words after a short delay. This is consistent with previous reports in the literature ascertaining deficits in free recall of verbal material for both Alzheimer's patients and Huntington's patients (Moss et al, 1986; Granholm & Butters, 1988). The discriminant function analysis separated the two patient groups from Control subjects with the same subtest, further confirming the findings of these previous studies. This area of functioning has been associated with the parieto-temporal areas, suggesting that predominantly cortical functioning is being assessed.

The Mini Mental State Exam failed to differentiate Alzheimer's patients from Huntington's patients though. No subtests between the groups were different, and no discriminant function could be derived to adequately separate the groups. These results confirm the fact that the Mini Mental State Exam is lacking in measures utilizing frontal functioning which could clearly distinguish Huntington's patients from Alzheimer's patients and Normal Control subjects. It also appears to be deficient in areas,

such as specific memory tasks, which could distinguish Alzheimer's patients from Huntington's patients and Control subjects.

The Mattis Dementia Rating Scale results suggest that this test is better than the Mini Mental State Exam at assessing cognitive areas impaired in both disorders. Both patient groups were impaired as compared to Control subjects on the Memory subtest, consistent with previous findings. Alzheimer's patients were also impaired as compared to Controls on the Initiation/ Perseveration subtest, which includes tasks of verbal fluency, verbal repetition, and double alternating movements, consistent with reports of language dysfunction early in the illness (Kempler, 1991; Salmon et al, 1991). Huntington's patients, on the other hand, exhibited poorer performance than Controls on the Construction subtest. Previous studies have reported deficient abilities on constructional tasks, possibly indicating a visuospatial dysfunction (Brown & Marsden, 1988; Folstein et al, 1990). A previous study examining the performance of these two patient groups on the Mattis Dementia Scale did not achieve the same results as found on this study (Salmon et al, 1989). However, the patients included in the previous study had an average total Dementia Rating Scale score of 114. The patients in this study were less demented, with average total scores of 123 for

Alzheimer's patients and 124 for Huntington's patients. This may have contributed to the different results found.

As with the Mini Mental State Exam results, the discriminant function analysis further supported the hypothesis that the patient groups could be differentiated from the Control subjects. The first function separated the patient groups from the Controls, consisting of the Memory, Attention, and Initiation/Perseveration subtests. This suggests that memory, attention, and language functioning, as assessed by the tasks included in this study, may be impaired in both groups.

Although none of the subtests were significantly different between the patient groups, the discriminant function analysis significantly differentiated groups with the Memory subtest. On this subtest, Alzheimer's patients performed worse than Huntington's patients, which is consistent with the previous study using this test (Salmon et al, 1991). This is an improvement over the Mini Mental State Exam, as on the Mini Mental no subtests differentiated the groups. This may indicate that the Dementia Rating Scale is assessing domains of memory more completely, enabling the test to differentiate cortical from subcortical dementias in this area. However, as no other subtests separated the groups, it appears that the test overall is deficient sampling areas known to be affected by subcortical dementia.

It appears from the above results that there is a fundamental lack of assessment of cognitive domains affected primarily in subcortical dementia on these traditional psychometric measures in the early phases of the respective dementing disorders. This includes such broad areas as executive functioning, and specific areas such as procedural memory. As Alzheimer's patients were differentiated from control subjects on all three tests both with MANOVA and discriminant function analysis results, there exists a bias in these tests towards assessing cortical dementing disorders. Thus, although, these tests may be adequate to assess cortical dementias, they are not sufficiently designed to assess subcortical dementias in the early phases of these dementing illnesses. This puts into question their widespread use in assessing dementing disorders in general, at least in their early phases.

