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A COMPARATIVE STUDY OF MEMORY RETRIEVAL AND SCANNING SPEED IN PARKINSON'S DISEASE AND SENILE DEMENTIA OF THE ALZHEIMER TYPE: IMPLICATIONS FOR THE CONCEPT OF FRONTO-SUBCORTICAL SYNDROME.

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Thesis presented to the School of Graduate Studies of the University of Ottawa as partial fulfillment of the requirements for the degree of Doctor of Philosophy

ISBN 0-315-40714-X

UNIVERSITÉ D'OTTAWA
UNIVERSITY OF OTTAWA

ACKNOWLEDGEMENTS

This research was carried out under the supervision of Donald T. Stuss, Ph.D. Dr. Stuss was, throughout, generous with his time and knowledge, and provided the much needed encouragement at those times when the perils of doing research with patient populations weighed heavily on me.

I also extend my sincerest thanks to my thesis board: Dr. D. Buchanan, Dr. H. Edwards, and Dr. T. Picton, for their much needed advice and criticism of the research project during the preparation phase. I would also like to thank the late Dr. P. McCormack, for his advice in the development of the memory paradigm.

Dr. R. F. Nelson's willingness to refer patients for the project, and his close collaboration with respect to neurological issues which arose, made this project possible.

My gratitude is also extended to Dr. D. Grimes of the Parkinson's disease clinic of the Ottawa Civic hospital, for refering patients.

I am especially indebted to Edna Leech, who developed the computer program that controlled the experimental procedure, Gilles Hamel whose technical expertise was invaluable, Sandra Champagne who helped in the testing of subjects, and Wayne Durham for his advice on statistical procedures. It is, however, not only their time and expertise that were appreciated, but also their friendship and support.

Finally, I would like to thank the Canadian Geriatrics Society -

for their partial funding of this research project.

CURRICULUM STUDIORUM

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Abstract

An experimental neuropsychological study was undertaken to investigate speed of short-term memory scanning, and the ability to retrieve learned material under two specified sets of conditions. In addition to a NC group, two groups were studied; one, a group of patients whose presumptive diagnosis implies primarily cortical pathology, and a second group of patients whose diagnosis implies primarily subcortical pathology. They were compared in order to determine whether slowed scanning and/or a retrieval deficit characterize subcortical dementias, and also to distinguish them from cortical dementia. Twelve non-demented Parkinsonian patients (M age = 58.3) were compared to twelve mildly demented patients with SDAT (M age = 67.0), and both of these groups were compared to a group of twelve normal control subjects (M age = 58.9) firstly on a task which allowed separation of the speed of specific cognitive operations from the speed of motor responses, and secondly on a memory task where both organization at learning and retrieval strategies were manipulated. The results of the memory scanning task showed that the groups differed neither on the motor component nor on the purely cognitive components. However, despite intact scanning abilities, some patients with Alzheimer's disease required a structured method of learning to achieve a successful performance of the task, while others could not perform it even with additional structure. The results of the memory

task revealed that, although both PD and SDAT patients show memory deficits, the impairment shown by PD patients is milder and can be restored to normal levels through cueing whereas cueing does not improve the performance of SDAT patients who show a large word loss independently of the method of learning or of retrieval. The pattern of memory deficit shown by the Parkinsonian patients is best described by the word 'forgetfulness' whereas 'amnesia' more accurately describes the deficit shown by patients with Alzheimer's disease. The theoretical implications of these results for the concept of subcortical dementia are discussed.

Introduction

The etiology of dementia, and the relationship between ageing and cerebral disease, are complex and not well understood. Ageing in an individual does not necessarily imply the presence of disease (Peiffer, 1981), but in a large population it is associated with an increased incidence of various diseases (Cummings & Benson, 1984; Eslinger, Damasio, Benton & Van Allen, 1985). In particular, it is associated with a markedly increased incidence of those diseases of the brain which can cause dementia. It has been predicted that the elderly population of the United States will reach 30 million just fifteen years from now. Given a prevalence of 6.5 percent amongst the elderly for moderate to severe dementia (Roth, 1985), it follows that by then the United States Health Department will have to provide services for at least 2 million demented patients. The Canadian elderly population by the end of the century is expected to reach 3.5 million, so that at least 230,000 demented patients will require services from Health and Welfare Canada (Health and Welfare Canada, 1984). Any effective attempt to provide essential medical, social, and psychological services for these individuals will have to be founded upon both a clear understanding of the concept of dementia, and on scientific demonstration of the specific effects of the various etiologies of dementia. These issues will be addressed in sections 1 and 2 following. Section 3 will describe one current theoretical

framework relevant to the present work. In particular, it will conceptualize the dementias as a variety of clinical syndromes which arise from various underlying causative diseases of two general sorts; namely, those thought to be secondary to cortical damage, and those thought to be secondary to subcortical damage. The validity and usefulness of this recent conceptualization will be examined.

Dementia: An Historical Perspective

An adequate history of the concept of dementia has yet to be written, and, to date the term has no single universally accepted definition (Wells, 1977). For this report a stated definition will be adhered to throughout.

For as long as individuals have been able to think and communicate, they have been able to notice the appearance of deficiencies in the higher functioning of others. For two-and-a-half millenia, observations of such deficits have appeared in legal and medical contexts. For example, in the 5th century BC Sophocles was accused of being demented by his son and was forced to demonstrate his own mental competence by writing a play (his tragedy, "Oedipus in Colon") (Roccatagliata, 1986). A physician in the 1st century AD, Celsus, made reference to dementia as a disorder that was well known at that time (Mahendra, 1984).

Surprisingly, dementia as understood as early as the 4th century AD already contained the three essential core concepts which

characterize present-day usage. At that time Oribasius "wrote of cerebral atrophy... (which) was thought to manifest itself in a loss of intellectual capacity...(and he) tried to relate the condition to the ageing process..." (Mahendra, 1984, p.3). The three core concepts here, which have remained central down to the present time, are that dementia refers to acquired deficits in higher intellectual functioning that are somehow related to ageing and/or cerebral disease. In the 19th century the term still retained this connotation. Esquirol (1845, p. 417), for example, defined "senile dementia" as "a cerebral affection ...characterized by a weakening of the sensibility, understanding and will, ...(which) results from the progress of age." Other 19th century writers did not differ conceptually from him. Rather, they furthered his careful description of the clinical findings characteristic of the dementias through attempts to refine their diagnostic classifications. Pritchard (1835) classified dementias into primary (e.g., mania, apoplexy) and secondary (paralysis). Willie (1873/4) differentiated the diagnosis of senile dementia from dementia due to general paresis, twenty years before the pathological diagnosis of general paresis became possible. Later, Binswanger (1898) introduced the distinction between pre-senile and senile dementia; and, Kraepelin (1898) introduced the concept of organic dementia in order to distinguish what was traditionally referred to by the term dementia from his new dementia praecox (now called schizophrenia). In addition, Lipowski (1980) has pointed out that during the 19th century the distinction between dementia on the

one hand, and mental confusion and delirium on the other, became clear.

At the turn of the present century, then, dementia clearly refered to higher functional losses, either due to organic disease of the nervous system, or a process in the senium (ageing) (Mahendra, 1984).

Although the term 'dementia' has sometimes been used loosely between the 4th and 20th centuries, and has consequently been confused at various times with madness or mental confusion, it nevertheless invariably included these three core concepts. Recently, its usage has become more restricted, and so more precise, and is largely confined to those three concepts. The obvious historical consistency of these central concepts, both over time, and between various writers at any given time, provides testimony for our accurate perception of the lived reality of the loss of mental functioning we can be heir to, either through brain disease or ageing.

Today, attempts to further refine the term persist (Isaacs, 1983; Jorm & Henderson, 1985; Mesulam, 1985). A typical modern clinical definition is the following one given by Cummings and Benson (1983):

> Operationally, dementia can be defined as an acquired persistent impairment of intellectual function with compromise in at least three of the following spheres of mental activity: language, memory, visuospatial skills, emotion, or personality, and cognition (abstraction, calculation, judgement, etc.) ....

> The stipulation that the intellectual impairment must be acquired distinguishes dementia from the congenital mental retardation syndromes .... Persistence is included as a criterion to exclude confusional states. (p. 1)

Having defined in detail these clinical characteristics of their manifest 'dementia syndrome', they go on to point out its connection with ageing and disease. They state that most dementias are found in people over the age of 65 years, and they then list various diseases which impair cerebral function so as to effect the clinically observed 'dementia syndromes'. They also make reference to the APA's DSM III (1980) definition of Primary Degenerative Dementia, a new term defined as 'organic mental deterioration without obvious aetiology' - a reference to those dementias traditionally seen as associated with, and possibly a consequence of, ageing, rather than of a discrete disease process. The increased precision, and the central core concepts are clear in this typical modern definition.

The present thesis arose from very recent published suggestions that there are two basic patterns of behavioural impairment that constitute two discrete, different dementias, within the wider dementia syndrome as we have known it over many centuries. In an unprecedented manner, each of the two types of dementia was said to be caused by a specified locus of pathologic change; one by cortical damage, the other by subcortical damage.

A Recent Controversy: Cortical versus Subcortical Dementia

A series of new classifications appeared during the course of the twentieth century. For example, the dementias were classified on the basis of their being either treatable (e.g. normal pressure hydrocephalus, pseudodementia) or untreatable (e.g. Alzheimer's disease, multi-infarct); or, according to the character of any underlying disease process, e.g. degenerative (e.g. Alzheimer's disease), infectious (e.g. cerebral disease), genetic (e.g. mongolism), etc., and so on. Sufficient confusion arose out of these numerous classifications for the term to fall into disuse in the United States in the 1950's for a brief period (Wang, 1977; Wells, 1977). It was replaced by the somewhat vague phrase 'chronic brain syndrome' (DSM-I, 1952). By the late 1960's, the term dementia was re-introduced as a sub-category of psychosis, associated with organic brain syndrome, and was classified into 'senile or presenile' (DSM-II, 1968).

Despite this confusion and the consequent changes in the popularity of the term, general agreement has emerged that it should continue to be used. Specifically, it is agreed that it should be used to describe an acquired loss of higher function secondary to underlying neuropathologic change due either to disease, ageing or both. Clearly, it has communicative value when used in this manner, and so has survived changes in diagnostic fashion.

More recently, a new clinical approach to the dementias has been described, based on the work of Albert, Feldman & Willis (1974), McHugh and Folstein (1975) and Cummings and Benson (1984). This classification, unlike the various 19th and 20th century classifications which preceded it, is radical in that it potentially widens the long-standing core concepts for the first time. It divides them on the basis of the presumed site of their primary causal pathologic changes, into 'cortical' and 'subcortical' (the latter is now sometimes called 'fronto-subcortical').

Having analysed the intellectual disturbances seen in five patients with supranuclear palsy, Albert et al. (1974) abstracted a clinical profile with the four following features: (1) "some form of memory deficit," (2) "a general slowing down of intellectual activity," (3) "alterations of personality -typically, inertia or apathy; occasionally with episodic irritability," and (4) "impaired ability to manipulate acquired knowledge" (p. 129). A review of the literature of other reported cases of progressive nuclear palsy provided supportive evidence for the occurrence of this clinical pattern. Other 'subcortical' diseases (for example, thalamic tumors, olivoponto-cerebellar degeneration, Parkinson's disease) also appear to share features of this clinical pattern.

The absence of difficulties in language and praxis, and the link between deficits in memory and learning and the slowness of intellectual function and inertia in these 'subcortical' diseases prompted Albert et al. (1974) to label the new clinical syndrome

'subcortical dementia' in order to contrast it with those different pattern of cognitive change traditionally thought to follow cortical damage.

In an independent report, McHugh and Folstein (1975) described a specific pattern of intellectual disturbances in eight patients with Huntington's chorea. They described their syndrome as consisting of (1) "a slowly progressive dilapidation of all cognitive powers", (2) "a prominent psychic apathy and inertia that worsens...", (3) "an absence of aphasia, alexia, cortical blindness or Korsakov-like amnesia" (p. 274). McHugh & Folstein believed it to be present in other diseases with subcortical pathology, such as Parkinson's disease, but they suggested that it was not present in diseases with a primary site of pathologic change in the cortex, such as Alzheimer's disease. They also used the term 'subcortical dementia' for the clinical syndrome they had described (McHugh & Folstein, 1975).

The characteristics of the cortical and subcortical syndromes are presented in Tables 1 and 2. As the Tables show, a primary conceptual difference is that, here-to-fore, 'dementia' referred to global deficits in higher cortical function (activities of communication, perception and praxis), rather than to deficits comprised of a group of several more specific losses such as inability to learn new material, set shifting, rate of information processing, along with the specific absence of aphasia, apraxia, etc. This is why this newest classification is more radical than any of its predecessors.

From its inception, the term "subcortical dementia" has been

Table 1

Subcortical Dementing Disorders: Behavioral Phenomenology

Activity	Slowing of thought, comprehension, verbalization movement (psychomotor retardation)
Memory	Forgetfulness
Cognition	Dilapidation
Personality	Decreased drive, apathetic, perplexed

From Benson, 1984

Table 2

Cortical Dementing Disorders: Behavioral Phenomenology

Activity	Spry, active
Memory	Amnesia
Cognition	Severely disturbed
Visuospatial Skills	Severely disturbed
Language	Anomia
Personality	Unconcerned, unaware

From Benson, 1984

controversial (Katzman, 1978; Roth, 1978). Marsden (1978) soon pointed out that alterations in mental function in the subcortical dementia of Parkinson's disease do not have the quality of a global decline in higher mental function characteristic of a "true dementia" (i.e., characteristic of the dementia of very long-established usage). Rather these patients "show a lack of drive and initiative" with "slowness of thought process and memory". He therefore argued that the term 'dementia' is incorrect when applied to these highly specific changes. He suggested the alternative term 'subcortical-frontal lobe syndrome' to emphasize the similarity he had observed between the changes observed with subcortical pathology, and those generally associated with frontal lobe pathology.

Shortly after introducing it, Albert (1978) himself expressed caution about the label "subcortical dementia". He described it as "shorthand", and stressed that he intended to describe "a fronto-subcortical problem". He suggested that "frontal system or fronto-subcortical dementia" might be more appropriate than simply subcortical dementia. Unlike Marsden (1978) and Roth (1980), he did not question the use of the term dementia in this context. This, despite the fact that his own results in 1978, four years after proposing the notion of subcortical dementia demonstrate unequivocally that the Parkinsonian patients, an example of his subcortical dementia, function in precisely the normal range when tested for dementia.

Roth (1980) states that the term dementia must be reserved for

"states of global deterioration of intellect and personality" (p.11) if we are to pursue ongoing useful refinement of the well-established concept, and maintain clear distinctions between discrete clinical syndromes. He clearly argues for our adherence to the long-standing usage outlined above, and maintains that the use of the term 'dementia' in the label 'subcortical dementia' is a misnomer which has caused unnecessary confusion. This is so, he suggests, despite the fact that the description of the observed clinical syndrome itself remains a useful contribution to our further understanding of one of the possible consequences of brain diseases.

Others, too, have opposed the division of the dementias according to a cortical-subcortical neuroanatomical model, pointing out that pure cortical or subcortical dementias do not exist (McHugh, 1978; Terry, 1978; Albert, 1978). On the one hand, in Alzheimer's disease neuronal loss has been reported in several subcortical nuclei, including the cholinergic cell bodies of the septum, the diagonal band of Broca, the Meynert nucleus, the noradrenergic neurons in the locus coeruleus, and the serotonic neurons in the dorsal raphe nucleus (Rubèrg et al., 1982; Whitehouse, Hedreen, White III, & Price, 1983; Whitehouse, Price et al., 1982). On the other hand, cortical changes have been reported in demented patients with Parkinson's disease (Alvord, 1971; Boller, Mizutani, Roessmann & Gambetti, 1980; Gaspar & Gray, 1984; Hakim & Mathieson, 1979; Jellinger & Grisold, 1982). These latter cortical changes are indistinguishable from some of those found in demented patients with Alzheimer's disease. Hence, it has

been suggested that these dementias should be called 'fronto-subcortical' or 'frontal system' dementias (Albert, 1978; Freedman & Albert, 1985; Freedman, 1985) rather than the more restrictive subcortical dementias.

This controversy remains unresolved (Benson, 1983; Benson, Cummings & Kuhl, 1981; Cummings and Benson, 1983). In a careful appraisal of the current situation, Whitehouse (1986) has recently pointed out that "systematic studies comparing different dementias have not been performed" (p.1). Specifically, he states "no comparative studies of the speed of mental processing have been published to determine whether slowness of cognition is more characteristic of subcortical than of cortical dementias (2)." He adds that "slowness of cognitive activity (bradyphrenia) is said to characterize patients with Parkinson's disease", and that "whether any actual differences in speed of mental activity (rather than physical activity) exist among different dementias should be tested experimentally" (p.2).

The present study addresses this suggestion by investigating memory retrieval and speed of memory scanning in three separate populations. It compares a group of patients with a subcortical disease with a group of patients with a cortical disease, and both of these with a group of normal control subjects.

Summary and the Present Project

Parkinson's disease, a primarily subcortical disease, is said to be characterized clinically by the presence of slowed thought, forgetfulness, apathy, and an absence of aphasia, agnosia, and apraxia; that is, it is said to be characterized by a subcortical dementia. In contradistinction, the presence of the three latter deficits is recognized as commonly characterizing the dementia of, for example, Alzheimer's disease, a primarily cortical disease, where they are accompanied by amnesia but not by slowed mentation.

An experimental neuropsychological study was undertaken to investigate two aspects of these dementias. In particular, speed of short-term memory scanning, and the ability to retrieve learned material under two specified sets of conditions, were measured in patients whose (presumptive) brain disease is primarily cortical (Alzheimer's disease), and these were compared with those observed in patient's whose brain disease is primarily subcortical (Parkinson's disease). Both were compared to similar measurements made on a group of matched controls.

Parkinson's Disease

Signs and symptoms.

In the early 19th century James Parkinson perceived that several motor signs and symptoms, taken together, formed a distinct clinical

entity. His 1817 monograph on the "Shaking Palsy" opens with this succinct description:

> Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and the intellects being uninjured. (p.1)

His perception was accurate and there has been no subsequent controversy over those signs and symptoms, with the one exception of his final statement that higher functions remained intact. His claim that signs and symptoms of deficits in higher function are uniformly absent has remained controversial throughout the 19th and 20th centuries, and has given rise to the above-mentioned confusion in the literature.

For persons over 50 years of age, the prevalence of Parkinson's disease is 1 in 200 (Marsden, 1983). Its clinical motor dysfunctions include tremor, rigidity, postural change, and bradykinesia. These dysfunctions often appear insidiously and progress gradually, with accompanying tremor and gait changes, ending many years later with severe disability resulting mainly from progressive akinesia and postural instability. Tremor is characteristically present at rest, as James Parkinson said, and in the early stages it is inhibited by limb movement. It has been reported as the initial complaint of 70% of patients with idiopathic Parkinsonism (Hoehn and Yahr, 1967). Rigidity, which is rarely symptomatic early in the disease, is detected clinically as resistance to passive movement: "Cogwheeling rigidity"

-a jerking sensation often observed on passively stretching a hypertonic Parkinsonian muscle --results from a combination of rigidity and tremor (Brain & Walton, 1969). Postural changes, including generalized flexion of the limbs, neck, and trunk, and postural instability during movement are not prominent in the early stages of the disease. Bradykinesia, the slowness and impoverishment of voluntary movement without weakness, includes an inability to initiate (akinesia), or to execute, (hypokinesia) normal movements. It is thought to partially account for several other signs of the disease, such as the mask-like facies, reduced blinking, and monotonous speech. It may also account for the characteristic early clumsiness of fine finger movements and micrographia (Barbeau, 1984; Rice, 1984).

Parkinson's disease and other extrapyramidal disorders are associated with abnormalities of the basal ganglia (Fahn, 1985), and are characteristically manifested by a combination of abnormal involuntary movements, alterations in muscle tone, and disturbances in postural stability. This clinical evidence has prompted Marsden (1982) to conclude that the basal ganglia is essentially an "organ of motor control" (Marsden, 1983). A summary of the relevant neuroanatomy of the brain regions associated with Parkinsons's disease is reviewed in Appendix 1. A summary of its pathology follows.

Pathology

James Parkinson hypothesized that the Shaking Palsy originated in a

damaged cervical spinal cord and lower brainstem. Preservation of intellectual function had suggested to him that the cerebral hemispheres were spared (Parkinson, 1817). The midbrain and substantia nigra were first implicated by Blocq and Marinesco (1893) who noted the presence of a circumscribed lesion in this region at necropsy. Trétiakoff (1919, in Calne, 1971) was the first to observe a variety of more detailed degenerative features and a reduction in the number of pigmented cells in the substantia nigra. Lewy (1913, in Brain & Walton, 1969) described concentric hyaline cytoplasmic inclusions (now called Lewy bodies) which can be seen in melanin-containing cells in the nucleus substantia innominata in almost every case of Parkinson's disease. However, he failed to observe the neuronal fallout in the substantia nigra. Foix (1921) observed a consistent fallout of pigmented cells from the substantia nigra, whereas Hassler (1938) found lesions of both the substantia nigra and locus coeruleus, the most marked neuronal loss being in the central part of the zona compacta of the substantia nigra. Cell loss was also observed in the substantia innominata. Lesions of the corpus striatum were present in some cases but not in others. Klaus (1940) confirmed Hassler's findings when he compared 32 cases of PD with 22 controls. All thirty-two cases had lesions in the substantia nigra, consisting of cell loss, degenerative cell changes, Lewy bodies, and gliosis. None of his 22 controls had any of these lesions. Greenfield and Bosanquet (1953) showed that nigral cell loss and Lewy bodies were constant findings in Parkinson's disease whereas striatal lesions corresponded

with those found in brains from non-Parkinsonian elderly subjects.

The primary pathologic abnormality found in the brains of patients suffering from Parkinson's disease is now generally agreed to be a degeneration and death of pigmented neurons in the pars compacta of the substantia nigra. This loss of nigral cells leads to a marked functional impairment of the nigro-striatal pathway and a reduction of the dopaminergic synaptic input to the caudate and putamen (Hornykewicz, 1966). The loss of dopamine content varies from one nucleus to another. For example, approximately 90% of the dopamine content in the putamen is lost, whereas a comparative reduction of approximately 64% has been measured in the caudate nucleus (Hornykiewicz, 1981). The unevenly depleted dopaminergic input into the neostriatum has been confirmed by Kish et al. (1985). The nigrostriatal fibers projecting from the medial section of the nigra to the caudate appeared to be the least depleted, whereas the caudal fibers projecting to the putamen were most depleted. The relationship between the uneven loss of dopamine, on the one hand, and the clinical picture of Parkinson's disease, on the other, remains unknown. Lewy bodies, eosinophilic inclusion bodies composed of protein of unknown origin, also characterize this disease and are located in the degenerating pigmented brainstem neurons of both the nigral neurons and locus coeruleus. It is noteworthy that Lewy bodies are found also in about 4% of brains from patients without Parkinson's disease. It has been hypothesized that these patients may have had subclinical cases of Parkinson's disease (it is known that 80 per cent of the zona

compacta must degenerate before clinical symptoms appear). Other areas where Lewy bodies are found in this disease include the substantia innominata, the lateral grey horn of the thoracic cord, and sympathetic ganglia.

The Prevalence of dementia in Parkinson's disease

The losses in higher function in Parkinson's disease are not as clearly documented as are its physical signs and symptoms, and its pathology. The first full report on any possible associated deficits in higher functioning in Parkinsonian patients appeared in 1880-82 (Mallié, 1908). Clinical observations on institutionalized patients had led several physicians to remark on the altered intellectual status of Parkinsonian patients (Charcot, 1875; Grasset, 1879; Luys, 1881). Charcot (1875) had pointed out that "à un moment donné l'intelligence s'obscurcit et la mémoire se perd", and said this appeared as a late complication in the course of the disease. Others, too, consistently stressed the impairment in memory, and the loss of intelligence (Grasset,1879; Luys,1881; Ball, 1882; Axenfeld & Huchard, 1883). Parant (1883) reported that all of the authors he had reviewed referred to "la débilitation mentale, et la perte, plus ou moins complète des diverses facultés." Compin (1902) thought that patients could be divided into two categories, one group with primarily emotional difficulties, and a second group with "des individus dont l'intelligence est réelement touchée, plus ou moins obtuse, suivant

les cas. La mémoire s'est dissipée; le sujet, plonge dans une hébétude intense" (p.15).

The controversy over the presence or absence of cognitive impairment in Parkinson's disease at Mallié's time (1908) led to at least three quite different positions being put forth. One suggested that there was no global impairment of higher mental functions in Parkinson's disease (Brissaud, 1895; Lamy, 1905; Parkinson, 1817; Wollenberg, 1899). A second suggested that any observed impairment was caused by other superimposed diseases (Ballet, 1903, Lamarche, 1898-99; Carrayrou, 1902-1903). A third view was that deficits in higher mental functions were common in patients diagnosed with PD and that the underlying disease process caused those deficits (Ball, 1882; Parant, 1883; Roger, 1885). Despite such controversy, virtually all writers agreed that the clinical picture included memory deficits, and many mentioned mental slowing (Ball, 1882; Compin, 1902; Mallié, 1908). There were, nonetheless, a small number of workers who agreed with James Parkinson's remark 80 years earlier, that there was no loss in higher function (Brissaud, 1895; Lamy, 1905; Wollenberg, 1899).

Early in the course of the disease, simultaneous with the memory deficit, patients appeared to respond more slowly than might be expected in social situations (Ball, 1882). For example, clinically they would respond slowly with answers to questions, one of the cluster of clinical characteristics that was subsequently labelled 'bradyphrenia' to indicate an assumed underlying slowness in thinking (Wilson, 1955). As early as 1882, Ball described one patient in the

following way: "La mémoire ...s'est affaiblis. Le travail de la pensée est lent et difficile. Un poids invisible semble écraser l'intelligence et ralentir à la fois les perceptions, les movements et les idées (p. 26)." Mallié (1908, p. 12) noted that "les idées sont lentes à se former comme à se combiner." Compin (1902) writes of the initial intellectual changes in the following manner:

> Malgré une certaine "raideur" de la pensée, un léger ralentissement de l'idéation, malgré aussi ce masque trompeur qui leur donne l'aspect de gens indifférents ou hébétés, les parkinsoniens conservent toute leur lucidité d'esprit au cours de l'affection dont ils sont frappés. Ce n'est habituellement qu'à la période ultime de celle-ci que l'intelligence est touchée...(p. 44)

thus stating that slowness of thought occurred in the presence of otherwise intact mentation.

Most early clinicians agreed that if dementia appeared in Parkinson's disease it did so only late in the disease and towards the end of life. Some writers took this to be evidence for the presence of a separate complicating disease (Ballet, 1890; Carrayrou, 1902-03; Lamarche, 1898-99), while others did not (Brissaud, 1895; Lamy, 1905; Parkinson, 1817; Wollenberg, 1899). Virtually all agreed there were memory deficits (Axenfield & Huchard, 1883; Ball, 1882; Charcot, 1875; Comprin, 1902; Grasset, 1879; Luys, 1881; Parant, 1883), and a few reported the presence of apparently slowed thinking (Ball, 1882; Mallié, 1908; Compin, 1902).

The attempt to clarify whether or not there are higher losses amounting to a dementia in Parkinson's disease continues today. Pirozzolo, Hansch, Mortimer, Webster and Kustrowski (1982) state that the question regarding changes in mental status in Parkinson's disease has generated more controversy than has the same question with respect to any of the other neurologic diseases characterized by central degenerative processes. Various investigative techniques which have attempted to establish the presence and nature of any dementia in Parkinson's disease have included community studies, clinical observations and neuropsychological studies. Table 3 summarizes those studies that have failed to find dementia as part of the complex of symptoms and signs of Parkinson's disease, whereas Table 4 presents those studies that have reported a strong clinical impression of the presence of a dementia specifically associated with Parkinson's disease. Table 5 presents some studies that have reported both specific neuropsychological deficits as well as more generalized (higher functional) deficits. Finally, Table 6 summarizes the actual incidences of global dementia recorded in Parkinson's disease in some of the reviewed studies reporting an associated dementia.

The studies summarized in Table 6 show an incidence of dementia varying from 14 percent to 93 percent. This wide range in prevalence rates may be partly accounted for by the methodological weaknesses in the design of these studies, including: 1. the pooling together of Parkinsonian patients of diverse etiologies; 2. the frequent use of poorly quantified mental status examination material; 3. the use of

Table 3

Authors, Dates, Methodology and, when Available, Number of PD Patients in Papers that Found no Association Between Dementia and Parkinson Disease. (C = Clinical Evaluation; P = Formal Psychological Tests; R = Literature Review)

Authors and Dates	Method	n
Parkinson, 1817	C	6
Wollenberg, 1899	C	-
Oppenheim, 1911	C	-
Konig, 1912	C	5
Wilson, 1921	C	-
Patrick and Levy, 1922	C	140
Bostroem, 1922	C	-
Schwab et al., 1951; Schwab, 1956	C	-
Diller and Ricklan, 1956	P	112
Doshay, 1960	C	-
Talland, 1962	P	45
Asso, 1969	P	31
Levita and Ricklan, 1970	P	32
Ajuriaguerra, 1971	P	142
Parkes et al., 1974	C	12
Damasio and Castro-Caldas, 1975	R	-
Matthews and Haaland, 1979	P	-

From Boller, 1980

Table 4

Authors and Dates of Papers Expressing the Clinical Opinion that Dementia can be Found in PD

Authors	Dates
Charcot and Vulpian	1861; 1862
Charcot	1875
Walshe	1955
McFie	1960
Ryan	1971
Drachman and Stahl	1975

From Boller, 1980

Table 5 ·

Authors, Dates, and Number of Patients of Studies that have Found a Neuropsychological Deficit in PD Patients

Authors and Dates	n
A. Specific Deficit:	
Talland and Schwab, 1966	50
Teuber and Proctor, 1964	38
Proctor et al., 1964	38
Horne, 1971; 1973	11
Bowen et al., 1972	136
Danta and Hilton, 1975	66
Bentin, Gordon, and Silverberg,	32
B. Generalized Deficit:	
Hardyck and Petrinovich, 1963	33
Warburton, 1967	140
Reitan and Boll, 1971	25
Pearce, 1974	-

From Boller, 1980 .

Table 6

Incidence of Dementia in Parkinson's Disease

Authors and dates	%
Mjones, 1949	40
Pollock and Hornabrook, 1966	20
Hoehn and Yahr, 1967	14
Loranger et al., 1972	37
Martin et al., 1973	81
Lieberman et al., 1974	22
Martilla and Rinne, 1976	29
Mindham, 1970	33
Sweet et al., 1976	33
Celesia and Wannamaker, 1972	40
Lieberman et al., 1979	32
Pirozzolo et al., 1982	93
Hakim and Mathieson, 1978; 1979	56
Boller et al., 1980	55

unclear and operationally undefined diagnostic criteria; and, finally, 4. the failure to include control groups.

