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NEUROPSYCHOLOGICAL SUBGROUPS OF PATIENTS WITH ALZHEIMER'S DISEASE

by

NANCY JUSTINA FISHER

A Thesis
Submitted to the Faculty of Graduate Studies through the Department of Psychology in Partial Fulfillment of the Requirements for the Degree of Master of Arts at the University of Windsor

Windsor, Ontario, Canada

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ABSTRACT

Neuropsychological test data from 134 patients diagnosed with probable Alzheimer's disease (AD) were studied, to investigate whether subgroups of patients with qualitatively distinct neuropsychological profiles could be identified. Three empirical classification approaches were undertaken in this regard: Q-type factor analysis, hierarchical agglomerative cluster analysis, and iterative partitioning (i.e., k-means). Past research has suggested that AD patients could be classified into three qualitatively different subgroups according to spared and impaired neuropsychological domains of functioning. Specifically, it has been reported previously that while the majority of AD victims undergo global decline, some patients may retain their visual-spatial/constructional abilities during the early period of the disease, while demonstrating impaired ability to access semantic/lexical systems. As well, it has been suggested that the opposite pattern may also occur amongst some patients (i.e., visual-constructional deficits in the face of relatively preserved accessibility of semantic knowledge). It was theorized that the above patterns may suggest different underlying pathways of neuropathological progression, such that the brains of those with spared semantic knowledge or visual-spatial/constructional abilities are initially affected asymmetrically. Furthermore, an earlier proposed neuropsychological model of AD accounting for these variations in early clinical presentation is extended and presented, in which three “ideal types” of AD are described and testable predictions made in their regard. In addition, it is suggested that past research in this area can be explained in terms of the Goldberg-Costa model of hemispheric specialization. As expected, the current research consistently identified 3 neuropsychological subgroups across the various clustering methods. Subgroup 1, comprising approximately half of the sample, is marked by severe anoma accompanied by moderate to severe constructional dyspraxia. Individuals in subgroup 2 display relatively spared visual-perceptual/constructional functioning, in the face of severe anoma. Members of subgroup 3 exhibit intact naming and non-verbal reasoning, with moderate difficulty copying overlapping figures. The 3 subgroups do not differ with respect to age, age at onset, duration of illness, educational level obtained or Hamilton depression rating. Results are discussed in terms of the subgroup and stage model approaches to the conceptualization of AD, and the theoretical model proposed.
ACKNOWLEDGEMENTS

Several people have graciously offered encouragement, advice, and/or assistance throughout the preparation of this thesis. I am greatly indebted to these individuals; were it not for their support, this project would not even remotely appear as it does today. First of all, I would like to thank the members of my committee: Dr. Rourke, my Chair and Mentor, for providing me with the intellectual development, self-confidence, and motivation necessary to see this project to completion; Dr. Bielniauskas, for his hospitality, encouragement, constructive criticism, and patience from the very start, over 19 months ago; Dr. Abraham, for his unique insights and feedback. Secondly, aside from the primary role played by Dr. Bielniauskas, the support of two other University of Michigan faculty, Drs. Giordani and Berent, was instrumental in assisting my struggle to gain access to the database employed in this research. Special thanks to Dr. Giordani, for the generosity with which he sacrificed his time in extracting suitable subjects from the database, in addition to the seriousness with which he regarded the project, and the unsolicited thoughtful suggestions he offered along the way. Thirdly, two individuals from Harper Hospital, Drs. Keenan and Fuerst, played key roles in keeping the project on track with respect to stringent study design. Dr. Keenan offered the early suggestion regarding the selection of a subject sample strictly adhering to research diagnostic criteria, and recommended the particular database which came to be utilized in this project. Dr. Fuerst provided helpful suggestions regarding the various statistical analyses, in addition to offering caring advice and encouragement on numerous occasions. I would also like to express my appreciation to my family and friends, for their tolerance of my mood-swings and island-like tendencies, in addition to their unconditional emotional support throughout. Thanks in this regard are due especially to my parents and Lou Cifa. Lastly, I wish to acknowledge the landmark investigations and theoretical writings of Dr. Alex Martin, which initially piqued my curiosity in this area of research. Combined with the teachings of Dr. Rourke, the work of Dr. Martin and his colleagues has laid the foundations upon which this thesis was conceived.

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CHAPTER I

INTRODUCTION

Alzheimer's Disease

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder, involving progressive dementia, or global loss of cognitive and integrative functions (Berg & Morris, 1990), which begins insidiously, most commonly in the later years of life. Memory loss is often the first symptom noticed by the patient and/or his/her significant others (Grady et al., 1988; Haxby et al., 1988; Price et al., 1993), although affective changes (e.g., depression, irritability), personality disturbance (e.g., suspiciousness, apathy), psychosis (e.g., hallucinations, delusions), and other cognitive deficits (e.g., word finding difficulty, impaired spatial perception and judgement) are also early symptoms of the disease (McKhann et al., 1984). Recent reports suggest that memory impairment is present in 95-99% of early AD cases, though it is almost always accompanied by deficits of variable degrees in other neuropsychological domains (Price et al., 1993).

As the disease progresses, impairment of memory and other cognitive functions becomes increasingly evident and pronounced, typically involving deficits in the following areas: orientation, comprehension, visual-spatial functioning, reasoning, abstraction, calculation, language (Bennett & Knopman, 1994; Katzman & Jackson, 1991; Weksler, 1994; Zec, 1993). While AD patients may be able to function adequately in routine situations, they become increasingly unable to adapt to novel environments or activities (Adams & Victor, 1993; Berg & Morris, 1990; Cummings & Benson, 1992). Ideational and ideomotor apraxia are often noted in the middle stages of the disease (Cummings & Benson, 1992). Eventually, as neuropsychological and neurological deficits become more widespread and severe, the individual becomes unable to care for himself/herself. In the later stages of the illness, patients may develop a disruption of the sleep/wake cycle (Prinz, Vitiello, Raskind & Thorpy, 1990), display a tendency to wander, and become episodically agitated, paranoid, and/or irritable (McKhann et al., 1984; Weksler, 1994). It is also during the later stages when motor deficits usually make their first appearance, typically manifesting as rigidity and gait disturbance (Chang Chui, 1987).

In the terminal stages of AD, the patient is typically unable to ambulate, becomes
incontinent, and is often confined to a wheelchair or bed. At this point, severe deficits in all neuropsychological domains are evident, although nonfluent aphasias are rarely observed (Cummings & Benson, 1992; Price et al., 1993). Neurological signs noted amongst patients in the late-stages of AD (and in some cases, in early AD) include: primitive reflexes (i.e., frontal lobe release signs), seizures, mild parkinsonism, myoclonus, and dysphagia (Berg & Morris, 1990; Chen, Stern, Sano & Mayeux, 1991; Funkenstein et al., 1993; Neary et al., 1986). The terminal position is that of quadraplegia in flexion (Adams & Victor, 1993; Cummings & Benson, 1992).

The sequence of neuropsychological/neurological and psychiatric disabilities may not follow in the above described order (Bennett & Knopman, 1994; Neary et al., 1986), and one or two deficits may take precedence (Price et al., 1993); the disease process putatively affects particular parts of the brain at different times from individual to individual (Adams & Victor, 1993; Jagust, Davies, Tiller-Borcich & Reed, 1990). However, in general, AD involves relative sparing of primary sensory and motor cortices; the hippocampus, amygdala, basal forebrain, and multimodal association cortex (P-O-T) seem to be the most affected (Moosy, Zubenko, Martinez & Rao, 1988). The course of AD can vary from 1-20 years; the average length of survival after diagnosis is approximately 8 years (Cummings & Benson, 1992). As of yet, the etiology of AD is unknown, although several different etiologic agents may be involved, and research strongly suggests a genetic defect as the source of AD in a subgroup of patients (Brandt et al., 1993; Fitch, Becker & Heller, 1988; Huff, Auerbach, Chakravarti & Boller, 1988; Katzman & Jackson, 1991; Saunders et al., 1993; St. George-Hyslop et al., 1987; see also Bennett & Knopman, 1994 for review). There is currently no effective treatment for AD, although recent drug developments appear promising in delaying disease progression early on in the course of the illness (Farlow, Grafon, Hershey, Lewis & Dolan-Ureno, 1992; Knapp et al., 1994). The end result for the AD patient is death, typically from pneumonia, urinary tract infection, or infection of decubitus ulcers (Adams & Victor, 1993; Cummings & Benson, 1992).

Alzheimer's disease represents a major health care problem. It is currently Canada's fourth largest cause of death, and is estimated to touch one family in three (Alzheimer
Society, 1992). Because of the rapid growth of the oldest age groups in our population, we can expect AD, given its age-related nature, to become increasingly more prevalent. Although currently only 12% of the Canadian population is above the age of 65, the elderly constitute the sole segment of the population that is expected to grow substantially in the next fifty years (Statistics Canada, 1992). It has been predicted that by the year 2031, one in five Canadians will be 65 years of age or older (Canadian Mental Health Association, 1988). Due to this aging of our population, without discovery of effective treatments or preventative measures, the prevalence of AD is expected to triple by the year 2050 (Terry & Katzman, 1992).

**Diagnosis and Classification: The Role of the Neuropsychologist**

The above described shifting demographic trends, which will inevitably lead to more cases of AD, the projected economic impact of AD (see McLachlan, 1991), and the morbidity effects of caring for AD victims (see Schulz, Visintainer & Williamson, 1990), render the search for an effective treatment of the utmost importance. The success of this quest depends, of course, on an adequate understanding of the disease. A crucial factor involved in understanding any disease is the ability to describe, conceptualize, and classify it appropriately. Although classification is of fundamental importance, research of this nature has been limited with respect to AD.

The diagnosis of AD is essentially one of exclusion. Neuroimaging may suggest the presence of AD (i.e., by revealing cortical atrophy and ventricular enlargement), but is inadequate as a definitive diagnostic tool (Burns, Jacoby & Levy, 1991; Cummings & Benson, 1992). There is currently no biological marker of AD identifiable by laboratory test, although of late, research in this area appears promising. The diagnosis of *probable* AD is based upon the presence of the clinical features discussed above; namely, evidence of insidious onset of progressive decline of cognitive functioning in two or more areas (one of which is typically memory), normal level of alertness, and the absence of any other identifiable disease which could account for the observed dementia (American Psychiatric Association, 1987; McKhann et al., 1984). Confirmation of the diagnosis of AD is
provided only by histopathologic evidence obtained at autopsy or biopsy\(^1\), involving identification of specified quantities of the classic neuropathological hallmarks of the disease, senile plaques and neurofibrillary tangles, in the absence of additional brain pathologies suggestive of other types of dementia (Khachaturian, 1985; McKhann et al., 1984).

Although AD is the most common cause of dementia (Berg & Morris, 1990; Katzman & Jackson, 1991), there are several other dementia producing conditions, which unlike AD, are reversible (e.g., hypothyroidism) (see Cummings & Benson, 1992). Thus, there is a dire need to rule out treatable causes of dementia, before hastily assigning a diagnosis of probable AD (Weksler, 1994). Given that antemortem diagnosis is based upon clinical presentation of progressive neuropsychological decline, coupled by exclusion of other dementing conditions, the role of the neuropsychologist has been assigned great importance in assisting with the differential diagnosis of AD, especially in identifying groups of AD patients for research purposes (McKann et al., 1984). This has resulted in attempts to identify a neuropsychological profile specific to AD, in order to facilitate identification of the disease (e.g., Fuld, 1984; Hom, 1992). Such an approach involves conducting assessments on large numbers of those suspected with the disease, averaging these data, and then comparing the means so obtained, with those generated from similar assessments of patients with other dementias, in addition to groups of normal elderly individuals. One product of this approach has been the FULD profile of the Wechsler Adult Intelligence Scale (WAIS) (Fuld, 1984). Fuld (1984), reasoning on the basis of the then popular cholinergic hypothesis of AD, claimed to have identified a characteristic AD profile based on seven WAIS subtests. Despite initial excitement however, the most positive studies have shown this profile to obtain in only approximately 50% of suspected AD patients, thus rendering it useless in ruling out AD as the appropriate diagnosis if it fails to emerge (see reviews by Goldman, Axelrod, Tandon & Berent, 1993, and Kaufman, 1990).

Martin (1990) points out two difficulties with the above described group

\(^1\) Biopsies are rarely conducted; the risk of the surgical procedure is seldom justified for the small benefit gained by the patient (Jarvik & Matsuyama, 1986; Jorm, 1987).
comparison approach for identifying an AD profile. First of all, due to the diagnostic uncertainty of AD, there is no way of knowing for sure whether all of the patients utilized in such research indeed have AD. Thus, the group profile may be distorted by misdiagnoses. To the extent that researchers control for this uncertainty with exclusionary criteria (e.g., all patients must have memory deficits), then to this same extent certain groups of patients with less common presentations are not included, resulting in a preselected sample. In support of his argument, Martin (1990) offers the example of Alzheimer's original patient, who presented with personality disturbance (i.e., delusional jealousy) long before memory and other neuropsychological deficits were evident. Thus, it can easily be appreciated that by excluding atypical presentations in research, we are in effect creating a more or less homogeneous sample, and constructing a biased definition of AD. This of course raises epistemological questions, and may lead us farther away from an adequate understanding of the disease.

A second problem with the group comparison approach pointed out by Martin (1988; 1990) is its reliance on “averaging of the data.” This approach assumes homogeneity of neuropsychological patterns of assets and deficits, which appears to be unfounded with reference to AD. (This thesis will be fully developed in Chapter II). Thus, averaging neuropsychological test data may obscure subgroups of patients with qualitatively distinct neuropsychological profiles.

Thus, taking it a step back, one could argue that the search for a “signature” profile of AD is theoretically unfounded, and methodologically difficult, if not impossible. Although granted, the cholinergic system is affected by AD, several other neurotransmitter systems also appear to be involved in varying degrees amongst distinct individuals (Bennett & Kropman, 1994; Mayeux, 1990). Furthermore, given the exclusionary nature of the diagnosis of AD, one could easily argue that it may represent several different, yet unexplained, degenerative entities, all leading to the same neuropathologic consequences (i.e., plaques and tangles), although possibly charting different pathways of progression through the brain. This is not unreasonable speculation, given that the neuropathological markers of AD are not specific to the disease (Hirano & Zimmerman, 1962; Tomlinson, 1982; see also McMenemy, 1963, for review). As McMenemy (1963)
points out, there are many examples in pathology of the same histological end result being brought about by distinct pathological processes and etiological agents. It appears as though due to pressing needs to identify the etiology, and develop an effective treatment of AD, we may have neglected the fundamental need to describe the disease adequately. This necessarily involves the provision of explanations for atypical presentations, and the development of a classificatory system to account for clinical variability.

**Clinical Heterogeneity: Subgroup versus Stage Models**

Many clinicians and researchers agree that patients with AD vary greatly in regard to their clinical presentation (Becker, Huff, Nebes, Holland & Boller, 1988; Jagust et al., 1990; Joanette, Ska, Poissant & Beland, 1992; Martin, 1990; Martin, Cox, Brouwers & Fedio, 1985; Neary et al., 1986; Price et al., 1993; Schwartz, 1987; Shuttleworth, 1984; Swash et al., 1991). In this manner, although memory deficits can almost always be shown to be present if adequate neuropsychological testing is undertaken, great inter-individual variability is apparent with respect to other areas of neuropsychological impairment, in addition to psychiatric and neurological symptomatology. There are two models of AD which attempt to explain the heterogeneity of symptom presentation amongst AD patients: the subgroup\(^2\) and stage models. Each will briefly be introduced here, due to their relevance to this project. Following this, the major limitations of the stage approach will be outlined, although direct support for the subgroup model is reserved as the focus of chapter two. The history of these two approaches within the specific field of neuropsychology will also be dealt with briefly in chapter two.

Proponents of the subgroup model of AD contend that patients vary with regard to their evolutionary pattern of neuropsychological/psychiatric/neurological degeneration. In this way, it is believed that individuals at comparable phases of the illness not only exhibit

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\(^2\) The term “subgroup” is used throughout this thesis to refer to homogeneous groups of patients according to some dimension, which may or may not be of etiologic significance (Jorm, 1985). The term “subtype” has been reserved for groups of patients with purportedly different etiologies (e.g., familial AD). The latter topic is not addressed directly in this thesis; the interested reader is referred to Chang Chui (1987) and Boller et al. (1992) for epidemiological reviews. This terminological distinction between “subgroup” and “subtype” (as per Jorm, 1985) is widely accepted and adhered to in the literature, and thus respected here to prevent confusion.
distinct patterns of spared and affected cognitive and functional abilities, but also, varying
degrees of impairment of these capacities. Furthermore, according to this view, not only do
the neuropsychological functions affected differ amongst individuals in the early and
middle stages of AD, but the patterns by which the subcomponents of these functions
breakdown also show inter-individual variability (Joanette et al., 1992; Jorm, 1985; Martin
et al., 1986). The goal of research conducted by those adhering to this conceptual
framework of AD is to identify subgroups of patients with similar patterns of degeneration.
Such identification would allow for study of these individual “subgroups”, which may
have etiologic, prognostic, and/or therapeutic import. Furthermore, within the field of
neuropsychology specifically, the study of the various patterns of neuropsychological
degeneration is of great interest in advancing our understanding of the organization of
functional neural systems (e.g., the organization of semantic knowledge). By identifying
double dissociations of function, and studying the ways in which these independent
systems breakdown, we become more aware of the functional organization of the brain.

In contrast to the view of individuals at comparable phases of AD as heterogeneous
in symptom presentation, opponents argue that deficits incurred by AD victims are
homogeneous, or, relatively equal across all domains. In this way, strict proponents of the
classical “stage model” approach contend that differences between AD sufferers merely
reflect the distinct stages of the disease, and hence, the severity and/or duration of the
disorder (Constantinidis, 1978; Hom, 1992; Reisberg, Ferris & Crook, 1982). Various
stage models have been presented in the literature (e.g., Cummings & Benson, 1992), each
assuming a more or less global, homogeneous deterioration of cognitive functioning,
which increases quantitatively as a function of disease progression. Qualitatively distinct
symptoms amongst AD victims are recognized by proponents of these models, but are
attributed to specific stages of disease progression (e.g., see Reisberg et al., 1982), and as
such, are thought to adhere to a strict timetable. Cummings & Benson (1992) and Chen et
al. (1991) adhere to a stage model of AD; this conceptual approach seems to be particularly
popular amongst neurologists (see Table 1 for an example of a widely accepted stage
model).

It must be emphasized that proponents of the subgroup approach recognize the
Table 1. A Popular Stage Model of AD

<table>
<thead>
<tr>
<th>Stage</th>
<th>(1-3 years)</th>
<th>(2-10 years)</th>
<th>(8-12 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>new learning defective, remote recall mildly impaired</td>
<td>recent and remote recall severely impaired</td>
<td>Intellectual functions severely deteriorated</td>
</tr>
<tr>
<td>Visuospatial skills</td>
<td>topographic disorientation, poor complex constructions</td>
<td>spatial disorientation</td>
<td>Motor-limb rigidity and flexion posture</td>
</tr>
<tr>
<td>Language</td>
<td>poor word list generation, anomia</td>
<td>fluent aphasia</td>
<td>Sphincter control urinary and fecal incontinence</td>
</tr>
<tr>
<td>Personality</td>
<td>indifference, occasional irritability</td>
<td>acalculia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>sadness or delusions in some</td>
<td>ideomotor apraxia</td>
<td></td>
</tr>
<tr>
<td>Motor system</td>
<td>normal</td>
<td>indifference or irritability</td>
<td></td>
</tr>
</tbody>
</table>

From: Cummings and Benson (1992)
progressive nature of AD, and generally agree that certain symptoms of AD appear to be
developmental markers of disease progression (e.g., myoclonus). However, they believe
that within this general framework, different patterns of progression exist, particularly with
respect to neuropsychological functioning.

There are several limitations of the stage model approach to the conceptualization of
AD. First of all, the fact that several different stage models are available in the literature,
some of which clash markedly in terms of the temporal sequence in which certain
symptoms are scheduled to first appear (e.g., personality disturbance; Martin et al., 1986),
raises questions concerning the validity of this approach (Liston, 1979; Schwartz, 1987).
Furthermore, there does not appear to be a consensus as to the appropriate number of
stages of the disease, or the approximate duration of each of the different stages (see
Schwartz, 1987 for a review of stage models).

A second difficulty with the stage approach is its failure to account for autopsy
confirmed case examples in the literature, which contradict the assumption of homogeneous
dissolution of memory, visual-spatial, and language functions (see model in Table 1). For
example, AD may initially present as an isolated memory impairment, in the face of
otherwise normal neuropsychological functioning (Haxby et al., 1988; Neary et al., 1986;
Price et al., 1993). Furthermore, individuals have been identified who exhibit severe
impairment on neuropsychological measures of visual-construction, while maintaining
relatively normal levels of performance on tests of word generation and naming, and vice
versa (e.g., Martin, 1990). Other contradictory autopsy confirmed examples include AD
initially presenting most prominently as a slowly progressive attentional deficit (Price et al.,
1993), fluent aphasia (Pogacar & Williams, 1984), and parietal lobe syndrome (Crystal,
Horoupian, Katzman & Jotkowitz, 1982). As a further blow to the assumption of
"homogeneous dissolution of function", not only do certain AD cases initially present with
"focal" impairment, but generally speaking, the most prominent initial area of deficit
remains salient during the course of the disease; preserved areas remain relatively less
affected, until the terminal stages are reached, at which time all areas of neuropsychological
functioning become disrupted profoundly (see Price et al., 1993, for several autopsy
confirmed examples).
A final major weakness of the stage approach is its adherence to a time schedule by which the appearance of certain qualitatively distinct symptoms are supposed to appear, as several autopsy confirmed cases of AD do not follow such a sequence. For example, motor deficits may appear early in the course of AD (e.g., Funkenstein et al., 1993; Jagust et al., 1990), but most stage models do not schedule this type of impairment to occur until the final stages of the disease. Similarly, personality and/or affective disturbance may present as an initial symptom in some patients, while in others does not occur until the later stages of AD (Adams & Victor, 1993).

As can be appreciated from the above critique of the stage model approach, the assertion that the deficits of AD progress in a parallel, and/or predictable sequence is weak on several grounds: strong contradictory evidence is readily available in the literature, and has been for at least the past decade. There is a tendency for proponents of the stage approach to dismiss as “atypical”, the cases mentioned above which contradict their models. However, since these cases were autopsy confirmed as AD and only AD, such a dismissal is irresponsibly unscientific. A subgroup model would appear to be much more adequate in terms of accounting for the case history literature to date; exhaustive support for this approach is offered in the following chapter, as the subgroup model represents the theoretical underpinnings of the project discussed herein.