Clinical Trial Batteries

The traditional clinical trial battery included in this study was the Alzheimer's Disease Assessment Scale, designed primarily for use with Alzheimer's patients. As the test was designed for this cortical dementing disorder, it includes cognitive measures impaired specifically in this disorders. Thus, it was expected that this test would differentiate Alzheimer's patients and Huntington's patients from Normal Control subjects, but would not be able to distinguish the two patient groups. These results were not

obtained. Significantly different multivariate profiles were found for the three groups. This in itself, though, is essentially meaningless from a regulatory and practical point of view as during a clinical trial it would be impossible to tell what particular cognitive area was improving for a patient. In determining where exactly the differences were between the groups, Alzheimer's patients were found to be significantly impaired as compared to Control subjects on the Recognition, Recall, and Orientation subtests, confirming previous reports of impairment in these areas. No subtests were significantly different between Huntington's patients and Control subjects or between Huntington's patients and Alzheimer's patients. The discriminant function analysis separated Alzheimer's patients from Huntington's patients and Normal Control subjects using the Orientation and Recall subtests, but failed to discriminate between Alzheimer's and Huntington's patients and between the latter and Controls. Thus, although Huntington's patients and Alzheimer's patients were matched for dementia level by Mini Mental State scores, the Alzheimer's Disease Assessment Scale could not distinguish between Control subjects and Huntington's subjects. This renders the test practically useless for clinical trials with Huntington's patients as cognitive impairment, which was established a priori by matching Huntington's and Alzheimer's patients for level of mental status compromise,

could not be identified with the ADAS by way of its subtests.

The Cognitive Drug Research Computerized Assessment Battery was designed more globally for dementing populations and was therefore expected to exhibit greater sensitivity in distinguishing between controls and demented patients and between patients with different dementias (Simpson et al, 1989). However, these expectations were not completely fulfilled. Significant multivariate profiles distinguished the three groups from one another. On subtest scores, though, as found in the Alzheimer's Disease Assessment Scale, only Alzheimer's patients were significantly impaired as compared to Control subjects, with all memory measures, except the Delayed Face Recognition subtest, exceeding the required alpha level. However, even the Delayed Face Recognition subtest approached significance ($p = .008$), but did not exceed the more stringent alpha level set to correct for multiple comparisons. No Huntington's subtest means were found to be significantly different from either group. This does provide support for the hypothesis that memory dysfunction occurring in Huntington's disease is a result of deficient retrieval but relatively intact encoding, as in all of the memory recognition tasks Huntington's patients performed as well as Normal Controls.

The only differentiation found between the patient groups occurred on the discriminant function analysis, which

separated Alzheimer's patients from both Huntington's patients and Normal Control subjects, creating a set of subtests including the Delayed Word and Picture Recognition subtests, and the Choice Reaction Time subtest. This further supports the hypothesis that on recognition tasks, Huntington's patients perform as well as controls.

Thus it appears that this test fails to measure domains specifically impaired in Huntington's patients, making the battery no more useful for clinical trials with Huntington's patients than the Alzheimer's Disease Assessment Scale.

The last clinical trial battery examined, the Repeatable Battery for the Assessment of Dementia, appeared to be the most useful test of the three clinical trial batteries in this context. Significantly different multivariate profiles were found, with Alzheimer's patients being differentiated from Control subjects on the Attention, Language, Recognition, Immediate Memory, and Delayed Recall subtests, confirming impairments in these areas documented in previous studies. Unlike the other two clinical trial batteries, Huntington's patients were also impaired compared to Control subjects on the Attention, Immediate Memory, and Delayed Recall subtests, impairment patterns consistent with previous studies. This separation of the recognition portion of the Delayed Recall subtest elegantly confirms the hypothesis that encoding takes place in Huntington's patients but that retrieval is deficient, as this group was

impaired on free recall tasks but not different from controls on the recognition task. Alzheimer's patients were impaired on both recognition and recall tasks, confirming that both encoding and retrieval are deficient (Litvan et al, 1991). The discriminant function analysis also served to separate Alzheimer's patients from Normal Control subjects with the Delayed Recall and Immediate Memory subtests. This further confirms the hypothesis that one of the earliest and most consistent deficits observed in Alzheimer's patients is in the domain of memory.