Community surveys such as Pollock and Hornabrook (1966), Martilla and Rinne (1976) and Rajput, Offord, Beard and Kurland (1984) estimate dementia incidences of 20%, 29% and 18% respectively. However, Pollock and Hornabrook (1966) did not have specific criteria for the diagnosis of dementia, and used the term to refer to non-specific mental change. Furthermore, their figure of 20% included many patients with an additional diagnosis, such as arteriosclerotic disorder. Martilla and Rinne (1976) developed their own criteria for the diagnosis of dementia and found the prevalence of dementia to be 29%. Like the former study, patients with arteriosclerotic Parkinsonism (54.6%) were found to be more often demented as compared to those without (18.2%) with a spread of 15%, mild, 5.8%, moderate and 5.4% severe. Furthermore, neither study was controlled. Rajput et al. (1984) used medical records as his source of information for both Parkinson's disease and medical-control subjects and estimated that dementia occured in 18.4% of patients as compared to 5.5% in the normal control.

In addition to the methodological weaknesses already mentioned, all three of these community studies also suffer from other difficulties such as failure to control for drug toxicity, depression and other psychiatric disorders, as well as for superimposed disease processes (such as metabolic or infective disorders), and trauma, all of which are known to affect memory (Brown and Marsden, 1984). It has

been proposed that a ratio of 10% to 15% represents a more realistic risk for global dementia in Parkinson's disease, once correction has been made for these design errors (Brown & Marsden, 1984). This ratio is close to that observed by Rajput et al. (1984), and is consistent with the 8% figure observed by Taylor, Saint-Cyr and Lang (1985) and the 15% reported by Lees (1985) who both did careful well-controlled prevalence studies.

Of particular interest in these studies is the consistent observation that mild memory deficits, of undescribed nature, are present early in the disease.

Matthews and Haaland (1979) suggest that heterogeneity of both patients and testing procedures used may have led to the disagreement amongst reported prevalences of dementia. In a well-controlled study, they confirmed the presence of cognitive impairment but described it as minimal. They stressed that the use of "the label 'dementia' in patients with Parkinson's disease is often inaccurate and misleading" (Matthews & Haaland, 1979, p. 955). They observed the deficits to be more common in patients with symptoms lasting more than 6 years, but found that the cognitive deficits in the 6 to 15 year group were still mild.

In another study of the prevalence of dementia in Parkinson's disease, Mindham, Ahmed and Clough (1982) suggested that, notwithstanding the methodological limitations of the mode of assessment used, there appears to be a sub-group of patients with Parkinson's disease in which global dementia is a regular feature.

They note that bradyphrenia, or slowness of thought, is taken to be a common component of Parkinson's disease whether or not there is a dementia, and it is therefore not a necessary precursor to the global dementia that they found had afflicted a minority.

Despite this controversy, there is general agreement that some form of cognitive impairment is present in Parkinson's disease, although its nature and incidence remain controversial. It has been suggested that some of the intellectual changes that occur are not due to the subcortical pathologic changes alone, but rather result from a superimposed Alzheimer's disease.

Evidence for the co-existence of Parkinson's and Alzheimer's diseases

Recent evidence (Alvord et al., 1974; Boller, 1980; Boller, Mizutani, Roessmann & Gambetti, 1980; Hakim & Mathieson, 1979; Victor, 1978) has suggested that the division of dementia into two well-delineated clinical types associated with anatomically localized pathologic changes (cortical-subcortical) has not fared well. The presence of Alzheimer-type cortical pathology (neurofibrillary tangles and senile plaques), and the depletion of cortical acetylcholine in the brain of demented patients with Parkinson's disease, has suggested that the (true) dementia sometimes observed in Parkinson's disease patients was due to the co-existence of Alzheimer's and Parkinson's diseases, the dementia being an expression of the cortical pathologic changes thought to characterize the former.

Alvord et al. (1974) published one of the earliest studies on the neuropathology of Alzheimer's disease in Parkinson's disease. In a retrospective investigation he examined 500 brains of patients who had suffered Parkinson's disease, and he found two distinct degenerative patterns. The first consists of Lewy bodies, which are associated with idiopathic Parkinson's disease; the second consists of the "Alzheimer tangle" type of Parkinson's disease, which is believed to be post-encephalitic parkinsonism. The severity of the motor symptoms and signs correlated well with the amount of nerve cell loss in the substantia nigra, whereas the severity of the dementia correlated well with the amount of nerve cell loss in the cerebral cortex.

Hakim & Mathieson (1979) presented a report on the histological features of the brains of 34 consecutive cases which at autopsy met the pathological criteria for Parkinson's disease, and they compared them to 34 age- and sex-matched control brains. Whereas only 6% of the controls revealed ante-mortem evidence for mental impairment, 56% of the Parkinsonians did so, with clinical features of mental impairment varying from disorientation and mild confusion to severe dementia. The authors provided evidence that the incidence of neuropathological changes of the Alzheimer-type were more frequent in the brains of Parkinson's patients.

Boller et al. (1980) confirmed the co-existence of cortical abnormalities, senile plaques and neurofibrillary tangles in the brains of patients with Parkinson's disease, and also correlated these anatomical changes with pre-mortem mental status. The group consisted

of 36 cases of which 7 were of indeterminate mental status. Of the 29 remaining cases, 16 had showed evidence of dementia ranging from severe (9, with 7 described as being mute, vegetative, or decerebrated at the time of death) to mild (7 patients with mild disorientation, and impaired memory for recent events). The remaining 13 patients were reported as having enjoyed a normal mental status except for slowed responses. Post-mortem findings on the severely demented group confirmed the diagnosis of Alzheimer's disease which had been made during life. Only three of the patients with mild dementia showed evidence of the Alzheimer-type pathology.

Ball (1984), however, gives telling criticisms of these reports which he refers to as examples of the ""Alzheimerization" of the central nervous system in Parkinson's disease" (p.182). He criticizes Hakim and Mathieson's paper (1979) on several grounds. Methodologically, he questioned the "crude" scoring system used to quantify the Alzheimer-type pathology, and he pointed out the absence of an inter-observer agreement for their scoring system. He also criticised them for not having explicitly reported the equivalent mean number of neurofibrillary tangles found in demented versus non-demented brains. So far, it appears to be difficult to conclude that the dementia found in Parkinson's disease is due to a superimposed Alzheimer's disease process because of the methodological differences amongst the several extant reports. It appears that not all global dementia found in Parkinson's disease can be attributed to such a process, because reports (Mann & Yates, 1983; Terry, Tomlinson,

Candy, et al., 1983) are now being published which show that: " concomitance of both SDAT and idiopathic parkinsonism would appear ... to be the exception, rather than the rule" (Ball, 1984, p.183).

Besides these findings of pathologic change thought to characterize Alzheimer's disease in the brains of patients with Parkinson's disease, there are also other sources of evidence which militate against specific associations between type of dementia and locus of pathologic change. This was provided by the discovery that lesions in some subcortical nuclear structures could play a significant role in the pathogenesis of Alzheimer's disease. Such evidence was provided by Whitehouse, Price, Clark, Coyle & Delong (1981) who, after reporting a loss of cholinergic neurons in the nucleus basalis of Meynert in one patient with a familial form of Alzheimer's disease, replicated the findings later in five other patients (Whitehouse, Price, Struble et al., 1982). A further report (Whitehouse, Hedreen, White III, & Price, 1983) suggested that both demented Parkinson's disease patients, and patients with Alzheimer's disease, shared a cell fallout in the nucleus basalis of Meynert. Other reports (Ruberg et al., 1982; Perry, Tomlinson, Candy et al., (1983) also stress the reduced activity of choline acetyltransferase in Parkinson's disease. Such biochemical alterations are relevant because a relationship between the severity of the dementia and measured reductions in choline acetyltransferase activity has been demonstrated (Perry, Tomlinson, Blessed et al., 1978). It thus appears that the distinction of dementia solely on the basis of any

associated anatomical pathology is unwarranted. Both diseases involve cortical and subcortical structures, and they have biochemical deficits in common.

As mentioned earlier, Freedman and Albert (1985) agree that the initial cortical-subcortical differentiation may have been incorrect. They suggest, however, that one should not throw out the baby with the bath water, in that the clinical observations remain valid. A description of the cognitive disturbances found in idiopathic Parkinson's disease preceeded the classification of Albert et al. (1974) and McHugh & Folstein (1975). Hassler (1965) used the term bradyphrenia to describe a neuropsychological syndrome which included a "failure of attention", a "delay in emotional responses", "slowness of thinking" and "indecisiveness". He hypothesized that these symptoms resulted from a cell fallout in the nucleus basalis of Meynert. It is of interest that neuronal fallout has been reported in the nucleus basalis of Meynert of patients suffering from SDAT.

Neuropsychological findings common to Parkinson's disease and frontal lobe pathology

There is an accumulating body of evidence documenting the similarity between the deficits found in patients with Parkinson's disease, and those of patients with frontal lobe damage. Freedman & Albert (1985) have stated that the pattern of dementia that had been called subcortical "can ... be distinguished as a clinical entity by

the presence of a characteristic cluster of neuropsychological deficits often related to frontal system dysfunction together with memory loss occuring without associated aphasia, apraxia and agnosia" (p. 314). Although at this stage the neuroanatomy and biochemistry of the syndrome remain unclear, nevertheless there appears to be, in Parkinson's disease, a frontal system disorder that includes damage to the subcortical structures which communicate with the cerebral cortex.

Bradyphrenia is a term that has been used in the past to encompass, amongst other features, such deficits as a lack of spontaneity, an increasing poverty of imagination, a paucity of initiative, etc. These are now redefined as difficulties in switching from one mental set to another, a delay in central processing time, deficits in attention and motivation, and perseveration. These changes are thought to result from pathologic changes in the mesocorticolimbic dopamine pathway (Agid, Ruberg, Dubois and Javoy-Agid, 1984; Delis, Direnfield, Alexander and Kaplan, 1982; Lees, 1985. These difficulties have also been observed in patients with frontal lobe pathology (Albert, 1978; Agid et al, 1984; Lees, 1985). The evidence pertaining to patients with Parkinson's disease who show frontal lobe like changes will now be reviewed to assess the validity of the new term 'fronto-subcortical dementia'.

Visuospatial. Teuber & Proctor (1964) challenged the expectation that damage to the basal ganglia produced little, if any, alteration in higher mental functioning. Having noticed the

similarity between the deficits in a delayed response task seen in monkeys with a lesion in the basal ganglia (caudate nucleus), and those with lesions in the cortex (bilateral frontal), they argued that similar deficits might result in humans who have either basal ganglia damage or frontal lobe damage. The Aubert experiment provided a crucial test since patients with frontal lobe damage had been shown to fail at a specific task (setting a luminous rod under condition of body-tilt) and Teuber and Proctor (1964) subsequently showed that Parkinsonian patients failed in exactly the same manner. This contradicted the earlier belief "that little or no alteraltion in higher functions should be expected, as long as the destruction is confined to the basal ganglia" (Teuber & Proctor, 1964, p.85).

Switching from one mental set to another. Bowen carried out a series of experiments to further study the visuospatial deficit uncovered by Teuber & Proctor (1964). Her results showed that PD patients were impaired on a route-walking test when the body position was not oriented to map coordinates (Bowen, Brady & Yahr, 1972); and, on identifying body parts (Weinstein body test) when stimuli were presented in a contralateral orientation (Bowen, Burns, Brady & Yahr, 1976). Under these two conditions, Parkinsonian patients were unable to reverse the information provided, or to shift their perceptual set to perform these tasks correctly. It became apparent that a lack of mental flexibility might, in part, be responsible for other similar results such as the deficits observed in the route-walking test (Bowen et al., 1972), the Weinstein body test (Bowen, 1976), and the

Wisconsin Card Sort (Bowen, Kamienny, Burns & Yahr, 1975).

Given that patients with frontal damage and those with basal ganglia damage exhibited similar clinical deficits, Bowen et al. (1975) reasoned that the two groups might share other symptoms related to cognitive functions. The authors chose a sorting task to assess concept formation in those patients who suffered subcortical damage because this had revealed impairments in the ability to shift sets in patients with frontal lobe lesions. A 'set' may be defined as a propensity of the brain to respond in one way, when other alternatives are available. Control of set requires the maintenance of one's strategy despite the pull of other possibilities, and also the ability to be sufficiently flexible to change strategy under new circumstances.

Using the Wisconsin Card Sort, Bowen et al. (1975) showed that Parkinsonian patients not only formed fewer concepts but also made significantly more errors than their normal controls. Parkinsonian patients were shown to be vulnerable to proactive interference, and to also to have short-term memory deficits. This suggested that these deficits might have interfered with the recall of the correct sorting criteria. In a further study on changes of personal orientation in patients with Parkinson's disease, (Bowen, et al., 1976), the deficits found in Parkinson's disease patients on spatial orientation tasks were also explained in terms of an impairment in switching from one type of perceptual organization to a different one. It was inferred that the deficits on both the route-walking test (Bowen et

al., 1972) and the body scheme test (Bowen et al., 1976) might be explained by a primary loss of mental flexibility shown through the inability to switch perceptual sets. These results are consistent with those observed in the Wisconsin Card Sorting Test (Bowen et al., 1975) and favoured a parallelism between the deficits found in patients with Parkinson's disease and those found in patients with damage to the convexity of the frontal lobe. However, Bowen (1976) favoured the primacy of the short-term memory deficits which leads to the conclusion that basal ganglia diseases produce deficits of their own, and which are only superficially similar to deficits secondary to frontal lobe damage (Stuss & Benson, 1986). Bowen (1976) felt that the overall behavioural deficits shown by the Parkinsonian patients were consistent with the "subcortical dementia syndrome" of Albert et al. (1974).

This reduced mental flexibility was demonstrated to be present very early in the course of Parkinson's disease by Lees and Smith (1983) who tested patients at the time of diagnosis, prior to the patients being treated. In a simplified version of the Wisconsin Card Sorting Test (only cards having single attributes were used), Lees and Smith confirmed that the patient group experienced difficulties in completing concepts, and showed an increase in perseverative errors. Contrary to Bowen et al. (1975) no short-term memory disturbances were found when tested for with a two-choice recognition memory test. The authors hypothesized that the impaired ability of these patients to form and shift concepts were likely due to damage to the

mesocorticolimbic pathway (Scatton, Rouquier, Javoy-Agid, 1982), secondary to dopamine depletion.

The loss of mental flexibility, or the inability to shift sets in Parkinson's disease patients reported by Bowen et al. (1975) and Lees and Smith (1983) was also reported more recently by Cools, Van Den Bercken, Horstink, Van Spaendonck & Berger (1984) who prefered to call it a "shifting aptitude". By shifting aptitude, the authors specifically mean the "ability to reorganize behaviour according to the requirements of the task" (p. 443). Patients with Parkinson's disease whose scores on standardized tests indicated an absence of dementia were examined on various specialized sorting tasks tapping the cognitive ability to both generate and alter categories, and also on motor sequences where the ability to correctly perform and quickly alternate into another sequence was required. Parkinson's disease patients showed deficits on both the cognitive and the motor shifting tasks, resulting in an overall reduction in "shifting aptitude". Using this evidence, together with that provided by animals with damage to the striatal system in the basal ganglia, the authors argued that the integrity of the basal ganglia is necessary for the preservation of 'shifting aptitude'. They grant that such deficits could be found in patients with frontal lobe damage. Such deficits in perseveration of incorrect responses and difficulty in maintaining sequences of correct responses have been demonstrated in patients with frontal lobe damage (Stuss, Kaplan & Benson, 1982; Stuss, Benson et al., 1983).

Flowers and Robertson (1985) attempted to dissociate the "cognitive impairments", i.e. the formation of concepts, from the "behavioural disturbances", i.e. the internal control necessary to apply concepts, in patients with Parkinson's disease. To do so, in their Experiment 1, they devised their own task (called the Odd-Man-Out) which is a choice discrimination task designed specifically to monitor the internal control of set. In the first trial, subjects were required to identify the one item amongst three items which differed in some way from the others. Parkinsonian patients produced almost as many concepts as the normal controls, which showed that the generation of correct concepts and their appropriate application to a rule is virtually unaffected by Parkinson's disease. On the second trial, the subjects were asked to choose the odd figure again but this time by following a different rule (to the same items) from that in the previous sequence. Parkinsonian patients were found to revert to the first applied rule and to oscillate between two known rules. They thus showed difficulty in maintaining a given set once an awareness of other possible choices had developed. Comments made after the experiment revealed that the control subjects had a tendency to revert to the prior set, but that they were able to self-correct spontaneously. Such observations have been made by Bowen et al. (1975), Lees & Smith (1983), and Cools et al. (1984). According to Flowers & Robertson, "Parkinson's disease interferes with the ability to maintain one rule against a possible second one" (p.523).

The authors replicated these results by manipulating other factors that could account for the findings (i.e. distractibility versus propensity to intrusions). Using a modified version of the Odd-Man-Out, the procedure followed in their Experiment 1 was repeated in their Experiment 2. The results found in the former experiment were replicated. Parkinsonian patients were still unable to prevent intruding alternatives from being given as responses, i.e. they failed not only at maintaining set but also at keeping in check competing responses.

These results, in conjunction with other results, led the authors to suggest that Parkinson's disease is not associated with a general dementia but rather shows very specific behavioural changes best described in terms of 'subcortical dementia', 'limbic system dementia' or frontal syndrome.

In summary, the ability to shift set (Bowen et al., 1976; Bowen et al., 1972; Bowen et al., 1975; Bowen et al., 1976; Flowers & Robertson, 1985 Lees & Smith, 1983; Tweedy et al., 1982) or the shifting of aptitude (Cools et al., 1984) has been found to be impaired in Parkinson's disease, although the ability to generate concepts has been shown to be intact (Flowers & Robertson, 1985). More specifically, Flowers & Robertson, clearly showed that Parkinsonian patients failed consistently to block competing responses from being put forth. This is similar to Milner's (1964) finding that frontal lobe patients were unable to overcome previously established response patterns on a similar test (Wisconsin Card Sort).

Memory. Most clinical reports stress that Parkinson's disease affects memory. In the subcortical dementias, memory is presumed to be affected in a way which clearly distinguishes it from memory changes seen in the cortical dementias. Qualitatively, subcortical damage is said to be associated with a deficit described as an inability to retrieve material that has been learned; a 'forgetting to remember' (Benson, 1978; Cummings & Benson, 1983; Caine, Ebert & Weingartner, 1977).

Published experimental investigations of the memory deficit in Parkinson's disease are few. One study (Tweedy, Langer & McDowell, 1982) directly addresses the claim that subcortical dementia does not produce a true memory deficit, but rather a pure retrieval deficit. In a paradigm designed to examine storage and retrieval capacity under conditions of free recall, cued recall, and recognition, Parkinsonian patients were presented with semantically related material. It was hypothesized that a true retrieval deficit would be reflected by a poor performance under free recall and a maximal performance under a forced-choice recognition condition. The evidence, in particular the improvement gradient from free-recall to cued recall, validates the contention that the primary higher deficit in Parkinson's disease is one of retrieval: a) patients with Parkinson's disease performed poorly at free recall; b) cues were of some benifit to access more of the learned material and c) the forced-recognition task almost restored memory to the level of the normal controls. With respect to the internal organization of the words, Parkinsonian patients

clustered words semantically as well as the two other groups.

In a second experiment, subjects were required to identify previously seen words or their synonyms (the discrimination between learned and novel material following a delay). Under this condition, Parkinsonian patients showed impaired recognition as compared to the other groups, particularly with respect to the recognition of synonyms which was interpreted as reflecting a specific deficit related to semantic content. It thus appears that the retrieval operation is not the only impaired process in Parkinson's patients.

In the third experiment, subjects were given a short-term recall task, a modified version of the Brown-Peterson test, consisting of semantically related words from four different categories. Parkinsonian patients were not impaired when immediate recall of the items was requested. However, the impairment shown under the various delays was proportional to the length of the delay. This performance was interpreted as being indicative of a faulty primary registration process which results in an accelerated loss of information. Such a deficit would be similar to that reported in Alzheimer's disease patients (Corkin, 1982; Miller, 1971).

The similarity, it was hypothesized, might be only apparent. In an attempt to create a release from proactive inhibition, the experimenters changed, without warning, the semantic categories of the words to be learned. The results showed that Parkinsonian patients were impaired on the release trial as compared to the other groups. The Parkinsonian group showed improvement at trial 2, suggesting that

a difficulty in switching sets (Bowen et al., 1975; Lees & Smith, 1983; Cools et al., 1984; Flowers & Robertson, 1985) might have been compounded to the memory deficit. Parkinson's disease patients may be more vulnerable to failure on this task due to the structure of the test itself, as it requires two switches, one from learning to counting and another from counting to retrieving. The observed deficits may thus partly reflect the operation of interference so that the failure in Parkinson's disease would result from qualitatively different reasons from those obtained in Alzheimer's disease. Failure as a consequence of interference, as defined by the Brown-Peterson technique, rather than as a consequence of a short-term memory deficit, has been demonstrated on patients with orbital-medial frontal leucotomy lesions (Stuss, Kaplan, Benson & Weir, 1982)

The results of Tweedy et al. (1982) are different from those of Caine, Ebert & Weingartner (1977) despite the use of a similar protocol. In a memory task involving immediate recall, delayed recall, cued recall, and recognition, Parkinsonian patients performed as well as normal controls.

Recognition memory was studied in a comprehensive manner by Flowers, Pearce & Pearce (1984). The chosen task minimized both motor and mental manipulation of material so that the dependent variable would give information about the effect of the disease on a patient's ability to learn and later recognize without error the learned material. Subjects were asked to remember lists of items (objects, histograms, words and numbers) and to then recognize the items amongst

other items (immediate testing with half the items and delayed testing of fifteen, thirty or forty-five minutes with the other half). It was hypothesized that a deficit in registering would be reflected by the immediate recall score whereas a loss of the information or an impairment in the consolidation mechanism would be reflected in the delayed tests. The results clearly showed the Parkinsonian patients performance to follow that of the controls despite a slightly lower level of accuracy. Furthermore, patterns of memory processing in both Parkinsonian patients and normal controls remained equivalent across the four test paradigms. Parkinson's disease, it was concluded, is not associated with a recognition memory deficit. One would therefore have to infer intact registering, encoding and retrieval of information during a passive memory task. Any deficit in an 'active' memory task would have to be related to a deficient retrieval mechanism.

Another line of investigation of recognition memory involved delayed response tasks (De Lancy Horne, 1971). In this protocol, subjects were required to identify, from a small array, modified Chinese symbols, previously learned, after delays of either 10 seconds or 60 seconds. Parkinsonian patients were observed to have slowed reaction time as compared to the control group, but were equally accurate. The results were interpreted as reflecting purely cognitive deficits, as the protocol excluded motor demands, and was considered to be secondary to basal ganglia damage. These results must be qualified, however, on at least three counts. Firstly, the use of

very complex visuo-spatial designs placed Parkinsonian patients at an immediate disadvantage by virtue of their symptomatology. Secondly, the patients used in this experiment represent a subgroup of Parkinson's disease patients as they had all suffered a thalamotomy operation. Lastly, all testing procedures were carried within one to three weeks following the operation so that the question of mental status at testing is unclear.

To summarize, deficits in mnemonic processes have been reported in non-demented Parkinsonian patients (patients who do not score within the demented range on a dementia rating scale). The impairment has been interpreted as being a retrieval deficit (Flowers et al., 1984; Tweedy et al., 1982) as revealed by intact recognition memory (Flowers et al., 1984; Caine et al., 1977; De Lancy Horne, 1971; Tweedy et al., 1982). When given a short-term recall task involving filled delays, Parkinsonian patients were reported to be vulnerable to interference (Tweedy et al., 1982), a finding also seen in patients with frontal lobe damage (Stuss et al., 1982b).

Memory and Reaction time. Reaction-time studies have most often focussed on the motor disorder in Parkinsonism (Cassel, Shaw & Stern, 1973; Evarts, Teravainen & Calne, 1981; Flowers, 1976; 1978a; 1978b; Heilman, Bowers, Watson & Greer, 1976; Velasco & Velasco, 1973; Wilson, 1925; Yokochi, Nakamura, Narabayashi, 1985). A small number of studies have attempted to determine whether subcortical lesions, such as those found in Parkinson's disease, produce a 'slowing of thought' (Albert et al., 1974; Albert, 1978). Wilson (1955) used the

word 'bradyphrenia' to refer to the "mental inertia and sluggish cerebration of not a few Parkinsonians" but he felt that the slowness of thought was "probably more apparent than real, being due to retarded execution but not perception" (p.933). This long-standing opinion has been challenged by results reported in a study of the rate of motor information-processing during movement (Sanes, 1985). In that study, Parkinsonian patients were observed to process a reduced amount of information per unit of time as compared to normal subjects, possibly due to some deficit in either the programming, retrieval, or execution stages of motor behaviours, or some combination of these.

Garron, Klawans & Narin (1972) studied a group of non-demented patients with Parkinson's disease on four verbal tasks. One task required the identification of synonyms, while another required reorganizing the letters of a given word so that it would make a new word, if possible. The third task was a recognition test in which a string of three to ten digits had to be recognized from another string. The last task required the judgement of whether a word did or did not belong to a group of words of a given category. Responses and timing were computer controlled. The results showed that the Parkinsonian patients clustered into two subgroups: one group that did not differ from the normal control subjects and another group that showed both slowness in response on all four tests and impaired intellectual function. The main characteristic of the slower patients was that they were significantly older and significantly more disabled than the patients with the faster response time. The slowing in the

older group was interpreted as reflecting the possible additivity of brain disease and ageing. Warburton (1967) had already noted that older Parkinsonian patients exhibited a significant degree of memory disturbance, and she too suggested that the deficit resulted from an interaction between the natural decline in memory function associated with increasing age (Craik & Simon, 1980; Poon, 1985; Simon, 1979) together with that arising as a result of the Parkinson's disease process.

The next three reviewed studies are of particular importance because their paradigm is similar to the one used in this dissertation. In the first study, Wilson, Kaszniak, Klawans and Garron (1982) investigated scanning speed in Parkinson's disease patients using the varied-set procedure of the reaction-time paradigm developed by Sternberg (1966). This is a particularly useful paradigm because it clearly separates the speed of mental events from the speed of motor events. The protocol requires the rapid search of memory for the retrieval of learned information. A group of old (over 65 years of age) and young (under 65 years) Parkinsonian patients were compared to matched control groups in a task requiring them to decide as quickly as possible whether a test digit was one of those seen amongst one, two or four digits that had been presented to them a few seconds earlier. If the decision was positive, the subject pressed a key with his/her right hand; if it was negative, the subject pressed a key with his/her left hand. Subjects were given 192 trials divided into 12 blocks of 16 trials each. Wilson et al. found that the older patients

were slower to scan the items in memory (61 msec per item) (as computed from the slope function of the linear regression performed on the data) as compared to the older normals (29 msec per item), the young patients (34 msec per item), and the young normals (36 msec per item). Accuracy of response was preserved in the older group. Because of the extreme variability of the data, a logarithmic transformation was performed on the reaction times, which when submitted to variance analysis, revealed that slowed mentation is a characteristic of older patients with Parkinson's disease. The authors used the term 'bradyphrenia' to describe this deficit. These findings are similar to those of Garron et al. (1972) in that both age and disease were, perhaps additively, linked to the slowness.

Since this dissertation was initiated, another study has been published (Rafal, Posner, Walker & Friedrich, 1984) using Sternberg's paradigm to investigate the characteristics of the slowed thinking which is central to the concept of frontal system dementia. It tested the hypothesis that mental slowing might be the cognitive equivalent to the motor phenomena of bradykinesia, and that both may be linked to the dopaminergic depletion. The subjects were ten patients, between the ages of 33 to 75, diagnosed as suffering from idiopathic Parkinson's disease. Four (ages 66 to 75, mean = 71) were tested prior to and after chemotheraphy. The six remaining patients (aged 33 to 70, mean = 58) were experiencing treatment failure. These patients were tested during the 'on-off' cycles of their fluctuations. All patients in this group were considered mentally normal, whereas

two patients in the former group were considered to have some mental impairment.

The subjects were shown a list of 1, 2, 4 or 6 digits, presented simultaneously, for a period averaging .5 seconds per item. Following a one second interval, subjects were shown one digit which they had to identify, as quickly as possible, as being a member of the learned set or not. The response mode was manual.

Results did not support Wilson's et al. (1980) finding of a mental slowing in Parkinson's disease. The speed of scanning was found to be approximately 40 msec per item, which falls within the normal range. The authors interpreted these result as evidence suggesting that bradyphrenia is not a component of Parkinson's disease in general, and that if it does exist, it is not related to either bradykinesia or dopaminergic dysfunction. They too, however, suggest that bradyphrenia may occur in subgroups of Parkinsonians who would have more severe deficiencies in mesolimbic or mesocortical dopamine pathways. These patients would differ from those having mainly a nigrostriatal dopamine deficiency, pathologically, as well as clinically.

Another more recent study (Hines & Volpe, 1985) investigated semantic activation in patients with Parkinson's disease using a lexical decision task which allows separation of motoric movement from mental processes. The task required subjects to decide whether groups of letters presented formed a word or not. In contrast to Wilson's et al. (1980) result where evidence of slowing of short-term memory was

reported, Hines and Volpe found no evidence of internal mental slowing. They interpreted their results as indicating that processes that require effort and attention are impaired in Parkinson's disease (as shown by the slower short-term scanning reported by Wilson et al. 1980) whereas automatic processes are spared.

In summary, the results with respect to the hypothetical bradyphrenia in Parkinson's disease remain controversial. Despite the fact that slowing on the basis of clinical impression has been frequently reported over a long period of time, there are only a few reports of measured slowing (Garron et al., 1972; Hansch et al., 1982; Wilson et al., 1980). An absence of slowing has been more often reported (Everts et al., 1981; Garron et al., 1972; Hines & Volpe, 1985; Rafal et al., 1984). Slowing, when it occurs, seems to appear in older and more disabled patients. One possibility is that early young Parkinsonians have mainly subcortical damage, as manifested by the motor symptoms, whilst older, longer-diseased patients have cortical damage with dopaminergic deficiencies which lead to bradyphrenia.

Alzheimer's Disease

In 1906, Dr. Alois Alzheimer described "a unique illness" at a meeting of the German Society of Alienists, opening with the following remark: "The clinical course and pathology of this distinctive process separate it from the known neurologic disorders". He provided

evidence of a disruption of neuronal function in the cortex of a 51-year-old woman which he associated with the gradual clinical deterioration in intellectual function and personality he had observed pre-mortem. Up to that time, dementia had been a functional clinical entity, a syndrome, treated by alienists (psychiatrists), rather than by neurologists. If Alzheimer's discovery did not facilitate diagnosis pre-mortem, it did allow a definitive diagnosis post-mortem, of one defined subgroup of clinically demented patients. His careful account of the progressive nature of the clinical signs and symptoms of the disease provided an impetus for subsequent workers both to follow its cognitive concomitants as they presented during life, and to stimulate research into the neuropathological changes at necropsy leading to advances in our understanding of the underlying disease process. His contribution was marked by Emile Kraepelin, who called the condition Alzheimer's disease.

Pathology

Macroscopically, reduction of cerebral substance is commonly present in the elderly. Brain atrophy is manifested by a relative increase in the volume of the ventricles, basal cisterns, and subarachnoid spaces. This change is viewed as a result of the normal process of ageing despite there being no evidence for such a reduction in cerebral substance in the 3% of over 65's who are disease free. It has not been found to correlate directly with the clinical severity of

dementia (Jacoby, 1981).