**Implications of Identifying Neuropsychological Subgroups**

Recognition that AD is not reducible to a single neuropsychological profile, but rather manifests itself as a few identifiable qualitatively distinct patterns of spared and impaired cognitive abilities in the early and middle stages, would have profound implications for professionals involved with the clinical neurosciences of aging, in addition to the patients they serve. Such enlightenment would facilitate the following: early diagnosis (i.e., by widening our understanding of presenting symptomatology)\(^3\), selection

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\(^3\) Early diagnosis is crucial; if delayed until advanced AD, neural degeneration may have occurred to the point at which the capacity for functional improvement or arrest/slowing of the pathological process may be limited or of little consequence (Swash et al., 1991). For example, current drug therapies (e.g., Tacrine) work by enhancing the function of intact remaining cholinergic neurons (Farlow et al., 1992; Knupp et al., 1994).
of appropriate therapies, assessment of interventions, our general understanding of the pathogenesis and classification of the disorder, and perhaps prognosis (Chang Chui, 1987; Martin, 1990). It is possible that neuropsychological heterogeneity may be of etiologic significance; it has been postulated that different etiologic factors may produce, via a final common pathway, the neuropathology of AD (Chang Chui, 1987; Jorm, 1985; McMenemey, 1963). These etiologic agents, and the pathways they follow, may be related to different patterns of neuropsychological degeneration. Delineation of this putative association between etiology and neuropsychological presentation may be of prognostic utility. Speculations aside, research will be more fruitful once manifestations of AD are reconceptualized at the outset (i.e., collectively regarded as heterogeneous in nature). This would hopefully prevent averaging of neuropsychological and other test data in research, which so often plagues studies in the field (Jarvik & Matsuyama, 1986; Martin et al., 1985), and may be hindering our understanding of the disorder.

Since neuropsychology plays a crucial role in identifying AD individuals for research purposes, it is imperative that efforts be made to recognize the possible existence of neuropsychological subgroups of patients; it is our determination which selects subjects for future study by various other disciplines. To move closer toward the goal of understanding the heterogeneity of AD noted by several fields (e.g., epidemiology, neuropathology, neurochemistry, etc.), neuropsychology must therefore assume responsibility for taking the first step.

Scope of Literature Review

The research project described herein involved the utilization of factor and cluster analytic techniques in an examination of neuropsychological profiles of AD patients. This investigation was conducted with the goal of reliably identifying homogeneous patterns of assets and deficits amongst groups of subjects. Before proceeding to further outline the rationale, hypotheses, methodology, and results of the current investigation, a literature review is in order, and will be presented in the chapter which follows.

Different groups of patients may have neuropsychological profiles implicating compromise of distinct neurochemical systems. The ability to identify patients in this way would facilitate appropriate assignment of AD patients in drug trials (Freed, Corkin, Growdon & Nissen, 1989; Martin, 1990).
In this review, converging evidence suggesting the heterogeneity of AD from several fields of study will be presented. This will be accomplished via a brief review of well designed studies (and those utilizing the NINCDS-ADRDA criteria for subject selection)\(^5\) employing the following schemas for the subgrouping of AD: (1) neurological signs, (2) neuroimaging findings, (3) EEG recordings, (4) patterns of neurotransmitter deficits, (5) morphological distinctions, (6) demographic variables, (7) progression rates, and finally, (8) neuropsychological profiles. Subsequently, an in depth review of the last schema (i.e., neuropsychological profiles) will be undertaken, in essence providing the rationale for the current investigation. The chapter concludes with a summary and critique of the neuropsychological subgrouping literature, followed by a discussion of the specific research questions and hypotheses suggested by the review and examined in this thesis.

\(^5\) Early studies revealed that the clinical diagnosis of AD was not confirmed on autopsy at an acceptable rate (Davies, Katz & Crystal, 1982; Tomlinson, Blessed & Roth, 1970). For example, Davies et al. (1982) found that only 46% of clinical diagnoses of AD were later confirmed histologically. Such reports created difficulty in interpreting the literature; how could one be certain of any research results in the face of this diagnostic uncertainty of the very group under study? As a result, a Work Group on the Diagnosis of Alzheimer's Disease was established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) in 1984 (McKhann et al., 1984). The interdisciplinary work group developed more stringent criteria for the diagnosis of AD, and these criteria are widely accepted as those to be met in any respectable research endeavour. Studies investigating the accuracy of the NINCDS-ADRDA diagnostic criteria have reported great improvement, with clinicopathologic agreement ranging from 64-100% (Bohler, Lopez & Moossy, 1989; Morris, McKeel, Fulling, Torack & Berg, 1988; Tierney et al., 1988). Furthermore, moderate levels of interrater reliability have been demonstrated in the utilization of the NINCDS-ADRDA criteria (Lopez et al., 1990), and the criteria have been demonstrated to have high sensitivity (.92) (Kukull et al., 1990). While generally only studies utilizing these criteria are included in the following literature review, those which did not explicitly state doing so, but whose criteria nevertheless matched those of the NINCDS-ADRDA, are also reviewed (e.g., studies undertaken before published criteria appeared). Similarly, studies conducted outside of North America are reviewed if they met criteria comparable to those outlined by the NINCDS-ADRDA Work Group.
CHAPTER II
REVIEW OF THE LITERATURE

SCHEMAS PROPOSED FOR SUBGROUPING PATIENTS WITH ALZHEIMER’S DISEASE

This literature review is organized according to different schemas by which AD patients may be categorized into subgroups, given that evidence for heterogeneity along these dimensions is noted in the literature. These parameters are by no means mutually exclusive. Indeed, it is hoped that subgroups identified according to these individual schemas will be demonstrated to overlap. Neuropsychological studies are reported throughout the coverage of these individual schemas; such measures are those best able to objectively and meaningfully distinguish individuals according to the various parameters. The last section, “Neuropsychological Profiles” is reserved for remaining neuropsychological studies which do not specifically correspond to the earlier presented schemas. It is demonstrated that although heterogeneity is observed via these several frameworks, investigation of neuropsychological subgroupings is the ideal mode of exploring clinical subgroups of AD.

Neurological Signs

Alzheimer’s disease has been generally thought to be characterized by a lack of sensory and motor symptomatology, especially in the early and middle stages of the disease. However, several neurologists have noted atypical clinical presentations, which were later confirmed on autopsy or biopsy as bona fide cases of AD. For example, Jagust et al. (1990) reported a case of AD initially presenting with judgement and coordination difficulties, accompanied by a slowly progressive left-sided hemiparesis. Crystal et al. (1982) reported on a woman presenting with a progressive right parietal lobe syndrome, characterized by astereognosis, pseudoathetosis, and extinction of the left visual field to simultaneous stimulation, who only two years later developed memory and other symptoms of higher order neuropsychological decline.

The presence of myoclonus and extrapyramidal signs on early neurological
examination have also been noted in some AD patients (Chang Chui, Teng, Henderson & Moy, 1985; Funkenstein et al., 1993; Neary et al., 1986), and may be related to a more rapid and severe decline in cognitive functioning (Chang Chui et al., 1985; Mayeux, Stern & Spanton, 1985; Stern, Mayeux, Hesdorffer & Sano, 1990), and a family history of dementia (Mayeux et al., 1985). The presence of extrapyramidal signs cannot be explained by the co-occurrence of Parkinson’s disease, as subjects with probable AD (McKern et al., 1984) cannot by definition have another CNS disease (Funkenstein et al., 1993). Some have attributed the presence of extrapyramidal signs to a “Lewy body variant of AD”, which accounts for a subgroup of AD patients who develop Parkinsonian symptoms insufficient for the diagnosis of Parkinson’s disease. At autopsy, in addition to sufficient amounts of the neuropathological markers necessary for the diagnosis of AD, Lewy bodies are found in the association cortex and brain stem, along with spongiform changes in the temporal lobe (Hansen, Maslia, Terry & Mirra, 1989; Hansen et al., 1990; Katzman & Jackson, 1991). Compared to typical AD brains, the Lewy body variant brains show significant neuronal loss in the nucleus locus ceruleus, substantia nigra, and substantia innominata, in addition to lower neocortical acetylcholinesterase levels, fewer mid-frontal tangles, and gross pallor of the substantia nigra (Hansen et al., 1989). Such patients typically develop masked facies, essential tremor, bradykinesia, decreased speed of rapid alternating movements, and mild gait disturbance; without the characteristic flexed posture, extremity rigidity, resting tremor, and other classic symptoms of Parkinson’s disease (Hansen et al., 1990; Katzman & Jackson, 1991). On neuropsychological examination they demonstrate AD features (e.g., progressive memory impairment, dysnomia, etc.), in addition to subcortical signs (e.g., poor Digit Span performance) (see Hansen et al., 1990, for a detailed description of the characteristic neuropsychological profile of these patients). However, the primary clinical presentation and history is that of AD. There is some suggestion that the Lewy body variant of AD has a more aggressive course, but this has not yet been substantiated (Katzman & Jackson, 1991).

Four possible subgroups of AD patients with regard to neurological symptoms and signs have been proposed on the basis of a longitudinal 4 year study of 50 DSM-III diagnosed patients: (1) **benign** - showing little progression (i.e., minimal decline in
functioning); (2) myoclonic - severe "intellectual" decline, myoclonus, and frequent mutism at a younger age of onset; (3) extrapyramidal - severe decline in cognitive functioning accompanied by psychotic symptoms, and extrapyramidal signs insufficient for diagnosis of Parkinson's disease; (4) typical - a gradual progressive decline in functioning without other distinguishing features (Mayeux et al., 1985).

**Neuroimaging Findings**

Positron emission tomography (PET) studies of mildly-moderately impaired AD patients have demonstrated that resting glucose metabolism is characteristically reduced in the parietal and temporal cortices relative to the frontal, periorbital, and occipital regions; hypometabolism of the frontal and anterior temporal areas occurs variably, related in part to overall disease severity (Chase, Burrows & Mohr, 1987; Friedland, Budinger, Koss & Ober, 1985; Haxby, Duara, Grady, Cutler & Rapoport, 1985; Haxby et al., 1986). Furthermore, inter-hemispheric asymmetry is evident in the frontal, parietal and temporal association areas, occurring with equal frequency in the right and left hemispheres¹ (Friedland et al., 1987; Haxby et al., 1986). Moreover, these metabolic asymmetries have been correlated with levels of language and visual-spatial functioning. In this manner, it has been demonstrated that patients with predominant language impairment as compared with visual-perceptual functioning show left-sided reduction asymmetry, and those with the reverse pattern of neuropsychological functioning demonstrate right-sided PET asymmetrical reductions (Haxby et al., 1985; Haxby et al., 1986; Martin et al., 1986). Furthermore, these asymmetries (i.e., PET and neuropsychological performance) remained stable at a 2 year follow up session (i.e., neuropsychological performance declined globally, but was relatively less affected in the originally preserved domain) (Grady, Haxby, Schlageter, Berg & Rapoport, 1986). Interestingly, mild AD patients without impairment in these two domains do not show this correlated resting PET asymmetry (i.e., on the basis of their patterns of strengths and weaknesses), although PET asymmetry is present. (Haxby et al., 1986). The results of Haxby and colleagues (1986) suggest that metabolic asymmetries precede corresponding neuropsychological deficits. However,

¹ Healthy elderly display inter-hemisphere symmetry of resting cortical metabolism (Friedland et al., 1987; Haxby et al., 1985).
follow up studies are necessary to determine whether the patients without initial language and visual-spatial deficits come to develop asymmetrical impairment of these abilities in line with their asymmetric PET patterns.

More recently, Haxby et al. (1988) investigated the *intra*-hemisphere distribution of metabolic reductions for evidence of heterogeneity. These researchers studied resting parietal-frontal distributions in mild to severe AD cases, and found them to be quite variable. The pre-motor association cortex was the most reduced frontal region. Severely functionally impaired patients demonstrated low metabolic activity in all regions except the occipital lobes when compared to controls; the greatest reductions were in the parietal and pre-motor cortices, while the smallest were in the sensorimotor and orbitofrontal regions. Moderately impaired patients differed from controls only by reduced pre-motor, parietal, and temporal activity; mild AD patients had significant reductions only in the parietal and lateral temporal lobes. Pre-motor reductions were related in part to disease severity, and in part to inter-individual differences independent of disease severity: Indices of pre-motor reductions were more strongly associated with overall severity than were parietal reductions; however, when considering the moderately to severely demented patients, the parietal/pre-motor ratios were highly variable. Equal numbers of patients demonstrated disproportionate parietal and pre-motor metabolic reductions. Furthermore, amongst the moderately impaired patients, these pre-motor/parietal discrepancies were related to patterns of performance on neuropsychological tests (severely demented patients could not complete these tests). In this manner, greater parietal reductions relative to pre-motor reductions were associated with impairments on measures of sentence comprehension, visual-construction, calculation, and immediate visual-spatial memory. Conversely, disproportionate pre-motor reductions were associated with poorer performance on tests of verbal fluency, graphomotor speed, and planning. These patterns were stable over a 1.5 year period.

In accordance with the above described PET research, single positron emission computed tomography (SPECT) studies have demonstrated reduced cortical perfusion in the associative temporoparietal cortex in early AD patients compared to matched controls; the overall degree and extent of decreased perfusion is positively associated with increases in AD severity (Schmitt, Shih & DeKosky, 1992). Furthermore, lateralized
neuropsychological impairment has been found to correlate with asymmetrical perfusion
deficits, in a manner similar to that discussed above with respect to the PET investigations
(Schmitt et al., 1992; see also Hendrie, Austrom, Hall, Farlow & Wellman, 1991 for
review).

Taking the study of cerebral blood flow in AD one step further, Bressi and
colleagues (1992), utilizing transcranial doppler sonography, reported significantly slower
blood flow velocities in the middle cerebral arteries (MCAs) of early AD patients compared
to healthy age-matched controls. Furthermore, in line with the above studies,
asymmetrical velocities in MCA flow were associated with corresponding asymmetrical
neuropsychological impairment: patients with more pronounced left hemisphere
dysfunction (i.e., those scoring poorly on the token test, word fluency test, and an object
naming task) demonstrated significantly slower blood flow in the left MCA compared to the
right, while the reverse asymmetrical pattern obtained in those with more prominent right
hemisphere dysfunction (i.e., those performing poorly on a line orientation test and the Rey
Complex Figure-copy).

Early reports (e.g., Naguib & Levy, 1982) suggested that AD subgroups could be
demonstrated via longitudinal serial Computed Tomography (CT) scanning procedures. In
this manner, one group of patients was reported to demonstrate relatively stable ventricular
size accompanied by little cognitive deterioration, while a second group evidenced
pronounced increases in ventricular size associated with cognitive decline (Naguib & Levy,
1982; see also Burns et al., 1991, for review). However, recent work strictly employing
the NINCDS-ADRDA criteria for subject selection does not suggest the presence of such
subgroups; although structural variability is evident (i.e., some patients show little atrophy
over time, while others demonstrate massive reductions), it does not appear to be clearly
related to level of neuropsychological decline (Burns et al., 1991).

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2 Velocities in the major intracranial arteries are presumably dependent on cortical levels of metabolic
activity in the regions they supply (Bressi et al., 1992). This study found reduced blood flow velocities
only in the MCAs (normal flow in other cerebral arteries). This is an expected finding since the MCA
supplies the temporoparietal region, that which was found in the PET and SPECT studies to be deficient in
early AD.
Electrophysiological Recordings

Increased slow-wave electroencephalographic (EEG) activity has been reported by some as characteristic of AD patients (Neary et al., 1986), and is noted by the NINCDS-ADRDA Work Group as consistent with the disease (McKhann et al., 1984). Although the subgrouping of AD patients by way of electrophysiological variation has not been consistently proposed as a sole method of accurately classifying these individuals, research in this area does support the heterogeneity of AD, and will be briefly mentioned here.

Soininen and colleagues (1989) analysed EEG spectra of patients with early AD (mean duration of illness=2 years), both at the time of diagnosis, and at a one year follow up period. Interestingly, for 50% of the patients, the EEG spectra\(^3\) were either normal or only mildly abnormal (i.e., mild slowing) at the first evaluation, and did not change at the follow up assessment. The situation was markedly different for the other half of the patients: their EEG spectra deteriorated significantly when comparisons between the baseline and follow up measures were made. The two patient groups (stable, deteriorating) did not differ significantly at either testing with respect to age, sex, duration of illness, age at onset of illness, or severity of AD: dementia progressed markedly in both subgroups. The authors attempt to explain these results by suggesting that cholinergic deficits may not be sufficient in all cases of AD to produce alterations of the EEG. Failure of the researchers to find a significant difference between the two groups in terms of disease severity, may have been due to the restricted neuropsychological tests utilized.

In a study partially mirroring the neuroimaging research discussed earlier, EEG activity from a group of AD patients whose initial and most striking symptom of the disease involved visual-spatial dysfunction, was compared to that generated from a group of AD patients whose earliest and most pronounced symptom was memory impairment. As might be expected, significantly less EEG activity in the parietal region was demonstrated in the visual-spatial group as compared to the memory group (Albert, Duffy & McAnulty, 1990). Unfortunately, this study did not investigate EEG differences in AD patients with disproportionate language deficits.

\(^3\) Only the EEG spectra from the T6-O2 derivation were analyzed in this study.
Patterns of Neurotransmitter Deficits

Autopsy studies comparing AD brains to normal aged brains reveal that many neurotransmitters are reduced in AD: the cholinergic, serotonergic, noradrenergic, glutaminergic, and dopaminergic systems show reductions (Bondareff et al., 1987; Gottfries, Bartfai, Carlsson. Eckernas & Svennerholm, 1986; Katzman & Jackson, 1991; Zubenko et al., 1989). While reductions of cholecystokinin and vasopressin are almost never involved, GABA and dopamine are sometimes reduced, and acetylcholine and somatostatin appear almost always to show reduced levels in AD brains (Mohr, Mann & Chase, 1990). Noradrenergic pathways are affected in some cases (Bondareff et al., 1987). Heterogeneity with respect to neurotransmitter levels is reflected by the recent findings that AD individuals vary in their responses to pharmacologic interventions (Forette, Bert, Breuil & Boller, 1992). The question has now become one of whether or not different patterns of neurotransmitter deficits can be meaningfully related to distinct patterns of neuropsychological dysfunction. This issue is of therapeutic significance; if subgroups of patients can be identified vis-a-vis patterns of neurotransmitter deficits (i.e., via neuropsychological correlation; the currently available direct in vivo measures of neurotransmitter levels are lacking), appropriate drug combinations necessary for symptomatic relief can be developed.

Morphological Distinctions

A subgrouping schema based upon amount of noradrenergic neuronal loss in the nuclei locus ceruleus of histopathologically confirmed AD cases has been proposed in the literature: $AD-1$ - with a mean neuronal loss of approximately 20%, and $AD-2$ - with a mean loss of approximately 80% in this region (Bondareff et al., 1987). $AD-2$ is associated with greater loss of nucleus basalis neurons, less choline acetyltransferase activity, reduced concentrations of somatostatin and norepinephrine, and increased counts of plaques and tangles in the cerebral cortex. No significant differences with respect to age at death, dementia severity, or duration of illness were found between the two groups. However, $AD-2$ is associated with an earlier age at onset (Bondareff, 1991). Failure of the researchers to find differences in dementia severity between the two subgroups may have been due to
the limited nature of the measure used in this determination.

**Demographic Variables**

Age of onset has been proposed as a differentiating factor in the course of AD. As such, the two classical forms of the disorder are still believed by some to exist: senile dementia (SD), with onset at or above age 65; presenile dementia (i.e., AD), with onset below age 65 (Lishman, 1978; Seltzer & Sherwin, 1983). Neuropathological and clinical evidence generally fails to support this distinction; indistinguishable densities of plaques and tangles are associated with the disease regardless of age, and the symptomatology of the senile and presenile forms are generally agreed to be similar (Adams & Victor, 1993; Berg & Morris, 1990; Cummings & Benson, 1992). However, at least one study has reported an association between early onset and greater cortical distribution of neurofibrillary tangles, while late onset cases show greater concentrations of tangles in the perihippocampal region (Zubenko et al., 1989). Further, some investigators have reported a faster progression rate amongst those affected by AD at younger ages (see below). Earlier age of onset has also been reported to be associated with more pronounced language impairment relative to other neuropsychological dysfunctions (Chang Chui et al., 1985; Filley, Kelly & Heaton, 1986), a family history of AD (Chang Chui et al., 1985), an initial emphasis on comportmental rather than cognitive deficits (Price et al., 1993), in addition to more widespread neuropathological and neurochemical disturbances (see Bondareff, 1991, for review), and an increased incidence of myoclonus and seizures (Chang Chui, 1985). However, other studies have not found these differences consistently (Becker et al., 1988; Grady, Haxby, Horwitz, Berg & Rapoport, 1987), one of which involved investigation of autopsy confirmed cases (Price et al., 1993). There is clearly no consensus on this issue.

Of note, Russians (Gavrilova et al., 1992) have always considered SD and AD separate entities, each with it’s own clinical picture and pattern of development, though united by similar neuropathology. Gavrilova and colleagues (1992) felt the need to document these differences via a comparative retrospective study of 40 patients (20 AD, 20 SD), as a comment on the current “Anglo-American subgroup controversy”. Their diagnostic criteria correspond to those of the NINCDS-ADRDA Work Group, and
somewhat convincing evidence is provided in support of substantial differences between AD and SD with respect to the following parameters: duration of the illness as a whole and of each individual stage (faster progression in AD); constitutional characteristics of the patient (i.e., AD cases more prone to have premorbidly low levels of functioning, in addition to aberrant personality traits); frequency of exogenous factors (e.g., toxin exposure, alcoholism, head injuries) in the premorbid period (more common amongst AD patients); types of psychopathological symptoms (e.g., SD patients more likely to exhibit paranoid behaviour); degree of mental disintegration in the final stage (much worse in AD than SD); neuropsychological disorders (i.e., SD initially more characterized by amnesia and semantic difficulties, followed by heterogeneous deficits, but limited neurological signs; AD associated with widespread homogeneous cortical deficits, expressive aphasia, and motor disturbances); insight into the illness (i.e., AD patients show insight, while those with SD are generally anosognostic); confabulation (only evident in SD patients); topography of atrophic changes in brain matter (frontal-temporal atrophy more marked in AD, parietal atrophy and decrease in the density of periventricular and semi-ovalar white matter more pronounced in SD) (Gavrilova et al., 1992).

Longitudinal studies report no differences in rate of progression of AD as a function of sex (Ortof & Crystal, 1989; Stern et al., 1992; Thal, Grundman & Klauber, 1988) or family history (Ortof & Crystal, 1989; Stern et al., 1992).