The Repeatable Battery for the Assessment of Dementia was also the only clinical trial to distinguish the two patient groups from each other. Alzheimer's patients were more impaired than Huntington's patients on the Delayed Recall subtest, suggesting that Alzheimer's patients exhibit a greater rate of forgetting than Huntington's patients. This would concur with previous findings with Alzheimer's patients (Salmon et al, 1991), as well as earlier studies examining savings scores (delayed recall minus immediate recall scores) of Alzheimer's and Huntington's patients (Troster et al, 1989). The second discriminant function also separated Huntington's patients from Alzheimer's patients and Normal Control subjects using the Attention subtest, with Huntington's patients showing more impairment. This is expected, as studies have shown this area to be more impaired early in Huntington's disease, with Alzheimer's

patients showing deficits in this area later in the course of the illness (Brandt et al, 1988; Pillon et al, 1991). Therefore, this was the only test which achieved a true double dissociation, even in the early phases of these two disease processes.

From these results it appears that the Repeatable Battery for the Assessment of Dementia may be the most useful test for dementing disorders in general. It clearly distinguishes the currently examined demented patients from control subjects, as well as differentiating between the patient groups on some measures. Thus, with overall cognitive impairment matched (Mini Mental Status Scores), profiles are exhibited by these patient groups which can be effectively differentiated. In turn, improvement due to pharmacological intervention may be therefore potentially detected.

The failure of the other tests to distinguish between the two dementing disorders appears to be due to a heavy reliance on cognitive domains affected principally in cortical dementias. Damage due to subcortical structures results in deficits observed in different cognitive areas, such as executive functioning. To be effective in clinical trials utilizing subcortical dementing disorders, these areas must also be assessed. This ensures that any improvement in these areas can also be assessed. However, in interpreting these results, a number of factors must be

considered. First, the patients used in this study were classified as mildly demented. Being closer to the beginning of their respective disorders, impairment levels may not be sufficient to be significantly different from control values. Also, as a stringent alpha level was employed to ensure an inflated Type I error did not occur, a concomitant increase in Type II errors may have occurred. This may have resulted in a decrease in sensitivity of the tests to detect significant differences. Further studies are needed using these tests with a greater number of patients in order confirm the results found in the present study.

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Appendix I. Patient Characteristics

ALZHEIMER'S PATIENT CHARACTERISTICS

PATIENT	SEX	AGE	EDUCATION
1	M	67	18
2	M	74	11
3	M	73	7
4	F	70	12
5	M	62	12
6	F	71	18
7	F	60	12
8	M	69	12
9	M	68	12
10	M	81	15
11	M	73	9
12	F	59	11
13	M	68	15
14	M	70	16
15	M	61	13

Appendix I. Continued

HUNTINGTON'S PATIENT CHARACTERISTICS

PATIENT	SEX	AGE	EDUCATION
1	F	30	12
2	F	56	12
3	F	76	12
4	M	60	7
5	M	33	15
6	M	55	12
7	M	45	15
8	M	45	6
9	F	33	12
10	F	31	12
11	F	55	10
12	F	44	15
13	M	40	10
14	M	36	10
15	F	31	12

Appendix I. Continued

NORMAL CONTROL PATIENT CHARACTERISTICS

PATIENT	SEX	AGE	EDUCATION
1	F	60	12
2	F	79	18
3	F	76	14
4	M	70	12
5	M	72	15
6	F	59	11
7	M	71	11
8	F	70	12
9	F	69	11
10	F	62	12
11	F	61	12
12	F	61	10
13	M	61	18
14	F	66	10
15	M	70	7

Appendix II. NINCDS-ADRDA and DSM-III-R Criteria for Alzheimer's Disease

NINCDS-ADRDA Criteria for the Diagnosis of Definite, Probable, and Possible Dementia of Alzheimer's Type (DAT)

A. Definite DAT

1. Patient meets clinical criteria for Probable DAT.
2. There is biopsy or autopsy evidence compatible with DAT.

B. Probable DAT

1. Dementia is established by a standardized mental status questionnaire and confirmed by neuropsychological testing.
2. There are deficits in two or more areas of cognition.
3. There is progressive worsening of memory and other cognitive functions.
4. There is no disturbance of consciousness (delirium).
5. The onset of the illness is between 40 years and 90 years of age.
6. There is no systemic illness or brain disease that could account for the progressive mental status changes.
7. The diagnosis of Probable DAT is supported by the following:
 - a. Progressive deterioration of specific skills such as language (aphasia), motor skills (apraxia), or perceptual recognition (agnosia).
 - b. Impaired activities of daily living and altered patterns of behaviour.
 - c. Family history of similar disorders, particularly if confirmed to be DAT neuropathologically.
 - d. Laboratory results such as:
 - i. Normal standard lumbar puncture;
 - ii. Normal or nonspecific EEG;
 - iii. Cerebral atrophy on neuroimaging procedures with progression on serial documentation.