The weight loss in the brain of demented individuals is 10 percent greater than that of non-demented aged brains (Terry & Davies, 1983), and, in part, that greater weightloss results from a reduction in the absolute volume of neuron-bearing cortex (Corsellis, 1976; Tomlinson, 1982).

Certain areas of the brain of patients with advanced Alzheimer's disease show more marked atrophy including the temporal lobes, especially its basal, medial limbic portion (hippocampus and amygdaloid nucleus) and the post-central parietal region. Encephalopathy is present, though, less severe, in the frontal lobes. In contradistinction to these areas, the primary projection areas such as the sensorimotor cortex and calcarine gyrus are well preserved (Brun, 1982; Brun & Gustafson, 1976; Brun & Gustafson, 1978).

Generally, brain atrophy has been found to have little diagnostic value. In presenile cases, it can be minimal, whereas in SDAT atrophy may be either minimal or overshadowed by the decrease in brain size taken to be consequent upon normal ageing (Perry, 1986). However, a consistent finding (both macroscopic and microscopic) is the reduction in size of the temporal lobes in brains showing Alzheimer's disease changes, as compared to age-matched brains without Alzheimer's disease (Hubbarb and Anderson, 1981; Tomlinson et al, 1984).

Cortical neuronal loss in Alzheimer's disease has been found to exceed age-dependent decline rates, with the losses being most severe

in the anterior temporal lobes (Brun and Gustafson, 1976; Colon, 1972; Shefer, 1973; Terry, Peck, DeTeresa, Schechter & Horoupian, 1981). However, the extent of total neuron loss from the cerebral cortex in Alzheimer's disease remains controversial (Tomlinson & Corsellis, 1984). Brains with Alzheimer's disease changes have been reported to show significant decreases in the number of large neurons in mid-frontal (40%), superior temporal (46%), and inferior-parietal regions (Terry et al, 1981) as compared to age-matched brains of non-demented patients.

The two classical pathological microscopic lesions associated with Alzheimer's disease are senile plaques (SP) and neurofibrillary tangles (NFTs). Senile plaques were first described over 80 years ago by Blocq and Marinesco (1892). Three main morphological constituents may be identified in the typical SP: a) abnormal neurites; b) abnormal glial cells; and c) amyloid fibrils --found predominantly at the central region of the plaques. Ultrastructural observations reveal that the number of presynaptic terminals seen in SPs suggest that the majority of their neurites are axonal, and contain abnormal mitochondria, dense bodies, paired helical filaments and lysosomes. Plaques are predominantly found in the gray matter of the cortex although they have been observed in the striatum and diencephalon (Rudelli, Ambler &.Wisniewski, 1984). The threshold hypothesis (Blessed, Tomlinson & Roth 1968; Tomlinson, 1979) predicts that, after a certain level, plaque counts continue to increase without further degeneration because close to maximum damage has been

achieved. Despite decades of research, the etiology and the effect of their formation on cortical neuronal function remains elusive (Perry, 1986).

NFTs were the main cortical microscopic abnormality reported by Alois Alzheimer (1907). They are intracellular, cytoplasmic structures which are believed to consist of abnormal fibrillary aggregates of protein. Tangles usually form in large pyramidal-shaped neurones, but may be observed in smaller, granular-type neurones or interneurons. In the neocortex, NFT's are located in mid- and deep-cortical regions (layers 3, 4, and 5), with preferential localization in the hippocampus. They also are present in the raphe nuclei of the brainstem and the neurons of the locus coereleus (Bondareff, Mountjoy & Roth, 1982; Hirano and Zimmerman, 1962; Ishii, 1966). The morphology of the NFT's differs from one area to the other, being flame-shaped in the hippocampal formation, curvilinear in the neocortex, and globose in the brain stem. Ultrastructurally, NFT's are composed of paired filaments that are twisted around each other in a helical fashion (Kidd, 1964; Terry, 1963), and terminate in a single filament (Wisniewski, Narang & Terry, 1976). Their precise chemical composition remains unknown, but it has been suggested that they may be derived from either neurofilaments or neurotubules (Grunde-Iqbal et al, 1979; Gambetti et al, 1980).

NFTs are a major histological hallmark of the disease and are generally essential to the pathological diagnosis of Alzheimer's disease. Contrary to the plaque formation, tangles are rarely found

in the neocortex, their extent being generally associated with length of time the disease has been present. The temporal lobe is often particularly affected, whereas the occipital lobe is much less so. Tangle formation is abundant in archicortical regions (Tomlinson & Corsellis, 1984) in terms of both density and proportions of neurons involved. In this latter area, tangles are distributed in the brains of both normal and demented individuals, as well as in other disease processes. For diagnostic purposes, the posterior hippocampus has been found to be the most useful region to examine, because tangle formation in this area was observed to be more extensive than in the anterior hippocampus and, quantitatively, estimates of tangles reliably diagnose cases of Alzheimer's disease (Ball, 1977).

The significance of the SP's and NFT's for the development of the clinical symptoms of Alzheimer's disease has been established through combined clinical and pathological studies (Perry et al, 1978; Wilcock & Esiri, 1982). These studies have demonstrated a correlation between the number of plaques in the neocortex and the severity of the cognitive deficits (Blessed and Tomlinson, 1965; Shefer, 1973).

The topography of the degenerative process has been mapped by Brun and Gustafson (1976) and has not been found to be uniformly severe in all regions. The hippocampus and amygdaloid nucleus show the most severe damage, whereas other areas, in order of decreasing severity, include the inferior temporal region (Brodmann area 20, 21), the post-central parietal areas (Brodmann 7b, 19, 39), the posterior

cingulate gyrus (Brodmann 23), and the frontal lobes anterior to the precentral gyrus. Relatively spared until late in the disease are the anterior cingulate gyrus (Brodmann 24), the sensorimotor region (Brodmann 4 - 7a), and the calcarine area (Brodmann 17). Figure 1 shows how Alzheimer's disease affects the cerebral hemispheres.

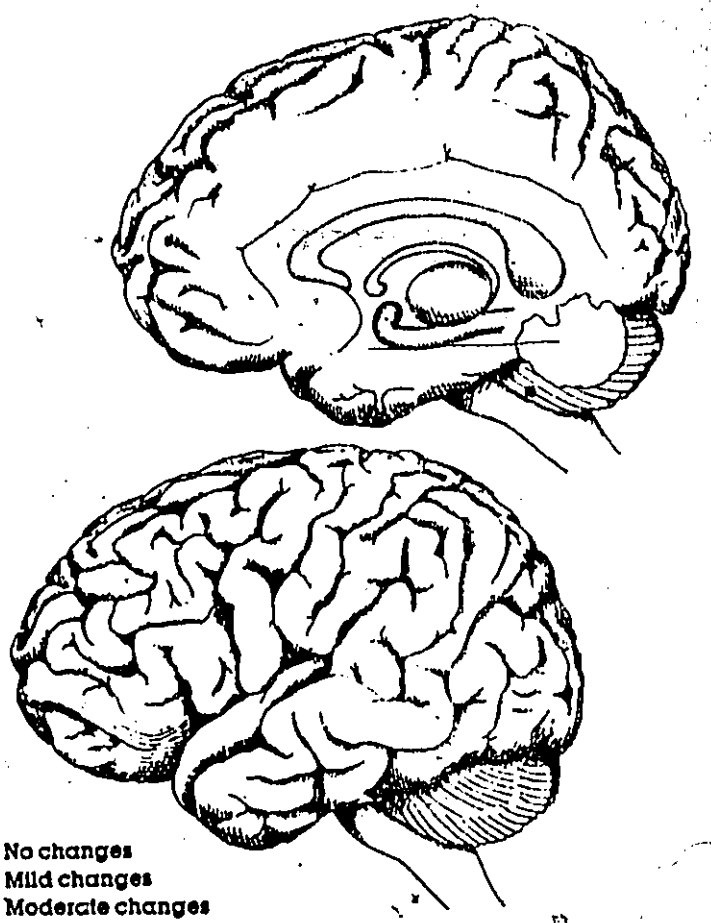
The clinical diagnosis of Alzheimer's disease remains a 'diagnosis by exclusion', while pathological diagnosis requires the examination of excized brain tissue. Recent technological advances have provided a method for the non-invasive in vivo quantification of cerebral rates of glucose use, from the use of positron emission tomography (PET) (Benson, 1982). This method has been applied to patients with presumptive Alzheimer's disease (see McGeer, 1986, for review).

A general pattern has emerged from the application of PET to presumptive Alzheimer's patients. Results indicate a significantly reduced cortical local cerebral metabolic rates for glucose utilization (Farkas, Ferris, Wolf, et al. 1982; Ferris, De Leon, Wolf et al., 1980; Foster, Chase, Fedio, Patronas, Brooks & Di Chiro, 1983; Freidland, Budinger, Koss & Ober, 1985). Although there was variation of glucose metabolism in the areas of the cortex involved, no consistent pattern could be identified.

Hypometabolism has been observed in the temporal-parietal cortex of Alzheimer's patients as compared to frontal cortex (Benson, Kuhl, Hawkins, Phelps & Cummings, Tsai, 1983; Chase, Foster, Fedio, Brooks, Mansi & Di Chiro, 1984; Friedland, Budinger, Jagust et al., 1985).

Figure 1. A view of the cerebral hemispheres as affected by Alzheimer's disease.

HOW DAT AFFECTS THE CEREBRAL HEMISPHERES



- ☐ No changes
- ☐ Mild changes
- ☐ Moderate changes
- ☐ Severe changes
- ☐ Total degeneration

Medial (top) and lateral (bottom) views show distribution of pathologic changes. Most severely affected are the posterotemporal, temporoparietal-junction, and medial-temporal regions (yellow, gray); corresponding abnormalities are memory impairment, visuospatial disturbances, cognitive alterations, and fluent aphasia. Lesser involvement of the frontal and anterior temporal cortices (blue, red) is reflected in cognitive impairment and personality changes. The primary visual, motor, and somatosensory regions are largely spared (white).

This finding compares well with the regional pathology of the disease as mapped by histological studies (Brun, 1984; Brun & Englund, 1981) which revealed that the areas most severely involved were the posterior temporal and parietal cortex.

Studies of glucose utilization have also revealed asymmetrical hypometabolism patterns depending on whether language or constructional apraxia were the outstanding disturbances. In the case of language, Foster et al., (1983) observed the largest reduction to be in the left frontal, parietal and temporal regions in patients with predominantly language disorders whereas the right temporal and parietal lobes were more affected in patients with constructional disturbances. When memory disturbances were the predominant deficit, no such asymmetrical hypometabolism patterns were observed.

PET provides an unprecedented approach to the in vivo quantification of aspects of neural pathophysiology. Findings of such studies correlate with the post-mortem histological findings and therefore offer hope for in vivo diagnosis in the future. To date, hypometabolism has been shown to be worst in the temporal-parietal lobes, and has revealed asymmetrical patterns which relate well to the behavioural features of the illness and may prove to also relate to the age of the patient (Koss, Friedland, Ober & Jagust, 1985).

Recent findings may challenge the view that the dementia in Alzheimer's disease is linked to the plaques and tangles. De Boni and McLachlan (Medical Post, 1986) have recently produced the first successful culture of paired helical filaments by altering the

environment of human brain cells in vitro with agents (glutamic and aspartic acids) that are part of the normal functioning brain but that become toxic when present at elevated levels. Unexpectedly, paired helical filaments were formed after having been exposed to normal concentration levels of these two agents. These two amino acids act as neurotransmitters and are reabsorbed by the neurons after completing their action, with the excess being broken down and leaving a momentary higher concentration of glutamic and aspartic acid. According to De Boni, the neurotransmitters in Alzheimer's disease are not broken down and dissipated as quickly or as completely as they are in normal brains which results in a toxic environment, without reaching toxic levels. The exposure to the agents results in the manufacturing of paired helical filaments which, over time, would become neurofibrillary tangles. Interestingly, De Boni suggests that, if this is so, plaques and tangles may be no more than an epiphenomenon and may not be related to the dementing illness.

The traditional view of the neuropathology underlying the progressive loss of higher mental function in Alzheimer's disease holds that it involves primary damage to the cerebral cortex where higher mental functions are taken to reside. However, subcortical nuclei have also been shown to be implicated in the disease (Mann, Lincoln, Yates, Stamp & Toper, 1980; Perry, Candy, Perry et al., 1982; Tagliavini & Pilleri, 1983; Whitehouse, Price, Struble, Clark & De Long, 1982).

The discovery that neuronal loss was also present in the region

of subcortical nuclei has challenged the traditional notion of a primarily cortical involvement in Alzheimer's disease. Current neuropathological research has focussed on a group of subcortical nuclei which give origin to axonal processes which project to the cerebral cortex. These include the cholinergic cell bodies situated in the basal forebrain region (septum, diagonal band, Meynert nucleus), the noradrenergic cell body located in the locus coerulus and the serotonergic cell body situated in the dorsal raphe nucleus. All innervate the cortex in a diffuse fashion. Table 7 presents the subcortical nuclei known to be affected in Alzheimer's disease.

Pilleri (1966) first reported neuronal loss in the Meynert nucleus in Alzheimer's disease and Davies and Maloney (1976) first recorded significant reduction of choline acetyltransferase in the brain tissue of patients with senile dementia of the Alzheimer's type. These were later confirmed by Whitehouse et al. (1982), Perry, Perry, Blessed & Tomlinson (1977), Spillane et al, 1977; and Rossor, Emson, Mountjoy, Roth & Iverson (1980). Because the neuronal loss from 75% to little or none was not observed to be proportional to the extensive loss (over 90%) of the acetylcholine synthesizing enzyme, choline acetyltransferase, from the Meynert nucleus (Perry et al., 1982), a retrograde axonal degeneration in response to abnormalities in their terminal fields was hypothesized. Evidence supporting this concept was provided by the retention of acetylcholinesterase histochemically in individual neurons of Meynert's nucleus, and absence of staining in the cortex (Candy et al., 1983). The role of the cholinergic system

Table 7

Status of Some Subcortical Nuclei in Alzheimer's Disease

Nucleus	Neurotransmitter type	Pathological changes	
		Neurone loss	Neurofibrillary tangle formation
Meynert nucleus (Basal forebrain)*	Cholinergic	Usually present, may be extensive in a minority of cases	Moderate number (up to 30%) of neurones involved
Substantia Nigra (Midbrain)	Dopaminergic	Present in less than 20% of cases	NFT formation rare but Lewy body formation may occur in a minority of cases
Mesocortical (A10) subgroup of substantia nigra (Midbrain -ventromedial)	Dopaminergic	Quantitatively not yet assessed	Moderate number of neurons involved
Ponto-mesencephalic reticular formation (Midbrain)	Mixed, includes cholinergic neurons	Quantitatively not assessed	Moderate number of neurons involved
Dorsal raphe (Midbrain/ Upper pons)	Serotoninergic	Conflicting reports; probably not extensive	Numerous up to 40 or 50% of neurones involved
Locus coeruleus (Pons)	Noradrenergic	May be present, particularly in advanced or younger cases	Only occasional neurones involved
Dorsal nucleus vagus (Medulla)	Cholinergic	May be present	Sparse

From Perry, 1986
* Location

in memory has been examined pharmacologically in studies examining the impact of cholinergic blockers on memory.

Noradrenergic neurons from the locus coeruleus have been shown repeatedly to be significantly impoverished in a proportion of patients with Alzheimer's disease (Forno, 1978; Tomlinson et al., 1981). This loss appears to be related to the severity of the disease (Tomlinson, Irving & Blessed, 1981), being minimal in less advanced cases and extensive in more advanced cases. One of the major areas of projection from this system is the cerebral cortex. It is therefore not surprising that abnormalities in noradrenergic activities have been noted at the cortical level (Adolfsson, Gottfries, Oreland, Roos & Winblad, 1978; Cross et al, 1981). A retrograde degeneration in the subcortical nucleus is again hypothesised to result from primary cortical abnormalities.

The involvement of the serotenergic nuclei projecting to the cortex is less well known but has raised interest as numerous tangles have been observed in the dorsal raphe nucleus (Ishii, 1966). Tangles have been observed only rarely in the locus coeruleus and to only a moderate extent in the Meynert nucleus. However, it appears that the presence of these tangles is not accompanied by substantial neuronal loss from this nucleus. The reduction in serotonin metabolite (Gottfries & Roos, 1973, Gottfries, Gottfries & Roos, 1969) suggests significant abnormalities in the serotenergic projections to the cortex. Consistently, functional changes in neurons projecting to the cortex are not correlated with primary subcortical neuronal loss

(Cross et al., 1985).

The cholinergic hypothesis (Perry et al., 1978) of Alzheimer's disease appears to correlate closely with a drop in test scores from normality to a moderate degree of dementia (assessed with the Blessed test) but less strongly with the further decline in mental function generally seen in Alzheimers's disease. The relation between cholinergic transmitter activities and Alzheimer-type pathological changes is not direct as can be seen by the fact that plaques and tangles are more prominent in layers III to V, whereas reductions in the cholinergic enzymes choline acetyltransferase and acetylcholinesterase are not confined or even more pronounced in these cortical layers (Perry et al., 1983). Therefore, the further progressive decline seen in Alzheimer's disease may be associated with abnormalities in other systems. However, the cholinergic hypothesis remains unchallenged (Perry et al., 1981; Cross et al., 1985) and provides a link between the cholinergic system and mental abnormalities.

Other neurotransmitter systems (dopamine, aminobutyric acid, glutamic acid) have been investigated but the results have indicated normal or inconsistent levels, the relationship of which, with respect to the neuropathological features, are unknown (Reisine, Yamamura, Bird, et al., 1978). Some neuropeptide systems have been investigated but it appears that the only consistent finding relates to somatostatin which has been found to be reduced in many cortical areas (Davies, Katzman & Terry, 1980), the temporal cortex only (Rossor,

Emson & Mountjoy et al., 1980; or in advanced cases only (Perry, Blessed, Tomlinson et al., 1981).

The disease Alois Alzheimer identified is held responsible for the most common form of dementia (Wells, 1978). The underlying pathology does not betray itself in bodily signs. To establish the presence of Alzheimer's disease, careful attention to the clinical picture is necessary, because there are at present no non-invasive methods that will confirm the diagnosis during life. The problem of identifying the disease process is well-documented (Freidland, Budinger, Jagust, Koss, Derenzo, Huesman & Yano, 1985; Davies, 1983; Terry, 1978; Roth, 1985). There have also been attempts to identify the constellation of cognitive deficits particular to Alzheimer's disease so that a neuropsychological diagnosis may be made during life.

Clinical characteristics

Sjogren (1952) provided the first clinical analysis of histopathologically verified cases of Alzheimer's disease in the following manner:

> In stage 1 in Morbus Alzheimer all the cases manifest amnestic disturbances, and, curiously enough, no fewer than 15 of the 18 cases show a predominant aspontaneity and reduced initiative. ... The observation that the

> aspontaneity and lack of initiative are as dominating as they are in my material contradicts the views frequently presented in the literature .... to the effect that a hyperactivity in the general behaviour is a characteristic feature for Morbus Alzheimer.(p.80).

Other striking features in the early stage included a rapidly progressive disorientation in space, followed by a disorientation in time. Stage II may begin on an average of 1 to 3 years after the first symptoms were noticed with the obvious presence of a progressive loss of higher mental functions. Language function is observed to deteriorate and apractic, aphasic and agnostic disturbances appear. In stage 111, such focal symptoms disappear in the face of diffuse loss of higher mental functions. The dementia is then complete, and a physical decline becomes apparent.

Other carefully detailed studies of the evolution of the slow loss of higher mental functions in histopathologically verified cases of Alzheimer's disease (Newmann and Cohn, 1953; Sims and Sussman, 1962; Sulkava, Haltia, Paetau, Wikstrom and Palo, 1983) have confirmed that the most prominent complaint is that of memory loss for recent events. Language deterioration either in the form of naming disturbances or word-finding difficulties in spontaneous speech followed. Disorientation to both time and place are seen early whereas apraxia appeared later in the disease. Depression appeared as a common symptom, even at the intermediate stage of the disease

whereas agitation, if present, appeared later. In the final phase, disorientation to person, stereotypy in movements and speech and paraphasias were evident.

Such descriptions confirm that patients with Alzheimer's disease undergo a progressive intellectual deterioration. Table 8 (Cummings & Benson, 1983) and Table 9 (Reisberg, Ferris and Cook, 1982) provide examples of summaries of the stages that describe the clinical course of the disease.

Alzheimer's disease is manifested through changes in cognition, amongst which disordered memory is the first and most prominent (Benson & Cummings, 1983; Lingren, 1952; Lishman, 1978; Sjogren, Sjogren & Lingren, 1952; Reisberg et al., 1982). The memory impairment remains the most consistent symptom throughout the course of the illness (Liston, 1977) and is a sine qua non for the diagnosis (Wells, 1979). The slow, progressive loss of memory and of other cognitive functions is taken to reflect both neuropathological and biochemical alterations in the brain tissue (Sulkava, Haltia, Paetau, Wikstron & Palo, 1983). The report of slowed thinking by Sjogren (1952) is an isolated one and his finding has never been mentioned in subsequent reports, despite some researchers having addressed the question experimentally (Ferris, Pirozzolo, Christensen, Ogle, Hansch & Thompson, 1981).

Diagnosis

Table 8

Principal Clinical Findings in Each Stage of Alzheimer's Disease

Stage I (duration of disease 1 to 8 years)

Memory-new learning defective, remote recall impaired
Visuospatial skills-topographic disorientation, poor construction
Language-poor word-list generation, anomia
Personality-apathy, occasional irritability or sadness
Motor system-normal

Stage II (duration of disease 2 to 10 years)

Memory-recent and remote recall more severely impaired
Visuospatial skills-poor construction, spatial disorientation
Language-fluent aphasia
Calculation-acalculia
Praxis-ideomotor apraxia
Personality-indifference and apathy
Motor system-restlessness

Stage III (duration of disease 8 to 12 years)

Intellectual functions-severely deteriorated
Motor-limb rigidity and flexion posture
Sphincter control-urinary and fecal incontinence

Adapted from Cummings & Benson, 1983

Table 9

Global Deterioration Scale (GDS) for Primary Degenerative Dementia (PDD)

GDS stage	Clinical phase	Clinical characteristics	Psychometric concomitants
1 No cognitive decline	Normal	No subjective complaints of memory deficit. No memory deficit evident on clinical interview.	Average or above average performance for age and WAIS vocabulary score on 3 of 5 Guild (4) memory subtests.
2 Very mild cognitive decline	Forgetfulness	Subjective complaints of memory deficit, most frequently in following areas: (a) forgetting where one has placed familiar objects; (b) forgetting names one formerly knew well. No objective evidence of memory deficit on clinical interview. No objective deficits in employment or social situations. Appropriate concern with respect to symptomatology.	Below average performance for age and WAIS vocabulary score on 3 of 5 Guild subtests.
3 Mild cognitive decline	Early Confusional	Earliest clear-cut deficits. Manifestations in more than one of the following areas: (a) patient may have gotten lost when traveling to an unfamiliar location; (b) co-workers become aware of patient's relatively poor performance; (c) word and name finding deficit become evident to intimates; (d) patient may read a passage or a book and retain relatively little material; (e) patient may demonstrate decreased facility in remembering names upon introduction to new people; (f) patient may have lost or misplaced an object of value; (g) concentration deficit may be evident on clinical testing. Objective evidence of memory deficit obtained only with an intensive interview conducted by a trained geriatric psychiatrist. Decreased performance in demanding employment and social settings. Denial begins to become manifest in patient. Mild to moderate anxiety accompanies symptoms.	One standard deviation or greater below average performance for age and WAIS vocabulary score on 3 of 5 Guild memory subtests. Often no errors on the Mental Status Questionnaire (MSQ). (5)
4 Moderate cognitive decline	Late Confusional	Clear-cut deficit on careful clinical interview. Deficit manifest in following areas: (a) decreased knowledge of current and recent events; (b) may exhibit some deficit in memory of one's personal history; (c) concentration decficit elicited on serial substractions; (d) decreased ability to travel, handle finances, etc. Frequently no deficit in following areas: (a) orientation to time and person; (b) recognition of familiar persons and faces; (c) ability to travel to familiar locations. Inability to perform complex tasks. Denial is dominant defense mechanism. Flattening of affect and withdrawal from challenging situations occur.	Frequent mistakes on 3 or more items on MSQ.
5 Moderately severe decline	Early dementia	Patient can no longer survive without some assistance. Patient is unable during interview to recall a major relevant aspect of their current lives: e.g., their address or telephone number of many years, the names of close members of their family (such as grandchildren), the name of the high school or college from which they graduated. Frequently some disorientation to time (date, day of week, season, etc.) or to place. An educated person may have difficulty counting back from 40 by 4s or from 20 by 2s. Persons at this stage retain knowledge of many major facts regarding themselves and others. They invariably know their own names and generally know their spouses and children's names. They require no assistance with toileting or eating, but may have some difficulty choosing the proper clothing to wear and may occasionally clothe themselves improperly (e.g., put shoes on the wrong feet, etc.).	Deficits evident on brief MSQ assessment.
6 Severe cognitive decline	Middle dementia	May occasionally forget the name of the spouse upon whom they are entirely dependent for survival. Will be largely unaware of all recent events and experiences in their lives. Retain some knowledge of their past lives but this is very sketchy. Generally unaware of their surroundings, the year, the season, etc. May have difficulty counting from 10, both backward and sometimes, forward. Will require some assistance with activities of daily living, e.g., may become incontinent, will require travel assistance but occasionally will display ability to travel to familiar locations. Diurnal rhythm frequently disturbed. Almost always recall their own name. Frequently continue to be able to distinguish familiar from unfamiliar persons in their environment. Personality and emotional changes occur. These are quite variable and include: (a) delusional behavior, e.g., patients may accuse their spouse of being an impostor; may talk to imaginary figures in the environment, or to their own reflection in the mirror; (b) obsessive symptoms, e.g., person may continually repeat simple cleaning activities; (c) anxiety symptoms, agitation, and even previously nonexistent violent behavior may occur; (d) cognitive abulia, i.e., loss of willpower because an individual cannot carry a thought long enough to determine a purposeful course of action.	5–10 errors on MSQ.
7 Very severe cognitive decline	Late dementia	All verbal abilities are lost. Frequently there is no speech at all—only grunting. Incontinent of urine; requires assistance toileting and feeding. Lose basic psychomotor skills, e.g., ability to walk. The brain appears to no longer be able to tell the body what to do. Generalized and cortical neurologic signs and symptoms are frequently present.	

From Reisberg, Ferris & Cook, 1982

The task force on the diagnosis of Alzheimer's disease (McKhann, Drachman, Folstein, Katzman, Price, Stadlan, 1984) under the auspices of the US Department of Health and Human Services has developed criteria for the provisional diagnosis of Alzheimer's disease (see Table 10). Probable Alzheimer's disease may be inferred if the onset of the memory and cognitive changes is insidious, and progressive, and if diagnosis of other possible systemic or brain diseases have been ruled out. When other significant diseases are present with a progressive dementia, a diagnosis of possible Alzheimer's disease may be made if the dementia is not accounted for by the other diseases. It can also be diagnosed if the presentation or course is atypical but does not fit other possibilities. A definite diagnosis of Alzheimer's disease can only be made post-mortem with histopathological evidence.

The Alzheimer-type dementia was originally described as a pre-senile illness, with early onset (Alzheimer, 1907). This illness was thought to be different from that where the dementia symptoms occured at the senium with age 65 being the artificial boundary separating these two illnesses. Pathological investigations, however, have suggested that the early and late onset forms shared common structural changes and the term 'senile dementia of the Alzheimer type' (SDAT) has been coined on this basis (Constantinidis, 1978; Terry, 1978; Terry & Davies, 1980).

Uncertainty has arisen towards the view that cases of early and late onset constitute a unitary condition in the light of both clinical (Loring & Largen, 1985; Roth, 1981) and neuropathological

Table 10

Criteria for Clinical Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

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

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

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65;

presence of trisomy-21; and

coexistence of other relevant conditions such as Parkinson disease.

From McKhann et al., 1984

evidence (Terry, 1978). Pre-senile Alzheimer's disease and senile dementia of the Alzheimer's type are probably the same disease, given their shared neuropathologic findings (senile plaques, neurofibrillary tangles, granuovacuolar bodies, Hirano bodies and the predominant transmitters deficiency (Terry, 1978). According to Constantinidis (1978), a number of authors have argued that it is possible to recognize qualitatively different subtypes of Alzheimer's dementia (Gustafson, 1985; McDonald, 1969; Heston, Mastri, Anderson & White, 1981). Structurally, the brain in the presenile form has been observed to be much smaller than that of both normal and SDAT patients (Terry & Davies, 1980). Neuropathologically, it appears that the neurons of the locus coeruleus, providing adrenegic projection to the rest of the cerebrum, have a 60-80% fallout in presenile cases of Alzheimer's disease. Patients with a later onset of disease (73-75) were found to have a fallout rate of approximately 20% as compared to normal controls (Bondareff, Baldy & Levy, 1981; Bondareff, Mountjoy & Roth, 1982). Further differences in concentration of both structural lesions and neurotransmitters and their markers in several brain regions were also observed in cases of early and late onset of the disease (Winblad, Adolfsson, Carlsson & Gottfries, 1982). Both plaque and tangle formation and neurotransmitter deficits were limited in the late onset types (Selzer & Sherwin, 1983; Evans et al., 1984; Rossor, Iversen, Reynolds, Mountjoy & Roth, 1984). Furthermore, neuronal fallout was not found to exceed significantly that found among normal aged individuals (Mountjoy et al, 1983).

Clinically, McDonald (1969) argued that two types of senile dementias could be distinguished, one occurring in a younger age group and having a 6-month life expectancy, and the other occurring in an older age group and having a longer prognosis. However, as Jorm (1985) pointed out, a definite demonstration of the existence of subtypes would have required a follow-up of the older group to exclude differences due to a variability in symptomatology, or a distinct developmental course. Being younger, patients with the presenile form are less susceptible to infections, arteriosclerotic disorders, tumors and other serious diseases and thus will more often go through all the stages of the dementia.

Three recent studies (Breitner & Folstein, 1984; Folstein & Breitner, 1981; Seltzer & Sherwin, 1983) appeared to give greater validity to the presence of subtypes in Alzheimer's disease. All three suggested that language disturbance is not invariably part of the symptomatology of Alzheimer's disease. Rather, the presence of language disturbance appears to be associated with an early age of onset, left handedness, an earlier death (Seltzer & Sherwin, 1983) and to a familial prevalence (Breitner & Folstein, 1984; Folstein & Breitner, 1981). All studies invoked the presence of a genetic factor underlying this particular subtype.

Mayeux et al. (1985) pointed out that Alzheimer's disease does not follow a formal predictable course. He identified four subgroups of patients with Alzheimer's disease, two of which showed myoclonic or extrapyramidal signs, the first being associated with severe

intellectual decline and often mutism after a younger age of onset and the second also with severe intellectual and functional decline but with frequent psychotic symptoms. The two other subgroups were without myoclonic and extrapyramidal signs and showed a typical course with the well known gradual pattern of decline of intellect and function.