**Progression Rates**

There is marked variability regarding the rate of progression of the symptomatology in AD: some patients deteriorate rapidly within the first year of diagnosis, while others seem to plateau for periods of time at certain levels of neuropsychological functioning (Grady et al., 1988; Katzman & Jackson, 1991; Morris et al., 1989; Price et al., 1993). This suggests rapid and slowly progressive variants of AD. Mann, Mohr and Chase (1989) investigated the existence of such subgroups based on neuropsychological test performance. They calculated an index of progression rate for 46 AD patients by subtracting each patient’s score on the Mattis Dementia Rating Scale from 140 (the lowest normal score), and dividing this figure by the number of years since onset of symptoms. Those
individuals who exceeded the median progression index value for the entire group range were classified as rapid progressors (n=13), while the remaining patients were considered slow progressors (n=33). The groups did not differ with respect to sex, education, age at symptom onset or Full Scale IQ. However, different neuropsychological profiles obtained for the two groups. The rapid progressors evidenced significantly poorer performances on Mental Control (subtest of Wechsler Memory Scale), the Vocabulary subtest of the WAIS-R, in addition to the Initiation and Perseveration, and Conceptualization subtests of the Mattis Dementia Rating Scale, compared to the slow progressors. There were no significant differences between the two groups with respect to performances on memory measures (e.g., Wechsler Memory Scale), the WAIS-R (i.e., Full Scale IQ), or visual-spatial tests (e.g., Block Design subtest of WAIS-R), as both groups performed poorly on these measures. The authors suggest that the rapidly progressive subgroup is characterized by more pronounced “frontal” impairment, while the slow progressors show only a posterior pattern of neuropsychological impairment.

In a later study (Mann, Mohr, Gearing & Chase, 1992), these researchers sought to explore their anterior(rapid)-posterior(slow) hypothesis by examining the PET scans of patients in the two neuropsychologically defined subgroups. Progression rates were calculated in the manner described above for all AD patients in the research group who had received PET scanning and extensive neuropsychological testing for the purpose of other studies (n=21). This resulted in 13 slow progressors and 8 rapid progressors. The two groups did not differ with respect to current age, age at symptom onset, or educational level. Similarly, as in the previous study, there were no significant differences between the groups with respect to global intellectual or memory performance (WAIS-R, WMS) or visual-spatial functioning; however, with this new sample, there was also no difference between the groups with respect to performance on the Vocabulary subtest of the WAIS-R. Performances on a word fluency task, Mental Control (of WMS) and the Ego State Inventory, were significantly poorer in the rapid group (the authors consider these tests to measure “frontal functions”). Examination of the PET scans revealed no significant differences between the groups with respect to the regional cerebral metabolism of the temporal, parietal, and occipital cortices and subcortical nuclei. However, cortical
metabolism was significantly lower bilaterally in the medial and posterior regions of the superior frontal lobes in the rapidly progressive group. Correlations computed between progression indices and regional metabolic values were significant only in relation to the superior frontal cortex; increasing rates of progression were associated with decreasing metabolism in the superior frontal cortex. The authors reasoned that these results suggest subgroups of the disease, rather than different stages of AD, because the two groups did not differ with regard to parietal/temporal metabolic reduction and posterior neuropsychological functioning.

Becker and colleagues (1988) also investigated the issue of rates of progression and differing neuropsychological profiles corresponding to this, and found no relationship between the pattern of neuropsychological functioning and the rate of AD progression. However, at least one other study has reported results consistent with those of Mann and colleagues (Nyth, Gottfries, Blennow, Brane & Wallin, 1991).

Several authors have investigated whether the tempo of AD progression varies as a function of age of onset (i.e., senile versus presenile dementia). There is a suggestion in the literature that the disease may progress more quickly amongst individuals with a younger age of onset. For example, Capitani, Della Sala and Spinnler (1990), studied the range of neuropsychological impairment amongst two groups of AD patients, who had suffered from the disease for approximately two years, and differed only in terms of the age at which onset of the first symptoms of AD were recognized: those with onset above age 60, but below age 70; those with onset below age 60. A wide variety of neuropsychological tests assessing general intellectual functioning, attention, memory, language and visual-perceptual functioning were administered, and subsequently, mean percentages of the numbers of tests each group showed impairment on were calculated. The mean for the earlier onset group was significantly higher. Other investigators have reported similar results (Gavrilova et al., 1992; Seltzer & Sherwin, 1983). Several longitudinal studies have failed to support these findings (Grady et al., 1987; Ortof & Crystal, 1989; Stern, Mohs, Bierer et al., 1992; Thal et al., 1988), and one study (Nyth et al., 1991) found the opposite results (i.e., the late onset group had faster rates of decline than the early onset group). However, a recent well-designed longitudinal study provides
convincing evidence for more rapid cognitive and functional decline in subjects with early onset AD (Jacobs et al., 1994). Interestingly in terms of this thesis, Jacobs and colleagues (1994) not only noticed level of performance differences, but also investigated pattern distinctions, reporting that early onset AD patients performed significantly worse on attentional measures than did late onset cases. Once again, there does not appear to be a consensus in the literature regarding this issue.

**Summary**

As is evident from the discussion thus far, several different lines of evidence suggest the heterogeneity of AD, and neuropsychological tests have been employed as functional measures of this suspected heterogeneity. It is easily appreciated that without corresponding neuropsychological evidence, the aforementioned proposed schemas are of questionable diagnostic utility. Schemas based on neurological signs are by their very nature subjective, and have little relevance unless demonstrated to be accompanied by deficits identified by more sophisticated and sensitive neuropsychological measures. The isolated case reports of unusual AD presentations are interesting, but the probability is high that subtle neuropsychological deficits were not noted by the neurologists reporting the cases. The Mental Status Exam is reported by many neurologists as a “measure of overall neuropsychological functioning”, which is clearly unacceptable from a neuropsychological standpoint. If reliable and valid relationships between demographic variables and disease presentation and/or progression exist, only standardized and comprehensive neuropsychological batteries will be adequate in this determination. Neuroimaging and electrophysiological differences amongst AD individuals are of questionable diagnostic utility unless consistently related to measurable neuropsychological patterns/levels of deficits. Similarly, while important in their own right, morphological distinctions and patterns of neurotransmitter deficits must also be shown to have corresponding neuropsychological sequelae before their diagnostic utility may be realized. Most importantly, we must remember that neuropsychological instruments are utilized in the selection of subjects for research by various other fields of study. Thus, it seems reasonable to begin looking for clinically-based classificatory subgroups of AD on the basis
of neuropsychological profiles. As mentioned earlier, research has tended (and understandably so) to focus on developing adequate treatments for AD; however, failure to precisely identify the diagnostic targets we intend to treat, may be hindering the development of effective therapies.

**Neuropsychological Profiles**

The neuropsychological research review in this section is conducted with an underlying goal of making a case for the presence of empirically derived qualitatively distinct neuropsychological subgroups of AD. Failure to recognize the neuropsychological heterogeneity in the past may have been due to unsophisticated neuropsychological measures, or the assessment of individuals at late stages of the disease, at which time patients are globally impaired and difficult to test (Joanette et al., 1992). Often the Mini Mental State Exam alone was used as a measure of neuropsychological functioning, which is of course, inadequate.

To begin with, the reader is provided with a brief historical overview of the conceptualizations regarding the nature of AD held by those within the field of neuropsychology. We next turn to a more or less chronological review of neuropsychological studies pertaining to the subgroup-stage debate. This review will demonstrate how the field has progressed in this regard, in addition to the manner by which the research results can be (or should be) accounted for by a more complex model of AD; that is, one which reflects an enlightened view of hemispheric specialization.

**History: Stage versus Subgroup Models**

As Joanette and colleagues (1992) point out, the degree to which the neuropsychological manifestations and heterogeneity of AD have been recognized, may be linked historically to the development and refinement of our neuropsychological measures. These authors note that Alois Alzheimer initially perceived the disturbance of his original patient as a personality change; it was not until some time later that he realized her memory and other neuropsychological functions were also deteriorating. It is quite possible (and probable on the basis of our current understanding of AD) that Alzheimer's patient
encountered neuropsychological difficulties earlier than had been noticed; at the turn of the century, neuropsychological measures were not available, and little was known regarding the evaluation of neuropsychological functioning.

Once measurable neuropsychological deficits were realized amongst AD patients, the predominant view in the field was that of homogeneous decline of functioning, resulting from generalized brain atrophy. There seemed to have been an *a priori* conception that AD “should” present as a diffuse disorder, and as a result, patients with focal presentations were excluded from research, and written off as suffering from another disorder, even though many of these cases were later autopsy-confirmed as AD (Schwartz, 1987). This idea that a particular brain disorder must produce the same deficits in all so afflicted, parallels the early situation with respect to learning disabilities (Rourke, 1989). The Geneva school held that AD manifested neuropsychologically as an “aphaso-agnos-oapractic syndrome”, or as homogeneous impairment of language, perception, and gestural functioning (Joanette et al., 1992). And as a result, it was believed that all neuropsychological functions were affected to the same degree at a given point in time (Joanette et al., 1992). This view is consistent with the contemporary stage model of AD.

The first published speculations of neuropsychological heterogeneity in AD did not appear until the late sixties (McDonald, 1969). McDonald (1969), recognizing discrepancies in the literature regarding the definition and features of senile dementia, undertook what appears to be the first attempt to subgroup patients with the disease on the basis of neuropsychological test performance. McDonald administered the Weigl Color Form Sorting Test, in addition to six tests assessing each of three domains of functioning (i.e., memory, “parietal” function⁴, and language), to a hospitalized group of patients diagnosed with senile dementia. Following this, he combined the results of the six tests from each domain into composite scores, resulting in a scale for each domain. He then examined data frequency distributions generated from these assessments in order to determine which domain of functioning best divided the patients into two groups. The distribution of scores on the parietal scale was blatantly bimodal (with the vast majority of patient scores falling at one of the two extremes), so he chose to subgroup patients on this

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⁴ Unfortunately, McDonald does not state which tests he utilized in assessing the 3 domains.
basis, and determine the characteristics of both the parietal function preserved and impaired groups. Interestingly, he reported that the impaired subgroup was significantly younger than the group with spared parietal function. McDonald (1969) subsequently replicated this study on a new, more representative sample, and found the same results. Furthermore, follow-up study of the patients revealed a poorer prognosis for the parietal group than for the subgroup with spared parietal function; six months later, 26% of the impaired parietal patients had died, as compared to only 4% of the group with spared parietal function.

Unfortunately, the study of McDonald (1969) did not appear to generate much interest at the time; although some authors wrote about the apparent heterogeneity of AD (e.g., Liston, 1979), no further subgrouping studies were attempted (or at least published), and the majority of clinicians and researchers seemed to cling to the “homogeneous dissolution” conceptualization of the disease. Perhaps due to ageism, or the distorted view of AD as involving normal age-related loss of memory and intellectual faculties, this view of AD as a homogeneous neuropsychological entity persisted until quite recently, and is evident in the group comparison approach to the study of AD (e.g., Fuld, 1984; Hom, 1992). Although still today, some remain entrenched in this belief, the acknowledgement of the possibility of AD representing a heterogeneous neuropsychological disorder is becoming increasingly evident in the current approach to the study of individuals so afflicted. This changing conceptualization of AD within the field of neuropsychology is likely associated with the mounting evidence from several fields (e.g., epidemiology, neurochemistry, neuropathology, etc.) suggesting the heterogeneity of the disease (see Boller, Forette, Khachaturian, Poncet & Christen, 1992).

Right-Left Studies

Martin and colleagues (1984, 1985, 1986, 1990) have conducted research involving the study of individuals at relatively equivalent stages of AD (i.e., in terms of duration of the illness), in search of subgroupings of patients with qualitatively distinct profiles of impaired and spared abilities. These researchers studied the performance of 42

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5 Of interest, the distribution of scores on the Weigl test was also bimodal.
AD patients in the early period of the disease process (mean symptom duration = 3 years), on measures assessing a wide range of neuropsychological functioning (see Martin et al., 1986). Particular attention was paid to the performances of the subjects on measures assessing accessibility of semantic knowledge (i.e., Boston Naming Test, Verbal Fluency subtest of Mattis Dementia Rating Scale, Associate Learning subtest of Wechsler Memory Scale-easy items only) and visual-spatial skills (i.e., Block Design subtest of the WAIS, Rey-Osterrieth Complex Figure-copy only, Mosaic Comparison Test). Qualitative interpretation of the results revealed that while the majority of patients under study exhibited deficits in all domains assessed, some demonstrated intact visual-spatial abilities, coupled with impaired access to semantic knowledge. Conversely, another small group of patients showed normal access to semantic knowledge accompanied by impaired visual-spatial functioning (see Figure 1 for examples).

In order to quantitatively verify these observations, Martin and colleagues subsequently subjected the results of the three measures of accessibility of semantic knowledge, and the three measures of visual-spatial functioning, to a factor analysis. Varimax rotation of the principal components solution yielded two relatively independent factors, each with high loadings for one set of tests (i.e., either those assessing semantic knowledge or visual-spatial skill), and low loadings for the other. This 2-factor solution accounted for 70.5% of the variance, suggesting the potential existence of subgroups of patients. In order to test this hypothesis, the factor scores assigned to each subject were utilized in plotting the patients graphically in two-dimensional space, which revealed a tendency for patients to cluster into different groups. To statistically verify these groupings, cluster analysis of the factor scores was undertaken, and revealed three qualitatively distinct subgroups: (1) those with relatively equal impairment of both semantic knowledge and visual-spatial skills (n=25), (2) those with impaired semantic knowledge coupled with relatively spared visual-spatial functioning (n=9), and (3) those with relatively intact access to semantic knowledge accompanied by visual-spatial impairment (n=8). Linear

6 Semantic knowledge and visual-spatial skills were chosen for study because aside from episodic memory impairments, these 2 areas had been both clinically observed by the researchers to be the most impaired domains of functioning, and those found to be most impaired in previous empirical studies.

7 A stage model of AD would predict a single general factor onto which all measures are highly loaded.
Figure 1. Examples of copies of the Rey-Osterrieth Complex Figure by patients with (A) relatively focal word-finding deficits and (B) relatively focal visuospatial and construction impairment. The number in parentheses under each drawing indicates the number of line-drawn objects from the Boston Naming Test that the patient was able to name before phonemic cuing (maximum score=85, normal range=50-85). [From: Martin (1990)]
discriminant analysis utilizing factor scores to predict subgroup membership successfully re-assigned 41 of the 42 patients, thus verifying cluster membership.

The first and largest qualitatively distinct subgroup identified by Martin and colleagues, those with relatively equal deterioration in both neuropsychological domains, was further broken down into 3 separate clusters: representing mild, moderate, and severe impairment. Thus, these patients exhibited qualitatively similar patterns of cognitive deterioration, and were differentiated only in terms of severity, hence conforming to a stage model of AD. However, the second 2 qualitatively distinct groups of patients identified lend credence to the subgroup model of the disease. Although the authors do not mention this, it is possible that these second two subgroups may have also clustered into smaller secondary severity groupings if a larger sample had been utilized. In short, it appears from this research that the stage and subgroup models are not mutually exclusive. If future studies utilizing more broad protocols and larger sample sizes confirm the findings of Martin and his colleagues, it would appear as though a conceptual model of AD combining the competing models may be indicated.

Following the above described statistical analysis, select patients (n=19) from each of the three subgroups underwent PET scanning to obtain estimates of cortical glucose utilization (Martin et al., 1986). Although the subgroups did not differ with respect to overall rate of cortical glucose metabolism, post-hoc comparisons indicated that metabolic differences were consistent with subgroup assignment: those with deficits in both cognitive domains (subgroup 1), displayed bi’lateral hypometabolism of the temporal and parietal lobes; those with impaired semantic knowledge accompanied by relatively spared visual-spatial abilities (subgroup 2), had significantly greater hypometabolism in the left temporal region relative to other cortical regions; those with the reverse cognitive pattern (subgroup 3), showed significantly greater hypometabolism in the right parietal region. Thus, it

8 The authors utilized Ward’s clustering procedure, which tends to combine clusters with small numbers of observations (Hair, Anderson, Tatham & Black, 1992).
9 Although it is possible that these findings could support a stage model alone, with “subgroup 1” indicative of this, and subgroups 2 and 3 representing dual- or mis-diagnoses, autopsies conducted on the patients in subgroups 2 and 3 who died shortly after the study confirmed the diagnosis of AD in all cases (Martin, 1990). Further, reports of single case studies of AD patients with similar patterns of cognitive decline to those members of subgroups 2 and 3 in Martin et al.’s research, have also been autopsy confirmed as having had AD (e.g., Crystal et al., 1982).
appears that the PET analysis provided external validation of the cluster analytic results generated earlier.

The patients involved in this ongoing research have been followed and re-tested on the six measures of verbal and visual-spatial functioning at one to two year intervals since the initial assessment in 1986. Martin (1990) reports that results of the re-evaluations indicate distinct patterns of deterioration based on subgroup membership. Those in subgroup 1, who initially displayed equal impairment in both domains, continued with this general global decline in functioning. However, patients in subgroups 2 and 3, exhibited significantly greater deterioration in the area (i.e., either verbal or visual-spatial) which was impaired at the initial evaluation. These results suggest that patterns of deterioration may be predicted with knowledge of initial subgroup membership. Moreover, AD may initially invade rather circumscribed regions in some patients and this region of most marked pathology may show inter-patient variability, thus producing qualitatively distinct neuropsychological profiles. If these findings are confirmed, they may have implications for models of AD progression (i.e., patterns of deterioration). In this way, unitary models of the course of AD (e.g., Zec. 1993) may need to be reconceptualized, or broadened, to account for subgroup differences. Each neuropsychological subgroup may very well correspond with distinctive neuropathological pathways of disease progression. Martin (1990) speculates on this issue, and offers what he refers to as a “minimal model” of AD progression.

Becker and colleagues (1988) have partially replicated the study of Martin and colleagues (1986) utilizing a larger sample of 86 patients. These patients underwent comprehensive neuropsychological evaluation, and subsequently, data obtained by measures of semantic knowledge and visual-spatial functioning similar to those utilized by Martin et al. (1986), were submitted to the same type of factor analysis conducted by Martin and colleagues. A two-factor solution was derived, accounting for 74.6% of the variance; the factors obtained were essentially the same as those reported by Martin and colleagues (1986). These researchers identified subgroups similar to groups 2 and 3 of Martin and colleagues, by calculating composite scores for the two neuropsychological domains, and utilizing the following criteria: (1) one composite score must be within the
normal range. (2) the other score must fall at least 2 standard deviations below it.
However, Becker and colleagues did not proceed with a cluster analysis of the factor
scores, as they were more interested in determining whether patients with predominant
language disturbance had a poorer prognosis as opposed to those with severe visual-spatial
deficits, than they were in verifying neuropsychological subgroupings.

The above described investigations strongly suggest a double dissociation between
accessibility of semantic knowledge and visual-spatial constructional skill, implying the
independence of corresponding neural systems. This suggests the presence of neuropsycho-
logical subgroups. While interesting in this regard, one must be careful not to
hastily conclude that a simple verbal (left) / non-verbal (right) dichotomy is at work here.
While “access to semantic knowledge”, or the neural representation of stored knowledge
can be considered a rather specific construct, it cannot be equated with language
functioning in general. It is quite possible that the patients who performed poorly on the
measures utilized to assess this domain may have performed adequately on other “verbal
measures”. Moreover, the assignation of all verbal functions to the left hemisphere is a
questionable assumption. Similarly, visual-spatial functioning is quite a broad construct, no
doubt involving several subcomponents, not all of which can be attributed solely to the
integrity of the right hemisphere.

**Spatial Processing**

Delis et al. (1992), realizing this conceptual difficulty with a simple verbal/non-
verbal dichotomy as representative of distinct subgroups of AD patients, investigated the
existence of dissociations within the realm of spatial processing. In accordance with the
above described studies, patients were divided into three groups on the basis of their
neuropsychological performance: (1) High Spatial (HS), Block Design performance at least
1 standard deviation above Boston Naming performance; (2) High Verbal (HV),
performance on Boston Naming Test at least 1 standard deviation above that on Block
Design; (3) Equal, similar performance on both measures. Comparisons of the groups
confirmed the expected significant superiority of the HV group over the HS group on the
Boston Naming test and WAIS-R Vocabulary subtest, and superiority of the HS group
over the HV group on Block Design. The groups did not differ with respect to Dementia Rating Scale total scores.

The subjects were administered a task involving the processing of local and global forms. Global-local figures representing letters or shapes (e.g., a large S comprised of small J's; see Figure 2) were presented separately to each subject for a ten second period, after which the subject was asked to draw each figure from memory. Following this, simple large and small figures (i.e., the size of the global and local forms) composed of solid-lines were presented in the same paradigm. For example, a simple large figure might be the letter "S", drawn as a solid line (i.e., not comprised of local stimuli). Simple small figures were the same as the local stimuli in the initial presentations (e.g., "#"). In the last phase of the procedure, the subjects were successively presented with all of the stimuli previously utilized (i.e., global-local, simple small, simple large), and asked to copy each of the figures, in turn. It was predicted, based on past research involving patients with left/right focal lesions, that during the global-local recall phase, the HS group would be superior to the HV group in processing global (configural) forms. Conversely, the HV subjects were expected to outperform those in the HS group in the processing of local (detail) stimuli.

As predicted, the HV patients obtained significantly superior local recall scores compared to the HS patients, while the HS patients outperformed the HV patients in terms of global recall scores. Local recall scores were highly correlated with Boston Naming Test scores, but not with Block Design scores; global recall scores correlated highly with Block Design scores but not Boston Naming scores. Furthermore, there was a great separation between the HV and HS groups in terms of their local-global difference score; as a result, the hit rate for classifying the patients into these subgroups via local-global difference score was 91%.

The global-local dissociation between the subgroups was not affected by the nature of the stimuli; the dissociation existed regardless of whether letters or shapes were utilized. In addition, the subgroups did not differ with respect to dementia severity or overall mean recall performance collapsed across global and local forms. Thus, their different patterns of performance cannot be attributed to overall level of neuropsychological dysfunction. Furthermore, the two groups did not differ with respect to performance on simple small
Figure 2. Examples of global-local stimuli. These stimuli were either linguistic forms (a) or nonlinguistic forms (b). Both (c) and (d) illustrate recall drawings by a High Verbal patient illustrating correct construction of the local forms and incorrect construction of the global forms. Conversely, (e) and (f) are recall drawings by a High Spatial patient showing accurate reproduction of the global forms and inaccurate reproduction of the local forms. [From: Delis et al. (1992)]
versus simple large recall trials. As a result, the authors suggest the dissociation between the subgroups as best accounted for in terms of the hierarchical relationship of global and local forms.

These researchers, later realizing that the above described study required the subjects to draw complex visual stimuli, thus involving visuoconstructional demands, conducted a further similar study without this constructional component (Massman et al., 1993). In this way, they sought to investigate whether the global-local dissociations could be demonstrated via a more elementary task, employing a directed-attention reaction time procedure. In addition, to reduce perceptual demands, only overlearned simple stimuli were utilized: either a “1” composed of small 1’s or 2’s, or a “2” composed of small 1’s or 2’s. The stimuli were presented on a computer screen, and in different blocks of trials, the patients were instructed to direct their attention to either the global or local forms, and hit one of two computer keys, dependent on whether a one or two was presented. As with the earlier study, new patients were grouped with respect to discrepant performance on the Boston Naming and Block Design tests. The authors predicted that the HV group would have more difficulty processing global forms (i.e., evidenced by lower accuracy and slower reaction times). the HS group would demonstrate more difficulty processing the local forms, and the “equal” group would show similar levels of difficulty for the two types of spatial processing. Pronounced dissociations in performance in accordance with these predictions were evident, both in terms of accuracy and reaction time.