C. Possible DAT

1. There are variations in the onset, presentation, or clinical course of a dementing illness that are unusual in DAT but for which there is no alternative explanation.
2. There is a second systemic or brain disease capable of producing a dementia syndrome that is not considered to be the cause of the dementia in that case.
3. There is a single gradually progressive deficit.

Appendix II. Continued

DSM-III-R Criteria for the Diagnosis of Primary Degenerative Dementia of the Alzheimer Type

A. Dementia

1. Demonstrable impairment of short-term and long-term memory.
2. At least one of the following:
 - a. Impaired abstracting abilities;
 - b. Impaired judgement;
 - c. Other disturbances of intellectual functions such as:
 - i. Aphasia;
 - ii. Apraxia;
 - iii. Agnosia;
 - iv. Constructional difficulty.
3. Mental status changes sufficiently severe to interfere with work or usual social activities or relationships with others.
4. The patient is not delirious.
5. The disorder cannot be attributed to any other disorder such as major depression.

B. Insidious onset with progressive deteriorating course.

C. Exclusion of all other specific causes of dementia by history, physical examination, and laboratory tests.

Appendix III. Consent Form

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Before you consent to participate in this study involving research, you must understand several general principles that apply to all who take part in our studies.

- a) Taking part in this study is entirely voluntary.
- b) Personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others.
- c) You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled.

Purpose of the Study: There is a lot of research being done to develop medications that will help improve the memory problems caused by different diseases. It is very important that tests used in this studies are useful in detecting different types of memory problems. This project will examine two new tests that are designed to test people's memory over time when they are on medication. People with different memory problems will be tested on these new tests to make sure that the different problems are picked up. Also some existing tests will be given so that the new tests can be compared with them.

Study Plan: If you agree to participate in this study, you will come to the Royal Ottawa Hospital for two visits. Each visit will involve three tests lasting approximately one to one-and-one-half hours each visit.

In these tests you will do some tasks such as remembering words, numbers and pictures. On one visit, for example, you will use a computer to do the tasks. You will watch the screen, which is like a TV screen, and make your answers by pressing one of two buttons.

Risks: You will not receive any treatments or undergo any medical procedures which might involve any risk to your health. You may find the memory testing mildly stressful and the appointments may cause some inconvenience to you.

Participation in this study will not help your memory. You will not derive any personal benefit from participating, but your involvement may indirectly benefit others in the future.

OTHER PERTINENT INFORMATION

1. **Confidentiality:** When results of this study are reported you will not be identified by name. Only hospital staff have access to your records from the study.

2. You will not be paid for taking part in this study.

3. **Problems or Questions:** Should any problem or question about this study arise, you should contact the principal investigator Dr. Erich Mohr, at the Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, Ontario, K1Z 7K4.

In case of emergency, please contact the Royal Ottawa Hospital at 722-6521. Ask that the duty physician for the Memory Research Program be paged. A physician will always be available in case of an emergency. For routine calls, please contact the Memory Research Program at 724-6551.

If you have questions about your rights as a patient, or if you have complaints about the study, you may speak to a patient representative. The patient representative is not associated with this research. To contact a patient representative call 724-6530.

4. You are free to refuse to participate and are free to withdraw from this study at any time without jeopardy to your future treatment.

Please keep a copy of this document for your personal records.

CONSENT FORM

COMPLETE APPROPRIATE ITEM BELOW, A OR B;

A. Patient's Consent.

I have read the explanation and have had the opportunity to discuss it and to ask questions. I consent to take part in this study.

_____ Name of Patient	_____ Signature of Patient	_____ Date
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B. Spouse/Guardian's Permission.

I have read the explanation of this study and have had the opportunity to discuss it and to ask questions. I consent to my ward's participation in this study.