The question as to whether these features constitute actual subtypes of Alzheimer's disease or are variants remains open. For example, none of the studies controlled for stage of the disease which means that patients at early and late stages of the disease may have been compared together. Thus, symptoms generally found in the late stages might have eventually been found in patients tested at an early stage had they been followed long enough. Evidence supporting such a possibility comes from Breitner and Folstein (1984), Constantinidis (1978) and Heyman (1984) who observed that patients without disorders of language, praxis and gnosias were more likely to be older at onset and to possibly not survive long enough to develop such deficits. Breitner & Folstein's (1984) younger group of patients had been institutionalized for longer periods than the older group. Heyman (1984) correlated the appearance of language disturbances in patients with Alzheimer's disease to the duration of the disease. In Heyman's group, the figure of patients with language disorder at initial diagnosis was 43%; however, it became 75% after a 3 year follow-up. Heyman (1984) did not observe the finding reported by Breitner & Folstein (1984) that patients with language disorder appeared to show

a greater familial incidence of the disease. Thus, the question of both subtypes of Alzheimer's disease and of a senile-presenile division is unresolved. Perry (1986) concludes that at this time the similarities between SDAT and presenile Alzheimer's disease outweigh the differences.

Memory disorder in Alzheimer's disease

An impairment in memory has perhaps been the most noted aspect of the cognitive decline associated with mild to moderate dementia of the Alzheimer-type (Coblentz et al., 1973; Katzman & Karazu, 1975; Semple, Smith, & Swash, 1982; Sims & Sussman, 1962). While in the early studies the memory deficit had been described as an inability to recall recent events (e.g., Blessed, Tomlinson & Roth, 1968; Torak, 1978), more recent reports have taken into account some of the multiple processes that are known to be involved in normal memory functioning (e.g., Corkin, 1982; Miller, 1978; Weingartner, Grafman, Boutelle, Kaye & Martin, 1983; Weingartner et al., 1982; Wilson, Kaszniak, Bacon & Fox, 1982).

The memory disorder secondary to Alzheimer's disease has been described as amnesia-like in which both recent memory and remote memory are affected. The experimental studies on memory processes in patients believed to suffer from either pre-senile or senile dementia will be reviewed. Such investigations have aimed at exposing the locus of failure of memory processes using a paradigm deriving from a

specific model of memory processes (Atkinson & Shiffrin, 1968; Craik and Lockhart, 1972).

Long-term memory and recognition in patients with senile and/or pre-senile dementia have been studied in paradigms using material such as pictures (Diesfeldt, 1978); faces (Ferris, Crook, Clark, McCarthy & Rae, 1980; Wilson, Kaszniak, Bacon, Fox & Kelly, 1982); and designs (Omer, Babayov & Menczel, 1985). Results suggested that non-verbal memory deteriorates at a faster rate than verbal memory (Omer et al., 1985), that high recognition is associated with a primacy effect in the recall serial curve (Diesfield, 1978); and that recognition of unfamiliar faces is preserved (Ferris et al., 1980), although this was later challenged (Wilson et al., 1982). The present review of the literature on memory processes in Alzheimer disease, however, will focus on experimental studies on verbal memory processes.

Miller (1971, 1972, 1973, 1975, 1977, 1978; Miller and Hague, 1975; Miller & Lewis, 1977), a pioneer in the experimental investigation of memory processes in Alzheimer's disease, studied the memory impairment of his patients using a framework which conceptualizes memory as a dual system. According to this system, two types of memory are hypothesized: (a) a short-term store (primary memory) which has limited storage capacity, holding information for no more than a few seconds, and dependant on phonemically coded information; and, (b) a long-term store (secondary memory) which has a greater capacity, and is thought of as a more permanent store which

relies heavily on semantic coding. Information, it was assumed, always travelled from short-term store to long-term store and also relied on the short-term store for its retrieval, moving in the opposite direction. Because most studies have used such a framework, the present review will organize the research according to the goal of the investigations such as, for example, short-term memory and long-term memory.

Experimental studies of memory processes in Alzheimer's disease

Studies focussing on short-term memory processes. Having hypothesized that the deficit in memory in Alzheimer's disease must lie at the short-term store, Miller (1971, exp. 1) attempted to verify this hypothesis using a free-recall condition of words learned. He observed that his demented patients did not show the usual primacy and recency effect indicating both a short-term and long-term store deficit. The long-term store impairment could be thought of as independant from that of short-term store but Miller reasoned that it could result from the deficit in the transfer of information from short-term store to the long-term store.

To test this hypothesis, Miller (1971, exp. 2) examined recall as a function of rate of presentation of words in a list, that is, if the transfer to long-term store was due to the short-term memory's reduced ability to transfer items from one store to another, then presenting the words at a slower rate should enhance the transfer. This would

result in an increase in the number of recalled words from the beginning of the list (primacy effect). The results, however, showed the manipulation to be helpful to the normal controls but not to the demented patients. He thus concluded that the memory impairment in senile dementia was composed of two independent deficits, one at the short-term and the other at the long-term memory.

The involvement of short-term memory in the memory deficit of Alzheimer's disease was verified following another methodological procedure (Miller, 1973). In this experiment, patients with pre-senile dementia failed to give back accurately an immediate replication of a short list of words after a single presentation. Furthermore, repeated presentations did not help this group to learn lists of words that exceeded the word span by one, two, or three items, although it did help the normals. Supra-span learning requires the use of the long-term memory in order to cope with the excess items.

Miller (1977), however, felt that the short-term store deficit could be an artifact, that is, that the actual problem could reside in processes preceding the insertion of information into short-term memory. Such processes could include disturbed attentional abilities or an impaired iconic memory, or the inadequate coding of the material in short-term memory. Using a procedure inspired by Baddeley (1966), he conducted an experiment to investigate the effect of acoustic similarity on recall from short-term memory. The results showed that the demented group were less able to utilize acoustic coding in

short-term memory.

Results by other authors support the impairment of short-term memory in patients with presumptive Alzheimer's disease. Corkin (1982) used the Brown-Peterson distractor method, and digit and block span test, and found that, in comparison to patients with global amnesia, patients with Alzheimer's disease showed, on the Brown-Peterson task, an impairment in both retention capacity and forgetting rates of short-term memory. She also noted that the performance on both digit and block span was impaired with the Alzheimer patients. Kopelman (1985) using a version of the Brown-Peterson and digit span tests, found that Alzheimer patients consistently performed poorly as compared to a group of control and a group of Korsakoff patients, thus displaying a severe impairment of short-term memory. Such results were also observed by Sullivan, Freely, Corkin & Growden (1984). However, the failure may be due to an interference effect as argued by Stuss, Kaplan, Benson, Weir, et al. (1982), since Corkin (1982) found that short-term memory processes were less impaired on tasks (e.g. digit span and block span) involving immediate memory without filled delays.

There are exceptions to the general finding that short-term memory is impaired in patients with Alzheimer's disease. In a study comparing two groups of patients (moderately and severely impaired) with probable Alzheimer's disease, to a normal control group, one group (severely impaired) was found to have a reduction of both primacy and recency effects whereas the other group (moderately

impaired) showed only a reduced primacy effect (Harris & Dowson, 1982). Long-term memory in the moderately impaired group was thus shown to be impaired but not short-term memory. Ober, Koss, Friedland & Delis (1985), using the selective reminding paradigm (Buschke, 1973; Buschke & Fuld, 1974), observed that mildly impaired patients with Alzheimer's disease relied on short-term memory for the recall of learned items much more than on long-term memory.

Despite such exceptions, the impairment in short-term memory is a well-replicated finding across laboratories and across techniques. Although one study (Harris and Dowson, 1982) found the impairment to be present only in the severely impaired group, another report (Corkin, 1982) in which subjects were divided according to severity reported the short-term memory deficit to characterize all patients.

Studies focussing on long-term memory processes: Miller (1975) investigated long-term memory in dementia using a procedure in which a list of words was presented to subjects. Following a filled interval three types of recall were initiated: a) free recall, b) a partial information recall (providing the initial letter of the word) and c) a recognition test in which the correct word was presented with a set of alternatives. In this study, the demented subjects performed poorly under both free recall and recognition but performed as well as the normals when provided with partial information. Interestingly, these results had been observed earlier with patients with other amnesic syndromes (Warrington & Weiskranz, 1970). Miller (1975) thus postulated that, rather than being a problem of acquisition, the

problem was one involving deficient retrieval mechanisms. A later study (Morris, Wheatley & Britton, 1983) replicated these results in a group of patients with senile dementia. Cueing, using partial information about the words, was found to be more effective than a recognition procedure. These authors also interpreted these results in terms of a faulty retrieval mechanism. However, such interpretations are questionable because it has been argued that cueing, by providing partial information about the words, produces enhanced recall due to weak and decayed residual traces (Pearcy, 1977; Squire & Wetzel, 1978; Woods & Piercy, 1974). Therefore, the enhancement of memory is likely to result from weak traces in long-term memory left by poor acquisition.

Miller (1974) investigated retrieval processes on the premise that new information entering long-term memory might be coded inefficiently or unusually. If this were so, then providing various types of cues might give some indication as to the encoding strategy used. An analysis of the type of errors made by demented subjects in a recognition test in which alternative stimuli differed from the correct one along several dimensions did not provide support for the hypothesis of a difference in encoding strategy. Although the Alzheimer's patients were poor at selecting the correct response, their type of errors were similar to those of the normal controls.

Miller (1975, 1977) insisted that both acquisition and retrieval were involved in the memory deficit since performance improved when retention was tested with partial information rather than a

recognition procedure, and since recognition worsened as the number of recognition alternatives increased. Whitehead (1975), however, showed that there was a trend toward a better recognition performance when Alzheimer's patients were tested with a forced-choice format rather than a "yes" or "no" response procedure. An error analysis revealed that it was not so much due to a reduction of the number of false positive responses but rather because it forced the subject to answer even when unsure. Ober et al. (1985) have shown that a deficit in retrieval of items is only a minor contributor to the overall memory deficit in Alzheimer's disease, and that the severity of dementia was an important factor with respect to the degree of impairment in long term memory. Thus, although mildly impaired subjects are less likely to encode information in long-term memory, they are more likely to retrieve items which appear to have been encoded into long-term memory. Moderately impaired subjects, on the other hand, encode more information into long-term memory but are less likely to retrieve the information. The results were interpreted in terms of allotment of already-impaired attentional processes.

The results of studies based on the "multistore" model have demonstrated that information fails to reach long-term memory. They have not determined, however, where the site of failure lies in those various stages. Weingartner et al. (1981) have shown that the memory problem in Alzheimer's disease is too complex to be understood solely within the multistore model of memory. Their results showed that the mnemonic deficits in Alzheimer's disease involved complex semantic

associative networks.

Organization of memory

Weingartner et al. (1981) explored the organizational quality and retrieval processes in patients with suspected Alzheimer's disease by comparing their performance on a series of laboratory tests designed to investigate learning and memory with that of normal subjects. The results showed the patients to have a severe memory failure on all of the tests, as might be expected, but their failure was shown to have identifiable characteristics. In the case of words learned over several trials, the patients showed a labile or inconsistent recall of previously remembered words. Words recalled on a prior trial had as much chance to be recalled at a subsequent recall trial as words that had not been recalled. In the learning of related and unrelated words, the Alzheimer patients consistently failed to use the "organizational or relational properties" of words which generally lead to successful encoding and thus to the making of reliable memory traces. In the retrieval of words that belonged to the same category, the patients, again, failed to use such organizational features which lead to a poor recall. The use of external strategies, repetition of the missed information; repetition of the list following the same sequence and presenting related words, all of which are known to facilitate encoding, were of little help to the Alzheimer's patients. They not only failed to relate events together and to abstract shared

attributes amongst events, but they also failed to actively organize the retrieved material and to use provided organizational structures. The patients were found to lack the semantic network necessary to reliably encode and retrieve verbal information. These results are consistent with the levels-of-processing theory (Craik & Lockhart, 1972) in that the failure to learn and retrieve could be explained by a failure of the encoding mechanism.

This interpretation was also supported by the findings of Corkin (1982). In her study, Corkin compared a group of patients with global amnesia with patients with the diagnosis of Alzheimer's disease divided into groups of mild, moderate and severe dementia (as measured by their disability in daily living activities). The goal of the study was to determine whether patients with global amnesia but otherwise intact cognitive functions differed from patients in whom a cognitive decline had paralleled the memory loss. Encoding processes and learning processes (verbal and non-verbal paired associate learning task) were investigated. Encoding processes were investigated within the depth of processing model whereby learning was facilitated at the sensory, phonological and semantic levels through a series of questions. The results of this verbal recognition memory task revealed that the integrity of cognitive functions other than memory are necessary for an effect of encoding strategies to occur, the Alzheimer group being the only group that did not profit from the various encoding strategies. Wilson, Kaszniak, Bacon, Fox & Kelly (1982) also reached a similar conclusion when their results indicated

a failure on the part of the Alzheimer patients to profit from semantic orienting questions at encoding.. The memory failure was interpreted as part of a complex network involving language functions.

The hypothesis that the memory failure of Alzheimer's patients may result from a failure to use attributes necessary to encode efficiently was given support in a study by Martin, Browers, Cox & Fedio (1985). Conducted within the levels-of-processing theoretical framework (Craik and Lockhart, 1972), several alterations were provided to the traditional method of controlling encoding. For example, each list was learned using different encoding strategies: subjects were requested to generate a word associate which either rhymed (phonemic level) with the word learned or to give a place where the object could be found (semantic level). Furthermore a "semantic-praxic" condition was added which required the patient to pantomime a movement or a sequence of movements which illustrated clearly the use of the word. Thus, not only was attention controlled at encoding but two modalities were used to enhance learning.

Such encoding techniques proved to be useful to both the normal subjects and the Alzheimer's disease patients under both semantic and praxic encoding conditions. Furthermore, both groups were found to encode semantically spontaneously which is contrary to the finding of Weingartner et al. (1981). A disruption of recall occurred for both groups only when asked to attend to the phonemic features of the words. Qualitatively, the pattern of recall of the Alzheimer's group was a miniature of that of the normal subjects suggesting that

patients in the early and moderate stage of the disease retain the ability to encode semantically.

The use of cueing (providing the generated associates given by the patient) failed to reduce the gap between the performance of Alzheimer's patients and normal controls. The retrieval deficit was therefore not supported as being the site of their failure. However, regardless of the technique used, encoding is still incomplete, due to other cognitive deficits, which limits the analysis of the material and leads to a lowered recall performance (Martin, Brouwers, Cox, & Fedio et al., 1985; Martin, Cox, Brouwers & Fedio, 1985). Therefore, as Corkin (1982) found, the memory disorder in Alzheimer's disease cannot be separated from other cognitive deficits.

Impaired learning and memory are thus two well-documented experimental findings in SDAT. Researchers are presently attempting to describe the processes characterizing the memory failure secondary to the disease (Martin, Browers, Cox, & Fedio, 1985; Martin, Cox, Browers, & Fedio, 1985; Ober, Koss, Friedland, & Delis, 1985). Attentional deficits and a general breakdown of cognitive functions have been found to contribute to the severity of that memory impairment.

Reaction time and Alzheimer's disease. Two studies report the use of choice-reaction task paradigms with cognitively impaired ("senile") patients (Ferris, Crook, Sathananthan & Gershon, 1976; Pirozzolo, Christensen, Ogle, Hansch, & Thompson, 1981). In the Ferris et al. study, although both simple and disjunctive reaction

times were slower in the 'senile' patients, dysjunctive reaction time alone distinguished the senile patients from the normal control subjects with 86% accuracy. There also appeared to be an association between the slowness of response and the patients' dependency on others.

In the Pirozzolo et al. study, subjects with Alzheimer's disease had significantly longer mean RT's on all three RT measures (auditory, visual and four-choice) but the difference between their performance and that of normal subjects was most pronounced when choice was required in the response. The increase in RT in the four choice task was interpreted as reflecting an index of cognitive impairment in these patients. As in the Ferris et al. (1976) study, the more complex task distinguished the patients from the normal control subjects with 92% accuracy. Nonspecific attentional or (unidentified) more specific dimensions of cognitive information processing deficits i.e. at the level of the decision process, were hypothesized to account for the slowing.

Findings on reaction-time tasks with Alzheimer's disease patients are therefore similar to patients with brain damage, i.e., both are slower to respond than age-matched controls (Benton & Joynt, 1958; Benton, 1977). A direct measure of speed of information processing using the item-recognition paradigm has not been applied to a population of patients suffering from Alzheimer's disease.

Summary, Description of Project and Hypothesis

It has been proposed that characteristic patterns of cognitive deficits and personality changes caused by disease processes in the central nervous system can be classified anatomically, on the basis of the site of the most significant underlying pathologic changes (Albert et al., 1974; Joynt & Shoulson, 1979; McHugh & Folstein, 1975). One constellation of symptoms, associated with subcortical pathology, (forgetfulness, inability to manipulate acquired knowledge with ease; personality changes characterized by apathy or inertia, and a general slowing of mental operations) has been called 'subcortical dementia' (Albert et al., 1974) or bradyphrenia (Hassler, 1965), whereas another, that associated with cortical pathology (amnesia, aphasia, cognitive deficits such as impaired judgment and abstraction, acalculia, etc., visual-spatial deficits, and personality changes characterized by unconcern and disinhibition) (Benson, Cummings & Kuhl, 1981; Benson, 1984), has been called cortical dementia (Albert, 1978; Albert et al., 1974; Cummings & Benson, 1983). The major distinguishing features of these two generic dementias are the presence of instrumental disorders (aphasia, agnosia, apraxia) in the cortical dementias (Albert, 1978; Benson, 1982; Freedman & Albert, 1985) and the preservation of such higher-order associative functions in the subcortical dementias (Huber & Paulson, 1985).

From its inception, this new classification of the dementias has been the subject of controversy. Firstly, it was pointed out that there are no pure cortical, or pure subcortical, dementias (McHugh,

1978). The literature on Parkinson's and Alzheimer's diseases clearly supports that. Secondly, the use of the term dementia has been criticized because it deviated from its historical meaning and therefore confuses rather than clarifies the issue (Marsden, 1978; Roth, 1980). Thirdly, because the neuropsychological deficits of patients with subcortical damage resemble those related to frontal system dysfunction, it has been suggested that the term 'fronto-subcortical' dementia or 'frontal system dementia' (Freedman & Albert, 1985) or 'frontal-lobe syndrome' (Marsden, 1978) might be more appropriate.

Although the anatomical classification of the dementias has suffered serious criticisms, the clinical distinction between the syndromes themselves has been generally accepted (Foster, 1986). Essentially, the clinical syndrome recently called fronto-subcortical dementia consists of specific acquired intellectual impairments, with forgetfulness and slowed mental processes being the outstanding ones; the intellectual deterioration is not a true one as in the cortical dementias but rather a difficulty in manipulating acquired knowledge. Finally, personality is affected, commonly in the form of apathy or depression. In contradistinction, the clinical syndrome which long-standing usage refers to as cortical dementia includes deficits in language, calculation, and learning with the salient features being amnesia, agnosia, aphasia and apraxia. Whitehouse (1986) has suggested that the distinction ought to be tested neuropsychologically.

This thesis is an experimental neuropsychological study of Albert's (1978) proposed distinction. It examines two prominent distinguishing features (slowness of thought processes and memory loss) of a group of patients with Parkinson's disease and then compares these with the results of similar investigations carried out on a group of patients with Alzheimer's disease. Both are compared with a controlled group.

Sternberg's item-recognition paradigm. The Sternberg procedure (Sternberg, 1969) was used in order to examine the potentially slowed but intact mental operations of the Parkinson's disease patients. It was chosen because it provides a robust experimental technique. An explanation of the Sternberg procedure follows.

The item-recognition paradigm. Sternberg's item recognition paradigm allows examination of internal scanning (Sternberg, 1963, 1966, 1969a), the rapid search of memory for retrieval of learned information. It is carried out experimentally in the following manner. A stimulus ensemble is chosen, which is comprised of all the members of the memory set and the test items set. From amongst the ensemble, a set of items is arbitrarily selected and defined as the positive set; they are the items presented to the subject for memorization. All remaining ensemble items are referred to as the negative set. A test stimulus or probe is always a single ensemble element presented for the subject to decide whether or not it is a member of the positive set. When shown a test item that has been memorized, the subject makes a positive response, in this case by

vocally saying "yes". If the test stimulus originated from the negative set, a negative response is given by saying "no". The term "item recognition task" derives from this last event of correctly recognizing the test stimulus, as either a member, or non-member of the positive set. The reaction time (RT) is measured from the onset of the test stimulus to the subject's response.

The paradigm can be carried out in one of two modes: either a fixed set can be used, in which a single memorized set is used for a series of trials; or a varied memory set can be used, in which a new memory set is presented with each given trial. Previous research has indicated that RT is independent of mode (Sternberg, 1975). Since at least one of our experimental groups (SDAT) had probable memory disorders other than those being investigated, the varied-set mode was used because it is dependent only on short-term memory. The number of items presented was within the digit span range of all subjects.

The study of reaction time (and index of retrieval time in recognition memory experiment) has given rise to a theory of the process of retrieval when learning and retention are essentially perfect. The processing that occurs between stimulus and response is conceptualized in terms of four sequential independent stages whose component latencies are additive. The suggested sequence is as follows: a) stimulus encoding or representation stage; b) a comparison and central scanning stage operating on the mental representation of the stimuli; c) a decision making stage and d) a

response execution stage. The events of Sternberg's (1966) item-recognition paradigm separates the four stages in the following manner. Stages one and two occur during the learning of the positive set and the subsequent comparison of the test item to this set. Stage three occurs when the subject has reached a decision as to whether the item has or has not been learned. Stage four occurs when the subject responds. This analysis is particularly useful in the present study, because, by isolating the stage or stages at which Parkinson's disease patients are deficient, it addresses the controversy as to whether or not patients with Parkinson's disease actually have slowed thinking (Wilson, 1955; Benson, 1984).

If the number of letters in the positive set is within the subjects' short-term retention capacity, the RT is a linear function of (positive) set size. This is thought to reflect the search, by an hypothesized comparator, in which the items in memory are serially compared with the probe.

A possible scanning strategy is to terminate scanning as soon as a match between the probe item and an item in short-term memory is detected. Under such circumstances, the hypothesized comparator would sometimes detect the positive item at the beginning of the scan, sometimes at the end, but on average, it would need to scan about half of the items. However, the comparator would always have to scan all the items in the set before concluding an absence of a match. Thus, the slope for negative responses should be approximately twice as steep as that for positive responses. Sternberg (1975) gives evidence

that scanning time has been observed to be the same for negative and positive responses. This implies that the comparator engages in an exhaustive comparison even when the item searched for is encountered part way through the memory set (Sternberg, 1969; 1975). The other possibility, a 'self-terminating' scan, wherein the memory search is terminated when identification of the appropriate memory set item is made, did not occur. An exhaustive scan would be reasonable on the assumption that it is much quicker to scan an item to make the decision that a match did or did not occur.

The Sternberg procedure has been proven to be robust as can be seen by the reaction-time functions obtained using a variety of stimulus ensembles. For example, stimuli used have included visual and auditory digits and letters, shapes, two- and three-digit numerals, pictures of faces, drawings of common objects, words of various lengths, colours, phonemes, and random forms (for examples, Burrows & Okada, 1973; Chase & Calfee, 1969; Clifton and Tash, 1973; Foss and Dowell, 1971; Hoving, Morin & Konick, 1970; Smith, 1967; Sternberg, 1969a; Swanson, Johnsen & Briggs, 1972; Wingfield, 1973). The slopes of the functions vary for different ensembles, but in a systematic manner.

Furthermore, the Sternberg procedure has been applied to various age groups: normals, alcoholics, schizophrenics, aphasics, Parkinsonians and brain damaged mental retardates (for examples, Anders, Fozard & Lillyquist, 1972; Eriksen, Hamlin & Daye, 1973; Harris & Fleer, 1974; Hoving, Morin & Konick, 1970; Mohs, Tinklenberg,

Roth & Kopell, 1979; Pharr & Connor, 1980; Swinney & Taylor, 1971; Warren, 1977).

With respect to normal aging, Anders et al. (1972) found that both the slope and the intercept of the scan function increased with the age of the subject. This led the authors to conclude that rate of scanning slows down with age, and this has been replicated by Ericksen, Hamlin & Daye (1973) and Anders and Fozard (1973).

At the time of the preparation of this project, there was only one study (Wilson et al., 1980) which had used the Sternberg procedure with one of our patient populations (Parkinsonian patients). The use of the same procedure will provide an extention of Wilson et al. (1980)'s study which concluded that rate of scanning is slowed in elderly Parkinsonian patients. Since the beginning of this project, another study has been published using a modified version of the Sternberg procedure. In the Rafal et al. (1984) experiment, the Parkinsonian patients were found to scan as quickly and effectively as the normal subjects. This study will, therefore, also provide further data that may help settle the issue as to whether Parkinsonian patients do, or do not, have slowed mental operations.

Although patients with Alzheimer's disease have been found to be slowed in choice-reaction tasks (Ferris et al., 1976), they have not been studied with the Sternberg technique. Such a study promised to be useful, because Sternberg's paradigm allows more accurate separate measurement of central scanning and extra-scanning processes than do choice-reaction tasks.

Finally, the study will compare the performance of these two groups to a group of normal, aged individuals.

Hypothesis to be Tested

Based on the review of the literature, the following questions may be raised. Is the slowness of mental function observed in Parkinson's disease greater than that observed in normal aging? Does Senile Dementia of the Alzheimer's type slow the rate of information processing more than normal aging and, if so, how does it compare to that found in Parkinson's disease? Can it be concluded that the Parkinsonian group is characterized by a 'bradyphrenia' (Wilson et al., 1980) which is not shared by the two other groups? Two of the questions may be stated in the form of a null hypothesis.

> There is no significant main or interaction effect between the diagnostic categories on the behavioural measures defined in terms of mean reaction time, and latency and slope functions.

> There is no significant main or interaction effect in the response type (yes or no) on the behavioural measure of mean reaction time.

One hypothesis is directional consequent on the procedure itself.

There is a significant difference between memory loading one, memory loading two, and memory loading three on the behavioural measure of mean reaction time.

Memory Paradigm. As reviewed in the introduction, memory failure is a constant feature of Alzheimer's disease. A disordered memory has also been reported to be part of the clinical picture of Parkinsonian patients who do not score within the demented range on dementia rating scales. In a second experiment, a comparison of the memory disorder suffered by the two patient populations was undertaken.

A memory paradigm was developed to study the differences on learning of material presented firstly without information, and, secondly with information, about the words to be learned. It was reasoned that if the difficulty experienced by Parkinsonian patients is one of abstraction and/or organization, then learning should be facilitated when subjects have been informed of the commonality amongst the words to be learned.

Furthermore, the memory paradigm was designed to allow comparison of various types of assisted recall, i.e., cued recall (where the patient is provided with categorical cues), and recognition (when the patient is required to discriminate between target items and new distractor items). It was reasoned that Parkinsonian patients' memory would be improved when assisted by cues or recognition if they have a retrieval deficit. Such strategies, however, were not expected to facilitate learning in the SDAT group because their memory disorder is

taken to be at the level of encoding.

Hypotheses to be Tested

A review of the literature prompted several questions. If the memory deficit in Parkinson's disease is a forgetfulness, a difficulty in retrieving memories, then one may be able to repair their deficit through the use of an appropriate strategy. Such a stategy should result in a performance increment as compared to what is recalled under simulated ordinary conditions (no priming free recall).

On the other hand, if the SDAT group does have a true deterioration of memory function, then the use of such strategies known to facilitate retrieval should not be effective.

Although memory function has been shown to decline with age, it is expected that normal aged subjects will have superior recall when compared with patients with Parkinson's disease or Alzheimer's disease.

Stated in terms of the major null hypotheses:

1. There is no significant difference between the diagnostic groups on the various recall measures.

2. There is no significant difference between the

method of learning on the number of words correctly recalled.

3. There is no significant difference between the retrieval strategies on the number of words correctly recalled.

4. There is no significant interaction effect between groups, condition and recall type on the retrieval measures.

Experiment 1

Method

Subjects

Three groups of subjects were investigated. The first (Group I) comprised outpatients diagnosed as having idiopathic Parkinson's disease (PD), and who were undergoing treatment for PD either at the Division of Neurology of the Ottawa General Hospital or at the Parkinson's Disease out-patient Clinic of the Ottawa Civic Hospital. The second group (Group II) comprised outpatients diagnosed as having Senile dementia of the Alzheimer-type (SDAT), referred from the Neurology Division and Memory Disorder Clinic of the Ottawa General Hospital. The third group (group III) consisted of normal control (NC) subjects who volunteered their participation. These were spouses of patients (2) and volunteers from the Senior Employment Bureau. All subjects gave informed consent for their participation and were paid $15.00 to defray minor expenses incurred due to the study. In the case of patients with SDAT, informed consent was also sought from the patient's next of kin.

General criteria for inclusion in the study for all subjects included (a) absence of a consistent history of hospitalization for psychiatric illness (in the case of a history of depression,

inter-rater reliability from two neurologists was used for inclusion in the SDAT group); (b) absence of a history of neurological disease other than that being investigated (no neurological disorder for Group III) and, c) the presence of the studied diseases (Group I & II) for at least one year.

For the patient groups, possible metabolic and biochemical disorders were investigated when required. Where clinically indicated, an EEG, CT-scan and Doppler were used. Blood tests included complete blood count, sedimentation rate, thyroid studies, liver and kidney function tests, folic acid, vitamin B-12, cortisol and VDRL. CSF analysis, RISA cisternography and angiography were not clinically indicated in any patients. The Hachinski-Ischemia score was applied to the SDAT group to rule out multi-infarct dementia (Hachinski et al, 1975). Brain biopsy was performed on one patient who was rejected from the study.

Although attempts were made to match all three groups according to age, education, and Wais-R (or Barbeau-Pinard for the French speaking subjects) vocabulary scores, this was not possible due to the SDAT group being at a more advanced age when referred. Primary emphasis was given to matching the PD and NC groups. For all subjects, the presence or absence of dementia was assessed at the time of initial evaluation using the Dementia Rating Scale (Coblentz, Mattis, Zingesser, Kassof, Wisniewski, & Katzman, 1973), which was developped for the clinical diagnosis of Alzheimer's disease (Mattis, 1976). Short examinations for dementia have been generally criticized

for failing to identify patients at the mild stage of the disease (Wells & Buchanan, 1977). The DRS clinical scale, however, has been shown to be a valuable instrument in distinguishing the Alzheimer-type dementia from other dementias, even at an early stage of the disease (Fuld, Katzman, Davies, Terry, 1981; Freedman, Rivoira, Butters, Sax & Feldman, 1984; Friedland, Budinger, Koss, & Ober, 1985; Martin & Fedio, 1983; Mattis, 1976; Moss, Albert, Butters & Payne, 1986; Vitaliano, Breen, Albert, Russo, Prinz, 1984; Volicer, Direnfield, Langlais, Freedman, Bird & Albert, 1985). When possible, this evaluation was repeated from 9 to 18 months following initial administration. This allowed assessment of any progressive decline in mental abilities. Subjects in the SDAT group who did not show a decline were excluded from the study.