Combining the results from both studies, there is a suggestion that the global-local dissociations occur at an early stage of visual hierarchical processing, and are apparent as well in visual-constructional and memory performance. The authors attribute this global-local dissociation to asymmetrical temporoparietal dysfunction; studies have shown that patients with unilateral focal lesions to this area demonstrate the same focal (left), global (right) impairments, and as was earlier mentioned, AD patients generally demonstrate metabolic reductions in the temporoparietal region. One might criticize the design of these studies for subgrouping patients solely on the basis of 2 measures. The results would have also been more powerful had the researchers conducted PET scanning, and subsequent comparisons between the two subgroups in accordance with their speculations. However,
these studies are valuable in terms of our understanding of the breakdown of neuropsychological functioning across the putative subgroups. It appears that a more complex right-left model than one simply involving a verbal/spatial dichotomy is in order.

Semantic Knowledge

In accordance with the above suggested subgroups of patients with respect to spatial processing, neuropsychological subgroups have also been searched for within the realm of semantic functioning. Studies conducted with this aim are particularly interesting, in that they reveal hints regarding the organization of stored knowledge within the brain.

Bandera and colleagues (1991) conducted an innovative study in this area. They tested mildly-moderately demented AD patients with a unique generative associative naming task, which represents a combined fluency/word association measure: the subject is presented with a stimulus word, and instructed to produce as many words as possible that are meaningfully related to it. They then proceeded to both quantitatively and qualitatively examine the responses in terms of the following parameters: adequacy, conventionality, word frequency, and lexical/semantic relation to the target (i.e., either propositional or hierarchical-categorical). Compared to controls, AD patients gave more idiosyncratic and fewer adequate responses, in addition to displaying a more perseverative response style. More interestingly however, within the AD group, 2 subgroups could be identified (representing the extremes of the bimodal hierarchical-categorical responses AD frequency distribution) which differed qualitatively on this measure, yet did not differ in regard to overall level of disease severity. Members of subgroup 1 produced low conventionality words, which were typically propositionally related to the target. Propositional responses refer to those which involve attributes or qualities of the stimulus word. On the other hand, members of subgroup 2 were conventional responders, and tended to give a high number of hierarchical-categorical associations (i.e., synonymous, antonymous, superordinate, subordinate or metonymical responses to the stimulus word). The authors suggest that each group differs with respect to their type of lexical-semantic impairment, suggesting that subgroup 1 members' typical production of unconventional, propositional responses may
represent disrupted access to a somewhat spared semantic network\textsuperscript{10}, while subgroup two represents patients demonstrating a breakdown of semantic knowledge (i.e., weaker lower-order propositional connections break down first, resulting in a greater frequency of hierarchical-categorical responses).

**Memory**

As demonstrated above, not only is it possible to broadly distinguish AD patients on the basis of differences in the relative preservation of domains of functioning, but qualitative differences between patients have also been identified within these individual domains. Becker (1988) proposed that working memory (i.e., primary memory capacity) and secondary memory (i.e., long term memory) are independent entities, and subsequently sought to dissociate these two types of memory, by demonstrating that they can be differentially affected in AD. Working memory impairments are thought by some to be related to disrupted functioning of a theoretical “Central Executive System” (CES), which results in disruption of divided attention, maintenance of information in primary memory, and the ability to retrieve information from semantic memory.

In this study, Becker (1988) considered reaction time, Digit Span, and Word Generation to Letter to be measures of working memory, or the integrity of the CES. Measures employed to tap the ability to maintain and consolidate information in secondary memory, and subsequently retrieve it, included Story Recall (similar to Logical Memory subtest of the WMS), a modified Rey-Osterrieth figure, and a Paired Associate Learning test (verbal pairs and face-name pairs). Seventy-one AD patients and 89 normal elderly controls were administered these measures. As is to be expected, the AD patients performed significantly poorer as a group on all measures compared to the normal controls. A principal components analysis was conducted on the patient data from the seven tests, yielding a two-component solution. As theorized, tests assessing secondary memory loaded

\textsuperscript{10} Assuming conventionality measures the strength of associative links between possible responses and the stimulus word, in semantic breakdown the spared associations would be the more conventional ones. Also, in semantic breakdown, propositional information is considered more vulnerable than hierarchical-categorical information. Thus, patients who characteristically offer low conventionality, propositional responses may be suffering from disrupted access to semantic knowledge, rather than a breakdown of semantic knowledge.
on component I, while those theorized as tapping CES dysfunction loaded on component II. Low correlations between the factors obtained, suggesting relative independence. Composite scores were then computed for these two types of memory for each individual. While the majority of patients evinced deficits in both areas, based on the two composite scores, Becker was able to identify two individuals whose scores differed by at least two standard deviations. One individual displayed marked impairment on the CES measures, with near normal performance on the secondary memory tests, while the other patient demonstrated the reverse pattern of performance. Becker speculates that secondary memory deficits may be the result of underlying hippocampal pathology, while CES/working memory dysfunction may be related to damage involving the projections from the nucleus basalis of Meynert to the frontal cortex.

Attention

Freed, Corkin, Growdon & Nissen (1988, 1989) also examined the memory functioning of AD patients in the hopes of identifying distinct subgroups. These researchers employed a picture recognition paradigm in the study of 20 mildly-severely demented AD patients and 20 age and education matched controls. The procedure involved 180 slides of pictures from 6 categories, 1/2 of which were utilized as targets, the other half of which were distractor slides. In the learning phase, patients viewed each target slide in succession for 4-16 seconds, while controls were exposed to each target for 1 second. This increase in exposure time for the AD cases was related to disease severity; the more severe cases required more exposure time to reach the same initial level of learning as the controls. By the end of the learning phase, patient and control performances were comparable. Recognition memory was assessed via a delayed-match-to-sample (DMS) paradigm at 10 minutes, 24 hours, and 72 hours after the end of the learning phase.

In addition to this procedure, all subjects were also administered a computerized attentional focusing test. This test involved 90 trials in which a “get ready” message first appeared on the screen, followed by a visual warning cue arrow which appeared on the centre of the screen. On a third of the trials, this cue arrow pointed right, on another third it pointed left, and on the remaining third of the trials the arrow pointed bidirectionally (i.e.,
double-headed arrow pointing both left and right). Following the warning cue, an "X" appeared either to the right or left of the arrow, and the subject was instructed to press a corresponding right or left response key, as soon as possible after the stimulus appeared. The subjects were informed that the appearance of a unidirectional arrow designated the correct location in which the X would subsequently appear most of the time, but when the bidirectional arrow appeared, the stimulus was equally likely to appear to its right or left. [Arrows were accurate (i.e., valid) in signalling the subsequent location of the stimulus 80% of the time]. Normal subjects benefit from the valid trials, demonstrating a positive value for the mean difference between invalid and valid cue trials.

The results of this study were quite interesting and unexpected. While the patients, as a group, performed worse than the controls on the picture recognition task 24 hours after learning, at the 72 hour testing, there was no difference in performance between the patient and control groups. This strange finding was due to the fact that 10 of the 20 AD patients demonstrated a rebound DMS performance at this time, while none of the controls displayed such aberrant performance improvements. Post hoc analyses revealed a significant relationship between this aberrant rebound effect on the recognition task, and abnormal performance on the attentional measure (i.e., a negative difference value between invalid and valid cue trials). The observation that only 50% of the AD patients displayed this unexpected performance, suggests the existence of subgroups of patients, with one subgroup characterized by selective attentional deficits.

Freed and colleagues (1989) looked to the experimental animal literature for an explanation of these unexpected observations. They cite a study by Rainbow & Flexner (1978) in which mice with neurochemical lesions of the noradrenergic system, displayed amnesia 24 hours after learning, but not at 72 hours post learning. Other reports demonstrate that rats with lesions of the dorsal bundle, the major efferent pathway of the locus ceruleus, display deficits in selective attention. Thus, there is a possibility that the "aberrant" subgroup of patients identified by Freed et al. may represent a group of patients with more extensive damage to the locus ceruleus. This is a well-grounded speculation, given the earlier mentioned morphological subgrouping of AD patients on the basis of reductions in locus ceruleus cell counts (Bondareff et al., 1987; Bondareff, 1991).
Due to the post-hoc nature of their results, Freed and colleagues (1989) proceeded to replicate their original study on a new sample, employing a slightly modified procedure. In this study, the recognition task included a delayed-non-matching-to-sample paradigm (DNMS)\textsuperscript{11}. They hypothesized that the DMS rebound effect observed earlier was attributable to an attentional disorder rather than a "spontaneously clearing amnesia", on the basis of the relevant animal research mentioned above. In accordance with this, they reasoned that in a subgroup of patients, DNMS would improve at the 24 hour post-learning period, while DMS performance would decline; if the DMS rebound effect observed earlier was due to an increased response to novel stimuli 24 hours post learning, DNMS recognition performance at this time should improve. If on the other hand the rebound effect is attributable to a spontaneously remitting amnesia, both DMS and DNMS performance should be reduced 24 hours after learning.

Again, the results indicated that 10 of the 20 AD patients displayed a rebound effect in their DMS recognition performance. Furthermore, the significant relationship between aberrant picture-recognition and reaction time performance found in the earlier study was replicated on this new sample, and the selective visual attention hypothesis was supported (i.e., DNMS performance improved at the 24 hr. post-learning test session). Moreover, the subgroup of patients with the apparent attentional difficulty, were later found to have significantly reduced levels of MHPG (a metabolite of noradrenaline) when cerebrospinal fluid analyses were conducted. The subgroups did not differ with respect to dementia severity as measured by the Blessed Dementia Scale, suggesting that the attentional subgroup was not a product of increased disease severity in terms of functional deficits\textsuperscript{12}, but rather of more severe compromise of the noradrenergic system. Again, these results are strongly supported by the earlier discussed reports of morphological subgroups based on cell reduction in the locus ceruleus.

\textsuperscript{11} In a DNMS recognition paradigm, the subject is presented with 2 slides and asked to point out which picture is new (i.e., not previously seen) rather than which picture is old (i.e., previously seen), as in DMS.

\textsuperscript{12} The Blessed Scale measures changes in self care, activities of daily living, and personality functioning (Blessed, Tomlinson & Roth, 1968).
A Study Demonstrating Regression to an Earlier Time

Hom (1992) administered the Halstead-Reitan Battery and other measures to 35 early AD patients (Global Deterioration Scale=4-5) and 30 medically normal age and education matched controls in an attempt to demonstrate widespread neuropsychological impairment amongst AD patients. He hypothesized that AD patients in the early stages of the disease would demonstrate both general (i.e., independent of location of brain impairment) and specific neuropsychological impairment, with a sparing only of motor and sensory functioning. As hypothesized, (and quite unsurprisingly), the results of the assessments indicated that the AD patients performed significantly poorer than controls in all neuropsychological domains, save for those of motor and sensory functioning.

On the basis of these results, Hom suggests that this neuropsychological pattern of impairment be utilized by all as an indicator of early AD. More disturbingly, he subsequently dismisses the subgroup issue, suggesting that all AD patients show the pattern he obtained, and criticizing the work of Martin et al. (1986) and others for their utilization of limited test protocols. There is a direct implication in his writing, that Hom (1992) believes that if more comprehensive measures were utilized by Martin et al. (1986), subgroups would not have emerged. Hom is unaware of the inherent weakness of his group comparison approach, and it is difficult to give him credit for much more than a brief scan of the ingenious arguments and research of Martin and colleagues. Martin and coworkers clearly demonstrated a double dissociation of function amongst AD patients, suggesting the separation of semantic and visual-perceptual systems. The study by Hom (1992) is reminiscent of the “old-school” approach, and it’s recency demonstrates that the stage-subgroup debate continues to be alive and well.

Material Specific Memory Loss?

Questions regarding the order by which cognitive systems breakdown in AD are recently being posed more and more frequently in the literature. The putative existence of qualitatively distinct neuropsychological subgroups suggests distinct patterns of breakdown corresponding to these groupings. The notion of relative sparing of certain domains of functioning in particular subgroups of early AD patients, raises several interesting
questions. Namely, should such groups of AD patients show material specific memory loss (i.e., preserved memory for material in the domain of functioning which remains relatively normal)? Moreover, if material specific memory loss is shown to occur amongst these individuals, is it secondary to primary visual-perceptual or semantic impairment? Or, is it a primary phenomenon (i.e., memory deficit) which in turn leads to impaired cognitive functioning in the respective neuropsychological domain?

It has been suggested that specific cognitive dysfunction may precede memory/learning deficits (i.e., the consolidation of new material) (Martin et al., 1985). For example, patients with predominant word finding difficulty may be in the process of undergoing a breakdown of semantic knowledge (impairment in lexical/semantic storage and retrieval), which results in reduced encoding ability specific to verbal information, ultimately manifesting as impaired recall of newly learned verbal information. By the same token, impairments in non-verbal recall may be secondary to visual-perceptual or constructional deficits. Thus, according to this theory, specific cognitive deficits limit analysis of similar material, and this results in reduced learning and encoding ability, which manifests as a material specific recall impairment (Martin et al., 1985). Such encoding impairment would appear to implicate specific cortical systems (Martin et al., 1985).

Another possibility is of course, that medial temporal memory systems breakdown asymmetrically, resulting in poor recall (i.e., consolidation) of information within a specific domain of functioning, in the face of relatively preserved pure neuropsychological functioning (i.e., encoding).

Very few researchers have ventured to investigate the issue of material specific memory loss in AD subgroups. The research of Martin and colleagues (1985) suggests that material specific memory deficits corresponding to neuropsychological subgroups may appear in some patients. They report on a subgroup of patients (n=9) presenting with severely impaired naming ability and verbal fluency, in the face of normal visual-perceptual and visual-constructive skills. When formal memory testing was undertaken, 4 of these patients demonstrated global memory impairments (i.e., severe impairment on Logical Memory subtest of Wechsler Memory Scale and Rey-Osterrieth Complex Figure). The remaining 5 patients scored within the normal range on the Rey-Osterrieth, while
demonstrating impairment on the Logical Memory subtest of the Wechsler Memory Scale (i.e., demonstrated a material-specific verbal memory deficit). When retested 1-2 years later, 4 of these 5 patients demonstrated memory impairments in both verbal and non-verbal domains. However, this change occurred while visual-constructional skill (i.e., Rey-Osterrieth-copy) remained within the normal range of functioning. The authors suggest that poor recall may occur before decline in the corresponding domain of functioning. This may reflect adequate encoding in the face of difficulties in retaining and/or retrieving information. This inability to retain or consolidate information would appear to implicate the amygdala/hippocampus as the initial source of impairment of episodic memory.

Becker, Lopez and Wess (1992) have supported and extended the work of Martin (1985). These researchers sought to confirm the presence of material specific memory loss in a subgroup of AD patients, and determine whether such deficits are secondary to primary visual-perceptual/constructional or semantic impairment. Neuropsychological tests assessing memory (modified Rey-Osterrieth, Logical Memory), visuospatial functioning, lexical/semantic abilities, and executive functioning were given to 191 early AD patients. Subsequently, the patients were classified according to their pattern of memory performance: those performing within normal limits on both memory measures, those with impaired verbal memory but normal non-verbal memory, those with impaired non-verbal memory but normal verbal memory, and those with global memory impairment. Twenty-five patients (13% of the sample) were identified as having material specific episodic memory loss: 13 patients demonstrated impairment on the verbal memory measures in the face of normal performance on the non-verbal memory tests, and 12 showed the reverse pattern. Thus, the results of Martin et al. (1985) were successfully replicated on a larger sample.

Becker and colleagues (1992) next sought to determine whether or not these groups classified according to material specific memory loss differed with respect to their performances on the remaining neuropsychological measures. Of interest here, lexical/semantic and visual-perceptual/constructional composite scores were formulated for all subjects, and comparisons were then made between the four different memory classified groups. Interestingly, selectively impaired non-verbal recall was not significantly
associated with visual-perceptual or visual-constructional deficits. Similarly, focal impairment of verbal memory was not significantly associated with performance on the semantic/lexical measures. Thus, material specific memory impairment was independent of impairment in particular domains of neuropsychological functioning (i.e., semantic, visual-perceptual/constructional), suggesting that such impairments were not primary factors responsible for disrupting performance on the memory measures.

Finally, Becker and colleagues (1992) conducted follow up assessments one year later on 94 of the patients (the remaining patients could not provide enough data to be adequately classified according to pattern of memory loss). Of interest, those originally focal patients in which the disease was thought to have progressed (on the basis of further reductions in mental status exam scores), demonstrated equivalent impairment in both verbal and non-verbal memory at the follow up assessment. Conversely, patients whose mental status exam scores remained the same, also retained the original material specific memory loss pattern.

In accordance with the results of Martin et al. (1985) this study implicates selective primary memory impairment in subgroups of AD patients, rather than impaired recall secondary to associated specific neuropsychological dysfunction. Thus, deterioration of memory seems to occur independently of other neuropsychological functions; other neuropsychological deficits are likely involved, but are not solely responsible. The results of both studies suggest a pattern of dysfunction in AD beginning at the level of medial temporal systems. Furthermore, the longitudinal nature of these investigations suggests an eventual spread of disease to contralateral medial temporal regions, likely prior to encompassing contralateral cortical regions. The asymmetrical memory loss noted by both Martin et al. (1985) and Becker et al. (1992), is supported by autopsy research reporting asymmetrical distributions of tangles, acetylcholine receptors, and acetyltransferase activity in the hippocampi of AD brains (Moossy et al., 1988; Zubenko et al., 1988).

**Integrative Summary and Critique**

It is apparent from the above review that the original conceptualization of AD as a homogeneous neuropsychological entity is in the process of undergoing a change; this is
evidenced by the research avenues pursued over the past ten years. The landmark research of Martin and his colleagues (1986), demonstrating a double dissociation of function between semantic knowledge and visual-constructional systems amongst AD patients, and the subsequent demonstration that corresponding inter-hemispheric asymmetrical metabolic dysfunction was associated with these neuropsychological subgroupings, strongly suggested a right-left factor contributing to heterogeneous neuropsychological presentations. This research implied that while some AD patients undergo a more or less homogeneous dissolution of neuropsychological functions (and thus conform to the classical stage model of AD), presumably reflecting underlying symmetrical neuropathology, qualitatively distinct subgroups of patients with pronounced deficits in one area of functioning, and relatively spared abilities in the other, could be identified, and these subgroups purportedly reflect asymmetrical neuropathology in the early stages of the disease. Becker and colleagues' (1988) partial replication added weight to these findings, although a large scale clustering replication has yet to be conducted. The putative existence of AD subgroups raises the possibility of material-specific memory loss involving the area of pronounced deficit; while this has been suggested to be the case by Martin et al. (1985) and Becker et al. (1992), this too has yet to be replicated within the context of a large scale clustering study.

Later studies, accepting the work of Martin and colleagues, investigated dissociations within the domains of semantic and spatial processing, revealing that the primitive verbal (left) - spatial (right) models of hemispheric specialization could not successfully be utilized in a neuropsychological model of AD. Furthermore, research investigating attentional and memory processing suggested that even a right-left model may be too limited for certain subgroups of AD patients.

Although Hom (1992) is to be commended for utilizing a comprehensive battery approach, and dispelling erroneous beliefs regarding early AD as merely involving memory impairment, he can be criticized with equal weight for his group comparison design, which in effect, precludes the possibility of identifying subgroups, and was anything but theoretically driven. His criticisms of Martin et al. (1986) and others, though important (i.e., subgrouping studies utilizing more comprehensive batteries should be conducted), are
not sufficient to render unwarranted investigations aimed at identifying neuropsychological subgroupings. Hom demonstrates his misunderstanding of the subgroup issue by employing a group comparison design. How much more interesting his results would have been had he made intra-AD comparisons.

**Towards a Neuropsychological Model of AD**

It may be helpful at this point to document what the literature suggests may be the state of affairs for the two subgroups of AD identified by Martin and colleagues (1986). First of all, we must look at the two groups of intra-correlated measures, and theorize about the respective systems they are tapping, in addition to their underlying neuroanatomical correlates. For the sake of simplicity, let’s refer to the subgroup of patients who performed poorly on the Verbal Fluency Test, Boston Naming Test, and Easy Paired Associates, as the “left” AD (LAD) group; and the subgroup who performed relatively well on these measures, but poorly on Block Design, the Mosaic Comparison Test\(^{13}\), and the Rey-Osterrieth Complex Figure Test, as the “right” AD (RAD) group\(^{14}\). It might be well to mention before proceeding that the deficits of RAD and LAD on the above described measures cannot be explained in terms of “spatial” and “verbal” memory loss (i.e., in terms of medial temporal lobe damage); patients with medial temporal lobe amnesia have no difficulty with tasks such as object naming and block design (Martin, 1992).

**RAD:** The PET studies reviewed earlier suggest that this group of AD patients evinces relatively focal right temporal-parietal involvement. The tests these patients performed poorly on all require adequate visual-perceptual-spatial integration, suggesting this is the area of dysfunction amongst RAD patients. However, recall the studies of Delis and colleagues (1992; 1993) in which a comparable group of patients could process local

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\(^{13}\) This test consists of a series of complex designs, which are displayed on a matrix partitioned by three columns and three rows. Each test item includes a master pattern and a test stimulus that differ only by a single block. The examinee is required to identify the column in which the master and test figure differ (Brouwers, Cox, Martin, Chase & Fedio, 1984).

\(^{14}\) These hypothetical “ideal types” are explicitly labelled, described, and theorized about following the suggestion of Morris & Flescher (1988). These authors point out that such formulation of a hypothetical classification enables one to predict subgroup differences, and test such predictions in the external validity component of classification studies.
forms, but had major difficulties dealing with global configurations. Knowledgeable of these results, we cannot conclude that the area of difficulty for this group can be accounted for solely in terms of a verbal-spatial dichotomy; RAD-like patients were able to perform a particular sort of spatial processing. Furthermore, case studies reported by Martin (1987) of individual members from this subgroup suggest that visual-spatial processing and construction for overlearned, familiar and meaningful stimuli, is preserved in this group of patients. It is only when the stimuli are complex and unfamiliar that these patients encounter difficulty (perhaps because in such a situation they cannot rely on their relatively intact left hemisphere systems).

**LAD:** The PET studies reviewed earlier suggest that this group of AD patients evinces relatively focal left temporal-parietal involvement. We cannot attribute their difficulties on the BNT to general visual difficulties (as some authors do) because they performed adequately on the 3 non-verbal measures, which rely heavily on visual perception. The difficulties of these patients would appear to lie within the realm of automatic/rote retrieval. One question that must be answered in this regard is --does the impairment on the “verbal” measures indeed represent impaired access to semantic knowledge (i.e., a retrieval problem)? Or, does it reflect a loss of the neural representations of stored knowledge? There is some indication that the latter may be the case.