_____ Name of Spouse/ Guardian	_____ Signature	_____ Date
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_____ Name of Investigator	_____ Signature of Investigator	_____ Date
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_____ Name of Witness	_____ Signature of Witness	_____ Date
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Appendix IV. Repeatable Battery for the Assessment of
Dementia

Subtests	Description
Immediate Memory	(A) A list of 10 words is read by the examiner and words recalled by the patient are recorded. This is repeated over four trials. Total words recalled over the four trials is scored. (B) A short story is read by the examiner and details recalled by the patient are recorded. This is repeated over two trials. Total details recalled on the second trial is scored.
Visuospatial/ Construction	(A) A complex figure is copied by the patient. Total details copied correctly are scored. (B) Two practice and 10 test items are presented to the patient. Each item consists of a stimulus appearing on the bottom page of the booklet and a response-choice display appearing on the top of the page. The patient is asked to identify the orientation of the two lines by finding the lines which had the same orientation in a 13 line array numbered from 1 through 13, each separated by an angle of 15 degrees.
Language	(A) Ten pictures are shown to patients to identify. Total correct is scored. (B) Patients are asked to generate as many items of a particular category (ie. sports) as possible in one minute. Total items generated are scored.
Attention	(A) A series of digits are read to the patient. The patient is asked to recite the numbers in the same order. For each series remembered correctly by the patient, a number is added to the next series. Total series remembered correctly is scored.

(B) A task similar to the Digit Symbol subtest of the WAIS-R is presented, however patients must fill in numbers according to symbols as opposed to symbols according to numbers. Total numbers correctly filled in on a 90 second time limit is scored.

Recognition

Twenty words are read to the patient. Ten words are from the word list read at the beginning of the test, with ten distracter words added. The patient is asked to respond yes or no as to whether the word is from the original word list.

Delayed Recall

At the end of the test, free recall of the word list presented at the beginning of the test, free recall of the story presented at the beginning of the test, and free recall of the complex figure is requested.

Appendix V. Cognitive Drug Research Computerized Assessment Battery

Subtests	Description
Immediate Word Recognition	A series of 12 words is presented. These words are re-presented with 12 distracter words. For each, the patient must decide whether or not the word was in the original sequence and press the 'YES' or 'NO' response button as appropriate. This task measures the ability to store and retrieve verbal information.
Simple Reaction Time	The word 'YES' is presented on the screen at random intervals and the patient is instructed to press the 'YES' response button as quickly as possible as he/she detects the stimulus. There are 20 trials. This task measures the speed of the early stages of information processing.
Choice Reaction Time	As in the Simple Reaction Time task but the stimuli 'YES' or 'NO' being presented randomly and the corresponding response button to be pressed as quickly as possible. There are 20 trials. This task measures the patient's simple reaction time together with the extra processing time necessary to identify the stimulus and to select the appropriate response.
Digit Vigilance	A digit is randomly selected and constantly displayed on the right hand side of the screen. A series of digits is displayed in the centre of the screen at the rate of 80 per minute, and the patient is required to press the response button when the two digits displayed match. This task measures sustained vigilance.

Appendix V. Continued

Memory Scanning	A series of 3 digits is presented for the patient to hold in memory. This is followed by a series of 18 probe digits for each of which the patient decides whether or not it was in the original series and presses the 'YES' or 'NO' response button as appropriate. This task measures the ability to hold information in short term memory and rapidly retrieve it.
Delayed Verbal Recognition	The series of 12 words which was presented at the beginning of the session is re-presented together with 12 distracter words. For each, the patient must decide whether or not the word was in the original sequence and press the 'YES' or 'NO' response button as appropriate. This task measures the ability to store and retrieve verbal information.
Delayed Picture Recognition	The series of 14 pictures presented at the beginning of the session is re-presented together with 14 distracter pictures. For each, the patient must decide whether or not the picture was in the original sequence and press the 'YES' or 'NO' response button as appropriate. This task measures the ability to store and retrieve pictorial information.
Delayed Face Recognition	The series of 10 faces presented at the beginning of the session is re-presented together with 10 distracter faces. For each the patient must decide whether or not the face was in the original sequence and press the 'YES' or 'NO' response button as appropriate. This task measures the ability to store and retrieve faces.

END

1 4 - 1 2 - 9 3

FIN