The presence of dementia was defined as follows: (1) the profile of behavioural disturbance was concordant with the definition that dementia is "an acquired persistent impairment of intellectual function with compromise in at least three of the following spheres of mental activity: language, memory, visuospatial skills, emotion or personality, and cognition (abstraction, calculation, judgment, etc.)" (Cummings & Benson, 1983, p.1); (2) the overall dementia rating score was below 133 (norms provided by Freedman, 1985); and (3) a progressive decline in functioning over time was observed. In one instance (SDAT group), the first and third but not the second criteria were met due to the patients superior premorbid abilities. The Washington Dementia Rating Scale (Cryer and Kissane, 1979) was used to

assess functional level. The Western Aphasia Battery (Ottawa General Hospital adaptation) was administered to ensure basic language capabilities; the presence or absence of depression was assessed through both the Zung (1965) and Beck (1961) depression rating scales. The Zung self-rating depression scale was proven to be a reliable instrument in the evaluation of the elderly (McGarvey, Gallagher, Thompson & Zelinski, 1980; Zung, 1967, Zung, Richards & Short, 1965).

Group I: Parkinson disease

Sixteen patients with idiopathic Parkinson disease were referred. One patient was rejected due to bilateral frontal lobe damage documented on CT-scan. Another was rejected due to an unusual history of juvenile Parkinsonism. Two other patients were rejected due to their having a severe dementia with the disease. Twelve patients were retained for the study. None of the patients showed a history of psychiatric illness. All patients had been diagnosed as suffering from Parkinsonism of the idiopathic type, for at least one year, and showed no evidence of other neurological disease. Patients were described as having altered cognitive functioning as compared to pre-morbid levels, but none showed evidence of presence of a dementia as defined by our criteria (see Table 11). All patients were on a variety of antiparkinsonian medications and were continued with chemotherapy extant at the commencement of the study (see Appendix 2 for drugs).

Signs or symptoms of parkinsonism were observed in all patients. These included cogwheeling (3 patients), akinesia (5 patients),

Table 11

Demographic Data for Parkinsons and Alzheimer's Diseases and Normal Subjects

Variables	Groups		
	Parkinson's Disease	Alzheimer's Disease	Normal Control
Sex			
Male	9	2	7
Female	3	10	5
Age (in years)			
M	58.3	67.0	58.9
SD	7.1	6.9	6.9
Range	49-70	57-80	46-70
Education			
M	13.2	12.6	14.3
SD	2.7	3.9	2.3
Range	9-17	8-22	10-17
Duration of Disease (in years)			
M	8.3	2.4	NA
SD	6.3	.99	NA
Range	1-21	1-4	NA
WAIS-R Vocabulary a)			
M	13.9	8.8	13.8
SD	1.8	22.6	3.0
Range	12-17	1-17	9-18
Dementia RS 1 b)			
M	140.1	118.7	142.2
SD	3.9	10.4	1.9
Range	132-144	105-143	139-144
Dementia RS 2			
M	141.6	99.5	NA
SD	1.9	24.7	NA
Range	138-144	63-136	NA
WDR c)			
M	.33	1.4	0
SD	.24	.63	0
Range	0-.5	.5-2.0	0
Zung Scale d)			
M	.46	.46	.35
SD	.08	.09	.09
Range	.31-.59	.34-.63	.26-.48
Beck Scale e)			
M	7.1	7.7	3.2
SD	4.3	6.9	2.9
Range	2-17	0-26	0-9
WAB f)			
M	99.2	91.8	99.8
SD	1.2	9.9	.62
Range	99-100	66-100	98-100

Hachinski Scale g)			
M	NA	1.6	NA
SD	NA	2.0	NA
Range	NA	0.6	NA

a) Vocabulary presented as a standardized scale score (Wechsler, 1981; Barbeau-Pinard (1951).
b) The Dementia Rating Scale is a composite score of several higher mental functions. Maximum score is 144.
c) WDRS-Washington Dementia Rating Scale.
d) Zung Depression Scale.
e) Beck Depression Inventory.
f) WAB-Western Aphasia Battery. Maximum score is 100.
g) Hachinski Ischemic score.

rigidity (8 patients), tremor (12 patients), masked facies (11 patients), seborrhea (4 patients) and various gait disturbances (all patients) including shuffling and festination. All patients with the exception of one showed bilateral involvement. Speech was generally of low pitch, and monotonous in tone for 11 patients. There was a range of severity of the Parkinson's symptoms (Hoehn and Yahr, 1967). One patient was at a functional level of stage 1, four patients were at stage 2; 2 were at stage 3 and 5 were at stage 4 of the disease. None of the patients had visual or auditory problems.

One patient was being treated successfully for hypothyroidism. Five were given an EEG, of which two showed diffuse slow background (6-7 Hz) with focal sharp waves at the left temporal area. Five patients were given CT scan. Results revealed that one patient had diffuse cerebral atrophy and another showed early cerebellar atrophy with considerable cerebral atrophy and some periventricular hypodensity. These patients did not show a corresponding deficit in general behavioral functioning as measured by the Dementia Rating Scale (DRS) and the Western Aphasia Battery.

The DRS has not been validated as an instrument for the purpose of identifying a dementia specifically attributed solely, or primarily, to underlying subcortical pathological change. In fact, there are, as of yet, no instruments capable of this (Cummings & Benson, 1984; Huber & Paulson, 1985; Whitehouse, 1986). However, useful indicators of the presence of a subcortical dementia may be provided from a qualitative analysis of patients' overall performance

(Cummings & Benson, 1984). If groups of patients with cortical or subcortical pathology both score within the range indicative of a dementia, on the DRS scale for example, the total score may be made up of qualitatively different characteristics for the latter group to be attributed to deficits in subcortical structure and function. Furthermore, the plotting of the subscale profile should follow a different pattern for one group as compared to the other. In this study, Parkinsonian patients were chosen so that they would not score within the range indicative of dementia on the DRS to ensure intact general cortical function.

Group II: Alzheimer Disease:

Fifty-five patients were referred with probable SDAT. Some patients were self-referred because of experienced memory disturbances and/or a decline in functional effectiveness either at home, or work, or both. Others were brought to their physicians (and subsequently to the neurologist or Memory Disorder Clinic) by family members with complaints of changed behaviour which precluded normal living. All patients had a history of employment and achievements indicating normal or higher premorbid intelligence.

Patients were submitted to a clinical-neurological diagnostic evaluation by a consulting neurologist, and to assessment of cognitive functioning, as described above.

Fourty-three patients were rejected. Nineteen patients were found to be too far advanced to participate in the experimental protocol;

sixteen either showed no progressive deterioration or had improved at time of re-test. Five patients who were provisionally diagnosed as having SDAT were rejected because of the atypical overall clinical picture and three patients were diagnosed as having multi-infarct dementia.

Twelve patients were accepted as members of the SDAT group on the basis of an agreement between two raters, a progressive loss of higher mental functioning as measured by the Dementia Rating Scale and the clinical-neurological assessment. Of these twelve patients three patients had historical features which required inter-rater consensus: one patient had had in the past two depressive episodes with hospitalization; one patient had had a closed head injury in his third decade; one patient had two different CT scan readings (one without contrast suggesting an infarct and a second one with contrast negating this). Patient's histories were otherwise insignificant. Demographic and neuropsychological characteristics of patients are shown in Table 11.

The SDAT group can be described as being mildly (105-146) demented using the Dementia Rating Scale. None of the patients studied were inpatients during the study; two patients were institutionalized within the follow-up period. All others were continuously cared for by their spouses. Patients in the mild dementia group were emotionally and behaviourally appropriate and could independently perform many activities, and could care for themselves.

Normal Controls

Twelve normal volunteers served as controls for the two other groups. These were members of the community who were leading normal lives, either still involved in their profession or retired. Three were volunteers from an Ottawa Curling Club while seven other volunteered from the Senior Employment Bureau. Two other volunteers were spouses of members of the SDAT group. Members of this group had no medical complaints and had no prior psychiatric history. Data on this group, including normal level of functioning, is presented in Table 11.

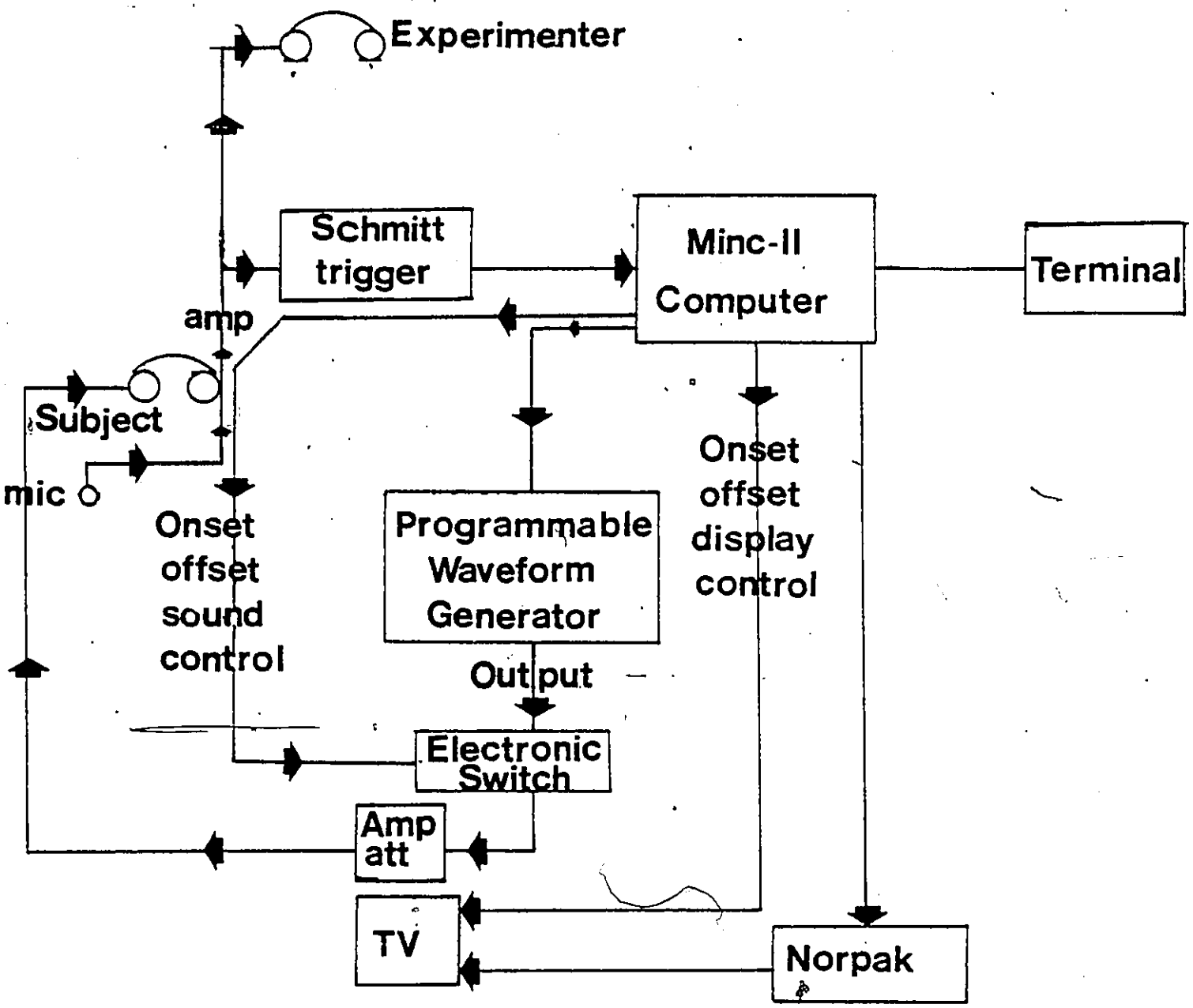
Materials

The varied-set procedure of the item-recognition paradigm (Sternberg, 1975) was used in this experiment. Onset and offset of all visual and auditory stimuli and timing of voice responses were controlled, processed and accessed through a Digital Equipment MINC 11 Computer. Figure 2 shows a schematic diagram of equipment used for presentation of the stimuli and collection of responses.

The visual display (letters of the alphabet) was presented on an Electrohome Contract Series 48 cm screen T.V. monitor (model C40 -852). Size, set and position on the visual display and generation of characters on the T.V. screen was done through a Norpak Micro Video Processor. Letters were 5 centimeters in height and 2 centimeters in width.

A 60 dB SPL, 1000 Hz warning tone was generated by a waveform generator (Wavetek model 159). The tone's onset and offset was computer controlled (5 ms rise and fall time) and was coupled to a set

Figure 2. Schematic diagram of equipment used for presentation of the stimuli and collection of responses.


Experimenter
Schmitt trigger
Minc-II Computer
Terminal
amp
Subject
mic
Onset offset sound control
Programmable Waveform Generator
Onset offset display control
Output
Electronic Switch
Amp att
TV
Norpak

of headphones (Telephonics, model TDH-49P) through a Grason Stadler amplifier (model 1288) and attenuator (model 1293).

An AKG microphone (model D40), along with an amplifier with gain of 5000, was used to pick up subject's voice response. The test letter was turned off by a Schmitt trigger circuit sensitive to voice amplitude. This trigger circuit sensitivity level was set so that the generated trigger pulse yielding RT would coincide with onset of the verbal response independently of subjects voice pitch variability. The trigger signal read by the computer gave an on-line measure of response time and initiated a routine to turn off the T.V. display. The response was also heard by the experimenter through a set of headphones.

Procedure

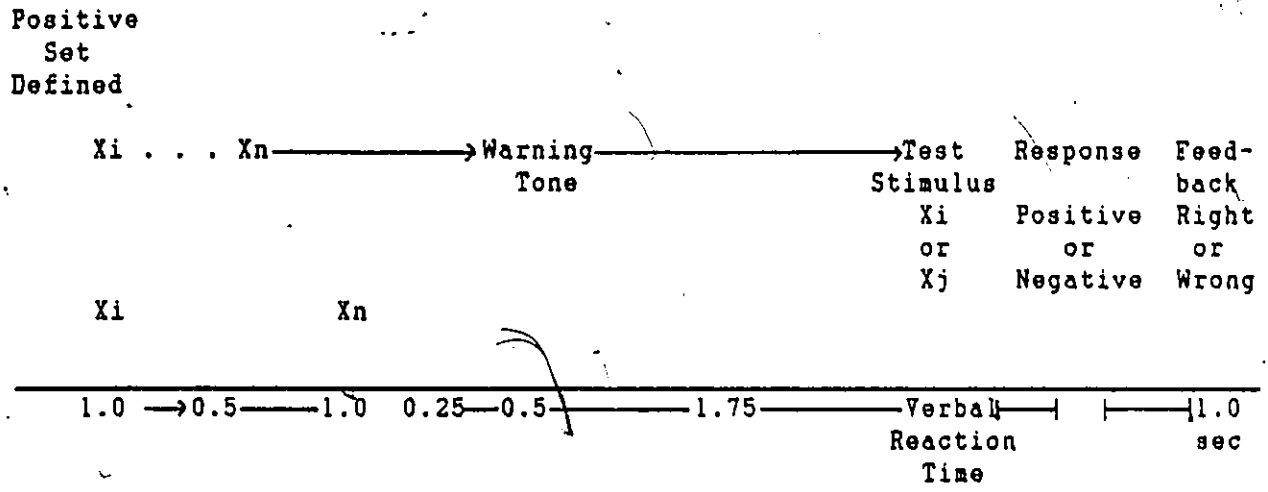
For the purpose of clarity, each trial will be artificially divided into three distinct phases: 1) the learning phase, 2) the testing phase and 3) the feedback phase. Figure 3 shows a schematic representation of the events of the item recognition paradigm.

Learning Phase

A trial began with the consecutive presentation of one, two or three letters of the positive memory set. Each letter was displayed for a duration of one (1.0) second with an inter-stimulus interval (ISI) of one half (0.5) second. The offset of the last letter of the memory set was followed in .25 msec duration by a warning tone of 0.5 second duration. This warning tone signaled to the subject the end of the learning phase and the onset of the testing phase which followed

Figure 3. Schematic representation of the events of the item-recognition paradigm.

TRIAL 1


Positive Set Defined
Xi . . . Xn
Warning Tone
Test Stimulus Xi or Xj
Response Positive or Negative
Feed-back Right or Wrong
Xi
Xn
1.0
0.5
1.0
0.25
0.5
1.75
Verbal Reaction Time
1.0 sec

the end of the tone by 1.75 seconds. The subject was free to rehearse during this short delay.

Testing Phase

At the offset of the retention interval, one single letter originating either from the positive or the negative set was displayed on the screen. The subject's task was to decide correctly, as quickly as possible, whether the displayed test letter was one of the items in memory. If the subject decided affirmatively, he answered "yes" or "oui" into a microphone, located approximately two inches from his mouth, thus making a positive response; otherwise he made a negative response by answering "no" or "non". The subject was instructed to respond as quickly as possible after the decision had been made. Verbal reaction time was measured on-line from the onset of the test stimulus to the onset of the verbal response. The verbal response also terminated the T.V. display of the test letter. A sample printout of one subject's results is presented in Appendix 3.

Feedback Phase

Subject's responses were heard by the experimenter via headphones after which he gave feedback through a display on the T.V. screen: the word "right", "bien" appeared if a correct answer was given or the word "wrong", "mal" appeared if it was incorrect. Feedback was displayed for 0.5 second. The response was then coded as "correct" or "incorrect" by the experimenter on the computer. In the event that the trial was invalidated by a technical difficulty, it was then coded "T" and replaced. Intertrial interval between feedback offset and the

beginning of the next trial was approximately 4 sec. Average inter-trial interval was approximately 6-7 seconds.

Experimental Protocol:

Each subject was seated in front of a television screen placed at eye-level 186 cm from the subject. Testing was carried out in a sound attenuated research chamber. Subjects received two sessions of 75 trials each separated by a short break. Sessions were broken into 10 blocks of 15 trials each. A word of encouragement to the subject separated the blocks. Instructions were given to each subject in the following manner. First the instructions were formally given as shown in Appendix 4a (English) and 4b (French). Then they were summarized in the manner described above informing the subject that in the learning phase, one to three letters would be shown. Then a warning tone would announce the end of the first phase and the arrival of the testing phase which consisted of a "yes" "no" answer given as quickly as possible. Finally, the subject was asked if he understood and if there were any questions.

Practice trials immediately followed the instructions. Each subject received a summary of the events for the first five practice trials whether the given answer was correct or incorrect. Then six other trials followed with instructions given only on the missed trials. Correctness of response was acknowledged only through feedback for all further trials. The experiment began after 15 consecutive successful trials were achieved. A maximum of 75 practice trials were allowed. Subjects who could not succeed within this limit were

assisted with an alternative "coached" technique as described further on. The instructions of the task were simplified as much as possible for subjects who had difficulty learning it. The experimental sessions lasted approximately 45 minutes with a five minute break halfway through the experiment.

One hundred and fifty trials were presented. For each trial, a different set (1 to 3 letters) of target stimuli, drawn from the "positive" set of eight letters (A,C,E,J,P,V,X,Z) was presented. The subject verbally responded "yes" or "no" to the test stimulus (a letter drawn from either the "positive" set or a second "negative" set (B,D,F,H,O,U,W,Y)), indicating whether or not the test stimulus had been presented as one of the memorized target stimuli. Selection of response type (yes or no) were made equiprobable. Selection of the target and test letters was random, with a restriction that each memory load size and the position of the test stimulus in the 1 to 3 letter memory sequence were made equally frequent.

A block of 15 trials was added to the total number to replace artifact contaminated correct responses, that is, those where the subject answered correctly but where the recorded reaction time was erroneous. The incorrect recorded reaction time could be either subject or machine related. In the first case, faulty triggering of the voice-operated response could be caused by manual contact of the microphone by the subject, too low a voice level, throat noises or coughing while the test stimulus was on. In the second, an erroneous recorded reaction time was due to faulty equipment. Such trials were

replaced at the end of the session and later included in the analysis of the results.

Simple error trials and outliers (responses which reaction time exceeded an arbitrary value of 4.0 seconds) of unknown contamination cause were rejected.

Coached-Learning Technique:

Subjects who could not successfully achieve 15 consecutive correct practice trials within 75 trials were given an alternative "coached-learning" procedure. The "coached learning" mode differed from the above only in that it contained instructions directing the subject more explicitly on the nature of the task. In this mode, the command "Learn" or "Apprenez" preceeded the appearance of the letter(s) to be memorized and lasted for 1.5 seconds on the screen. The question "Was it?" "C'était?" appeared for 1.4 seconds following the warning signal and preceded the appearance of the test stimulus. Finally, the words "yes" "oui","no" "non" appeared with the test stimulus and lasted until the subject answered. This method was designed to assist those subjects who experienced difficulty in ordering the events in a sequential meaningful manner as they appeared on the screen. Again, instructions were clarified at each missed trial. Subjects who failed to reach 15 consecutive correct responses within 50 trials were rejected from the study.

Results

Group Characteristics

Analysis of the data was done using SPSS Oneway programme with Tukey's a posteriori contrasts. Despite attempts to match the three groups, the analysis of group-defining variables revealed that the Parkinson's disease group (PD), the normal control group (NC) and the Alzheimer's disease group (SDAT), differed in the following characteristics. The demographic variable of age revealed a significant main group effect, $F(2, 33) = 5.33$, $p<.001$. Post hoc analysis showed the SDAT group to be significantly older ($M = 67.0$) than the PD group ($M = 58.3$) and the NC group ($M = 58.9$).

All three groups had equivalent educational level (SDAT $M = 12.6$; PD $M = 13.2$; NC $M = 14.3$). The main effect for vocabulary scaled score was significant, $F(2, 33) = 10.62$, $p<.001$. Tukey's a posteriori contrast analysis showed that the SDAT group had, as might be expected, achieved significantly lower scores on vocabulary (8.8) as compared to the two other groups (PD = 13.9, NC = 13.8). Both measures of cognitive (Dementia Rating Scale, DRS) and functional (Washington Dementia Rating Scale, WDRS) dysfunction revealed significant main effects, $F(2, 33) = 47.95$, $p<.001$ and $F(2, 33) = 42.73$, $p<.001$ respectively. Again, Tukey's revealed the SDAT patients' DRS score to be significantly lower ($M = 118.7$), and they were found to be functionally more impaired as rated by the WDRS ($M = 1.42$). Comparatively, the PD group (DRS $M = 140.1$ and WDRS $M = .333$) was both cognitively and functionally equivalent to the NC group (DRS

M = 142.2; WDRS M = .00).

Results on the Dementia Rating Scale subtests for each group are shown in Table 12. Analysis of variance revealed significant main effects for the following subtests: initiation and perseveration, $F(2, 33) = 16.89$, $p<.001$, conceptualization, $F(2, 33) = 9.15$, $p<.001$, and memory $F(2, 33) = 10.39$, $p<.001$. As indicated in Table 12, post hocs from the Tukey's analysis revealed that for all subtests, the SDAT group achieved significantly lower scores than both the PD and NC groups.

Language examination as measured by the Western Aphasia Battery (WAB) revealed a significant main effect, $F(2, 33) = 10.15$, $p < .001$) with the SDAT group (M = 91.8) having significantly more overall language impairment than the two other groups (PD, M = 99.3; NC, M= 99.8), as evidenced by the Tukey's post-hoc analysis. Again, the SDAT group differed significantly from the two other equivalent (PD and NC) groups on all subtests. The mean scores and analysis of subtests revealed that the SDAT patients were impaired primarily for complex items.

Analysis of scores achieved on the Zung depression rating scale revealed a significant main effect, $F(2, 33) = 8.33$, $p < .001$. Tukey's analysis showed that, although still within the non-depressed range, both the SDAT (M = .48) and the PD (M = .46) had significantly more complaints than the NC group (M = .34). Scores on the Beck Depression Inventory also revealed that, although all three groups were within the normal range, the PD and the SDAT groups had

Table 12

Means and Standard Deviations of SDAT, PD and NC on the Dementia Rating Scale Subtests

	Groups					
	SDAT		PD		NC	
Subtests	M	SD	M	SD	M	SD
Attention and concentration	35.9	0.9	36.5	0.9	37	0.0
Initiation and perseveration	27.8	6.5	35.8	1.6	36.1	1.7
Construction	5.5	1.0	6.0	0.0	6	0.0
Conceptualization	31.6	6.7	37.5	2.6	38.4	1.2
Memory	18.5	6.4	24.3	1.1	24.9	0.3

significantly more complaints than the NC group.

Covariate analysis between age and Vocabulary scale scores, DRS, WDRS, Zung scale of depression and the WAB were all found not to be significant. All results remained significant when age was used as a covariate.

Item-recognition paradigm

Practice trials. Subjects of the PD and NC groups had no difficulty in learning the steps of the item-recognition paradigm as evidenced by the small number of practice trials necessitated to master the task (PD M =17.8 and NC M =18.2). However, eleven of the 12 SDAT patients did not reach the criteria of 15 consecutive correct trials within the 75 practice trial limit. The "coached" method for learning was implemented for these patients. Three of the patients were rejected because they did not benefit from external structuring of the task. The eight other patients were able to achieve the criteria of 15 consecutive trials within an average of 36 trials.

Error rates. Mean error rates were equivalent for the normal subjects (1.5%) and the Parkinsonian patients (1.2%). However, the error rate in the SDAT group was variable in comparison to the two other groups. One patient of the SDAT group was rejected because of a 25% error rate, which exceeded the 20% set limit. Another patient was rejected because he could not re-establish set for continuing the task after the half time-break. His error rate for 75 trials was 13%. Finally, one other patient, who had to be verbally assisted to respond having failed to understand the significance of the non-verbal events

of the paradigm, was rejected because the RT means were longest for memory loading one and fastest for memory loading three. This patient had learned that the maximum number of letters to be shown was three and therefore responded promptly only when the memory loading was of three letters. Error rate for the remaining five SDAT patients was 1.9% which is equivalent with the NC and PD groups. It thus appears that successful subjects for all groups were equally good at registering and storing the list materials, providing an independent assessment of the three group's retrieval processes. Decision times for incorrect responses were deleted from the analyses.

Treatment of outliers. Mean RTs of subject's responses were computed separately for the PD group (N = 12), NC group (N = 12), and the SDAT group (N = 5) for each memory loading (one, two, and three), as well as for response type (positive and negative). These means were corrected for extreme scores ("outliers") for each subject, as suggested by Grubbs (1969), by excluding trials in each condition in which reaction times exceeded critical values at the .05 level of significance. Elimination of extreme responses following a method recommended by Grubbs was used by Pharr and Connor (1980) in a similar experiment. Rejected trials were of 1.3% for the NC group, 1.1% for the PD group and 1.4% for the SDAT group. Because the number of outliers was small, no attempt was made to analyze the percentage of rejected trials statistically.

Revised means excluding these outliers were retained for all further statistical analyses. Because of the unequal number of

subjects, two separate group analyses were performed, the first comparing the SDAT, PD and NC groups (N = 5); and the second comparing the PD and NC groups (N = 12).

Performance of patients with Senile Dementia of the Alzheimer's Type. Seven of the twelve patients with Alzheimer's disease were unable to learn to perform the Sternberg task, even when a structured coaching method was provided. The mean DRS score of these patients was 114.7 whereas the mean WAB score was 93.4. Four of the five patients who did perform the task were unable to do so until a structured method was used. The mean score of the DRS scale for these patients was 120 whereas their mean WAB score was 94. Three of these four patients, when retested after a six-month to a year delay, were unable to perform the task even under structured conditions. Their DRS mean score at this time was 109. The single patient who had been able to perform the task without a structured setting (DRS = 143 and WAB = 100) was unable to do so at retest, but could do so when given structure (DRS = 136 and WAB = 99). None of the Parkinsonian patients or the normal subjects required such structured assistance.

Latency analysis of the three groups. Five subjects from the PD (M age = 65.6) and NC (M age = 65.6) groups were age matched to the SDAT (M age = 67.6) patients who succeeded in doing the task. Mean RTs were computed for the PD group, N = 5 and the NC group, N = 5, for each memory loading and for response type. Analysis of variance was performed using SPSS Manova on mean RTs with response type (positive and negative) and size of memory set (one, two and three) as

within-subject variables and with groups (SDAT, PD and NC) as between-subject variables. Because of the size of the sample within each group, only univariate statistics were used. The data was analysed separately for the three groups and submitted to regression analysis.

The 3 (Group) x 3 (Memory set) x 2 (Response type) analysis of variance performed on the reaction times yielded a non-significant main effect for Groups ($F(2,12) = 2.68$, $p>.05$), and Response Type ($F(1,12) = 4.48$, $p>.05$). The interactions Groups x Response Type ($F(2,12) = 1.07$, $p>.05$), Groups x Memory-set Size ($F(4,24) = 1.26$, $p>.05$); and Groups x Response Type x Memory-set Size ($F(4,24) = .64$, $p>.05$) were also not significant. The stated null hypothesis for these results must therefore be accepted. However, as predicted, the memory-set size main effect was significant, $F(2, 24) = 31.25$, $p<.01$. Tukey's a posteriori comparison revealed that, as expected, memory-loading one was significantly different from memory-loading two, and that memory-loading three was significantly different from both memory-loading one and two. Grand means and standard deviations for collapsed positive and negative responses are summarized in Table 13.

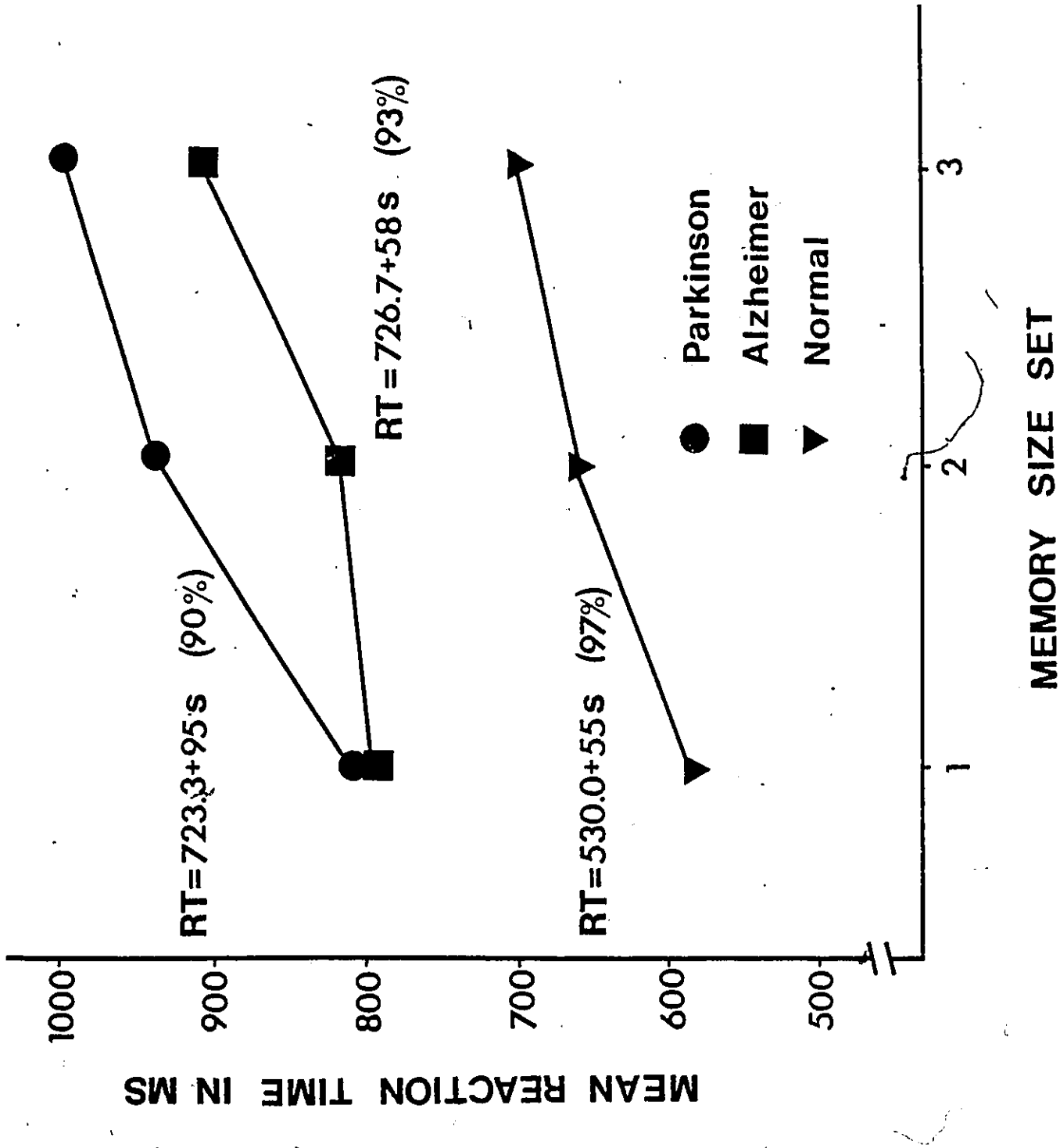
Figure 4 presents the mean reaction time of the SDAT, PD and NC groups as a function of the three memory-set sizes. In this Figure, the reaction times for yes and no are averaged together since the analysis of variance revealed that neither the main effect of type of response nor its interactions were significant.