Error analysis of performances on the BNT reveals that AD patients are apt to make semantic errors. In this way, their object naming errors consist mainly of the names of objects from the same semantic category as that of the item presented (e.g., socket for plug), or of the name of the category to which the object belongs (e.g., bird for pelican) (Martin, 1992). These types of errors differ markedly from those of frontal lobe patients (i.e., with damage to Broca's area), who tend to perseverate, and do not generate many semantic errors (see Martin, 1987). Further, on fluency tests, AD patients tend to perform worse on the semantic category trial (i.e., when asked to name as many types of animals as possible), than they do on the letter trials (e.g., when asked to name as many words as possible that begin with the letter “C”), although they perform poorly on both (Butters, Granholm, Salmon, Grant & Wolfe, 1987). This is interesting, because normal individuals
typically perform exceedingly better on the category trial. This suggests that AD patients have difficulty generating lists of items within one category.

Martin (1987) provides evidence for this breakdown of semantic knowledge, which is theorized to progress hierarchically from loss of specific object attributes or examples, to disruption of specific categories, and then finally to higher order superordinate categories. He suggests that knowledge is mapped along the temporal lobe in a posterior-anterior gradient, with specific attributes (i.e., lower levels of hierarchical knowledge representations) represented most posteriorly, and successively more general levels represented anteriorly. Disease progression proceeding in a posterior to anterior fashion would thus destroy the lower levels of the hierarchy first, resulting in the types of qualitative errors observed amongst early AD patients on measures of semantic knowledge. This explanation corresponds nicely with the work of Delis et al. (1992, 1993), which suggests that not all visual-spatial functioning is preserved in this group of patients. Recall that a grossly comparable group of patients had difficulty with local stimulus processing. Thus, there is a suggestion that in LAD, general global processing (i.e., higher order), is relatively better preserved, than local, detail processing. Could it perhaps be that rather than knowledge being mapped in the temporal lobe from specific (posterior), to general (anterior), it is mapped from right to left (i.e., with higher order, more general abstractions represented in the right hemisphere, or requiring the integrity of right hemisphere systems for their access)? This explanation would also seem to explain the deficits and types of errors made by LAD patients.

The Goldberg-Costa Model and the White Matter Connection

Goldberg and Costa (1981) introduced a model of hemispheric specialization based on neuroanatomical distinctions between the cerebral hemispheres. They noticed that the right hemisphere is more diffusely organized than the left, has a lower grey to white matter ratio (i.e., implying more long myelinated fibres), and has a greater representation of the association areas. On the other hand, the left hemisphere is more focally organized; distinct modality specific cortical areas are more prominent. Following the suggestion of Gur and colleagues (1980), Goldberg and Costa interpreted the grey to white ratio as a marker of
structural organization with respect to intra- versus interregional integration. As such, they theorized that the structural organization and patterns of connectivity in the right hemisphere make it more organized for interregional integration, while the neuroanatomical structure and connectivity of the left hemisphere make it more suitable for intraregional integration.

On the basis of these structural asymmetries, Goldberg and Costa hypothesized that the right hemisphere has a greater capacity to deal with complex information (i.e., due to its greater representation of association areas), and also has the capability to process several modes of representation within a single cognitive task (i.e., due to its interregional connectivity). One implication of this is that the right hemisphere has a greater ability to process novel stimuli for which the individual has no pre-existing code or descriptive system (i.e., for which the individual does not have rules or codes to routinely apply). On the other hand, it was theorized that the left hemisphere would function more effectively on tasks requiring the utilization of a single mode of processing, due to its greater representation of unimodal sensory and motor areas and intramodal connectivity, and was particularly suited for the stereotypic application and storage of codes or descriptive systems that have already been learned.

The neuropsychological patterns of RAD and LAD can readily be interpreted, in terms of this model, as breakdowns of the respective hemispheres (initially in relative isolation). Members of the LAD group are not able to access their descriptive systems effectively, as they are in the process of disorganizing, or breaking down. Thus, overlearned material is gradually being lost, depending on the strength of the associations, with weaker associations (assuming less redundancy or compensatory systems) most vulnerable. This is likely the result of the degeneration of left hemisphere grey matter. I propose that they have a tendency to give semantic errors on verbal tests because general, higher levels of the hierarchy of knowledge representation within the right hemisphere (or activated by the right hemisphere) are functioning adequately; but they are unsuccessful in searching down a hierarchy, due to impaired left hemisphere systems, which deal with these specifics or attributes. These patients will be able to perform tasks which do not rely on previously learned descriptive systems, depending on their level of attention and severity of memory deficits. The deficits of the RAD group are best explained in terms of
the breakdown of the essential white matter patterns of connectivity in the posterior right hemisphere.

The designation of AD as a "cortical" dementia is erroneous on several grounds. It is now known that several subcortical structures are involved (e.g., nucleus basalis of Meynert, locus ceruleus, raphe nucleus) to varying degrees in AD (Bondareff et al., 1987; Mann & Esiri, 1988). More interestingly, several investigators have reported white matter degeneration in AD brains (Brun & Englund, 1986; Gottfries et al., 1986). Indeed, a recent report suggests that white matter lesions are common in patients with AD, even when great effort is expended in ensuring those with vascular risk factors, cerebrovascular and cardiovascular disease are specifically excluded (Bennett, Gilley, Wilson, Huckman & Fox, 1992). Bennett and colleagues (1992) noted the white matter lesions appear most commonly in the centrum semiovale and other subcortical regions surrounding this centre. Disruption of this area is of great significance, as this mass of white matter contains commissural, association, and projection fibres (Carpenter, 1991).

The neuropathology of AD tends to target populations of projection neurons important for feedback/feedforward projections amongst the limbic system and association cortices, resulting in disconnections (Hyman et al., 1993). For example, the entorhinal cortex receives projections from the association cortices, and passes this information on to the hippocampus via the perforant pathway, and as such, is the major afferent link between the multimodal association areas and the hippocampus. During the course of AD, the entorhinal cortex is particularly hard hit by tangles (Hyman et al., 1993), and this eventually destroys the perforant pathway, isolating the hippocampus from the cortex. Similarly, the CA1 zones and subiculum, which give rise to the major efferent pathways of the hippocampal formation, are also the targets of massive AD neuropathology (Hyman et al., 1984). Thus, the high densities of tangles in the afferent neurons of the entorhinal cortex, and the efferent neurons of the subiculum and CA1 zone serve to functionally disconnect the hippocampus from the rest of the cerebral cortex.

Of greater import to this thesis, is the other major area of the brain severely affected by the neuropathology of AD, the multimodal association cortex. This area is highly prone to neurofibrillary generation and neuritic plaques. In particular, the large pyramidal
interassociational neurons of layers III, V, and VI are the primary recipients of damage (Chang Chui, 1989; Lewis, Campbell & Terry, 1987). This is of significance because it is the long axons of these neurons which form cortico-cortical connections. Given that these are the pivotal layers for cortico-cortical projections, some authors have suggested that, just as the pathology in the entorhinal cortex and subiculum disrupts the input and output of the hippocampus, pathology in layers III, V, and VI of the association cortices disrupts the input and output of each area (i.e., the feedforward and feedback projections that conjoin cortical areas of different hierarchies) (Damasio, Van Hoesen & Hyman, 1990). Thus, it is argued that the association cortex becomes functionally disconnected. The parietal association cortex is the major posterior multimodal association area. Reductions in input to this area from unimodal association regions may account for the deficits observed in RAD.

Possible Neuroanatomical Routes of Degeneration

Little is directly known regarding the evolution and progression of AD with respect to underlying loci of pathology (Mann & Esiri, 1988; Martin, 1990), and this issue becomes even more complex when clinical subgroups are considered. It is known from autopsy studies, for example, that certain brain regions are affected more than others, and that the neuropathology is generally symmetrical (Moossy et al., 1988; Zubenko et al., 1988). However, we must remember that these brains represent the end stage of the disease, when global neuropsychological decline is evident in all cases, and hence do not provide any concrete evidence regarding the early distribution of neuropathology. Interestingly, although symmetry of pathology at autopsy seems to be the rule in AD, in a small percentage of AD brains, significant left-right asymmetries in the numbers of plaques, tangles, and cholinergic enzymes in homologous brain regions have recently been observed (Moossy et al., 1988; Moossy, Zubenko, Martinez, Rao, Kopp & Hanin, 1989), although the clinical correlates of these asymmetries have not yet been studied. Another intriguing finding is that this right-left asymmetry in the density of plaques (though not tangles) appears to diminish with increasing neuropathological severity (Moossy et al., 1989). This suggests that right-left asymmetry decreases as the disease progresses, so that by the time of death the neuropathology is more or less symmetrical. This author could not
locate any autopsy studies which involved early AD brains (i.e., of patients dying of other, non-neurological causes), which is the precise type of evidence needed for a true understanding of the progression of AD. In the absence of such information, there is a need to put forth hypotheses regarding the course of pathologic changes, both on the basis of end stage pathology, serial longitudinal neuroimaging, and comprehensive clinical history. Such a task necessarily involves an interdisciplinary approach seeking answers to the following questions: Does the brain invariably become affected in the susceptible areas simultaneously? Or, can distinct patterns of progression be delineated? If so, how do these patterns correspond to different neuropsychological subgroups of patients?

The neuropsychological literature provides some clues regarding the above questions. Much of the literature suggests memory impairment as the most pronounced and initially appearing symptom in AD (Damasio et al., 1990; Grady et al., 1988; Price et al., 1993; Welsh, Butters, Hughes, Mohs & Heyman, 1992). In addition, the studies investigating material specific memory loss reviewed earlier, suggest that memory impairment precedes other neuropsychological dysfunction (Becker et al., 1992; Martin et al., 1985). Based on the literature, it seems reasonable to assume that this impairment reflects underlying pathology in the region of the hippocampus and amygdala (Hyman, Van Hoesen, Damasio & Barnes, 1984; Milner, Corkin & Teuber, 1968; Mishkin, 1978; Van Hoesen & Damasio, 1987). Mann and Esiri (1988) mention that these areas may be at high risk due to their connections with the olfactory bulb, which has been proposed as a point of entry for an AD pathogen. Martin (1990) provides the following supporting evidence for the hippocampus/amygdala as the initial locus of pathology in AD: (1) autopsy evidence of severe and perhaps universal involvement of this region; (2) the established role of these structures in learning and memory; (3) reports of isolated amnestic impairment in biopsy-proved cases of AD (e.g., Neary et al., 1986).

Further evidence supporting the amygdala/hippocampus as the initial locus of pathology in AD is provided by autopsy studies of the brains of Down’s syndrome patients who die before 50 years of age. It is well known that individuals with Down’s syndrome who live past the age of 50 years have comparable distributions and quantities of plaques and tangles in their brains to those observed in AD (Whalley, 1982; Wisniewski,
Wisniewski & Wen, 1985). However, those with Down’s syndrome who die at 20 years of age or younger, rarely have any plaques and tangles at all (Mann & Esiri, 1988; Whalley, 1982). Thus, between the approximate ages of 20 and 50, the changes which occur in Down’s syndrome brains can be viewed as a pathological model of AD pathogenesis and progression (Mann & Esiri, 1988). In line with this reasoning, Mann and Esiri (1988) performed autopsies on nine patients with Down’s syndrome who died before age 50 (ages 13-49), in order to investigate the topographic distribution of plaque and tangle formation corresponding to the different evolutionary periods. Three groups of patients were identified (ages in parentheses): (1) those with no plaques or tangles anywhere in the brain (13, 31), (2) those with numerous plaques and tangles present in a distribution similar to that of AD brains (42, 48), and most interestingly, (3) those with an “intermediate” pathological picture, in which “mature” plaques were observed in the amygdala-hippocampal region, and “primitive” plaques were seen in the neocortex (37, 40, 42, 43, 49). The tangles in group 3 brains were most heavily concentrated in layer II of the entorhinal cortex. This research suggests that initial plaque and tangle formation arises in the area of the hippocampus and amygdala, and then spreads to other areas (i.e., neocortex, nucleus basalis, locus ceruleus).

Martin (1990) speculates that from the medial temporal region, the disease progresses to the posterior temporal and parietal cortex, and then proceeds in a posterior to anterior fashion, eventually reaching the frontal cortex and then also the subcortical nuclei (e.g., basalis, locus ceruleus, raphe). These formulations are certainly consistent with the PET studies reviewed earlier, in addition to autopsy studies reporting that the frontal cortex is affected to a much lesser extent than the other regions (Brun & Englund, 1986). The neuroimaging studies reviewed earlier suggest that parietal and temporal regions are more heavily affected early in the disease, and that frontal involvement is associated positively with disease severity. These studies, coupled by reports that motor signs appear late in the course of the disease in most cases (Cummings & Benson, 1992), suggests that the frontal cortex does not become sufficiently involved until late in the disease. Thus, as Martin

15 Mature plaques refer to those with a well-defined amyloid core surrounded by several dystrophic neurons, while primitive plaques consist of only a few neurites with an ill-defined amyloid core (Mann & Esiri, 1988).
(1990) suggests, a posterior to anterior pattern of progression appears to be a reasonable speculation.

It next behooves us to theorize about RAD and LAD. Martin (1990) suggests that perhaps the disease initially invades the medial temporal region asymmetrically in some individuals, and continues to proceed in an asymmetrical fashion initially (see Figure 3). The questions next become: When does this asymmetry begin (i.e., at what level)? How long does it persist? Why would some individuals be relatively spared from pathology on one side of the brain?

Although granted, I do not believe it is within the realm of neuropsychology to figure out the answer to question 3. I propose the following hypothetical explanations to questions 1 and 2. It has been mentioned by others that AD appears to carve out functional systems (Duyckaerts, Delaere & Hauw, 1992). In this manner, plaques and tangles appear to accumulate in certain regions, before spreading to others. Duyckaerts et al. (1992), suggest that plaques and tangles are not mere representations of neural degeneration, but that they play active roles in attracting healthy cells and destroying them, thereby creating destruction systematically, within neural networks. These authors believe that AD is not a random process of neurodegeneration, but follows discrete neuroanatomical boundaries. Thus, it can be inferred from their theory, that the location in which AD pathology initially begins will have important localizing behavioural sequelae, and patterns of progression of these sequelae, thus producing the functional heterogeneity of early AD. In line with this reasoning, I propose the following16:

(1) Typical AD: In most cases of AD, the original locus of pathology arises in the central region of the hippocampal formation. It then spreads out bilaterally, encompassing two putatively distinct functional systems of the hippocampal formation: one left, and one right. Thus, in these global AD cases, anterograde memory loss will be general (i.e., there will be no evidence of material specific impairment). From here, the pathology progresses systematically, concentrating in this region, particularly the entorhinal cortex, until it reaches connections to the association cortices, eventually spreading to posterior temporal

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16 Many of these formulations were inspired by the speculations of Martin (1990).
PATHWAYS OF NEUROPATHOLOGICAL PROGRESSION OF AD*

[Based in part on the speculations of Martin (1990)]

Figure 3. (1) In this model, the amygdala and hippocampus are the initial loci of pathology. This is consistent with memory deficits and affective-personality disturbance (amygdala) presenting as early symptoms. In the typical patient, the disease progresses to the posterior temporal and parietal regions, resulting in a more or less homogeneous set of verbal and visual-perceptual deficits (2). From here the disease spreads in a posterior to anterior fashion, eventually reaching the frontal lobes and subcortical nuclei (e.g., nucleus basalis, locus ceruleus) (3). In subtype B, the amygdala and hippocampus are not affected bilaterally to the same extent, with more left sided pathology in evidence. In subtype C, the right side is more severely affected. Asymmetrical degree of involvement continues, but otherwise, as described for A, proceeds in a posterior to anterior fashion. [**Note: 1 should realistically be placed between and below 2 and 3.**]

This hypothetical model raises several important questions. (1) Does the asymmetrical neuropathology in B and C begin at the amygdala/hippocampus, or at the temporal/parietal level? If the former is true, one would expect material specific memory loss; while if the latter were the case, global memory impairment would be evident, in the presence of preserved pure visual-perceptual or semantic ability unrelated to intact limbic (i.e., medial temporal) memory systems. (2) Does the disease spread anteriorly and to the contralateral hemisphere simultaneously? Or, does it rapidly encompass one hemisphere before spreading extensively in the other (i.e., posterior → anterior → contralateral → posterior)?
and parietal regions as Martin (1990) suggests. At the same time, the pathology spreads from the hippocampal formation to the basal forebrain. From here, it destroys projections to the pre-frontal lobe. This explains why the pre-central and post-central gyri are spared until the very late stages of the disease.

(2) \textit{RAD}: In RAD, the hippocampus/amygdala is also the origin of pathology. However, the pathology arises not medially, but laterally to the right. Thus, the putative right functional memory system is carved out first, resulting in material specific memory loss for complex spatial information. Several studies have demonstrated the role of the right hippocampus in tactile and visually-based learning tasks involving spatial information and orientation, and it has been reported that the greater the removal of tissue from this area, the greater the memory impairment (Corkin, 1965; Milner, 1965; Smith & Milner, 1981). This direct relationship between cell loss and increasing deficit would appear to explain the progressive nature of the memory impairment in AD. While proceeding to the temporal and parietal association cortices, the disease spreads also to the contralateral hippocampus/amygdala. From the contralateral hippocampus/amygdala, the disease spreads to the parietal and temporal cortices on this side as well. Thus, in RAD, the general pattern of neuropsychological deficits should be: material specific memory loss (spatial), followed by spatial deficits, followed by global memory impairment, followed by global cortical deficits (i.e., both visual-spatial, and semantic, but more severe visual-spatial). This is consistent with the material specific memory loss research of Martin et al. (1985) and Becker et al. (1992). From here the disease progresses in the typical pattern outlined in (1).

(3) \textit{LAD}: The opposite pattern of RAD (see above). The role of the left hippocampus in verbal learning of a rote nature (e.g., recall of word lists) has been demonstrated, and as with the right hippocampus, there seems to be a direct relationship between amount of hippocampus removed, and the extent of memory impairment (Petrides & Milner, 1982).

(4) Nucleus Locus Ceruleus AD (\textit{NLCAD}): One could also speculate regarding the sequence of pathology for a subgroup of AD patients with pronounced attentional
difficulties. For example, in the nucleus locus ceruleus variety of AD, pathology may begin at this level, possibly via spinal fluid entry of the pathogen. The pathology may then progress upward to the central hippocampal/amygdala complex and follow the same pattern of (1) above. The possible existence of a NLCAD subgroup will not be explored in this thesis.

Admittedly, these are rough formulations; they are, however, testable.

**Purpose of Present Study**

The work of Martin and colleagues (1986), although commendable, is limited by the small sample size utilized and the failure of the authors to replicate their results across cluster analytic methods (i.e., evaluate the reliability of their results). The partial replication of Becker and his colleagues (1988) adds weight to the work of Martin et al., but did not employ cluster analytic techniques. The primary goal of the current research project was to replicate the findings of Martin et al. (1984, 1986, 1990) on a larger sample, utilizing comparable neuropsychological test results from the University of Michigan’s Alzheimer’s research database. It was predicted that the current similar investigation will support the results of these researchers on a larger scale. Namely, 3 subgroups will be identified: (1) those with relatively equal impairments in both (a) accessing semantic knowledge, and (b) visual-spatial functioning; (2) those with relatively intact ability to access semantic knowledge but impaired visual-spatial skills; and (3) those with impaired accessibility to semantic knowledge accompanied by relatively normal visual-spatial functioning.

A secondary goal of the present research involves model building. Drawing heavily on the “minimal model” and speculations offered by Martin (1990), in addition to the available neuropsychological and neurological literature, I have created a testable model outlining potential pathways of AD progression corresponding to distinct neuropsychological profiles. This model predicts that material specific memory loss in subgroups 2 and 3 will only be present in the early period of the disease. Primary motor deficits will not appear until the later stages of the disease, and should to some degree be reflective of subgroup membership.
Hypotheses

1. Principal components analysis will produce 2 factors, when semantic knowledge and visual spatial measures are included in this procedure: the visual spatial measures (i.e., Block Design, Figure-Ground, Copy task) will load highly on Factor I, while the semantic knowledge measures (i.e., BNT, Verbal Fluency, Easy Paired Associates) will have negligible loadings on this factor. Factor II will be characterized by the reverse pattern (i.e., high loadings for verbal measures, low loadings for non-verbal measures). This 2 factor solution will account for a substantial proportion of the variance, estimated at approximately 70%.

2. When the individual patient T-scores on the neuropsychological measures of interest are subjected to Q-type factor analysis and various cluster analytic techniques, 3 subgroups are predicted to emerge. Subgroup 1 will be comprised of individuals displaying relatively equal neuropsychological impairment in both domains of functioning. Subgroup 2 will comprise patients exhibiting relatively intact visual-spatial functioning, coupled by impaired semantic abilities. Subgroup 3 will comprise those individuals with relatively normal access to semantic knowledge, in the face of impaired visual-spatial abilities. Subgroup 1 will comprise the majority of individuals, with the other two subgroups roughly equally represented by the remainder of the patients. Secondary severity groupings will be apparent in all three subgroups, when a priori criteria are utilized in their determination. However, subgroups 2 and 3 will contain less severely impaired patients than subgroup 1.

3. All subjects will show deficits on the memory measures. However, subgroups 2 and 3 will evidence relatively greater impairment in the domain maximally impaired. In this way, subgroup 2 will be relatively more impaired on a measure of verbal memory (i.e., Logical Memory subtest of WMS), compared to their performance on a task of visual-spatial memory (i.e., Visual Reproduction subtest of WMS). Subgroup 3 will demonstrate the reverse pattern.
4. Correlations calculated between motor impairment and disease severity will be positive, regardless of subgroup membership. However, lateralized differences for subgroups 2 and 3 will be apparent, in addition to being consistent with neuropsychological profiles, and putative underlying neuropathology.

5. Lastly, in accordance with the Goldberg-Costa model of hemispheric specialization, those with the RAD pattern will evince lower PIQ compared to VIQ, while those with the LAD pattern will demonstrate the reverse pattern of performance on the Wechsler Adult Intelligence Scale -- Revised (WAIS-R) (i.e., VIQ<PIQ).
CHAPTER III
METHODOLOGY

Subjects

Data from 134 patients (57 males, 77 females) diagnosed with probable AD (McKhann et al., 1984), housed in the University of Michigan's Alzheimer's Disease Research Databank, were utilized in the current investigation. These patients were selected from a larger group of more than 3000 individuals, referred to the University of Michigan Medical Center (Neurology Clinics, Psychiatry Department, or Neuropsychology Program) or the Michigan Dementia Program, for inpatient/outpatient consultation regarding suspected dementia. This referral area has a population of over 10 million, spanning the entire state of Michigan, in addition to northwestern Ohio and northeastern Indiana. All patients met the following criteria for inclusion, as established by the NINCDS-ADRDA Work Group, and outlined by McKhann et al. (1984):

(1) Alzheimer's dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests:

(2) deficits in two or more areas of cognition:

(3) progressive worsening of memory and other cognitive functions:

(4) no disturbance of consciousness:

(5) onset between ages 40 and 90, most often after age 65; and

(6) absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

All patients in the study sample also met the following research diagnostic exclusionary criteria: (1) no history of severe ongoing cardiac, hepatic, pulmonary, or renal disease (or other significant medical illness such as malignancy or HIV seropositivity); (2) no history of substance abuse; (3) no history of head injury with loss of consciousness exceeding one hour; (4) no history of anoxia or diffuse ischemia
resulting in cognitive decline; (5) no major psychiatric disorder unrelated to the present illness; (6) no history of consistent noncompliance with medical treatment. In addition, the following research diagnostic inclusionary criteria were met by the subjects: (1) adequate hearing and visual acuity, (2) cognitive symptoms remain present even when CNS drugs are withdrawn, (3) if depressed, neuropsychological deficits are not reversed with psychotherapy or antidepressants. (4) cognitive decline must have occurred over a period of at least 6 months, and must be interfering with activities of daily living.