Table 13

Grand Mean Reaction Time and Standard Deviations for Collapsed Probes as a Function of Size of Memory Set

		Memory set size					
		1		2		3	
Group	n	M	SD	M	SD	M	SD
SDAT	5	.795	.23	.822	.21	.901	.14
PD	5	.805	.20	.933	.23	.995	.27
NC	5	.587	.09	.654	.09	.698	.08

Figure 4. Line of best fit to the mean latencies of collapsed positive and negative responses as a function of memory set.


MEAN REACTION TIME IN MS
1000
900
800
700
600
500
RT=723.3+95s (90%)
RT=726.7+58s (93%)
RT=530.0+55s (97%)
Parkinson
Alzheimer
Normal
1
2
3
MEMORY SIZE SET

Inspection of the figure suggests that (1) the mean reaction time for the SDAT, PD and NC groups increases approximately linearly; (2) PD patients show the slowest reaction time as revealed by the greatest slope; the NC and SDAT groups show similar reaction times as revealed by their comparable slopes and (3) PD and SDAT patients show similar time taken for non-scanning processes as revealed by their having similar intercepts. NC subjects, however, show a faster time taken for non-scanning processes as revealed by their lower intercept.

Analysis of slope and intercept. For each subject the equation expressing RT as a linear function of memory set size was calculated using the least-square regression method. The function relating RT to set size(s) is: RT = 723.3 + 95 s for the PD group; RT = 726.7 + 58 s for the SDAT group; and RT = 530.0 + 55 s for the NC group. The linear trends accounted for 90% to 97% of the variance. The scanning rate as suggested by the slopes of the reaction-time function was 10.5 items per second for the PD group, 17.2 items per second for the SDAT group, and 18.2 items per second for the NC group. Analysis of variance showed that both the rate of scanning and the vocal response (and other processes taken to be reflected in the intercept) were not statistically different across groups despite an apparent trend towards slower scanning for the PD group and slower non-scanning processes for both patient populations. Table 14 summarizes the analysis of variance of the mean slopes and intercepts of the SDAT, PD and control groups.

Analysis of Latency: NC and PD Groups. Latency data were

Table 14

Analysis of Variance on Mean Slope and Mean Intercept Data of the SDAT, PD and NC Groups

Slope data:

Group	n	M	SD	df	F	p
SDAT	5	58.0	.06			
PD	5	95.0	.05	2,12	1.16	.34
NC	5	55.0	.01			

Intercept data:

Group	n	M	SD	df	F	p
SDAT	5	726.7	.30			
PD	5	723.3	.17	2,12	1.4	.28
NC	5	530.0	.10			

analysed, using the SPSS Manova-programme, in which response type (positive and negative) and size of Memory Set (one, two and three) were the within-subject variables, and Groups (PD vs NC) was the between-subject variable. Because of the size of the sample within each group, only univariate statistics from this program were used. Mean RT from each group were also submitted to a regression analysis.

The main effect of groups was found to be non-significant ($F(1,22) = 3.57$, $p>.05$). Type of response proved to be a significant main effect ($F(1, 22)= 7.10$, $p<.01$). Negative responses were faster than positive responses for the PD group. There is no explanation for this finding. Although not unusual, the more expected finding in studies of young normal subjects is that positive and negative trial slopes are equal (Sternberg, 1975). Groups x Response Type, however was not significant ($F(1,22) = 1.79$, $p>.05$), indicating that the two groups responded in the same manner. Size of memory set showed, as predicted, a significant main effect ($F(2, 44) = 81.71$, $p<.001$). Tukey's a posteriori comparison revealed that memory loading one was significantly different from memory loading two, and that memory loading two was significantly different from both memory loading one and three. Finally, the interaction Groups x Response Type by Memory Set Size was not significant ($F(2,44) = .03$, $p>.05$) suggesting that the positive and negative responses within and between the groups were statistically similar to each other. Grand means and standard deviations for positive and negative responses are summarized in Table 15.

Figure 5 presents the mean latencies of correct responses as a function of memory set size, for both the Parkinsonian patients (N=12) and for normal control subjects (N=12). The left panel represents the reaction times for the yes responses whilst those for the no responses are presented in the right panel.

A qualitative analysis of the figure suggests that: (1) as the list is lengthened, latency also increases for the PD and NC groups; (2) there is a trend toward a slower overall reaction time for the PD group; and (3) the 'yes' responses are slower than the 'no' responses for the PD group.

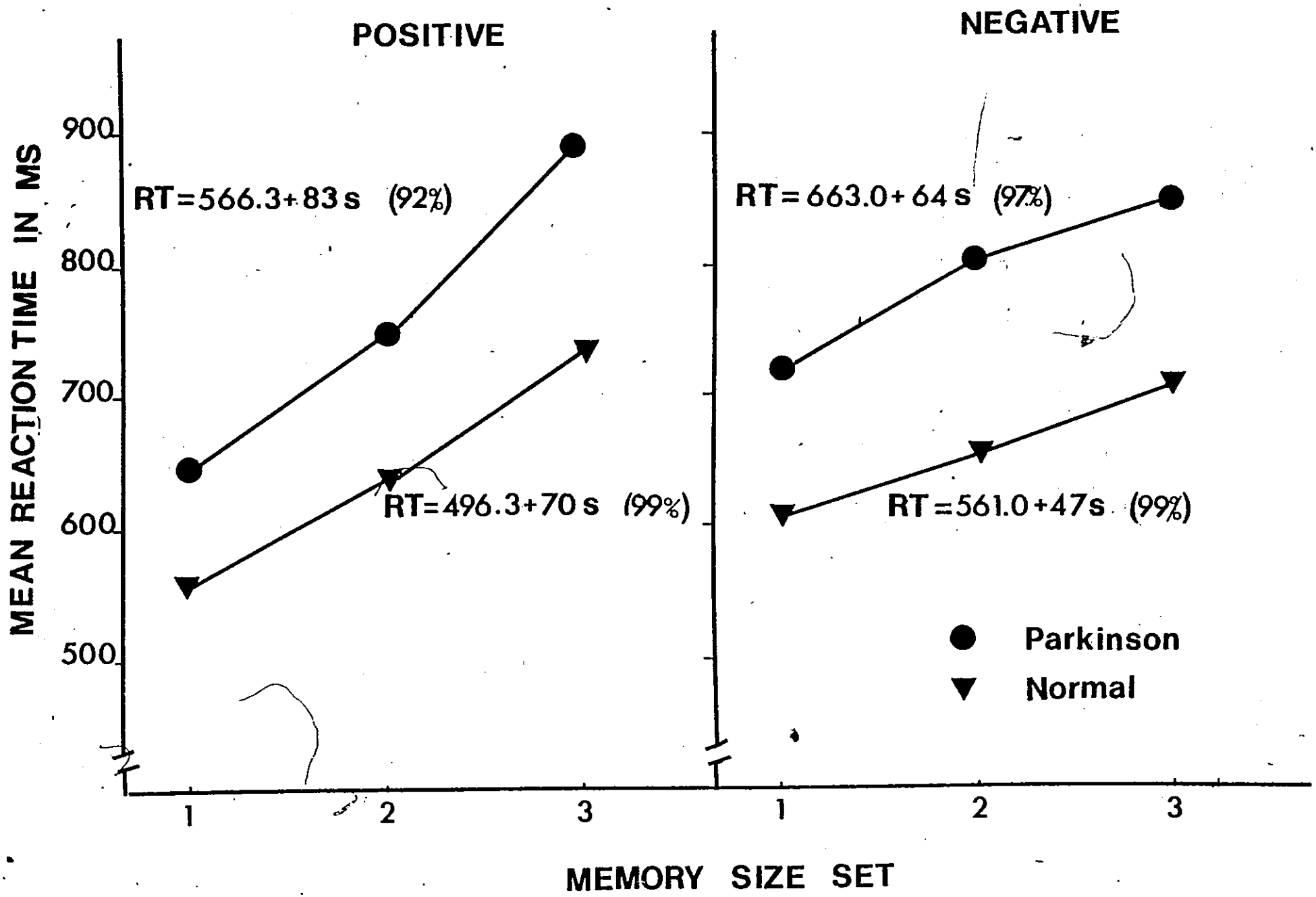
Analysis of Slope and Intercept. Again, for each subject the equation expressing RT as a linear function of memory set size was calculated. The least-square regression functions computed were as follows: (a) For the positive probes, the PD group mean reaction time was 567.4 + 82.4 s and the NC group mean reaction time was 496.4 + 70.0 s; (b) for the negative probes, the PD group mean reaction time was 662.7 + 63.9 s; the NC group mean reaction time was 561.2 + 46.6 s. The slopes for both positive and negative responses were not found to be significantly different between groups, although the PD group showed a trend towards slower scanning. For the Parkinsonian patients, linear equations accounted for an average of 92% of the variance in the positive RT and 97% of the variance for the negative RT. For the controls, linear equations accounted for an average of 99% of the variance in both positive and negative RTs. The slopes for the PD group suggest a scanning rate of 12.1 items per second for the

Table 15

Grand Means and Standard Deviations for Positive and Negative Responses for PD and NC Groups

		Memory set size											
		Positive responses						Negative responses					
		1		2		3		1		2		3	
Group	n	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
PD	12	.805	.20	.933	.23	.995	.27	.720	.19	.805	.23	.848	.27
NC	12	.587	.09	.654	.09	.698	.08	.608	.07	.657	.06	.701	.08

Figure 5. Line of best fit to mean latencies of positive responses (left panel) and negative responses (right panel) as a function of memory set.


POSITIVE
NEGATIVE
MEAN REACTION TIME IN MS
900
800
700
600
500
RT=566.3+83 s (92%)
RT=496.3+70 s (99%)
RT=663.0+64 s (97%)
RT=561.0+47s (99%)
Parkinson
Normal
1
2
3
1
2
3
MEMORY SIZE SET

positive trials and of 15.6 items per second for the negative trials. The slope for the NC subjects indicated a rate of scanning of 14.3 items per second for the positive responses and 21.5 items per second for the negative responses. The NC group showed a trend towards processing a larger number of items per second when giving negative responses as compared to the PD patient's positive and negative responses and their own responses. Table 16 summarizes the t-test analyses of the mean slopes and intercepts of the PD and control groups at each response type.

Intercepts were slightly greater on negative trials than on positive trials, a usual result with the use of this procedure (Sternberg, 1975). As Table 16 indicates, neither the slopes nor the intercepts between Parkinsonian patients and normal controls reached statistical significance on either positive or negative trials.

Discussion

Subjects. From the outset of this project, an attempt was made to match groups for age. However, although the pool of provisionally diagnosed SDAT patients was substantial, the residual number of probable SDAT subjects after follow-up was small. Those who were excluded tended to be younger. This resulted in a significantly older sample of SDAT patients. As only twelve patients with PD were available for the study, it was not possible to raise the mean age of this group to match that of the SDAT group. Finally, matching of the

Table 16

T-test on Mean Slope and Mean Intercept Data of the PD and NC Groups

Positive slope data:

Group	n	M	SD	T	df	p
PD	12	82.4	.27	.96	22	.35
NC	12	70.0	.04			

Positive intercept data:

Group	n	M	SD	T	df	p
PD	12	567.4	.18	1.28	22	.22
NC	12	496.4	.07			

Negative slope data:

Group	n	M	SD	T	df	p
PD	12	63.9	.07	.85	22	.41
NC	12	46.6	.03			

Negative intercept data:

Group	n	M	SD	T	df	p
PD	12	662.7	.19	1.70	22	.11
NC	12	561.2	.08			

control subjects was done concomittantly with the referral of the PD and SDAT patients so that, in the end, the control group was closely matched to the PD group but not to the SDAT group. To control for age, analyses of variance were performed on the vocabulary, the Zung, the WDRS, the DRS and the WAB tests with age used as a covariate. All results remained significant, differentiating between the SDAT and the PD and NC groups. The lower scores cannot be accounted for by the fact that the SDAT patients were older, but rather appear to be a function of the disease process itself.

The diagnosis of Alzheimer's disease is difficult to establish clinically. Follow-up studies reported in the literature indicate false positive rates ranging between 27 to 57% (Nott & Fleminger, 1975; Ron, Toone, Garralda & Lishman, 1979). To minimize false positive diagnosis in this study, strict criteria were used to establish the initial presumptive diagnosis (see methodology section). These criteria have been used elsewhere (for example, Hughes, Berg, Danziger, Cohen, Martin & Knesevich, 1982; Freedman et al. 1984; Freedman et al.,1986; Vitaliano et al., 1984). In addition, only those patients who showed clinical deterioration at 6 - 12 month follow-up were kept in the study.

All three groups had an equivalent educational level. Generally, the correlation between education and IQ has been shown to be strong (Matarazzo, 1972; Matarazzo & Herman, 1984). It is thus justifiable to infer equivalent premorbid abilities on the part of the SDAT group, despite significantly lower scores on the vocabulary scale. This is

particularly so as the correlation between education and verbal IQ on the Wais-R has been shown to be highly correlated (Matarazzo & Herman, 1984).

The diagnosis of Alzheimer's disease is also supported by the results of the language examination. Only the SDAT patients showed deficits on the language examination. Although it was not possible to identify a particular aphasic profile (Kertesz, 1979), the pattern of results was similar to that described in SDAT patients (Cummings, Benson, Hill & Read, 1985). Patients with Alzheimer's disease have been shown to have problems with the semantic aspect of language (Bayles, 1982), in particular with finding words in spontaneous conversation, and with the naming of objects. The SDAT patients were significantly impaired in the subtests comprehension and fluency. Disruptions in comprehension and fluency in free speech have been observed (Appell, Kertesz & Fisman, 1982; Irigaray, 1967; Miller & Hague, 1975) in patients with moderate SDAT. Disruption of performance has also been observed with mild cases of Alzheimer's disease on the verbal fluency task (Appell et al., 1982; Huff, Corkin & Growden, 1986; Martin & Fedio, 1983; Ober, Dronkers, Koss, Delis & Friedland, 1986; Rosen, 1980). The language impairment in this group of SDAT patients is also consistent with other reports that verbal fluency is a sensitive measure for the discrimination of patients with mild SDAT from non-demented subjects of the same age (Eslinger, Damasio, Benton & Van Allen, 1985; Storandt, Botwinick, Danziger, Berg & Hughes, 1984).

The Dementia Rating Scale (DRS) was developed specifically for the

study of presenile and senile dementia (Mattis, 1976). This scale was validated with a population of cortically demented patients and was found to correlate highly with cerebral blood flow through grey matter (Mattis, 1976). Preliminary results have indicated that examination with the DRS with a six month interval was a good predictor of the rate of progression of the disease in a given individual over the subsequent two years (Mattis, 1976). Therefore, the DRS, used as a screening instrument, provides inferential support for the presence of cortical pathology in general; further, when put within the context of a general diagnostic battery, and a 6 - 12 months follow-up examination, it is useful for the diagnosis of Alzheimer's disease in particular.

Results of both the Zung and Beck depression scales revealed the SDAT, PD and NC groups to be within the non-depressed range. However, the scores on the Beck depression inventory revealed the SDAT and PD patients to have significantly more complaints than the normal control subjects. An item analysis showed that the two patient groups reported some degree of fatiguability, indecisiveness, reduced interest, irritability and inefficiency. Patients thus endorsed items which are consistent with the existential experience of aging and/or being diseased. Patients or normal control subjects did not report self-destructive thoughts (item I), guilt (item E), being a failure (item C), etc., attributes highly characteristic of a depressed mood (DSM-111, 1980). The present results are consistent with those obtained from Parkinsonian patients by Gotham, Brown and Marsden (1986).

Summary of the project. Patients with subcortical brain pathology

have been reported to show a recognizable clinical pattern of cognitive deficits. These deficits have been referred to as a subcortical dementia (Albert et al., 1974; McHugh & Folstein, 1975), or, more recently, as a frontal system dementia (Freedman & Albert, 1985) since they have a "frontal lobe flavor" (Stuss & Benson, 1986). This pattern of cognitive deficits has been contrasted with that which is taken to arise from cortical pathology (Cummings & Benson, 1984). Parkinson's disease is one of several diseases that has been said to give rise to a subcortical dementia (Albert, 1978; Cummings & Benson, 1984), whereas Alzheimer's disease is the commonest cortical dementia, and perhaps the prototypical example. Amongst the clinical characteristics said to differentiate these two dementias from each other is the presence of slowed mentation in subcortical dementia, and its absence in cortical dementia. This study examined that proposition by experimentally investigating the speed of memory scanning in a group of patients suffering from Alzheimer's disease, and in a group of patients suffering from Parkinson's disease, as well as in a group of normal control subjects. It was hypothesized that if subcortical pathology leads to mental slowing, then such slowing should be manifested in the reaction time function, both in the slope and intercept values as measured with the memory scanning procedure.

Wilson et al. (1980) had reported that memory scanning was slowed in elderly Parkinsonian patients but not in younger patients. However, when this thesis was initiated no other laboratory had attempted to replicate their results. One purpose of the present study was to

confirm or disconfirm their work. It directly addresses the question of possibly slowed scanning in Parkinson's disease. It goes farther by addressing the question of possibly impaired memory retrieval in those same patients. These data were compared with identical measures taken on SDAT patients, in an attempt to determine whether mental slowing is more characteristic of subcortical than of cortical dementia. Since the onset of this study Rafal et al. (1984) disconfirmed the reported slowing of scanning at least in some patients with Parkinson's disease. It was hypothesized, in this study, that the memory scanning speed of the SDAT patients and the NC subjects would be equivalent and significantly faster than that of the PD patients.

High-speed memory scanning. The results of the present investigation describe search processes underlying the retrieval of information from short-term memory. As documented by Sternberg (1966, 1969), the search strategy underlying the retrieval of information from short-term memory is characteristically of high speed, serial and exhaustive. In the present experiment, PD patients and NC subjects were found to employ a serial search as revealed by the finding of significant linearity in the slopes of the response latencies plotted as a function of list length. This means that mean response latencies increased linearly with the number of elements in memory. The search was exhaustive as revealed by equivalent positive and negative slopes (PD, NC & SDAT comparison) and by the longer search time for positive items (in the PD & NC comparison). Some SDAT patients, but not others, can process information in a short-term memory task. Those patients

who did perform, exhibited the same qualitative memory-processing characteristics as the normals and the PD subjects.

Theoretically, the slope of the RT function represents a measure of the rate of memory scanning of the positive set. The finding that positive and negative slopes were unequal (PD & NC comparison) is not unusual (Clifton & Birenbaum, 1970; Forrin & Morrin, 1969; Mohs, Tinklenberg, Roth & Kopell, 1978; Mohs & Wescourt, 1973; Stuss et al., in press). There is no agreement amongst investigators as to what produces unequal slopes.

As reflected in the reaction time slopes, the NC and SDAT groups showed comparable scanning speed. Although the slope of the PD group indicated a slower scanning rate, it did not prove to be significantly different from those of the two other groups. The finding that PD patients' scanning speed did not differ statistically from that of the control group in a short-term memory task might appear at first glance to challenge Wilson et al.'s (1980) report of mnemonic slowing in elderly Parkinsonian patients. It is, however, consistent with Rafal et al.'s (1984) study.

In the above-mentioned two studies, the slopes of the reaction time for the older Parkinsonian patients and normals was 61 msec and 34 msec, respectively (Wilson et al., 1980) and 40 msec (there were no normal control subjects) (Rafal et al., 1984). In the present study, the slopes for letters was of 95 msec (PD), 58 msec (SDAT) and 55 msec (NC). Although there was a trend for the Parkinsonian patients to be slower, the variability was such as to produce an overlap across groups

so that the difference did not reach significance. This was so even with the larger number of subjects (N = 12). Wilson et al. (1980) reported a statistically significant slowing of speed of memory scanning in their older Parkinsonian patients, as compared to their younger Parkinsonian patients and normal controls. None of their patients were demented. They argued that the slowing they observed in the older Parkinsonsian group, was not part of a generalized memory breakdown because their error rate was low. Wilson et al. (1980) suggested that the slowing represented an interaction between the disease process and the process of ageing and that the term 'bradyphrenia' could appropriately describe this element of cognition in Parkinsonism. It is important to note here that one of the essential major clinical characteristics of the proposed subcortical dementia, namely "slowing of thought" (Benson, 1984) is present in non-demented patients with subcortical disease.

The difference observed between the scanning speed of Wilson et al.'s Parkinsonian group and the scanning speed recorded in the present study may be, in part, attributed to an age-disease interaction because the mean age of his older patients (M = 69.4) exceeds by more than a decade that of our patients (M = 58.3). In fact our group matches his young group of Parkinsonian patients (M = 58.1). We cannot compare either the duration of the disease, nor the length of the treatment, because they are not reported in the Wilson et al.'s paper. It may be that their results will be found to hold in a study carefully controlling for both age and length of disease . Supportive data has

been reported by Garron et al. (1972) and Warburton (1967). The former found that his older and longer diseased Parkinsonian patients were significantly slower than his younger and less disabled patients on a number of verbal-memory tasks. The latter noted that memory impairment was significantly more severe in older Parkinsonian patients, and she suggested that the impairment might result from an interaction between ageing and the disease process.

In the Rafal et al. (1984) paper, Parkinsonian patients were not found to have slowed scanning speed. Both mean group age (M = 57.8) and mean length of disease (M = 11.8) of their patients are similar to ours (M age = 58.3; M duration of illness = 8.3).

Studies on normal, aged, subjects have reported a slowing in the rate of memory scanning which occurs between 45 and 50 years of age (Anders, Fozard & Lillyquist, 1972; Anders & Fozard, 1973; Ericksen, Hamlin & Daye, 1973; Ford, Roth, Mohs, Hopkins, & Kopell, 1977; Lorsbach & Simpson, 1984; Puglesi, 1986; Thomas, Waugh & Fozard, 1978). In fact, Birren (1974) has stated that the ageing process results in a generalized slowing of central, as well as peripheral, nervous system functioning. The slope of the RT functions for the normal, older, subjects in studies using a paradigm similar to that used in this study have been reported by other workers as follows: 71 msec (Anders & Fozard, 1971); 45 msec (Anders & Fozard, 1973); 43 msec Eriksen et al., 1973); and 80 msec (Ford et al., 1979). Our range largely overlaps the range reported in the literature.

The intercept is an estimate of the time needed for stimulus input

and identification, response selection and initiation, and those other unknown facets of performance not affected by the number of items in memory. In this study, none of the between-group intercept values achieved the level of significance. Significant differences in the intercept values have been observed, in other studies in normal, aged subjects as compared to younger populations. For example, in the older, normal, aged subjects intercept values were reported at 892 msec (Anders & Fozard, 1973; 816 msec (Anders et al., 1972); 905 msec (Ford et al., 1979); and 440 msec (Eriksen et al., 1973). In the analysis in which there were five subjects per group, the intercept values were 723 msec for the PD; 727 msec for the SDAT, and 530 msec for the NC group. In the second analysis with twelve patients per group, the intercept values were, for the positive responses, 567 msec for the PD patients, and 486 msec for the NC subjects; and, for the negative responses, 662 msec for the PD group and 561 msec for the NC group. Higher intercept values in older subjects are generally attributed to the motor component of the task (Eriksen et al., 1973; Ford et al., 1979). In this study the use of a vocal response mode eliminated any motor factors which might have produced a differential intercept value caused by a manual response. In the Wilson et al. (1980) study, where a manual response was used, the intercept value was not less for the Parkinsonian patients as compared to normal control subjects.

The Rafal et al. (1984) study attempted to validate the hypothesis that Parkinson's disease results in a slowing of thought processes

which could be the mental counterpart of the bradykinesia observed in the motor domain. Should this be so, they suggested that a dysfunction of dopaminergic basal ganglia mechanisms would be implicated in cognitive functioning. However, the authors could not find a relationship between bradyphrenia and drug treatment and failed "to validate the concept of bradyphrenia in any sense that can be related to bradykinesia or to dopaminergic dysfunction" (p.1088). The authors suggest that the mental impairment in some Parkinsonians might be due to coexisting Alzheimer's changes (from mild to severe) as these have been shown to be almost always present (Boller et al., 1980; Hakim & Mathieson, 1979). However, as seen in our study, patients with Alzheimer's disease perform in a qualitatively different manner, even at the mild stage of the disease process. Furthermore, their scanning speed is equivalent to that of normal subjects, suggesting that the ability to scan remains intact in the presence of substantial cognitive deficits. Rafal et al. (1985) further proposed that bradyphrenia (as defined by the slowing of thought) occurs only in "Parkinsonians who have substantial deficiencies in mesolimbic or mesocortical dopamine pathways" (p.1093). It would not occur in patients with dopaminergic deficiency limited to the nigrostriatal system. The validation of such an hypothesis would require the use of sophisticated brain imaging technology, and would be well worth pursuing. If this were done, it could demonstrate the biochemical correlates of what has been called 'fronto-subcortical dementia'.

In our study, scanning was not shown to be slowed statistically

in either patients with Parkinson's disease or with Alzheimer's disease. This does not exclude the possibility that slowed mentation occurs in Parkinson's disease, or in Alzheimer's disease, but rather that high-speed short-term memory scanning, which is one aspect of mentation, is normal. The hypothesis of slowed mentation should be further investigated under more demanding memory scanning protocols or using subgroups defined on the basis of age and length of illness.

Performance of the SDAT. Unexpectedly, SDAT patients as a group, with the initial exception of one patient, showed a consistent inability to learn how to perform the Sternberg task regardless of the amount of coaching provided. This is in direct contrast to the PD patients and the NC subjects who understood the requirements of the task after having been given the initial instructions once. This result was quite unanticipated because patients at the mild stage of the disease, as indicated by their DRS score, were chosen for the study. Furthermore, the Sternberg procedure has been successfully applied to retarded subjects (with low level intact cognitive functioning) (Dugas & Kellas, 1974; Harris & Fleer, 1974; Maisto & Jerome, 1977; Silverman, 1974), which suggests that the failure of these SDAT patients results not from their lowered level of functioning per se but from their general cognitive deterioration. The DRS norms used in this study (provided by Dr. Morris Freedman) had a cut-off score of 133, with scores above constituting the normal range, and scores below constituting the impaired range. Ober et al. (1986) defined their mildly demented group as having obtained scores

of 95 and above on the DRS, and their moderately to severely demented group as having achieved scores of 87 and below. In this study, the SDAT mean DRS score was 118.7, which places these subjects within the mildly impaired range. In the Vitaliano et al. (1984) study, the severity of the dementing illness was defined in terms of instrumental and maintenance activities of daily living (Kane & Kane, 1981). The mildly demented group showed some impairment in language and recreation but little impairment in such functions as mobility, feeding and dressing. The moderately impaired individuals, however, showed impairments at all levels of functioning. In terms of the DRS, the recall and orientation subscales were found to be the most useful in differentiating between normal and mildly impaired subjects, whereas the recognition of items and attention subscales or tests were found to be the most useful in the grading of the severity of impairment between mildly impaired and moderately impaired SDAT patients, the latter showing the poorest scores. In fact, these authors concluded that an accurate classification can be achieved by using only the attention, recall and recognition tests. A scale measuring activities of daily living was not employed in this study. However, the scale which was used indicated impaired functionality in the mild range. Following the Vitaliano et al. (1984) suggestion, analysis of the recall and recognition tests revealed that both the recall and orientation tests were impaired. Recognition of items and attention were within normal limits. This, again, confirms that our subjects were within the mildly impaired range.

When investigating dementia, significant differences on almost any cognitive variable measured on groups of demented and aged-matched normal controls are to be expected. Therefore, instances in which differences are not found can be of more interest than are cases where positive results are found (Miller, 1981). What proved to be of interest in this study was the fact that despite significant cognitive functional differences on numerous variables, five Alzheimer patients were able to scan items in short term memory at the same rate as the NC subjects and similarly to the Parkinsonian patients. This is particularly interesting in light of the fact that prior to coaching, they were quite unable to do the task.

The Sternberg procedure is a relatively easy task to learn to perform, as can be seen from its instructions in Appendix 3. However, only one SDAT patient was able to learn the task in the same manner as the PD and NC subjects and only four of the eleven remaining SDAT patients were able to perform with the structured method. The performance of these five patients will be examined.

Short term memory was found to be intact as evidenced by their low error rate. This suggests an adequate capacity to retain one to three letters in short-term memory. These patients also showed normal scanning ability under the structured method. As Figure 4 attests, scanning in this group is as efficiently carried out as in the two other groups, and furthermore follows the same qualitative characteristics, as discussed earlier. If the SDAT patient is able to complete the task, there does not appear to be any evidence of slowing

in memory-scanning speed.

The fact that the intercept value of the SDAT group was similar to that of the PD and NC group, suggests that the processes of stimulus encoding, stimulus identification, response selection and response initiation, as well as other processes thought to be represented in the intercept have remained functional.

The Sternberg task consists of a sequence of events, each event being a necessary unit of information for the following event. To achieve a successful performance on the Sternberg task, subjects must have the ability to integrate each event within the sequence in a meaningful whole. They must also be able to use this integration to anticipate the events, store information in short-term memory, anticipate the test and provide an answer. Eleven patients with SDAT were unable to follow the sequence of events of the Sternberg's task. However, four patients were able to follow the sequence when orienting instructions had been built in the paradigm. One patient who had been able to perform the task without the structured method required it at re-test. Her performance was otherwise identical to her prior one. It thus appears that one aspect of the failure of the SDAT patients involves an impairment in the ability to organize and maintain information in a proper sequence. However, once the segments of the sequence were organized for the subjects, the task became possible for some of the subjects.

The SDAT group's failure to perform the Sternberg's task could have been interpreted as being due to an inability to switch mental

sets. That is, subjects repeat an answer when another alternative is the correct answer. An inability to switch mental set may be involved with a moderate cognitive deterioration as evidenced by one patient who was able to get into set for the first part of the trials but failed to do so again after having taken a pause. This was also noted in another patient who would get into and fall out of set repeatedly during the experiment. It is of relevance that these two patients were not able to get beyond the practice trials at later testing. The patients who successfully completed the task under the structured method showed no evidence of perseveration or mental inflexibility, once within the structured mode. Rather, the subjects responded as appropriately and as rapidly as the two other groups.

Two general anatomical bases are frequently proposed to explain these deficits. The integrity of the frontal lobes have been reported as being necessary for maintaining and organizing segments of information in meaningful sequences (Stuss & Benson, 1986). Generalized brain damage also produces disturbances which are not unlike those secondary to focal frontal damage (Robinson, Shoemaker, Schlumpf, Volk & Bloom, 1975). As stated by Kinsbourne (1977):

> A diffuse loss of neurons might handicap the victims in such general mental skills as flexible problem solving, the ability to change sets and entertain improbable outcomes as possibilities, as well as to focus, maintain and then adaptively detach attention in a task" (p. 227).

Providing built-in instructions to the SDAT subjects appears to compensate for the sequencing dysfunction so that performance becomes possible. It is as if the instructions become the patient's monitoring system (Stuss & Benson, 1982). Verbal regulation can be effective in some patients with frontal lobe damage, particularly if the dysfunction is not severe (Luria, 1973; Stuss, Delgado & Guzman, in press). This, however, lasts only shortly as seen by the inability of four patients to complete the task under these conditions at retest, within a year of testing.

It is uncertain whether the disorder in SDAT patients is due to focal frontal dysfunction or more diffuse brain damage. Frontal damage is certainly common in SDAT (Cummings & Benson, 1984). However, it has been suggested that the frontal region is intact until late in the disease process (Cummings & Benson, 1983). In this case, the influence of the frontal lobes over posterior brain regions would be hindered by the more diffuse brain damage. However, the fact that external monitoring is helpful to achieve a successful performance suggests that the frontal system itself may be involved early in the disease process and then becomes overshadowed by a further general deterioration.

Alzheimer's disease causes a progressive decline in cognitive skills from previous levels. Jorm (1986) argues that general cognitive damage specifically produces a major decrement in the capacity for controlled processing (Shiffrin & Sneider, 1977) early in the disease whereas automatic processing remains intact until the late

stages of the disorder. This would result in mildly demented patients having problems with unfamiliar cognitive tasks necessitating attentional resources. The Sternberg procedure is an unfamiliar cognitive task and thus would require attentional resources to be focussed. We will first discuss the notion of attention and then relate attention to the Sternberg procedure.

A universally accepted definition of attention has yet to be put forth. For the purpose of this discussion, definitions provided by Picton, Stuss & Marshall (1986) and Moscovitch (1979) will be used. As defined by Picton et al. (1986) "attention can describe a state, a resource, or a process"(p. 19). Attention defined as a state requires effort as one "expects particular information and prepares to perceive and act on that information"(p. 19). As a resource attention is "allocated to particular mental processes ... (or) paid out on demand to facilitate selected aspects of information processing"(p.19). Attention as a process "chooses particular information for further evaluation and response while ignoring other available information" (p.19). All these concepts are integrated in Moscovitch's (1979) definition of attention: it is "a control process that enables the individual to select, from a number of alternatives, the tasks he will perform, or the stimulus he will process, and the cognitive strategy he will adopt to carry out these operations."(p.422).

The performance on the Sternberg procedure requires "active" attention by which a central controlling process directs and maintains the state of attention and allocates attentional resources. Such an

attentional process is dependent upon the functional integrity of various interconnected areas of the brain. Three known areas important for attentional behaviour are the parietal lobe (sensory information), the hippocampus (orienting response to new stimuli) and the frontal lobes (attentional direction of behaviour) (Picton et al., 1986). These areas are also known to be damaged in Alzheimer's disease (Cummings, 1982).

Attention in this study was measured with the DRS and was found to be within normal limits. However, the attentional tasks in this test are very easy to perform, and perhaps are best related to the 'state' or 'resource' concepts of attention. Therefore, it is likely that more demanding tasks assumed to measure the control aspect of attention such as the Wisconsin Card Sorting Test would have shown an impairment.

In the Sternberg paradigm, controlled (Shiffrin & Schneider, 1977) or effortful processing (Hasher & Zacks, 1979) may be seen as a pre-requisite to scanning, which is an automatic process (Sternberg, 1975). According to Jorm (1986) "early dementia is characterized by problems with cognitive tasks of an unfamiliar sort (which by their nature require attentional resources), and by difficulties in learning (because controlled processing is essential to learning)"(p.79). The Sternberg paradigm fits these criteria in that it is a highly unfamiliar task which, further to intact attentional processes, requires the ability to abstract, sequence, switch mental sets, and use short-term memory. The results show clearly that scanning is not

impaired in a mildly impaired patient but, rather, that other impaired structures are responsible for the failure. Although the difficulties experienced by the SDAT patients can be explained by the notion of diffuse brain damage, it also appears that specific deficits due to loss of the directive, controlling function of behaviour, either through direct frontal damage or through diffuse damage including the frontal lobes can be identified at the mild stage of the disease.

The study of cerebral metabolic function provides some insight into why SDAT patients were incapable of learning how to do the Sternberg paradigm despite being only mildly impaired on the DRS, regardless of the brain area involved. Generally, positron emission tomography has revealed significant overall cortical hypometabolism, with the amount of metabolic abnormality being proportional to the degree of cognitive impairment (Chase et al., 1983a; Chase et al., 1983b; Foster et al., 1983). Chase et al. (1984), however, noted only a slight difference in cortical glucose metabolism between mild and severely affected patients. It could be that our mildly impaired Alzheimer's patients had marked metabolic dysfunction compared to normals. They suggested that a high threshold of cortical metabolic dysfunction must be exceeded before its effects become clinically evident. Once the threshold is reached, small further decrements in cortical metabolism will be associated with large increases in the clinical severity of the dementia. The brain is thus able to compensate for major metabolic dysfunction as measured by decreased glucose metabolism. However, there is a threshold beyond which it can

no longer compensate. It is at this point that cognitive dysfunction becomes apparent and the DRS begins to measure the appearance of the mildest dementia. It is probable that our SDAT subjects who succeeded in the task with the structured procedure were at this level.

Although we do not have measures of brain glucose metabolism for our subjects, their performance within the demented range allows us to postulate that the required threshold had been reached. Furthermore, a small decrease in the DRS score appears to be associated with a much larger decrease in functional abilities as evidenced by their performance on the Sternberg procedure. For example, the one subject who did perform the task without difficulty, a very gifted patient whose slowly developing inability to cope with familiar responsibilities forced her to leave an executive position, achieved a DRS score of 143. Her loss of memory and of cognitive abilities had been documented over a two year period. At retest, one year later, her DRS score was 136. At that time she failed to perform the Sternberg paradigm and required assistance with the structured method.

It is of further interest that the DRS range of the patients who performed on the Sternberg with the help of structure was 114-125 whereas it was 109 to 112 at retest when they failed to perform with this coached technique. It thus appears that a loss of 7 to 10 points on the DRS scale corresponds to a much larger loss of cortical dysfunction, and thus, in itself, gives very little information as to the actual loss of ability incurred. It is probable that the failure of the SDAT subjects to perform the task regardless of instructions

reflects this greater cognitive dysfunction.

EXPERIMENT 2

Method

Subjects

Subjects of each group (SDAT, PD and NC) included in Experiment 1 also participated in Experiment 2. Experiments 1 and 2 were conducted on the same day.

Materials

Eight words were chosen from each of the following six familiar semantic categories: occupations, furniture, flowers, musical instruments, animals, and fruits. Most words were selected from clusters 7 and 8 of the Toglia and Battig (1978) word frequency norms. All words were restricted to between five and eight letters (see Appendixes 5a (English) and 5b (French) for categories and words frequency).

Four words belonging only to clusters 7 or 8 of the Toglia and Battig norms (1978) were chosen from each category as test words (see Appendixes 6a (English) and 6b (French) for list of test items). The remaining four words per category were used as distractors in the recognition test (see Appendixes 7a (English) and 7b (French) for distractors).

The six categories were divided arbitrarily into two groups of three, one comprised of "flowers", "musical instruments" and "occupations", the other, of "animals", "fruits", and "furniture".

To avoid an order of presentation effect within groups, randomly structured lists were derived using the 5000 Random Digits (Glass and Stanley, 1970). Twenty lists containing the categories "fruits, animals and furniture" comprised Aggregate 1 (A1) (see Appendixes 8a (English) and 8b (French) for Aggregate 1). The other twenty lists containing test words from categories "flowers, musical instruments and occupations" comprised Aggregate 2 (A2) (see Appendixes 9a (English) and 9b (French) for Aggregate 2). A presentation order was derived by numbering the twenty lists (from 1 to 20) within A1 (fruits, animals, furniture) (see Appendixes 8a (English and 8b (French) for A1) and by giving letters (A to T) to the lists within A2 (flowers, musical instrument, occupation) (see Appendixes 9a (English) and 9b (French) for A2). Presentation of lists from the two Aggregates was counterbalanced within each group so that two consecutive subjects would not begin with identical group categories (see Appendixes 10, 11 and 12 for 'list order' within each group). Furthermore, the presentation of the lists were counterbalanced across groups to prevent a word-order effect (see 'organization within list' of Appendixes 10 to 12 for order of lists presentation).

Design and Procedure

Each subject saw 12 words, presented one at a time, projected via a Kodak 750H carousel on a white wall, located at a distance of 255

centimeters from the subject, in a darkened room. The words were composed of individual letters 23 cm in height, with widths varying from 5 cm to 22 cm, and were presented at a rate of one word every four seconds. Slide presentation control was done by a logic timing apparatus (Digitimer D4030).

Two test procedures (condition A, non-organized acquisition and condition B, organized acquisition) were administered in a fixed order. Conditions were separated by the item-recognition procedure described in Experiment 1. To control for attention and capacity to read the words to be learned, subjects were asked to read each word aloud as they were presented (see Appendixes 13a (English) and 13b (French) for instructions). Although time for recall was not limited, it generally did not exceed two minutes.

Condition A (non-organized acquisition). Under non-organized acquisition, a list of 12 words was presented for memorization, without subjects receiving any prior information about the words. Retention was measured immediately after the projection of the last word with three separate tests, two measuring recall, and a third measuring recognition. First, for a measure of free recall, subjects were given a sheet of paper on which were printed 12 blank lines and they were asked to recall, and write down, as many words as they could in any order (see Appendix 14 for recall sheet). Immediately following this, a second test, measuring cued recall, was initiated. They were given a second sheet of paper which had on it the three semantic categories, as well as twelve blank lines (see Appendixes 15

a, b (English) and 16 a, b (French) for cued recall sheet). Subjects were asked to write down as many words as they could, in any order, including those they had recalled on the previous test. A third test measuring recognition of the twelve learned words embedded in a sample of twenty four immediately followed the cued recall test (see Appendixes 17 a,b (English) and 18 a,b (French) for recognition sheet). Subjects were asked to underline only the words they recognized having learned.

Condition B (organized acquisition). Under organized acquisition, learning was primed, that is, subjects were informed of the semantic categories to which the words to be learned belonged prior to their being presented. For reference, a sheet with the semantic categories printed on it was placed in front of subjects (see Appendixes 19 a,b (English) and 20 a,b (French) for category sheet). It was removed after presentation of the last word.

Data Scoring

Four dependent variables were extracted from the free and cued recall performance within each condition (A and B): a) the total number of correct words; b) the positive and negative increment; c) the semantic clustering and, d) the intrusion score. A fifth dependent variable, a discriminability and response bias measure were calculated from the recognition test. These are defined below.

Proportions of correct words recalled. Proportions of correct words recalled were calculated from the total number of correct words retrieved at free recall and cued recall under non-organized

(Condition A) and organized (Condition B) acquisition.

Positive and negative increment. The words retrieved at cued recall were compared with those that had been retrieved at free recall. Normally, a word retrieved at free recall should also be retrieved at cued recall (Buschke, 1984). The correctly retrieved words at cued recall in both conditions were analysed for any negative increment, this being defined as any correct word that had been retrieved at free recall but forgotten at cued recall (old words); and positive increment, being defined as any correct words not retrieved at free recall but retrieved at cued recall (new words).

Positive and negative increments were scored as follows. Each correct word that was lost from free recall to cued recall was given a minus value. Therefore, the value for four forgotten, or old, words would be '-4'. Each correct word that was not in free recall but that was added in cued recall was given a plus value. Thus, a score of '+3' was given if three unrecalled, or new, words were added in cued recall. Two formulas were derived (see appendix 21 for formulas) in order to calculate proportions of positive and negative increment for each subject.

Intrusions. Intrusion scores, that is the reporting of words not present in the learned list, were also calculated.

Recognition. Recognition was assessed by requiring the patient to identify the test words embedded in semantically related distractors. Indices of discriminability (the failure to distinguish target items (signal) from distractor items (noise)), and response

bias, (the inclination towards "yes" or "no" responses independently of stimulus type) were calculated using nonparametric formulas because a ceiling effect was present. Patients with SDAT, for example, have been shown to favor "yes" responses (Post, 1975). These nonparametric formulas (see Appendix 22 for formulas of indices of discriminability and response bias respectively) have been found to correlate highly with parametric measures derived from signal-detection theory (Underwood, 1974).

Results

Recall of Words. For each subject, four recall scores were calculated: the total number of correct responses for free and cued recall under conditions A (non-organized acquisition) and B (organized acquisition). An analysis of variance was performed, using SPSS Manova, on the total number of correct words recalled with groups (PD, SDAT, NC) as the between-subject variables, and with condition (non-organized and organized acquisition) and type of recall (free recall and cued recall) as the within-subject variables. Only univariate statistics were used, as explained. A posteriori contrasts were done using the Tukey's procedure with a $p < .05$ significance level.

The proportions of correct words recalled for each of the groups are presented in Table 17. The analysis of variance on the proportion of correct words recalled revealed a main effect for Groups ($F(2,33) =$

Table 17

Mean Proportions of Correct Words Recalled

	Proportion of words recalled							
	Without categories				With categories			
	Free		Cued		Free		Cued	
Group [a]	Mean	SD	Mean	SD	Mean	SD	Mean	SD
PD	.56	.14	.60	.16	.59	.16	.54	.19
SDAT	.25	.10	.14	.12	.24	.16	.18	.15
NC	.67	.16	.67	.16	.72	.15	.68	.15

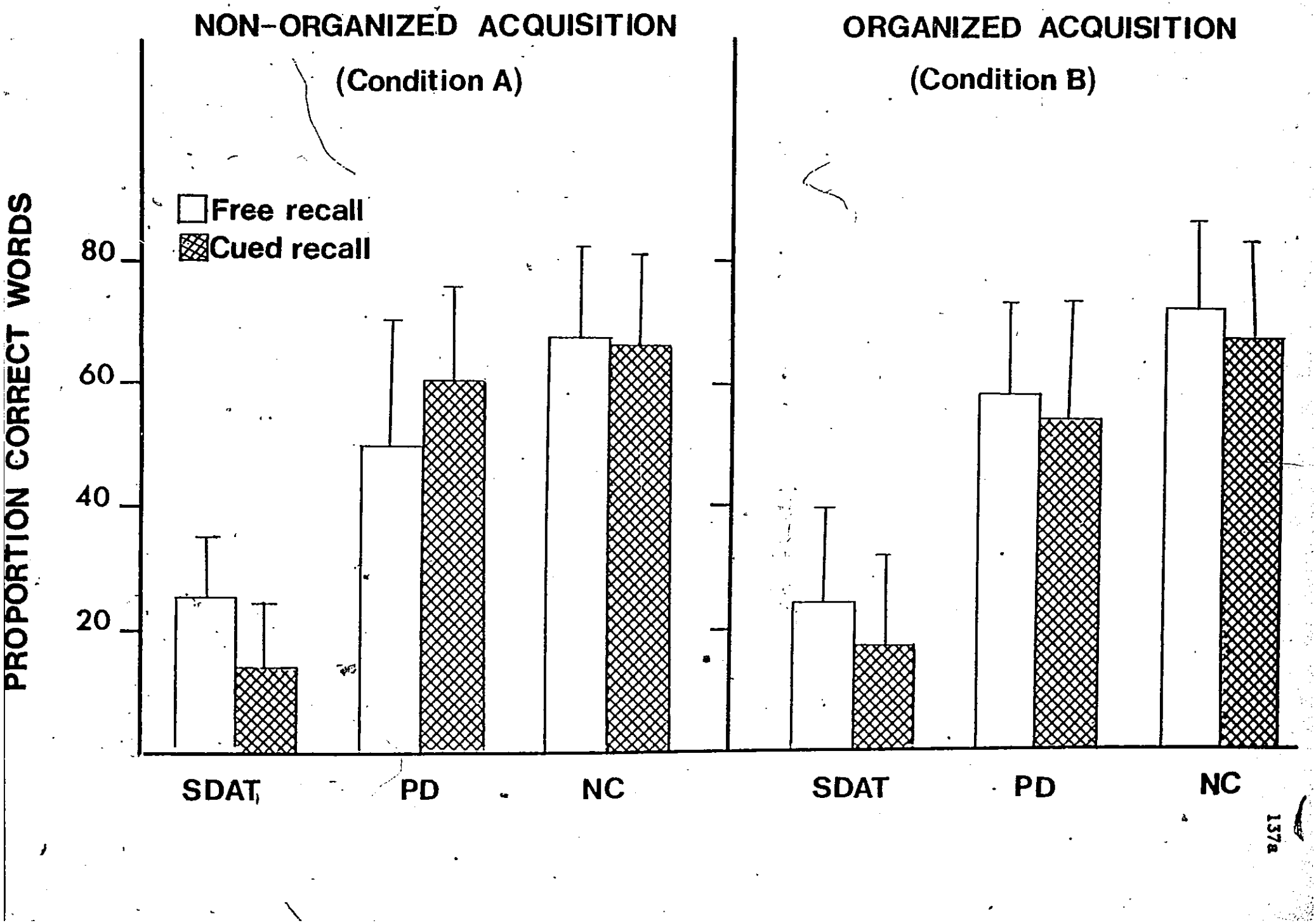
a n = 12 for each group

45.28, $p<.001$), Recall Type ($F(1,33) = 10.38$, $p<.001$) but, not for condition ($F(1,33) = .20$, $p>.05$). A significant Groups-by-Recall Type ($F(2,33) = 4.49$, $p < .01$) and Group-by-Condition-by-Recall type interaction, $F(2, 33) = 3.14$, $p = 05$ but not for Condition-by-Recall Type ($F(1,33) = 1.12$, $p > .05$) or groups by condition ($F(1,33) = .20$, $p > .05$ is also revealed. A posteriori contrasts suggest memory patterns specific to each group.

As shown in Figure 6, for both types of acquisition (organized and non-organized, condition A and B), PD patients recalled significantly fewer words at free recall than the NC subjects. They, however, recalled significantly more words than the SDAT patients. Under cued recall of non-organized acquisition, PD patients benefited from retrieval cues. Their performance was restored to the level of the NC subjects. This, however, was not observed under organized acquisition. The SDAT patients recalled significantly less words than both normal controls and PD patients under all encoding and retrieval conditions. Since both PD and SDAT patients showed significantly more complaints on the Zung and the Beck's depression scales than the NC group, the scores on these scales were correlated with the proportion of words recalled. The results did not reveal any association on these three measures. The poorer performance of these two patients populations cannot be attributed to factors related to somatic complaints.

For both condition A and condition B, cueing did not result in the recall of a significant number of words in the PD and NC groups as

Figure 6. Mean proportion of words recalled by SDAT, PD and NC groups under non-organized and organized acquisition.


NON-ORGANIZED ACQUISITION
(Condition A)
ORGANIZED ACQUISITION
(Condition B)
Free recall
Cued recall
PROPORTION CORRECT WORDS
80
60
40
20
SDAT
PD
NC
SDAT
PD
NC

compared to their performance at free recall. For the SDAT group, a decay of memory over time is suggested by the recall of significantly fewer words at cued recall than at free recall. This is shown in Figure 7.

The use of priming, that is, providing information to the subject about the semantic affiliation of the words to be learned (Condition B) did not facilitate learning in any of the groups either under free recall or cued recall.

Words Gained and Words Lost. Cued recall allows the assessment of storage and retention since free recall alone does not recover all items available in storage (Tulving & Pearlstone, 1966). Under such recall strategy, the expectation is that items retrieved by free recall should also be retrieved under cued recall (Buschke, 1984). However, in this experiment, a qualitative analysis of the words retrieved at cued recall as compared to those retrieved at free recall, under each encoding condition, indicated a lack of consistency of recall on the part of the PD patients and a consistent loss of words on the part of the SDAT patients. The NC subjects, however, appeared to be more stable. An analysis of words gained (positive increment) and words lost (negative increment) at cued recall under both encoding strategies was carried out. Two-way anovas were performed on both the positive and the negative increments (Table 18). Both anovas had groups as the between-subject variables and condition (non-organized and organized acquisition) as the within-subject variables.

Figure 7. Mean proportion of correct words recalled at free and cued recall under non-organized and organized acquisition.

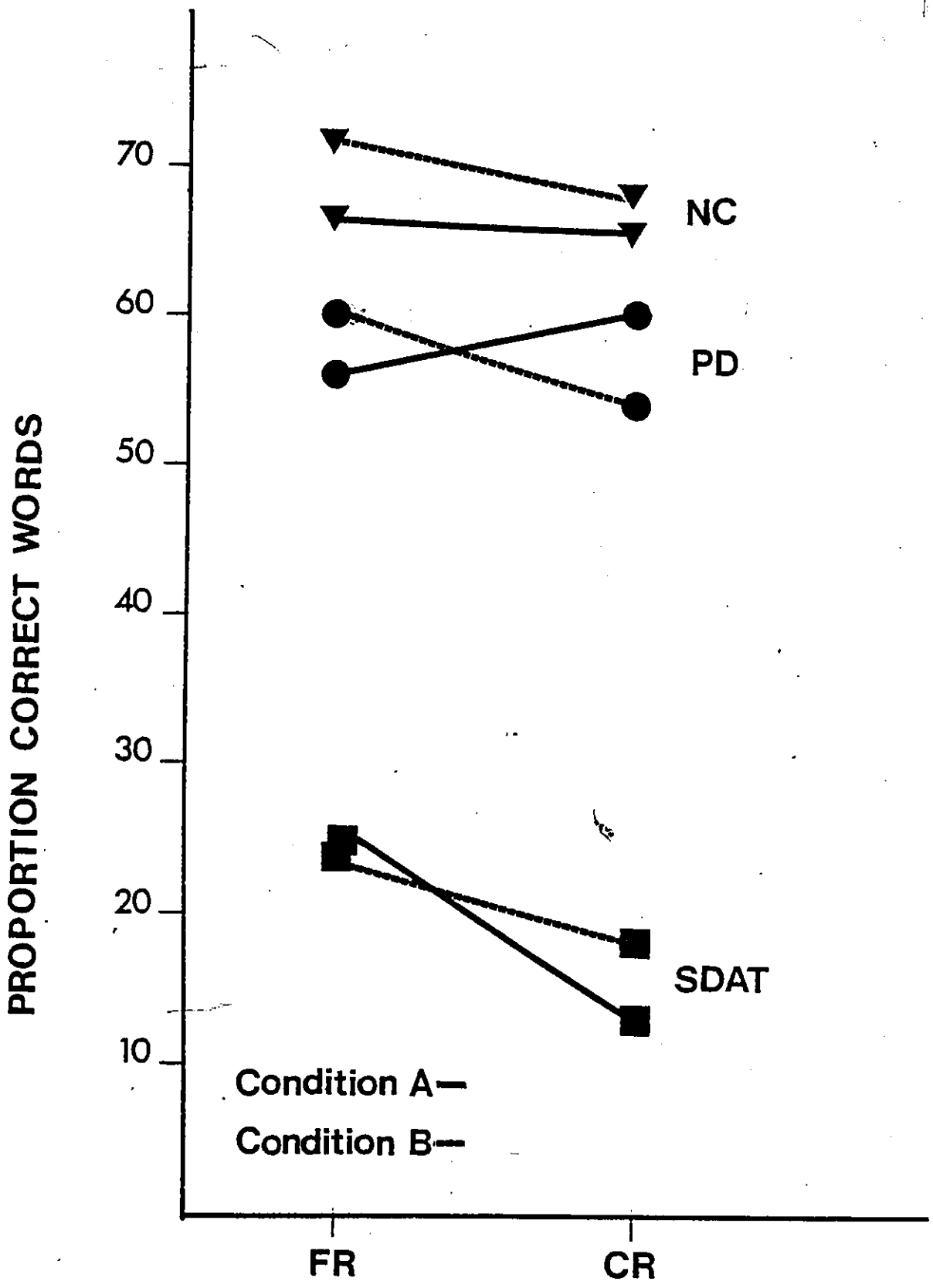

PROPORTION CORRECT WORDS
70
60
50
40
30
20
10
NC
PD
SDAT
Condition A—
Condition B—
FR
CR

Table 18

Mean Proportions of Positive and Negative Increment at Cued Recall

Group a	Condition: Without categories Mean	SD	With categories Mean	SD
Positive increment:				
PD	.27	.17	.06	.11
SDAT	.07	.08	.07	.08
NC	.14	.14	.08	.12
Negative increment				
PD	.20	.27	.17	.16
SDAT	.59	.36	.63	.36
NC	.09	.09	.12	.13

a n = 12 for each group

The analysis of variance on the positive increment revealed a significant main effect for Groups ($F(2,33) = 3.98$, $p<.03$) and for Condition ($F(1,33) = 11.19$, $p<.01$) and a significant Groups-by-Condition interaction, $F(2, 33) = 9.22$, $p<.001$), whereas that on the negative increment revealed only a significant main effect for Groups, $F(2, 33) = 27.93$, $p<.001$. A posteriori contrasts were performed on the interaction of the positive increment and the main effect of the negative increment.

As shown in Figure 8, the analysis of consistency of recall in condition A, when subjects are requested to learn the list of words without the benefit of external organization, revealed that providing the cues after free recall resulted in PD patients adding significantly more new words to the list at cued recall; that is, they retrieved from memory significantly more words that had not been recalled under free recall. This effect was not observed in either the NC and SDAT groups who both retrieved a small and equivalent number of new words. The effect was not found in Condition B so that the net gain was significantly larger in Condition A as compared to Condition B.

As Figure 9 indicates, and confirmed by the analysis of variance on negative increment, the SDAT group lost a significantly larger number of words from free recall to cued recall under both conditions. A posteriori contrasts on the groups confirmed that the SDAT group lost significantly more words than both the PD and NC groups. The PD and NC groups lost equally.

Figure 8. Positive increment at cued recall in non-organized acquisition (left panel) and organized acquisition (right panel) for the SDAT, PD, and NC groups.

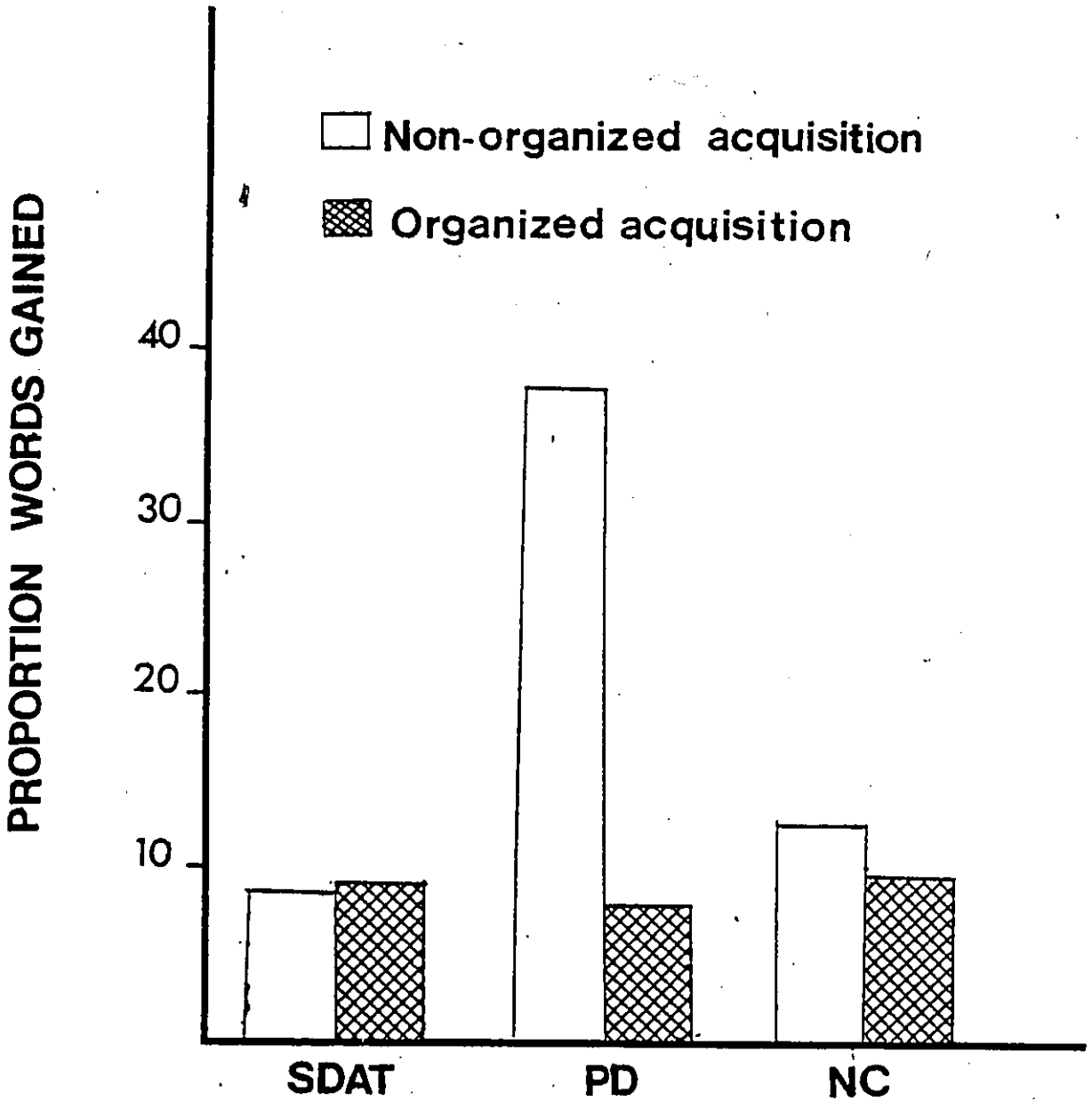
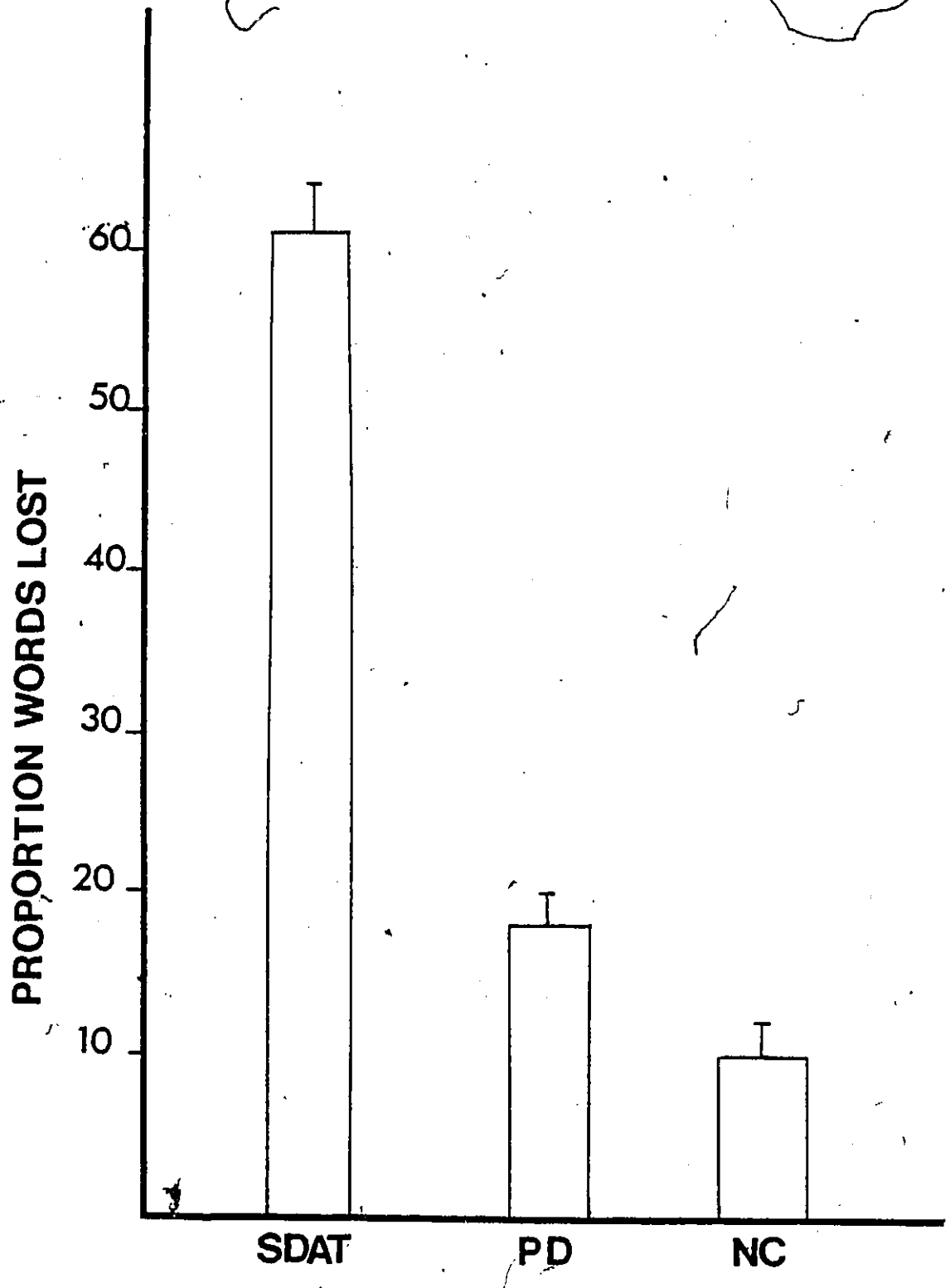

Non-organized acquisition
Organized acquisition
PROPORTION WORDS GAINED
40
30
20
10
SDAT
PD
NC

Figure 9. Negative increment at cued recall on combined non-organized and organized acquisition for the SDAT, PD, and NC groups.