All patients received medical, neurological, and neuropsychological examinations. The following laboratory screening studies were conducted on each subject, revealing no abnormalities: complete blood count (CBC); electrolyte, glucose, blood urea nitrogen (BUN), and creatinine level analysis; liver and thyroid function tests; B12 and folate level assessment; FTA-Abs test for syphilis; sedimentation rate; urinalysis. No patient displayed focal primary motor or sensory findings on neurological exam, and all had modified scores of less than four on the Hachinski Ischemic Scale (Hachinski et al., 1975). All patients underwent CT and MRI scanning, which failed to reveal any significant focal abnormalities.

Aside from the above inclusionary/exclusionary criteria, all patients registered in the database were included in the current investigation, if sufficient neuropsychological data were available. Psychometric evaluation included the following: Mini Mental State Exam (MMSE) (Folstein, Folstein & McHugh, 1975), Hamilton Depression Scale (Hamilton, 1967; Warren, 1994), Grip Strength Test (Reitan & Davison, 1974), Finger Tapping Test (Reitan & Davison, 1974), Blessed Dementia Scale (Blessed, Tomlinson & Roth, 1968), Wechsler Memory Scale (WMS) (Wechsler, 1945), Wechsler Adult Intelligence Scale - Revised (WAIS-R) (Wechsler, 1981), Boston Naming Test (Kaplan, Goodglass & Weintraub, 1983), Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1989; Spreen & Benton, 1977), Animal Name Fluency Test ( Isaacs & Kennie, 1973; Spreen & Strauss, 1991), Southern California Figure-Ground Visual Perception Test (Ayres, 1966). Several other neuropsychological tests were administered in a flexible fashion to selected patients, but were not included as variables in the current investigation due to the inconsistency of their use.
Demographic and test data were retrieved directly from the database, and doublechecked manually via file review. Best estimates of symptom duration were gleaned from reports of the referring physicians and file notes recorded by a neuropsychologist (or supervised intern) during interviews conducted with family members/friends of the subjects. In the rare event that these two information sources differed, a mean estimated length of symptom duration was calculated, weighing each value equally. A descriptive chart comprising the demographic characteristics of the sample and their average level of performance on the WAIS-R, MMSE, Blessed, Hamilton, and other neuropsychological tests of interest is provided on the following page. All subjects employed in this study were born between the years 1903 and 1941. The majority were right-handed (96.3%), and only 11% of the sample tested positive for the presence of extrapyramidal signs. As can be appreciated from Table 2, this sample is somewhat highly educated; 43% of the subjects had completed high school and some college (mean educational level=12.8 years). Of note however, this is an improvement from the mean educational level obtained by Martin and colleagues (1986) of 14.5 years. The age range of the current sample (50-91) is also an improvement over that of Martin and colleagues (1986) (i.e., 43-74 years), including representation of the "very-old" elderly. Forty-one percent of the subjects were 75 years-old or older; 16% were ≥ 80 years of age. Occupational representation of the sample is demonstrated in the pie chart on page 58c (Chart 1), given the categorical nature of this variable. Eighty-three percent of the subjects were classified as "not depressed" by clinicians' ratings on the Hamilton Depression Scale (see Chart 2).

The following patient raw scores were converted to T-scores1, averaged, and expressed graphically (see Graph 1) to demonstrate the goodness of fit of this sample, as

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1 Raw scores were converted to T-scores (Mean=50; Standard Deviation=10) demographically corrected for age (in addition to education and gender, when such normative information was available), using normative data presented by the following authors (tests in parentheses): Van Gorp, Satz, Kiersch and Henry (1986) (BNT, age and educational level; if education ≥ 12 years); Ross, Lichtenberg and Christensen (1994) (BNT, age and educational level; if education < 12 years); Bielanskas, Newberry and Gerstenberger (1988) (Figure-Ground, sex-corrected only); Reud (1987) (COWAT, Animals; age and education); Wechsler (1945) (Easy Associates, MQ; age corrected only); Wechsler (1981) (Block Design, VIQ, PIQ; age corrected only). As no norms were available for the copy task scoring system created for this project, a T-score of 50 was considered the normal mean [corresponding to a perfect score of 5; normal elderly have no difficulty copying the figures (Folstein et al., 1975)], with scores of 4, 3, 2, and 1, assigned T-scores of 40, 30, 20, and 10, respectively.
Table 2. Characteristics of the Sample

<table>
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<th>Demographic Variable</th>
<th>Mean</th>
<th>S.D.</th>
<th>Range</th>
</tr>
</thead>
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<td>Age (yrs.)</td>
<td>72.2</td>
<td>7.6</td>
<td>50-91</td>
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<tr>
<td>Estimated Age of Onset</td>
<td>67.7</td>
<td>8.5</td>
<td>42-86</td>
</tr>
<tr>
<td>Education (yrs.)</td>
<td>12.8</td>
<td>3.1</td>
<td>5-20</td>
</tr>
<tr>
<td>Duration of Illness (yrs.)</td>
<td>4.5</td>
<td>3.3</td>
<td>1-19</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Psychological Test</th>
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<th>S.D.</th>
<th>Range</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS-R -- VIQ</td>
<td>82.3</td>
<td>14.4</td>
<td>53-123</td>
<td>121</td>
</tr>
<tr>
<td>-- PIQ</td>
<td>79.3</td>
<td>14.5</td>
<td>57-120</td>
<td>121</td>
</tr>
<tr>
<td>-- FSIQ</td>
<td>80.5</td>
<td>13.9</td>
<td>50-123</td>
<td>133</td>
</tr>
<tr>
<td>WMS -- MQ</td>
<td>75.3</td>
<td>13.5</td>
<td>50-117</td>
<td>133</td>
</tr>
<tr>
<td>-- Logical Memory</td>
<td>2.5</td>
<td>2.4</td>
<td>0-20</td>
<td>133</td>
</tr>
<tr>
<td>-- Visual Reproduction</td>
<td>3.0</td>
<td>1.9</td>
<td>0-9</td>
<td>133</td>
</tr>
<tr>
<td>Hamilton Depression Scale</td>
<td>5.5</td>
<td>4.2</td>
<td>0-20</td>
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<tr>
<td>MMSE (Total)</td>
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<td>5.2</td>
<td>1-27</td>
<td>134</td>
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<td>Blessed</td>
<td>6.8</td>
<td>3.9</td>
<td>0-19.5</td>
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</table>
Chart 1. Occupational Representation

- Homemaker
- Factory Worker
- Services
- Office/Clerical
- Skilled Labourer
- Sales
- Civil Servant
- Teacher/Counsellor
- Profess./Managerial
- Other

Chart 2. Distribution of Subjects by Hamilton Depression Rating

- No Depression
- Minor Depression
- Missing Data
- Major Depression
Graph 1.

T-Scores Comparing the Present Sample to that of Martin et al. (1986)

-10 0 10 20 30 40 50
VIQ PIQ MQ SM VP

- Current Sample
- Martin et al. (1986) Sample

SM = Semantic Memory  VP = Visual-Perception
compared to other AD samples: VIQ, PIQ, MQ. Semantic Memory (sum of T-scores from COWAT, Animal Fluency, Boston Naming and Easy-Paired Associates=4 for each individual), Visual-Perception (sum of T-scores from Block Design, Figure-Ground and Copy task=3). The typical pattern evinces depression of VIQ, PIQ, and MQ; with PIQ slightly lower than V·Q, MQ lower than PIQ, and relatively equal means for Semantic Memory and Visual-Perception. Graph 1 illustrates the pattern obtained with this sample, in comparison to that reported by Martin et al. (1986) for their group of patients. As can be easily seen from this graph, when mean overall performance across all patients is considered, the current sample fits the above outlined pattern of performance normally observed amongst AD samples in general, in addition to that obtained by Martin et al.'s (1986) sample, in terms of VIQ>PIQ>MQ. However, the present sample is a great deal less impaired than the patients studied by Martin and colleagues. Furthermore, with respect to semantic and visual-perceptual/constructional functioning, the current sample obtained the opposite pattern to that of Martin et al.'s (1986) sample; visual-perceptual-constructional abilities appear slightly more impaired than semantic knowledge. This may be due to slightly different visual-perceptual tests utilized in the current research (e.g., Figure-Ground, Pentagon Copy Task). In addition, the method by which T-scores were calculated for the Figure-Ground test (due to the lack of age-appropriate normative data), likely overestimated levels of impairment on this measure.

Neuropsychological Measures

Data from the following tests were utilized in this research: Animal Name Fluency Test, Blessed Dementia Scale, Boston Naming Test (BNT), Controlled Oral Word Association Test (COWAT), Finger Tapping Test, Grip Strength Test, Hamilton Depression Rating, Mini Mental State Exam (MMSE), Southern California Figure-Ground Visual Perception Test, Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler Memory Scale (WMS). Each will be briefly described here in turn, and mention of it’s utility made. More detailed test descriptions are provided by Benton and Hamsher (1989), Cummings and Benson (1992), Kaufman (1990), Lezak (1983), Spreen and Strauss (1991), Walsh (1991), and Wechsler (1945, 1981).
Animal Name Fluency Test (Isaacs & Kennie, 1973; Spreen & Strauss, 1991): This test requires the examinee to name aloud as rapidly as possible, as many types of animals (e.g., lion, elephant, snake etc.) he/she can generate within a 60 second time period. It is utilized in this research as a reflection of within-category accessibility of semantic knowledge.

Blessed Dementia Scale (Blessed et al., 1968): This 22 item behavioural rating scale comprises questions regarding changes in the patient’s habits (e.g., sphincter control), memory (e.g., ability to recall recent events, shopping lists etc.), ability to care for him/herself (e.g., eating, dressing), activities of daily living (e.g., ability to perform household tasks, deal with small sums of money), and personality/emotional functioning (e.g., degree of emotional control, egocentricity), over the previous 6 months. It generates a “dementia” score, which may be viewed as a measure of AD severity. Total inability to complete an activity is given a score of 1, intermittent incapacity is assigned a score of 1/2, and complete retention of an ability generates a score of zero. Questions regarding eating, dressing, and continence are rated on a 0-3 point scale, with 0 representing no dysfunction, and 3, major impairment. Occurrences of the listed changes in personality, interests, or drives, are scored as 1 for each item present; absences of such alterations are scored as zero. The dementia score is calculated by simply summing the scores allocated for each item. Special scoring allowances are made when the presence of a recently acquired physical disability served to restrict activities. The total score ranges from 0 (fully preserved functional capacity/socioemotional functioning) to 28 (extreme impairment of self-care and personality functioning). This questionnaire was completed in an interview format with the aid of a close family member and/or friend (ideally, the primary caregiver). It is utilized in this research as an overall estimate of functional competence.

Boston Naming Test (BNT) (Kaplan, Goodglass & Weintraub, 1983): This test comprises 60 line drawings ranging from familiar items at the beginning (e.g., house), to more difficult ones at the end (e.g., abacus), which the examinee is asked to name. If the patient is unable to name a drawing, the examiner offers a semantic cue (i.e., definition or attribute of the object); if still unable to name the item after the semantic cue is given, a
phonemic cue is provided (e.g., for "latch", it begins with the sound "la"). A point for the correct naming of each item is awarded only if the examinee either spontaneously names the object, or does so after provision of a semantic cue (i.e., no points are awarded if the subject correctly names the item after a phonemic cue is given, although this information is qualitatively important). The maximum score on this test is 60. The BNT is utilized in this project as a measure of accessibility of semantic knowledge.

Controlled Oral Word Association (COWAT) (Benton & Hamsher, 1989; Spreen & Benton, 1977): During this test, the patient is required to name orally, in a 60 second period, as many words as possible that begin with a particular letter of the alphabet. In this version, 4 sixty second trials are given, with the target letters being D, C, F, and L. This measure is utilized in the factor and cluster analyses as a measure of accessibility of semantic knowledge.

Finger Tapping Test (Reitan & Davison, 1974): The patient is required to tap a key with his/her index finger, as rapidly as possible, for 5 ten second trials. The right and left hands are tested separately. This test is utilized as a measure of motor speed.

Grip Strength Test (Reitan & Davison, 1974): The patient is required to squeeze a dynamometer as tightly as possible, with the arm extended and the instrument pointing toward the floor. Each hand is tested separately for two trials. This test is utilized as a measure of motor strength.

Hamilton Depression Rating Scale (HDRS) (Hamilton, 1967): The Hamilton Depression Scale data included in this research were obtained via the clinician rating form of this measure (i.e., as opposed to the self report version). This is a 17-item scale, in which the clinician inquires about and rates the subject on relevant symptom areas (e.g., guilt feelings, insomni, depressed mood etc.) within a clinical interview format. The maximum score on this measure is 52. The following score ranges correspond to the presence and severity of symptoms: ≤10, not depressed; 11-16, minor depression; 17-25, major
depression: ≥26. severe depression. Test data from the HDRS was utilized in this project to rule out depression as an influencing factor on the neuropsychological test performance of the majority of subjects.

Mini Mental State Exam (MMSE) (Folstein et al., 1975): The MMSE is a gross screening instrument containing 30 items designed to assess areas such as orientation, recall, language, perceptual-motor functioning (e.g., copy design), and attention/concentration. It yields a single score, as an estimate of dementia severity. A cut-off score of 23 is recommended in determining the presence of cognitive impairment (normal range=24-30; maximum score=30) (Folstein et al., 1975). The following score ranges were employed in severity stratification of the sample: mild, ≥ 24; moderate, ≥ 19 and ≤ 23; severe, ≤ 18 (Welsh et al., 1992). This instrument was utilized as a measure of dementia severity in the current investigation, given its widespread use in research, and established psychometric properties (Galasko et al., 1990; Salmon, Thal, Butters & Heindel, 1990). The figure-copy subcomponent of this test is utilized as a measure of visual-construction. This task requires the examinee to copy a picture of 2 overlapping pentagons. The drawings were scored on a 5 point scale, ranging from a score of 5 which was earned by perfect reproductions, to a score of zero, which was given to totally deficient drawings (see the Appendix for scoring criteria developed for this project, and a copy of the stimulus figures).

Southern California Figure-Ground Visual Perception Test: (hereafter referred to simply as "Figure-Ground") (Ayres, 1966): This test is composed of 16 stimulus cards, half of which contain overlapping figures depicting common objects; the other half, geometric figures embedded within larger geometric designs. A response card for each stimulus card is provided, containing 6 possible responses (i.e., either common objects or geometric figures), of which 3 (the correct responses) are represented somewhere on the test stimulus card. The subject is instructed to point out the objects/figures on the response card which are present (i.e., in either an overlapping or embedded fashion) on the test stimulus card, within a 60 second time limit (per card). The maximum score on this test is 48, as there are
3 correct choices on each of the 16 cards, each worth one point. This test is utilized as a measure of complex visual-perception.

*Wechsler Adult Intelligence Scale - Revised (WAIS-R)* (Wechsler, 1981): One subtest from this measure of general cognitive functioning was utilized in this research as a measure of visual-perception, construction, and visual-motor integration: Block Design. The Block Design test requires the subject to construct replicas of two designs made by the examiner, and seven designs displayed two dimensionally on printed cards, utilizing 4, 6, and then 9 plastic blocks.

*Wechsler Memory Scale (WMS)* (Wechsler, 1945): The Associate Learning (Easy Paired Associates only), Logical Memory, and Visual Reproduction subtests from this general memory measure were utilized in this project, the first as a measure of accessibility of semantic knowledge, the second as a measure of immediate verbal recall, and the third as a measure of immediate visual-spatial recall. The Easy Paired Associates measure comprises the 6 easy items of the Associate Learning subtest of the WMS. During each of three trials, the examiner slowly reads aloud a list of 6 easily associated word pairs (e.g., baby-cries), and upon completion, the first word of each pair is successively offered, and the examinee is to provide its mate. The Logical Memory test includes two prose passages which are read aloud by the examiner. Following each reading, the examinee is required to recall as many ideas and details from the passage as possible. During the Visual Reproduction subtest, the subject is exposed to three cards containing geometric figures, one at a time for 10 seconds each. Immediately following each 10 second presentation, the card is removed out of sight, and the patient is asked to draw the figure(s) from memory on a blank sheet of paper. The Memory Quotient (MQ) score generated from the subtests of the WMS, was utilized in this research to compare the extent of overall verbal memory impairment averaged across all patients in the study sample, to other samples; namely, that of Martin and colleagues (1986).
On Cluster Analysis

Cluster analysis is a term applied to a set of objective multivariate techniques utilized for grouping a large number of individuals into smaller subgroups (i.e., clusters), so that those in the same subgroups are more similar to each other on some predetermined criteria than they are to individuals in other subgroups (Hair et al., 1992). The resulting clusters should demonstrate high within-cluster homogeneity, and high between-cluster heterogeneity, reflective of natural relationships within the data (Morris, Blashfield & Satz, 1981). The application of cluster analysis involves many subjective decisions by the researcher, including the choice of similarity measure, algorithm, and overlying clustering approach and method to be utilized. Several different approaches are available, including the following: hierarchical agglomerative methods, hierarchical divisive methods, iterative partitioning techniques, factor-analytic variants, graphic methods, clumping procedures, and density searching techniques (Blashfield & Aldenderfer, 1988; Everitt, 1974; Morris, Blashfield & Satz, 1981). Each of these approaches, in turn, have various specific algorithms and procedural options. As well, many different measures of inter-individual similarity/dissimilarity are available, each varying in sensitivity to profile elevation, shape, and scatter (see Blashfield & Aldenderfer, 1988). Euclidean distance is the most commonly used measure of similarity between two individuals (Hair et al., 1992). In essence, this is the measure of the length of a straight line drawn between the two observations, and is sensitive to differences in severity, shape, and scatter between subgroup profiles (Hair et al., 1992). The Pearson product moment correlation is another commonly utilized similarity measure (Blashfield & Aldenderfer, 1988). This measure is disproportionately sensitive to the pattern (i.e., shape) of subgroup profiles, at the expense of loss of information regarding scatter and elevation (Aldenderfer & Blashfield, 1984; Everitt, 1974; Morris & Fletcher, 1988). Because of the multitude of approaches, algorithms, and similarity measures available, and the lack of appropriate criteria for their selection in particular situations, different solutions are often obtained with the same data set, across different methods (Blashfield & Aldenderfer, 1988; Everitt, 1974; Morris, Blashfield & Satz, 1981). There is no consensus in the literature as to the criterion by which to select the appropriate number of clusters in a data set, allowing subjectivity to creep in. For all the
above reasons, investigators must clearly outline the methods utilized, in addition to the rationale behind their decisions. Furthermore, due to the unreliability of one particular analysis, clustering studies should necessarily include replication of the initial solution across two or more similarity measures, algorithms, and methods (Everitt, 1974; Hair et al., 1992; Morris, Blashfield & Satz, 1981).

Clustering Methods Utilized in Data Analysis

Q-Type Factor Analysis: This procedure involves the factoring of an intercorrelation matrix of subject profiles, in order to condense large numbers of heterogeneous individuals, into distinct subgroups of similar individuals (Hair et al., 1992). Factors are extracted from the inter-correlation matrix using standard procedures (e.g., principal components analysis) and then rotated. Each factor is then interpreted as a cluster; individuals are assigned to clusters (i.e., factors) on the basis of their highest single factor loading (Blashfield & Aldenderfer, 1988; Everitt, 1974).

Average Linkage Between Groups: This method is often referred to as UPGMA (unweighted pair-group method using arithmetic averages). In this method, the similarity between two clusters is defined as the mean similarity between all pairs of cases in which one member of the pair is from each of the clusters (Norusis, 1990). Thus, the cluster criterion is the mean similarity between individuals in one cluster and those in another.

Average Linkage Within Groups: This method combines clusters in a manner such that the mean similarity between all cases in the new cluster is as high as possible. It does this by considering the similarity between two clusters as the average of the similarities between all possible pairs of cases in the resulting cluster (Norusis, 1990).

Ward’s Method: This method combines clusters which result in the smallest increase in overall sum of the squared within-cluster variance (Hair et al., 1992; Morris, Blashfield & Satz, 1981; Ward, 1963).
**K-Means:** This method produces clusters by estimating cluster centers based on the values of the variables and assigning cases to the centers that are the nearest (measured by squared Euclidean distance). As each case is added to a cluster, the center is updated to a mean for the cases that are thus far in the cluster. After each case is classified in this manner, the algorithm reassigns each case to the nearest cluster centers: if the case is closest to the centroid (mean) of its own cluster, it is left in that cluster, otherwise, it is reassigned to the cluster with the closest centroid (MacQueen, 1967; SPSS-X Manual, 1988). This procedure is repeated until a stable solution is reached, in which no individual case changes cluster membership.

**Overview of Statistical Analyses**

As many different statistical procedures/strategies were employed in this research, a synopsis of the major paths taken, and the rationale behind each is provided here, before proceeding to report the results. The reader (especially if unfamiliar with well-designed classification research) may find it helpful to examine the accompanying descriptive diagram, which outlines the major steps taken in the course of data analysis (see Chart 3, next page), either before, during, and/or after reading this summary.

The first step of data analysis involved the conversion of raw patient scores on seven measures [BNT, COWAT, Animal Fluency, Easy Paired Associates, Block Design, Figure-Ground, Pentagon Copy task (from MMSE)] to demographically corrected T-scores (see footnote on page 58), for comparative purposes. Subsequently, the T-scores were submitted to an R-type factor analysis, using Varimax rotation of the principal components solution. These tests were chosen for analysis due to their similarity to those utilized by Martin et al. (1986) and Becker et al. (1988). A two-factor solution was expected to emerge, with a high degree of intercorrelation between the verbal measures and between the spatial measures, but minimal relations across the two domains, suggesting the possibility of subgroups. Following the R-analysis, a Q-type factor analysis (i.e., inverted matrix with columns representing the subjects and rows the variables) was undertaken, in which product moment correlations were calculated between all possible column pairs (i.e., between subject profiles). Factors extracted were retained and rotated to Varimax criterion,
Chart 3. Overview of Method

Raw Test Data

Calculation of T Scores

Preparation of NxP Matrix

Transposition to PxN Matrix

Computation of NxP Matrix of Intercorrelations

R-Type Factor Analysis

Rotation of PC Solution

Confirmation of 2 Orthogonal Factors

Computation of NxN Matrix of Intercorrelations

Q-Type Factor Analysis

Retention of Single Loadings ≥ 0.50

Ward's Method

ALWG

MJHG

Calculation of T-Score Means & Profile Plotting for each Subgroup

Misclassification Analysis

Cluster Analysis Utilizing Correlation as Similarity Measure

K-Means Cluster Analysis

Comparison of Q-Derived Subgroups on Neuropsychological Tests and Demographic Variables

*Inspired by Del Dotto & Rouke (1965)

N = cases  P = variables
ALWG = Average-Linkage Within Groups
ALHG = Average-Linkage Between Groups
if the eigenvalues equalled or exceeded the ratio of number of subjects/number of variables (Del Dotto & Rourke, 1985). An initial Q-type factor analysis was thought beneficial in that this alternative "clustering" method has no bias against creating relatively small clusters; many cluster analysis techniques are biased toward creating clusters of equal size (D. R. Fuerst, personal communication, August 10th, 1994). Furthermore, Q-analysis controls for the presence of outliers, as every case is not necessarily required assignment to a cluster (D.R. Fuerst, personal communication, August 10th, 1994).

If, as predicted, the Q-analysis identified significant qualitatively distinct subgroups of individuals (as evaluated via multivariate analysis of variance and profile analysis procedures), various cluster analyses were to be performed on the T-score data, in an attempt to generate similar subgroupings across multiple methods (i.e., establish internal validity). Only those clusters emerging via the majority of methods would be accepted as reliable. The product moment correlation coefficient was chosen as the primary similarity measure (i.e., utilized in 3 of the 4 analyses), given that the prime interest of this study involves qualitative pattern (i.e., shape) variability (Aldenderfer & Blashfield, 1984; Everitt, 1974; Morris, Blashfield & Satz, 1981). The above described hierarchical agglomerative methods (average linkage between groups, average linkage within groups, and Ward's method) were utilized first, followed by an iterative partitioning procedure (i.e., k-means) in which squared Euclidean distance served as the similarity measure. The appropriate number of clusters in the data were determined by inspection of the cluster fusion coefficients at each stage (i.e., for sudden drop), in addition to the corresponding icicle plots and dendograms (Everitt & Dunn, 1991).

Demographic and other neuropsychological data are provided for each of the subgroups which emerged. Comparisons were made between the subgroups to determine whether age, duration of illness, severity of the illness, and other such factors differ between the groups, in addition to whether the groups display distinct patterns of performance on verbal and non-verbal memory measures, and tests of motor functioning. As discussed earlier, on the basis of prior smaller scale research, it was predicted that three qualitatively distinct groups of individuals would be identified: (1) those with global impairment (reduced scores on all measures); (2) those with relatively spared accessibility
of semantic knowledge but impaired visual-perceptual/constructional functioning; (3) those with impaired ability to access semantic knowledge, but relatively unimpaired visual-perceptual and constructional functioning. Furthermore, it was predicted that patients with spared semantic knowledge in the face of impaired visual-spatial abilities would perform significantly better on measures of verbal memory (Logical Memory) and crystallized intelligence (VIQ), while those with the opposite pattern would demonstrate superior performance on tests of figural memory (Visual Reproduction) and fluid intelligence (PIQ).
CHAPTER IV
RESULTS

Initially, a correlation matrix (P x P) of the 7 test variables (Animal Fluency, BNT, COWAT, Easy Associates, Block Design, Copy task, Figure-Ground) was computed and examined. The majority of coefficients were above .30, and each variable had large correlations (i.e., .40 and over) with at least one other variable. Bartlett's test of sphericity revealed that the correlation matrix was unlikely to be an identity matrix (Norusis, 1990). As well, the anti-image correlation matrix had exceedingly low coefficients, and the value of the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was high (.78). All of these findings suggested the appropriateness of the factor model (Norusis, 1990).

R-Factor Analysis

The T-score data from the AD patients on the four measures of lexical/semantic access and three measures of visual-perceptual/constructional skill were subsequently submitted to a principal components factor analysis using Varimax orthogonal rotation of the principal components solution (SPSS-X FACTOR procedure, version 4.0). The criterion for factor extraction was an eigenvalue of greater than 1 (i.e., Mineigen=1: the latent root criterion) (Afifi & Clark, 1990; Hair et al., 1992; West, 1991). This criterion for selecting the appropriate number of factors was observed to correspond with that suggested by examination of the scree plot, in addition to the commonly utilized rule of thumb regarding selection of only those components which explain at least 100/N (N=the number of variables) percent of the total variance (100/7, or at least 14.3% in this sample) (Afifi & Clark, 1991). A two-component solution emerged, accounting for 61.6% of the total variance (see Table 3 for component loadings). The eigenvalues for the first and second components were 3.3 and 1.04, respectively. As expected, the variables loading highly on Factor I were as follows: BNT, COWAT, Animal Fluency, and Easy-Paired Associates. Those with significant loadings on Factor II included: Block Design, Figure-Ground, and

\footnote{1 A solution accounting for at least 60% of the total variance is considered a satisfactory solution (Hair et al., 1992).}
Table 3. Principal-Components R-Type Factor Analysis Loadings

<table>
<thead>
<tr>
<th>Test</th>
<th>Factor 1</th>
<th>Factor 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT</td>
<td>.68</td>
<td>.15</td>
</tr>
<tr>
<td>COWAT</td>
<td>.75</td>
<td>.25</td>
</tr>
<tr>
<td>Animal Fluency</td>
<td>.81</td>
<td>.27</td>
</tr>
<tr>
<td>Easy Associates</td>
<td>.73</td>
<td>.16</td>
</tr>
<tr>
<td>Block Design</td>
<td>.28</td>
<td>.82</td>
</tr>
<tr>
<td>Figure-Ground</td>
<td>.22</td>
<td>.62</td>
</tr>
<tr>
<td>Copy Task</td>
<td>.14</td>
<td>.85</td>
</tr>
</tbody>
</table>

Table 4. Results of Q-Type Factor Analysis

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Factor I</th>
<th>Factor II</th>
<th>Factor III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eigenvalue</td>
<td>55.58</td>
<td>30.04</td>
<td>21.53</td>
</tr>
<tr>
<td>Variance</td>
<td>.42</td>
<td>.22</td>
<td>.16</td>
</tr>
<tr>
<td>Cumulative Variance</td>
<td>.42</td>
<td>.64</td>
<td>.80</td>
</tr>
<tr>
<td>Number of Subjects with SL</td>
<td>58.00</td>
<td>36.00</td>
<td>30.00</td>
</tr>
<tr>
<td>% of sample with SL</td>
<td>43.28</td>
<td>26.87</td>
<td>22.39</td>
</tr>
</tbody>
</table>

SL=Significant Loadings (i.e., above .50)
the Copy task. Thus, the dissociation between accessibility of semantic knowledge and visual-perceptual/constructional functioning amongst AD patients reported by Martin and colleagues (1986) was replicated on this independent sample, utilizing similar neuropsychological test data, and substantially less impaired patients. However, the resulting split was not as extreme as that reported by Martin et al. (1986).

Q-Factor Analysis

Q-type factor analysis involves the factoring of individuals rather than variables (i.e., tests, as in the above R-method) (McKeown & Thomas, 1988). This was accomplished by creating a correlation matrix in which the individual respondents represented the rows, and the test variables the columns. The resulting matrix was then transposed, and correlation (i.e., similarity) coefficients were calculated between the profiles of each pair of subjects in the sample, creating a 134x134 (i.e., NxN) matrix of intercorrelation (SPSS-X procedure PROXIMITIES). Subsequently, this new matrix was submitted to a principal components factor analysis (SPSS-X procedure FACTOR). Only those factors with eigenvalues ≥ the ratio of the number of subjects to the number of variables (i.e., 134/7, or 19.14) were retained (Del Dotto & Rourke, 1985). This criterion yielded three factors, accounting for 80% of the common variance. An additional principal components factor analysis was then run, including a command limiting the number of to be extracted factors to three [CRITERIA=FACTORS(3) subcommand of FACTOR, SPSS-X]. The three emerging factors were subjected to Varimax orthogonal rotation (see Table 4 for factor loadings). Patients were assigned to each subgroup on the basis of the factor for which they demonstrated a loading at or above .50. Subjects without at least one loading of .50 on a factor, in addition to those with significant loadings (i.e., ≥.50) on more than one factor, were not considered in the determination of subgroups. This assignment procedure resulted in the subgrouping of 97 patients, or 72.39% of the sample. Thirty-four percent of these subjects were assigned to subgroup I (i.e., Factor I); subgroups II and III were comprised of 21.64% and 17.16% of the reduced sample, respectively (see Table 5).

Following this, T-score means from the seven test variables used in the R- and Q-type factor analyses were computed for each subgroup and plotted graphically (see Graph
Table 5. Breakdown of Subjects by Pattern of Significant (≥ .50) Factor Loadings

<table>
<thead>
<tr>
<th>Loadings</th>
<th>Number of Subjects</th>
<th>% of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor I only</td>
<td>45</td>
<td>33.58</td>
</tr>
<tr>
<td>Factor II only</td>
<td>29</td>
<td>21.64</td>
</tr>
<tr>
<td>Factor III only</td>
<td>23</td>
<td>17.16</td>
</tr>
<tr>
<td>Factor I &amp; II</td>
<td>11</td>
<td>8.21</td>
</tr>
<tr>
<td>Factor II &amp; III</td>
<td>2</td>
<td>1.49</td>
</tr>
<tr>
<td>Factors I &amp; III</td>
<td>13</td>
<td>9.70</td>
</tr>
<tr>
<td>Factors I, II &amp; III</td>
<td>1</td>
<td>.75</td>
</tr>
<tr>
<td>No SL on any Factor</td>
<td>10</td>
<td>7.46</td>
</tr>
</tbody>
</table>

SL = Significant Loading
2). Examination of these profiles revealed that all three subgroups performed similarly on some of the measures. For example, all three groups demonstrated similar levels of performance on the Figure-Ground test, earning mean T-scores of 19.98 (subgroup 1), 20.97 (subgroup 2), and 21.52 (subgroup 3); suggesting that this variable has little or no utility as a discriminator between the groups. Multivariate analysis of variance (MANOVA) was undertaken to investigate whether the three groups differed significantly, utilizing the Q-defined subgroups as the independent variable, and the seven neuropsychological measures as the dependent variables. Utilizing Wilks’ Lambda as the criterion, such analysis revealed that the groups were significantly different from each other on the combined dependent measures $F(14, 176) = 26.44$, $p < .001$. The same results obtained when Pillai’s criterion $|F| (14, 178) = 25.89$, $p < .001$ and Hotelling’s trace criterion $|F| (14, 174) = 26.98$, $p < .001$ were utilized in the MANOVA (see Table 6). A commonly employed equation for calculating the proportion of variance accounted for by this significant subgroup effect ($\eta^2 = 1-\lambda$), indicated that 89.6% of the variance in the best linear combination of test scores is accounted for by subgroup assignment (Tabachnick & Fidell, 1989). Subsequent univariate $F$ tests revealed that the BNT $|F| (2, 94) = 52.5$, $p < .001$, Block Design $|F| (2, 94) = 26.04$, $p < .001$, and Copy Task $|F| (2, 94) = 69.68$, $p < .001$, were significant contributors to these overall group differences (see Table 7). Because there were significant pooled within-group correlations amongst the test variables, a stepwise analysis was also performed, as suggested by Tabachnick and Fidell (1989). This involved an original univariate $F$ test for the first variable (i.e., BNT), followed by

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2 Prior to such analysis, the graphic distributions of test data for each subgroup were examined to ensure the assumptions of MANOVA were adequately met. No major deviations from the assumptions that would invalidate the procedure were noted.

3 Due to the increased Type I error rate resulting from computation of multiple ANOVA’s, more stringent $\alpha$ levels were set via a Bonferroni type adjustment. Conservative $\alpha$ values of .001 (.0014286, to be precise; i.e., .01 / 7) were assigned for each of the 7 variables, and the overall level considered necessary for a significant result for the set of dependent variables (i.e., .01) conformed to the following equation: $\alpha = 1 - (1-\epsilon_1) - (1-\epsilon_2) ... (1-\epsilon_7)$ (Tabachnick & Fidell, 1989).

4 The problem with performing multiple univariate $F$ tests on correlated dependent variables involves the likelihood that correlated measures assess overlapping aspects of the same construct. Thus, the univariate $F$'s are not independent, making adjustment of the error rate difficult.
Graph 2. Mean Scores of the Three Subgroups Derived by Q-Factor Analysis

BNT = Boston Naming Test, COWAT = Controlled Oral Word Association Test, ANIM = Animal Fluency, EA = Easy Associates, BD = Block Design, FG = Figure Ground, COPY = Pentagon Copy Task
Table 6. MANOVA Significance Table

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Value</th>
<th>Hypoth. df</th>
<th>Error df</th>
<th>$F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pillai’s</td>
<td>1.34</td>
<td>14</td>
<td>178</td>
<td>25.89*</td>
</tr>
<tr>
<td>Hotellings</td>
<td>4.34</td>
<td>14</td>
<td>174</td>
<td>26.98*</td>
</tr>
<tr>
<td>Wilks'</td>
<td>0.10</td>
<td>14</td>
<td>176</td>
<td>26.44*</td>
</tr>
</tbody>
</table>

*p < .001

Table 7. Univariate Analyses of Variance Results (df=2,94)

<table>
<thead>
<tr>
<th>Variable</th>
<th>$SS_B$</th>
<th>$SS_W$</th>
<th>$MS_B$</th>
<th>$MS_W$</th>
<th>$F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT</td>
<td>22545.86</td>
<td>20167.62</td>
<td>11272.93</td>
<td>214.55</td>
<td>52.54†</td>
</tr>
<tr>
<td>COWAT</td>
<td>200.96</td>
<td>13155.13</td>
<td>100.48</td>
<td>139.95</td>
<td>.72</td>
</tr>
<tr>
<td>EASSOC</td>
<td>172.50</td>
<td>2505.54</td>
<td>86.25</td>
<td>26.65</td>
<td>3.24*</td>
</tr>
<tr>
<td>ANIM</td>
<td>1422.27</td>
<td>26883.07</td>
<td>711.14</td>
<td>285.99</td>
<td>2.49</td>
</tr>
<tr>
<td>BD</td>
<td>3097.36</td>
<td>5590.48</td>
<td>1548.68</td>
<td>59.47</td>
<td>26.04†</td>
</tr>
<tr>
<td>FG</td>
<td>40.69</td>
<td>11755.68</td>
<td>20.34</td>
<td>125.06</td>
<td>.16</td>
</tr>
<tr>
<td>COPY</td>
<td>28862.71</td>
<td>19467.62</td>
<td>14431.35</td>
<td>207.10</td>
<td>69.68†</td>
</tr>
</tbody>
</table>

*p < .05 †p < .001

[BNT=Boston Naming Test, COWAT=Controlled Oral Word Association Test, EASSOC=Easy Paired Associates, ANIM=Animal Fluency, BD=Block Design, FG=Figure-Ground, COPY=Pentagon copy task]
analyses of covariance (i.e., a series of ANCOVAs) for each of the remaining variables, one at a time. Thus, the remaining six variables were evaluated as to the amount of new information (i.e., in terms of variance accounted for) they added to the combination of dependent variables already tested, controlling for the effects of all previously entered variables, in a manner analogous to hierarchical stepwise analysis of the independent variables in multiple regression. Retaining the previous α adjusted for inflated Type I error rate, similar results emerged, with COWAT, Easy Associates, Animal Fluency and Figure-Ground F's failing to reach significance (see Table 8). Subsequent profile analysis indicated that the overall patterns of performance on the 7 tests were significantly different between the 3 groups [(Wilks' U = .063) F(12, 162) = 40.15, p < .001] (see Table 9). Indeed, eta square (i.e., the strength of the association; η² = 1 - Wilks' Lambda) revealed that 94% of the variance about adjacent line segments of the profiles is accounted for by the varying shapes of the profiles.

Cluster Analyses

In order to evaluate the reliability of the Q-derived subgroups mentioned above, four different clustering algorithms were utilized on the same data, in an attempt to replicate identification of the three Q-groups across various methods. As mentioned previously, such replication is required, because cluster analysis often generates inconsistent results across different approaches (i.e., Q-analysis, hierarchical agglomerative methods, iterative partitioning procedures), algorithms (e.g., Ward's versus average linkage), and similarity measures (e.g., correlation versus Euclidean distance) (Afifi & Clark, 1990). In this manner, it was reasoned that if indeed subgroups exist, a design incorporating different approaches, algorithms, and similarity measures, should produce consistent results. Only then, can one be assured that results obtained are not simply an artifact of the particular methodology utilized (Campbell and Fiske, 1959). Four widely used techniques were chosen, given their availability, and success in previous studies (see Blashfield & Aldenderfer, 1988; Everitt & Dunn, 1991): Ward's method (Ward, 1963), average linkage between groups (Sneath & Sokal, 1973), average linkage within groups (Sneath & Sokal,
Table 8. Roy-Bargman Stepdown $F$ Test Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypoth. MS</th>
<th>Error MS</th>
<th>Stepdown $F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT</td>
<td>11272.93</td>
<td>214.55</td>
<td>52.54†</td>
</tr>
<tr>
<td>COWAT</td>
<td>406.37</td>
<td>116.07</td>
<td>3.50*</td>
</tr>
<tr>
<td>EASSOC</td>
<td>32.69</td>
<td>21.85</td>
<td>1.50*</td>
</tr>
<tr>
<td>ANIM</td>
<td>705.13</td>
<td>252.84</td>
<td>2.79</td>
</tr>
<tr>
<td>BD</td>
<td>1279.11</td>
<td>48.35</td>
<td>26.45†</td>
</tr>
<tr>
<td>FG</td>
<td>464.42</td>
<td>100.45</td>
<td>4.62*</td>
</tr>
<tr>
<td>COPY</td>
<td>8938.83</td>
<td>169.16</td>
<td>52.84†</td>
</tr>
</tbody>
</table>

*p < .05  †p < .001 (adjusted criterion for significance)

[BNT=Boston Naming Test, COWAT=Controlled Oral Word Association, EASSOC=Easy Paired Associates, ANIM=Animal Fluency, BD=Block Design, FG=Figure-Ground, COPY=Pentagon copy task]

Table 9. Profile Analysis (of Parallelism) Results

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Value</th>
<th>Hypoth. df</th>
<th>Error df</th>
<th>$F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pillai's</td>
<td>1.47</td>
<td>12</td>
<td>164</td>
<td>38.04†</td>
</tr>
<tr>
<td>Hotellings</td>
<td>6.35</td>
<td>12</td>
<td>160</td>
<td>42.31†</td>
</tr>
<tr>
<td>Wilks'</td>
<td>.06</td>
<td>12</td>
<td>162</td>
<td>40.15†</td>
</tr>
</tbody>
</table>

†p < .001  (*one way MANOVA on line segments testing parallelism hypothesis)
1973), and k-means iterative partitioning (MacQueen, 1967). The correlation coefficient was selected as the similarity measure for the hierarchical analyses, while squared Euclidean distance was employed in the k-means procedure. The SPSS-X version 4.0 implementations of these methods were utilized, the hierarchical algorithms with procedure “CLUSTER”, and the k-means iterative algorithm with the “QUICK CLUSTER” procedure.

Inspection of the amalgamation coefficients, icicle plots, and dendrograms generated by the three hierarchical methods suggested the presence of distinct homogeneous clusters of individuals. The average linkage (within groups) and Ward’s algorithms clearly suggested a three group solution. The other hierarchical technique, average linkage between groups, suggested either three or four group solutions as optimal. However, when a three group solution was forced, each and every individual from the fourth group joined group one. As no qualitative distinction could be made between the patterns of performance of group one and four, the three cluster solution was considered to best explain the structure of the data. The SPSS-X k-means procedure requires the researcher to select the number of clusters to be derived from the data. As the Q-analysis and 2 of the 3 hierarchical procedures clearly suggested the presence of three groups, \( k \) was set at 3 for the iterative partitioning procedure. Initial cluster seeds were randomly selected by the program. When the procedure was re-run utilizing the Q-derived means of the seven variables for the 3 subgroups as the initial cluster seeds, the results were nearly identical.

The results of the five analyses were evaluated in three ways, in a manner similar to that of previous well designed clustering studies (Del Dotto and Rourke, 1985; Fuerst, Fisk & Rourke, 1989): (1) visual comparison of graphic profiles constructed by plotting the means of each subgroup on the seven measures (i.e., for each of the five methods), (2) misclassification analysis, and (3) construction of a multiprofile-multimethod matrix (Campbell & Fiske, 1959). Profile plotting and subsequent inspection of the patterns each method generated for the three subgroups were qualitatively judged as highly similar (see Graphs 3A-D). Misclassification analysis involved the use of the Q-defined groups as the criterion subgroups. Counts were made as to the number of subjects misclassified to the Q-
Graphs 3 (A), (B), (C), (D). Comparison of Subgroups Derived from Three Cluster Analysis Algorithms (B. Ward's Method; C. Average-Linkage Between Groups; D. Average-Linkage Within Groups) with the Q-Defined Groups*.

A. Q-Factor Derived Subgroups

B. Ward's Method Derived Subgroups

C. Average-Linkage (Between Groups) Derived Subgroups

*Continued on next page
Graph 3 (*continued)

D. Average-Linkage (Within Groups) Derived Subgroups

Q-Factor Derived Subgroups*

*Reprinted for ease of comparison
Graph 5. Total Mean T-Scores for the 3 Subgroups for each Domain of Functioning*

*Calculated by summing mean T-scores for each of the average-linkage (within groups) derived subgroups on (SM): BNT, Verbal Fluency ([COWAT+Animals]-2), EA, and (VP). Fig. BD and Copy.
Graph 4. K-Means Subgroups (A) Compared to Q-Derived (B) Groups

Note that the k-means procedure utilized a distance similarity measure, accounting for the more defined groups in terms of levels of performance, and minor deviation of pattern [compare top left of (A) to that of (B)].
factor groups by the other four clustering methods (see Table 10). As can be seen in Table 10, misclassifications were evident for each of the methods. However, the vast majority of subjects (81-93%) were correctly classified by each method. The average-linkage within groups and Ward’s algorithms were most successful in correctly classifying the subjects. These two methods classified all of the Q-derived subgroup 1 subjects correctly. The k-means procedure performed the worst (although still, quite well) of all the algorithms. This is explainable in that a distance measure was utilized as the similarity measure with this algorithm: distance measures are not as sensitive to profile shape as are correlation coefficients.

As a third, and perhaps most powerful means of assessing the similarity of the three subgroups generated by each of the five clustering approaches, a multiprofile-multimethod matrix of intercorrelations was constructed (see Table 11). In a classic (and brilliant) methodological paper on construct validation, Campbell and Fiske (1959) presented what they labelled the hypothetical “multitrait-multimethod matrix”, as a systematic means of assessing convergent and divergent validity. The multitrait-multimethod matrix involves reliability and validity coefficients computed between several traits assessed by several methods. The validity coefficients represent the correlations obtained for the same trait across methods. In this manner, independent measures of the same construct are correlated. Obviously, the higher the correlation coefficients, the more valid the measures (and the construct). The matrix also contains correlations between different traits assessed by the same method, and correlations between different traits and different methods. Campbell and Fisk (1959) argued quite well that in order to demonstrate satisfactory validity of a construct, one is obligated to demonstrate high correlations between the same traits measured by different measures (i.e., validity coefficients). As well, one must also demonstrate that these coefficients are higher than those between different traits measured by distinct measures, in addition to those between different traits measured by the same method. My interpretation of the multitrait-multimethod design is presented in Table 11 as a “multiprofile-multimethod matrix.” Notice that the correlations computed between the same subgroup profiles across different methods are extremely high, ranging from .79 to .99. Notice as well that the majority of heteroprofile-heteromethod and heteroprofile-
Table 10. Misclassification Analysis: Number of Patients Wrongfully Assigned to each Q-Factor Group by the Cluster Analytic Methods

<table>
<thead>
<tr>
<th>Clustering Method</th>
<th>Q-Derived Subgroups</th>
<th>Total Misclassifications</th>
<th>% Correctly Classified</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 45)</td>
<td>2 (n = 29)</td>
<td>3 (n = 23)</td>
</tr>
<tr>
<td>Ward's</td>
<td>0</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>ALGi</td>
<td>5</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>K-Means*</td>
<td>8</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>ALWG</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

*ALGi = Average Linkage Between Groups  ALWG = Average Linkage Within Groups
*Also known as nearest centroid sorting
Table 11. Multiprofile-Multimethod Matrix: Intercorrelations between Q-Derived Subgroup Profiles and those Identified via Cluster Analytic Techniques

<table>
<thead>
<tr>
<th>Q-Factor</th>
<th>Ward’s</th>
<th>ALB</th>
<th>K-Means</th>
<th>ALW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td>32.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W1</td>
<td>.96</td>
<td>.43</td>
<td>.54</td>
<td></td>
</tr>
<tr>
<td>W2</td>
<td>.41</td>
<td>.99</td>
<td>.03</td>
<td>.47</td>
</tr>
<tr>
<td>W3</td>
<td>.27</td>
<td>.08</td>
<td>.96</td>
<td>.46</td>
</tr>
<tr>
<td>A1</td>
<td>.96</td>
<td>.47</td>
<td>.52</td>
<td>.99</td>
</tr>
<tr>
<td>A2</td>
<td>.37</td>
<td>.99</td>
<td>.02</td>
<td>.43</td>
</tr>
<tr>
<td>A3</td>
<td>.30</td>
<td>.08</td>
<td>.96</td>
<td>.48</td>
</tr>
<tr>
<td>K1</td>
<td>.98</td>
<td>.35</td>
<td>.40</td>
<td>.98</td>
</tr>
<tr>
<td>K2</td>
<td>.43</td>
<td>.99</td>
<td>.06</td>
<td>.99</td>
</tr>
<tr>
<td>K3</td>
<td>.61</td>
<td>.38</td>
<td>.50</td>
<td>.79</td>
</tr>
<tr>
<td>B1</td>
<td>.98</td>
<td>.44</td>
<td>.03</td>
<td>.99</td>
</tr>
<tr>
<td>B2</td>
<td>.38</td>
<td>.99</td>
<td>.02</td>
<td>.44</td>
</tr>
<tr>
<td>B3</td>
<td>.43</td>
<td>.21</td>
<td>.97</td>
<td>.64</td>
</tr>
<tr>
<td>Q1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>W2</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>W3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K1</td>
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<tr>
<td>K2</td>
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<tr>
<td>K3</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>B1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ALB* = Average-Linkage Between Groups  
*ALW* = Average-Linkage Within Groups

Inspired by Campbell & Fiske (1959)
monomethod coefficients are low.

Given that the three methods evaluating the reliability of the Q-factor analysis derived subgroups strongly supported the predicted existence of three qualitatively distinct subgroups, difference tests (i.e., ANOVAs) between the groups on measures not employed in their derivation were undertaken (Aldenderfer & Blashfield, 1984; Fletcher, 1985) (see Table 12). The groups did not differ significantly in terms of age, estimated age of onset, duration of illness, or educational level obtained. As well, the mean Hamilton depression scores for each of the three groups fell within the non-depressed range, and the Blessed scores demonstrated similar mild levels of functional impairment across the three groups.

Univariate $F$ tests were also conducted in order to test the $a priori$ hypotheses that (1) one subgroup would demonstrate relatively lower performance on tests of visual-figural memory and fluid intelligence, while (2) another would show significantly more impairment on tests of verbal memory and crystallized (i.e., overlearned) verbal intelligence. Due to the multitude of $F$ tests conducted, the corrected alpha level required for significance became $0.0006$, in order to maintain a conservative total alpha of $0.01$. However, two measures demonstrated differences between the groups at the $0.002$ level (equivalent to less than total $p < 0.05$), and thus are reported. Subsequently, multiple pairwise comparisons were conducted for the variables which yielded significant differences between the groups via the univariate $F$ tests, in order to determine specifically which of the three groups differed from each other. Tukey’s alternate procedure was selected as appropriate for the multiple comparisons (Jaccard, Becker & Wood, 1984).

The most striking results obtained with respect to the first hypothesis mentioned above. Subgroup 1 displayed a significantly lower PIQ mean (70.75) than subgroups 2 and 3 (83. and 86.5 respectively) ($p < 0.05$). Furthermore, subgroup 1 also demonstrated significantly lower performance relative to subgroups 2 and 3 on the Visual Reproduction subtest of the WMS ($p < 0.05$). Some support for the second hypothesis, was also apparent; subgroup 3 obtained superior VIQ scores to those of both subgroups 1 and 2 ($p < 0.05$). However, there were no differences between the groups on the Logical Memory subtest of the WMS. With regard to mean FSIQ, subgroup 1 performed the most poorly ($M=74$), followed by subgroup 2 ($M=80$), and then subgroup 3 ($M=87$) ($p < 0.05$). Similarly,
Table 12. Means and Standard Deviations for the Three Q-Factor Analysis Derived Subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup 1 Mean (S.D.)</th>
<th>Subgroup 2 Mean (S.D.)</th>
<th>Subgroup 3 Mean (S.D.)</th>
<th>Significant (p &lt; .05) Paired Comparisons‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>71.16(8.17)</td>
<td>69.72(8.21)</td>
<td>73.87(7.26)</td>
<td>None</td>
</tr>
<tr>
<td>EAO</td>
<td>67.42(9.09)</td>
<td>65.68(8.69)</td>
<td>69.00(7.99)</td>
<td>None</td>
</tr>
<tr>
<td>LOI</td>
<td>3.73(2.82)</td>
<td>4.00(2.39)</td>
<td>4.91(3.23)</td>
<td>None</td>
</tr>
<tr>
<td>Education</td>
<td>12.69(3.12)</td>
<td>13.59(2.31)</td>
<td>12.52(3.33)</td>
<td>None</td>
</tr>
<tr>
<td>PSIQ</td>
<td>74.27(14.94)</td>
<td>80.48(9.23)</td>
<td>87.17(13.51)†</td>
<td>1&amp;2, 1&amp;3</td>
</tr>
<tr>
<td>VIQ</td>
<td>78.66(12.70)</td>
<td>79.46(9.93)</td>
<td>90.53(14.38)*</td>
<td>1&amp;3, 2&amp;3</td>
</tr>
<tr>
<td>PIQ</td>
<td>70.75(11.38)</td>
<td>83.00(12.06)</td>
<td>86.47(11.40)††</td>
<td>1&amp;2, 1&amp;3</td>
</tr>
<tr>
<td>MMSE</td>
<td>14.82(5.16)</td>
<td>18.03(4.32)</td>
<td>18.83(4.52)*</td>
<td>1&amp;2, 1&amp;3</td>
</tr>
<tr>
<td>Blessed</td>
<td>7.48(3.67)</td>
<td>6.02(3.67)</td>
<td>5.76(3.11)</td>
<td>None</td>
</tr>
<tr>
<td>Hamilton</td>
<td>5.34(3.30)</td>
<td>5.04(4.12)</td>
<td>5.50(4.01)</td>
<td>None</td>
</tr>
<tr>
<td>TVR</td>
<td>40.69(4.56)</td>
<td>45.03(5.89)</td>
<td>47.83(6.56)††</td>
<td>1&amp;2, 1&amp;3</td>
</tr>
<tr>
<td>TLM</td>
<td>35.33(10.72)</td>
<td>34.62(4.79)</td>
<td>38.35(9.81)</td>
<td>None</td>
</tr>
<tr>
<td>TTAPD</td>
<td>39.55(13.37)</td>
<td>45.93(14.01)</td>
<td>45.59(10.77)</td>
<td>None</td>
</tr>
<tr>
<td>TTAPND</td>
<td>37.84(15.02)</td>
<td>42.97(12.90)</td>
<td>44.24(10.27)</td>
<td>None</td>
</tr>
<tr>
<td>TVRIIPD</td>
<td>38.89(9.25)</td>
<td>38.38(11.36)</td>
<td>40.09(8.88)</td>
<td>None</td>
</tr>
<tr>
<td>TVRIIPND</td>
<td>38.50(10.70)</td>
<td>38.54(13.52)</td>
<td>41.09(9.47)</td>
<td>None</td>
</tr>
</tbody>
</table>

‡Tukey's Alternate Procedure

*p < .002  †p < .0002  †† p < .00001

EAO = Estimated Age at Onset of AD  
LOI = Length Since Onset of Illness (yrs.)  
TTAPD = T-Score for Finger Tapping (Dom.)  
TTAPND = T-Score for Finger Tapping (Non Dom.)  
TVRIIPD = T-Score for Grip Strength (Dom.)  
TVRIIPND = T-Score for Grip Strength (Non Dom.)
subgroup 1 exhibited more severely impaired performance on the MMSE as compared to subgroups 2 and 3. No differences on the motor measures (i.e., grip strength, and finger tapping) were apparent across the three groups. However, correlations computed between finger tapping performance and disease severity (i.e., as assessed by MMSE scores; higher MMSE scores indicate lower levels of impairment) were positive [dominant $r = .45$, $p < .01$; nondominant $r = .33$, $p < .01$]. Correlations between grip strength and level of symptom severity failed to reach significance.
CHAPTER V
DISCUSSION

Summary of Results

The results of this study demonstrated that reliable subgroupings of patients diagnosed with mild to moderate probable AD, each displaying qualitatively distinct patterns of performance on neuropsychological measures, can be identified via Q-type factor analysis. These findings were replicated via three different hierarchical agglomerative cluster analysis algorithms, in addition to a non-hierarchical iterative partitioning technique. Such results are in sharp contradiction to a “stage model” approach to the conceptualization of AD: the subgroups did not differ in terms of duration of illness, and the presence of simultaneous (i.e., non-AD) CNS processes accounting for the qualitative variation is unlikely, given the stringent exclusionary and inclusionary criteria for subject selection. In accordance with previous research, three subgroups were identified. Although all three groups performed similarly on measures of verbal fluency, easy (verbal) paired associates, and perception of overlapping and embedded figures, significantly distinct patterns on other measures were evident. Overall, subgroup 3 appears as the highest functioning of the three groupings. This subgroup demonstrated preserved naming abilities and Block Design performance, although encountered some difficulty copying simple overlapping figures. Subgroup 2 demonstrated severe anomia, in the context of relatively spared visual-perceptual/constructional functioning. Subgroup 1 is marked by severe anomia, mildly to moderately impaired Block Design performance, and a virtual inability to copy a simple drawing of two overlapping figures.

The subgroups identified in this study are not inconsistent with those reported by Martin and colleagues (1986). For example, their globally impaired group may correspond to subgroup 1 of the current study. Furthermore, although clearly less impaired than the subjects studied by Martin et al. (1986), subgroup 2 demonstrates a pattern which may be a precursor to the spared visual-perceptual functioning in the face of severe impairment of accessibility of semantic knowledge pattern identified by these researchers (i.e., LAD). In a similar fashion, subgroup 3 may represent a precursor to the group identified by Martin and
colleagues (1986) as exhibiting relatively intact access to semantic knowledge in the face of impaired visual-perceptual/constructional abilities (i.e., RAD).

Evaluation of Hypotheses

The first hypothesis concerned the initial R-type factor analysis. It was predicted that such analysis would produce two factors, accounting for approximately 70% of the variance, when the following seven test variables were submitted to the procedure: Block Design, Figure-Ground, Copy Task, BNT, COWAT, Animal Fluency, and Easy Associates. The first three measures were predicted to load highly on Factor I, and the second four, on Factor II, as had occurred in the analyses of Martin and colleagues (1986) and Becker and colleagues (1988). This hypothesis was generally supported: two factors did emerge, accounting for just over 60% of the total variance. Variables loading on each factor were as predicted. However, unlike prior studies, Factor I represented the verbal measures rather than the visual-perceptual/constructional ones, and Factor II was characterized by high loadings from the visual-perceptual/constructional measures. Thus, for the current sample, the semantic measures appear to account for a greater proportion of the variance. The measures utilized in the earlier studies appear to be more sensitive than those utilized in this research. Many of those used presently, did not demonstrate significant group differences (i.e., Figure-Ground, Easy Associates, Animal Fluency), resulting in a factor solution accounting for less variance than predicted. This is likely related to generally higher levels of functioning of the subjects in the current sample compared to those utilized in past studies, resulting in a restricted range of scores.

Hypothesis two predicted that three subgroups would be identified by the various clustering techniques. The largest such subgroup was predicted to be comprised of individuals displaying relatively equal neuropsychological impairment on both measures tapping accessibility of semantic knowledge and those gauging visual-perceptual/constructional functioning. A second subgroup was predicted to comprise patients exhibiting relatively intact visual-perceptual functioning coupled by impaired semantic abilities; a third subgroup was predicted to display the opposite pattern. These second two subgroups were predicted to account for approximately equal numbers of the
remaining patients. Furthermore, based on the theoretical model of disease progression presented in chapter two, it was predicted that the first subgroup would contain subjects at all severity levels (i.e., mild, moderate, and severe), while the second two subgroups would only represent mild and moderate cases. It was theorized that the asymmetrical patterns of impairment underlying these groups eventually gives way to global pathology and corresponding diffuse neuropsychological dysfunction. In general, this cluster of hypotheses was supported. The Q-type factor analysis and three hierarchical clustering approaches suggested the presence of three subgroups, and the groups were successfully replicated by the k-means iterative partitioning procedure.

Subgroup 1 is analogous to the first group predicted to emerge. This group represented the majority of patients and was marked by severe anemia and moderate to severe compromise of constructional abilities. Support for the theoretical model of progression was also obtained, in that subgroup 1 evinced significantly greater levels of impairment on the MMSE and FSIQ as compared to the two remaining subgroups. Thus, individuals classified to this globally impaired group (i.e., corresponding to the hypothetical "GAD" subgroup) were more likely to evince greater overall impairment than those assigned to the other two subgroups.

The correspondence of subgroups 2 and 3 to those predicted is less striking, yet present. In accordance with prediction, these two subgroups are comprised of relatively equal numbers of the remaining subjects. Subgroup 2 would appear to correspond to that predicted to exhibit impaired access to semantic knowledge, accompanied by relative sparing of visual-perceptual constructional abilities. This group displayed poor BNT performance ($T$-score = 9.66), while scoring within borderline normal limits on the Block Design ($T$-score = 40.55) and Copy ($T$-score = 39.23) tasks.

Subgroup 3 resembles the group predicted to display sparing of semantic knowledge accessibility in the presence of visual-constructional impairment (i.e., BNT $T$-score = 46.82; Copy $T$-score = 36.61). However, the mean Block Design performance of this group falls just within normal limits ($T = 42.7$), clouding the interpretation of this subgroup’s constructional performance. This subgroup is the least defined, and the discrepancy between the scores on the Block Design and Copy tasks is puzzling. It may be
that this seeming contradiction can be accounted for in terms of the global-local demands of the two tasks. In this manner, while Block Design can be approached with both local and global strategies, it would appear that the pentagon copy task is more dependent on preserved global processing abilities.

The third hypothesis predicted that subgroups 2 and 3 would demonstrate material specific memory loss in the domain maximally impaired. Thus, it was predicted that subgroup 2 would evince higher levels of performance on the Visual Reproduction subtest of the WMS as compared to their score on Logical Memory, while subgroup 3 would demonstrate the reverse pattern. This hypothesis was only partially supported: While the performance of subgroup 2 on the Visual Reproduction test exceeded that on the Logical Memory test, all three subgroups performed better on the Visual Reproduction test than on the Logical Memory test, suggesting that this subtest may be easier for AD patients in general.

Hypothesis four predicted that correlations calculated between scores on the motor measures (i.e., finger tapping and grip strength) and decreasing severity of cognitive symptoms would be positive. This hypothesis originated from the disease progression model. It was theorized, on the basis of past research, that the frontal cortex (and specifically, the motor areas), are spared AD pathology until the advanced phase of the disease. As such, it was reasoned that degree of impairment on these measures should be correlated with MMSE scores. This hypothesis was supported with respect to finger tapping performance: as finger tapping performance declined, MMSE scores dropped, indicating greater degrees of disease severity. However, the correlation between grip strength performance and MMSE scores failed to reach significance.

In accordance with the Goldberg-Costa model of hemispheric specialization, the final hypothesis predicted that those with the RAD pattern (i.e., impaired visual-constructional functioning in the context of relatively better preserved accessibility of semantic knowledge), would display a PIQ < VIQ pattern of performance, suggesting impaired fluid abilities as opposed to overlearned crystallized knowledge. Conversely, the LAD-like group was predicted to display the reverse WAIS-R pattern (i.e., PIQ > VIQ). This hypothesis was supported, as subgroup 2 (LAD-like subgroup) displayed superior
PIQ compared to VIQ, while subgroup 3 (RAD-like subgroup) displayed the reverse pattern.

Limitations of the Present Study

Although the present study yielded some significant findings, several limitations must be noted. The reliability of the scoring criteria developed for the pentagon copy task is unknown. Each individual's drawings were scored by only one investigator, precluding the assessment of interrater reliability. Hence, these results must be interpreted cautiously. Similarly, given the lack of geriatric norms for the Figure-Ground test, and the observation that the three subgroups performed similarly on this measure, these results must also be viewed with caution. Because inappropriate age norms were utilized in calculating the T-scores for this measure, it is quite possible that the suggested impairment across all subgroups represents a normal age-related decline.

Secondly, given that the current sample consisted mainly of highly educated, white, upper middle class individuals, the generalizability of these results is limited to this population. As well, the sample is biased in terms of individuals willing to participate in research.

Thirdly, outliers were not removed from the data prior to analysis. As a result, it is possible that such deviant individuals distorted the patterns obtained. However, given that the same three groups were apparent across clustering approaches, algorithms, and similarity measures, it is unlikely that they interfered in any significant way. Nevertheless, detection and removal of outliers would serve to increase the reliability of the results reported herein. Another limitation of the present research involves the sample size. Although meeting the minimum number of subjects for powerful factor/cluster analytic research, utilization of a larger sample may have improved the stability of the results obtained.

As more of a conceptual limitation, neuropsychologically heterogeneous manifestations of AD may reflect inter-individual differences in brain organization (and hence, distinct patterns of breakdown corresponding to these differences), differential changes in brain organization as a function of age, or the heterogeneity of the normal aging
process itself, which leaves individuals differentially vulnerable to losses in certain areas (Joanette et al., 1992). It is quite possible that cognitive decline associated with normal aging may not proceed in a homogeneous fashion. Thus, neuropsychologically identified subgroups of AD may merely reflect differences in pre-morbid levels of functioning (i.e., pre-morbid strengths and weaknesses). As such, distinct weak areas of neuropsychological functioning before AD strikes may become more pronounced when AD initially begins. If this is true, heterogeneity may not be attributable to AD itself, but to pre-morbid individual differences. Thus, the significance of neuropsychologically defined subgroups may represent regional neuropathological susceptibility rather than distinct evolutionary sequences related to different etiologies (Chang Chui, 1987).

Some support, though minimal, for this potential confounding factor is provided by a cluster analytic study of neuropsychological data collected from healthy elderly individuals (Valdois, Joanette, Poissant, Ska, & Dehaut, 1990). This analysis yielded 6 subgroups, most of which represented quantitative differences, but two of which represented uninterpretable though qualitatively distinct profiles of neuropsychological functioning. Notably, these qualitatively distinct clusters were comprised only of the most severely impaired subjects and they did not overlap with those determined by Martin et al. (1986), Becker et al. (1988), or the present study. Furthermore, the researchers failed to elaborate the extent of their exclusionary screening process beyond simply stating that the subjects were, “without obvious clinical signs of brain damage or psychiatric disorders” (p. 589). Given these weak inclusionary criteria, it is quite possible that early AD patients with subtle signs were not screened out. In spite of these limitations, the Valdois et al. study is valuable as a caveat to overinterpretation of subgroup study results. More stringently designed studies (i.e., utilizing health screening criteria similar to those suggested by the NINCDS-ADRDA Work Group) of normal elderly individuals will surely resolve this issue.

Another limitation of this study, which could not be controlled, involves the source of the data. Due to the research criteria for the diagnosis of AD, which require deficits in at least two areas of neuropsychological functioning, one of which is memory, AD patients presenting atypically may have been excluded from the database utilized in this
investigation (Becker et al., 1992; Martin, 1990). Identification of subgroups very early in their development represents a challenging task, and clearly the results of the present study are limited in this regard.

Directions for Future Research

Future research should be directed toward improving upon the above noted limitations of the current investigation. In such a manner, this research requires replication on a larger, independent, more representative (i.e., of minorities and low SES groups) sample. In addition, it would be beneficial to repeat the current analyses utilizing data collected from cognitively intact normal elderly controls (e.g., spouses of current subjects; non-neurological medical sample), in order to ensure that the three subgroups do not exist amongst such individuals. As well, longitudinal research in which individuals from the three subgroups are followed and re-evaluated yearly would be beneficial in directly delineating further patterns of progression. Such outcome research would be beneficial in determining prognostic differences. Future subgrouping studies should include patients with possible AD, in order to prevent exclusion of atypical early presentations of AD. Neuroimaging studies on members of the individual subgroups would allow for external validation of the classification scheme suggested herein. Finally, research endeavours involving neuropsychological functioning of AD patients should perform within-group comparisons, in order to allow differences between these subgroups to be realized.
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Appendix

Scoring Criteria for Pentagon Copy Item from the MMSE

A. Figures are rotated correctly* (1 point)
B. Two distinct figures are apparent* (1 point)
C. The two figures are approximately the same size* (1 point)
D. One figure overlaps the other* (1 point)
E. The figures have 5, roughly equal sides (i.e., less than 1 cm discrepancies) (1 point)

Maximum score = 5
Tremor is not penalized by the scoring system

*Regardless of whether the figures are pentagons
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