PROPORTION WORDS LOST
60
50
40
30
20
10
SDAT
PD
NC

A fourth analysis of variance was performed to evaluate the total shift of old and new words, the combined gain and loss scores, with groups as the between-subject variables and condition (organized and non-organized) as the within-subject variable.

Results indicated a group interaction, F (2, 33) = 14.15, p < .001. A posteriori contrasts revealed that the NC group showed the least shift of old-new words amongst the groups. The PD group showed significantly more shift than the NC group but significantly less shift than the SDAT group.

Recognition: Indices of Discriminability. A two-way analysis of variance was performed on the recognition scores with the indices of discriminability as the dependent variable. Group (PD, NC and SDAT) were the between-subject variables and condition (A and B) was the within-subject variable.

Results revealed a Group main effect, $F(2,33) = 29.81$, $p < .001$. A posteriori contrasts showed that both PD and NC subjects had little difficulty in distinguishing target items from distractor items whilst the SDAT group had significantly greater difficulty as seen in Table 19.

Recognition: Response Bias. A two-way analysis of variance was performed with response bias as the dependent variable. Again, group (PD, NC, SDAT) was the between-subject variable and condition (A and B) was the within-subject variable.

Results did not reveal a Group main effect ($F(2,33) = 2.73$, $p > .05$) but did reveal a main effect for Condition ($F(2,33) = 47.58$,

Table 19

Indices of Discriminability and Response Bias

Indices of discriminability:

	Condition			
	Without categories		With categories	
Group [a]	Mean	SD	Mean	SD
PD	.92	.08	.88	.12
SDAT	.62	.12	.64	.18
NC	.83	.07	.90	.08

Response bias:

PD	.59	.32	.25	.45
SDAT	.48	.27	.00	.00
NC	.73	.29	.25	.45

[a] n = 12 for each group

$p < .001$). Analysis of response bias means indicated that whereas there had been a bias towards answering with 'yes' responses in condition A, this tendency was not present when learning under conditions of organized acquisition.

Intrusions. The PD group was 97% accurate in retrieval under all recall types and conditions. That is, only 3% of the words they reported were not learned words. The NC group were 100% accurate in their free recall in Condition A and Condition B. At cued recall, they showed 99% accuratly in condition A and 98% accuratly in Condition B.

In contrast, the SDAT group revealed a propensity to recall incorrectly remembered words that were not presented as items to memorize. Furthermore, it appears that the closer recall is to the presentation of the memory list, the smaller is the number of intrusions. Thus, SDAT patients were 83% accurate at free recall in Condition A versus 61% at cued recall. Organized acquisition appears to result in an increase in the number of intrusions.

This was verified in a three-way analysis of variance with groups (PD, SDAT, NC) as the between-subject variable and condition (non-organized and organized acquisition) and recall type (free and cued) as the between-subject variables. Results revealed a group-by-condition-by-recall type interaction, $F(2,33) = 3.34$, $p < .04$.

The results showed that under free recall in condition A, (non-organized) the number of intrusions was equivalent across all groups. However, under cued recall, the SDAT group produced a larger

number of intrusions as compared to the two other groups.

Under free recall in organized acquisition, the SDAT group generated a larger number of intrusions than the two other groups providing information about the material to be recalled has the effect, in SDAT patients, of triggering the release of words from the same category as the words learned without appropriate blockage. This effect is more evident in free recall, conditon B, which showed a significantly larger number of intrusions as compared to condition A.

Discussion

The present findings demonstrate that Parkinson's disease and Alzheimer's disease are each associated with their own particular memory deficit. The deficit found here in patients suffering from Parkinson's disease has been described in the literature either as "forgetfulness" (meaning, "a difficulty in initiating the retrieval of stored memories" (Benson, 1984, p. 187)), or as "forgetting to remember" (Albert et al.,1974). These descriptions intend to convey that PD patients are able to learn new material but have difficulty retrieving it once it is stored. The deficit evidenced here in patients suffering SDAT, in contrast, could not be so described. Rather, they showed a rapidly progressive amnesia that occurs as part of a wider cognitive deterioration, an amnesia which arises from an underlying difficulty more profound than impaired retrieval.

Self-reports of the present patients suffering from Parkinson's disease are fully consistent with the above clinical descriptions; and, the above characterization of the loss in patients in the SDAT group accords fully with collateral accounts given by members of their families.

Overall memory performance

The results showed that (1) the SDAT patients were significantly impaired in comparison to both other groups under all encoding procedures and recall strategies; (2) compared to the NC subjects, the PD patients were significantly impaired on free recall non-organized acquisition, and both free and cued recall of organized acquisition; (3) providing an encoding strategy (organized acquisition) did not improve performance in any of the groups; (4) with cues after non-organized learning, PD patients and normal control subjects performed at the same normal level, whereas providing cues to the SDAT group regardless of method of encoding, was of no benefit to them; (5) decay in memory occurs for all groups under all conditions with the SDAT group showing a very much greater decay than the PD and NC groups who show the same decay as each other (these data are summarized in Table 20 and 21); (6) on tests of recognition, PD & NC groups showed ceiling effects under both conditions, SDAT showed no ceiling effect under both conditions; and finally, (7) the measured memory impairment in both PD & SDAT groups was independent of their

Table 20

Summary of Results for the Non-Organized Acquisition Condition

Non-organized acquisition

Groups	Free Recall	Cued Recall	Recognition
NC	normal spontaneous organization	no performance change	ceiling effect
	No gains ---------->		
PD	reduced memory capacity	improved performance	ceiling effect
	GAINS---------->		
SDAT	no evidence of organization.	worsened performance	no ceiling effect
	No gains ---------->		
	LOSS---------->		

Table 21

Summary of Results for the Organized Acquisition Condition

Organized acquisition

Groups	Free Recall	Cued Recall	Recognition
NC	organization given by experimenter, and used by subject No gains ---------->	no performance change	ceiling effect
PD	organization given by experimenter: results equal to cued recall of non-organized condition. (was equal to NC) No gains ---------->	no performance change	ceiling effect
SDAT	organization given by experimenter: no evidence of its use by patients. LOSS---------->	worsened performance	no ceiling effect

scores on both depression rating scales.

Encoding and retrieval strategies

Total words recalled. The method of acquisition (non-organized and organized) was varied, with recall stragegy (free and cued) being held constant. This was done in order to test the hypothesis that changing the encoding strategy from non-organized to organized would directly improve recall. With one exception, it did not. Regardless of whether information about the material to be learned was provided or not prior to learning, the number of words recalled was equivalent for the NC and SDAT groups under free and cued recall, and for the PD group under free recall of organized acquisition only. This was so despite the fact that none of the groups showed a ceiling effect for word recall.

When the dependent measure was the total number of words recalled, providing an organized method of encoding did not statistically significantly affect the performance of any of the three groups. This may be secondary to the experimental design. The stability of the information learned, however, as described in the section 'words gained and words lost' (below) was different amongst the groups.

Retrieval strategy did not facilitate recall within groups across learning conditions. In the literature category names used as cues have been reported to be facilitative when the words are presented in

random order and the subjects are informed of the categories just prior to the test (Pollio & Gerow, 1968). Certain constraints on this usefulness of cueing with normal subjects have, however, been reported. For example, categorical cueing is effective only when the number of categories exceeds the number that subjects are able to retrieve spontaneously (Bellezza & Hartwell, 1981). Superiority of cued recall is reportedly not observed when only three categories are used with normal controls, because three is well within normal memory capacity, i.e., list length of 12 items, with 4 items per category (Tulving & Pearlstone, 1966). Cueing under such conditions provides little advantage, if any, over the already high recall of the three categories (Cohen, 1966; Mandler, 1966; Tulving & Pearlstone, 1966). Selection of the experimental paradigm in this research was primarily based on the expected abilities of the two patient groups, not on the expected performance of the NC group.

As expected (Tulving & Pearlstone, 1966), all NC subjects recalled all three categories at free recall non-organized acquisition (i.e., they recalled at least one word for each category). In contrast to the NC group, only nine of the PD patients, and none of the SDAT patients produced words from each of the three categories. Since all of the SDAT patients had unaccessed categories, they might have been expected to benefit from cueing, but they did not. On the other hand, three PD patients had unaccessed categories, and for them cueing was beneficial.

Semantic information provided at cued recall under non-organized

acquisition allowed access to words within missed categories for those 25% of the PD patients who had not accessed all three categories. There was a trend towards an increased number of words recalled following cueing for all PD patients, but it does not achieve statistical significance (see also Tweedy et al., 1982, for a similar result). It does, however, result in the following interesting finding; namely, that before cueing the PD group recalled statistically significantly fewer words than the NC group, but following cueing, they recalled as many.

Semantic cues did not facilitate recall in the NC group for the reason given above (Bellezza & Hartwell, 1981). In the literature, with tests using three categories, cueing has been shown to provide virtually no advantage in normal, aged, subjects (Mandler, 1967), as we found in the present study's NC group. In the PD patients, cueing operated primarily on a minority (25%), and yet the group achieved a statistically significant improvement when they are compared to the NC subjects. In the SDAT patients, cueing should theoretically be efficacious because all subjects in this groups failed to recall at least one category. However, there was no improvement; rather, there was a substantial loss.

In summary, patients with long-standing PD have a relatively mild memory deficit that is decreased by cueing, while recently-diagnosed patients with mild SDAT have a profound memory deficit that is not helped by cueing.

Kirsher, Webb & Kelly (1984) have provided a possible explanation

for the failure of cues to enhance the SDAT patients' performance. They point out that patients with senile dementia appear to experience difficulty in remaining within the limits of 'semantic boundaries'. That is, rather than grouping words under the general class they belong to, Alzheimer's patients will sometimes convert a word to a class as part of their idiosyncratic encoding strategy. For example, rather than using the general class "occupation" for dancer, 'dancer' itself will be substituted, and represent a class to which other words will be assigned. The distortion of meaning inherent in such a classification system may be one factor underlying the finding that ordinarily meaningful semantic cueing does not help SDAT patients.

Words gained and words lost. An analysis of the retrieved words at cued recall as compared to free recall, as measured by 'words gained' and 'words lost' was carried out to compare the internal structure of recall across the three groups. This analysis revealed a differential effect of encoding strategy on retrieval processes only for Parkinsonian patients. Under non-organized encoding (see Figure 8), cueing resulted in PD patients gaining significantly more words than it did under organized recall. They also gained a significantly larger number of words than either the NC or SDAT subjects under both conditions. This indicates that the words had been recorded in memory but had not been accessed without cues. However, they suffered the same small loss with time as the NC subjects. Nevertheless, the resulting net gain allowed PD patients to perform at the level of the NC subjects under cued recall following non-organized acquisition.

Under non-organized acquisition, subjects are simply told that they will be given a list of words to learn and that they will be asked to recall them later. They are thus left to use their own mnemonic strategies. Under these conditions, cueing helped Parkinsonian subjects to retrieve words that had not been accessed at free recall. Cueing was not effective for either the NC or the SDAT subjects.

Successful retrieval of encoded events has been shown to depend upon (a) the availability of the appropriate event in memory storage and (b) the access to that information at the desired time (Tulving & Pearlstone, 1966). A retrieval failure may thus be a function of the physical deterioration of the stored event itself, or of the inaccessibility of successfully stored information at recall (Tulving & Madigan, 1970)). The efficacy of the retrieval cues under the non-organized condition for the Parkinsonian patients indicates that the information in memory had not deteriorated but that it could not be accessed without cues. In contrast, the failure of cues to improve recall in the SDAT group suggests that the information is not available for retrieval and/or that the small amount of information that has been encoded, may have been organized within a meaningless classification system (Kirsher, Webb & Kelly, 1984), and is therefore not accessible even with semantic cues.

<u>The performance of the Parkinsonian patients</u>

There are at least two ways in which the performance of the Parkinson's disease patients might be explained. One is based on a clearly significant finding of the present study; the other is based on a trend that did not reach significance.

For the first explanation, consider the measures of memory capacity, and the effects of cueing. It is clear that the PD patients have a smaller overall memory capacity than the NC subjects. This finding is consistent with that of Tweedy et al. (1981), and that of Pillon, Dubois, Lhermitte and Agid (1986). Tulving and Pearlstone (1966) have shown that the effectiveness of cueing is related to the memory capacity of the subjects being tested. Specifically, it is directly related to the excess of categories in the test being used, over the maximum number of categories that the tested subjects can retrieve spontaneously. That is, if NC subjects can normally retrieve six categories spontaneously, then a test using seven categories will lead to the disappearance of the ceiling effect found with fewer categories. Further, the effectiveness of cueing would then make itself apparent, as Mandler (1967) described. It is possible that the pathologic changes in Parkinsons's disease act so as to reduce overall memory capacity, such that at three categories, a substantial minority (25%) of PD patients are already not showing a ceiling effect. Cues would then begin to improve their performance in the same manner as seen in normals at six categories. Baddeley (1981) has offered a detailed theoretical conceptualization of how reduced overall memory capacity might result in the observed poorer performance.

A second possible explanation, perhaps a weaker one on the basis of the present findings, arises out of the data on the impact of cueing. From non-organized free recall to non-organized cued recall, there exists the same trend towards improved recall as from non-organized free recall to organized free recall. Those trends suggest that the poorer performance of PD patients, when left to organize the information themselves, results in part from their failing to organize semantically in the manner allowed by the cues. That is, they may recall words on the basis of differently organized strategies, perhaps idiosyncratically organized ones. It is well established in the literature (Bowen et al., 1976; Cools et al., 1984; Flowers & Robertson, 1985; Lees & Smith, 1983; Smith, 1983) that PD patients exhibit a specific difficulty in switching sets. This particular function, the ability to vary sets being looked at and to choose tentatively from amongst them, is required for spontaneous semantic organization (Bower, 1981). If further work were to establish the observed trends as significant, through using a more extensive paradigm and larger experimental groups, then it could be said (Pillon et al., 1986) that the memory deficit found in patients with Parkinson's disease is one of those several higher losses which comprise the frontal system syndrome.

Performance of the Alzheimer' disease patients

The ability to encode or learn requires the proper working of

memory which is intimately linked to the integrity of "multiple and discrete psychobiological mechanisms" (Weingartner, Grafman et al., 1983, p. 382). One mechanism specific to the performance of the SDAT patients that has been identified as being associated with the memory failure is an inability to access previous knowledge (semantic memory). This finding has been repeatedly replicated (Martin, Browers et al., 1985; Martin & Fedio, 1983; Ober et al., 1986; Weingartner, Graftman et al., 1983; Weingartner, Kaye et al., 1981). This failure results in an inability to either use, or to impose organization on, material to be learned. This inability is clearly seen in the failure of the SDAT group to use a clustering strategy, even under conditions where a possible organizational strategy is offered to them.

Another often neglected factor that may have contributed to the SDAT patients' poorer overall performance is that of attentiveness. There was, during testing, behavioural evidence of attentional difficulties in the SDAT group, but not in the PD or NC groups. For example, SDAT patients were more likely to comment while looking at the words to be learned regarding their inability to memorize anything anymore, or they had to be reminded to read the words aloud, or could easily turn around and make a comment on a word per se or the number of words. Therefore, part of their failure to learn may be at least partly attributed to an inability to focus properly on incoming information. Such difficulties in sustaining focussed attention and learning have been noted by others (Ober, Dronkers, et al., 1986; Ober, Koss et al., 1985; Wilson, Bacon, Fox, Kramer et al., 1983; and

Wilson, Bacon, Fox & Kaszniak, 1983).

The memory deficit caused by Alzheimer's disease is known to be rapidly progressive. Our SDAT subjects, as discussed earlier, were no more than mildly impaired as determined by the Dementia Rating Scale. Despite this, they showed a severe anterograde deficit. Other workers have also reported this finding (Corkin, 1982; Weingartner, Kaye et al., 1981; Wilson, Bacon, Fox, Dramer et al., 1983; Wilson, Bacon, Fox & Kasniak, 1983).

The dementia in Alzheimer's disease involves widespread neocortical, as well as subcortical, pathology with documented damage at the posterotemporal, temporoparietal-junction, and medial-temporal regions (Brun & Guftafson, 1978). The amnesia has been particularly associated with medial temporal damage (Martin et al, 1985). This association is supported by the observation of a severe cell loss in the hippocampus (Ball, 1972) and the amygdala (Herzog & Kemper, 1980). Evidence of damage is also provided from in-vivo hypometabolism in the temporal-parietal cortex of Alzheimer's patients (Benson et al., 1983; Foster et al., 1984; Friedland et al., 1983; Friedland et al., 1985; Haxby, Grady, Duara, Schlageter, Berg & Rapoport, 1986).

Whereas an accessibility problem appears to be the core of the Parkinsonian patients' memory difficulties, the deterioration of the stored information observed in the SDAT patients recall from free recall to cued recall under both non-organized and organized acquisition suggests the more serious problem of the reduced availability of the appropriate event-information in memory storage

(Tulving & Pearlstone, 1966). The use of the term amnesia to describe their memory failure is therefore appropriate (Benson, 1984). The presence or absence of retrieval cues do not affect the performance of the SDAT patients; systematically recalled significantly less words under cued recall as compared to free recall. This indicates that not only are encoding processes impaired in SDAT patients, but also memory traces are weak and easily disrupted, or are inaccessible due to their having been organized idiosyncratically.

There are quantitatively and qualitatively different profiles in the PD and SDAT groups supporting the hypothesized distinguishing features of fronto-subcortical syndrome (forgetfulness) and cortical dementia (amnesia). More specifically, the retrieval deficit hypothesis which is suggested as a behavioural manifestation of subcortical dementia (Benson, 1984) is supported under conditions of non-organized free recall. The problem of accessibility is also shown by the Parkinsonian patients' results on the recognition task under both conditions, which was the same as the NC subjects', within the limitation implied by the presence of a ceiling effect. This effect, however, was not seen at cued recall when semantic cues are provided prior to learning. The fact that the same reduced number of words are recalled at non-organized and organized recall was interpreted as evidence for a reduced overall memory capacity on the part of PD patients. The mechanisms underlying this reduced overall memory capacity are unknown. The failure of memory of the SDAT group, however, was interpreted as a much more reduced overall memory

capacity arising out of diffuse damage of the brain and consequent physical decay of stored information, with the particular involvement of the medial-temporal area.

General discussion

1. Theoretical implications for the concept of subcortical dementia

As has been pointed out in the introduction, the word dementia has been defined over many centuries, impressionistically, but nevertheless consistently, on the basis of every day experience. A more modern heuristic allows us to define members of the demented class through measurement. In the present century, a number of dementia rating scales have been developed which enable us to separate demented from non-demented patients more objectively. One question posed by the concept of subcortical dementia can be put as follows: should the term 'demented' refer to patients who score in the non-demented range while having an identifiable pattern of demonstrable higher losses arising from subcortical pathology?

With this question in mind, notice that the present experimental findings include one measured difference and one measured similarity between the higher functioning of demented patients suffering from Alzheimer's disease and non-demented patients suffering from Parkinson's disease. Each of these two findings can be seen to point towards its own consequences for the study of dementia in general, and

for the recent concept of subcortical dementia in particular.

As Miller (1981) has pointed out, when experimentally comparing two subgroups, one demented group and the other not, the finding of a similarity is to be less expected than the finding of a difference. So a measured similarity can actually be more striking than can a difference.

The difference was found on a measure of memory retrieval. When compared with normal controls, patients suffering from Parkinson's disease had a reduced capacity for recall that was restored to normal through cueing (under non-organized acquisition). By comparison, patients suffering from Alzheimer's disease clearly evidenced a very much larger reduction in memory capacity which was not improved through cueing.

It could be said that the patients in these two groups are similar in that they both show decreased memory capacity, even though they show a different sized decrease. Taking this in conjunction with other clinical findings (as described by Benson, 1984) it could also be said that these patients are likewise similar in that they are demented, albeit one group cortically, and the other subcortically (Albert et al., 1974; McHugh & Folstein, 1975; Albert, 1978; Freedman & Albert, 1985). To then attempt to qualify those statements by pointing out that the measured difference between the size of their memory impairments helps characterize the differences between the respective dementias (that is, that amnesia characterizes dementia, while the more subtle memory deficits of Parkinson's disease

characterize subcortical dementia) over-emphasizes minor similarities while de-emphasizing major differences. This is one reason why the attempt to define the subtle higher losses associated with subcortical disease as a dementia (Albert, 1978) in the sense of Roth's 'true' dementia (1980), has brought about the confusion that it has (Albert, 1978; Foster, 1986; Freedman & Albert, 1985; Huber & Paulson, 1985; Katzman, 1978; Marsden, 1978; Roth, 1980; Whitehouse, 1986).

There can be no question that a general pattern of clinical and neuropsychological findings has been accurately associated with a diverse group of diseases loosely called subcortical. Diseases in this group, that are said to cause subcortical dementia, include supranuclear palsy, thalamic tumors, olivopontocerebellar degeneration; progressive pallidal degeneration (Albert et al., 1974), and, most recently, Parkinson's disease (Albert, 1978). The pattern of clinical neuropsychological findings associated with this group of diseases has not yet been defined with adequate precision, and it has been suggested that it might vary from one subcortical disease to another (Cummings & Benson, 1983). Nevertheless, it could reasonably be seen either as a clinical syndrome, on the basis of its phenomenology, by a term like bradyphrenia (Hassler, 1965), or as an anatomically-based syndrome by a phrase like frontolimbic syndrome, or frontal-system syndrome or fronto-subcortical syndrome (Marsden, 1978), without introducing any unecessary confusion. However, to attempt to establish this clinical pattern as more than a syndrome, for example as a variant of Roth's true dementia, will cause

unecessary confusion.

The second experimental finding, the similarity, was that there was no statistically significant difference between the rate at which Parkinsonian patients, Alzheimer's disease patients, and normal control subjects, scanned their short term memory traces. The long-accepted clinical slowing of thought of Parkinson's disease, taken in conjunction with its apparent absence in Alzheimer's disease, could reasonably have yielded the expectation that Parkinson's disease patients might scan more slowly. Such an expectation would arise from the assumption that slowed scanning might effect slowed thinking. There is already some experimental work which would lend support to such an assumption (Wilson et al., 1980), although one subsequent experimental report failed to confirm it (Rafal et al., 1984). Whitehouse has recently pointed out that "no comparative studies of the speed of mental processing have been published to determine whether slowness of cognition is more characteristic of subcortical than of cortical dementias." The present study was specifically designed to provide data on the question Whitehouse (1986) raised subsequently. He correctly points out that "the validity of this distinction (between cortical and subcortical dementia) has not been established"(p.4), and that its validity can only be determined through "comparison of several types of dementias, using neuropsychological instruments..." (p.4). The present comparison has revealed that slowed scanning does not underlie the bradyphrenia of Parkinson's disease, and, slowed scanning is not part of the rapid

generalized, profound cognitive decline that characterizes early Alzheimer's disease. Both results are somewhat surprising. Given that the results are somewhat unexpected, it is unfortunate that there still are no other comparative studies whose results could be compared with the present study, a point that will be further considered in the next section, 'Methodological Issues and Future Research'.

This provides a further example of a similarity obscuring a difference. It is true to say that when patients with Alzheimer's disease and patients with Parkinson's disease scanned their short-term memory within the present experimental paradigm, they did so at the (statistically) same normal rate. However, all Parkinsonian patients were able to carry out the experimental instructions at first sitting without help. Alzheimer's disease patients, on the other hand, varied in that, at first sitting, one could do it without assistance, four could do it only with coaching, and the other seven could not do it at all. At retest within a year, the four who could do it with coaching joined the ranks of those who could not do it at all, and the one patient who had done it without coaching now required coaching. It is clear that whatever it is that forms the basis for the higher losses in these two patient groups, it does not involve decreased scanning speed. However, the mode of performance of the Alzheimer's disease patients is typical of Roth's (1980) true dementia, whereas the performance of the PD patients is not.

A second question arises about whether or not those higher losses found in Parkinson's diease patients who appear to suffer from a true

dementia (i.e. those who score in the demented range on rating scales) are different from those higher losses in non-demented Parkinsonian patients and/or from the losses characteristic of Alzheimer's disease patients. A preliminary study aiming at investigating some of these differences has recently been published by Freedman & Oscar-Berman (1986). Their results indicate broad similarities between the dementia of Alzheimer's disease patients and that of 'truly' demented Parkinsonian patients. They do, however, stress one fine difference which they suggest indicates that these (cortical) dementias may arise from pathologic changes in physically close, but functionally separate areas of the same cerebral region, namely, the frontal cortex.

Regarding the notion of subcortical dementia, Freedman and Albert (1985) stated that "It is important to stress that this new terminology is only offered tentatively as an approximation of our current state of knowledge until such time that it can be replaced with better labels" (p.314). The present findings, and other findings in the literature on the clinical characteristics associated with subcortical diseases, would be better represented by a term such as 'fronto-limbic syndrome' (Albert, 1978) or 'fronto-subcortical syndrome' (Marsden, 1978), than by the controversial notion of a new (subcortical) dementia.

2. Methodological issues and future research

Exclusion criteria were used for the selection of members of both

patient groups. Patients with Alzheimer's disease represented the most problematic group because the disease does not reveal itself by physical signs, but rather by cognitive changes over time, and so final confirmation of the diagnosis can only be established post-mortem. Close monitoring of the progressive cognitive changes is therefore necessary to minimize false positives. In this study, careful attention was given to diagnostic issues with the further step of a six months to one year follow-up. This latter step distinguishes the present study from previous efforts to study the cognitive losses associated with Alzheimer's disease. The methodological characteristic of the present paper that distinguishes it from all others is that it incorporated a follow-up confirmation of the earlier tentative diagnosis of SDAT. This procedure resulted in the exclusion of all but twelve patients of twenty-four referred cases of early Alzheimer's disease. Had we included these patients in the study as the published studies do, then the marked memory impairment difference might have been smaller.

An attempt will be made to obtain post-mortem confirmation of the diagnosis of the twelve patient with provisional Alzheimer's disease who participated in this study.

Exclusion criteria were also used for the sample of Parkinsonian patients in order to include only patients with idiopathic Parkinsonism. In this study, patients who showed signs of a dementia were excluded because of reports of superimposed Alzheimer's disease in demented patients with Parkinson's disease. Such a strategy was

used to avoid the possible difficulty in interpretation which might have resulted had positive findings been found. In this case, positive findings can clearly be attributed to the effect of the disease process of idiopathic Parkinsonism. It is, however, recommended that future research on the subject of cortical and subcortical dementia include both demented and non-demented Parkinsonian patients. Freedman and Oscar-Berman (1986) provide a good model for future research.

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APPENDIXES

Appendix 1

Brief Summary of Relevant Neuroanatomy

The basal ganglia comprise the following subcortical structures of the telencephalon; the caudate nucleus, the putamen, the globus pallidus, and the amygdaloid nuclear complex (Carpenter, 1978). The caudate and putamen together comprise the neostriatum or striatum; the neostriatum together with the globus pallidus comprise the corpus striatum. Two nuclei which have become unofficial members of the basal ganglia because of their important connections to the neostriatum are the substantia nigra (located in the midbrain (mesencephalon)) and the subthalamic nuclei (located in the diencephalon (FitzGerald, 1985).

Within the basal ganglia, the striatum and pallidal complex (consisting of the globus pallidus and the pars reticulata of the substantia nigra) may be divided in terms of their respective input and output functions. The major afferent connections include the corticostriatal, and nigrostriatal systems. The efferent system which will be reviewed here is the mesocortical-dopaminergic pathway. It is important because pathologic changes affecting it have been hypothesized to be responsible for some of the cognitive deficits found in Parkinson's disease.

The afferent connections

1. Corticostriatal afferent system. The striatum receives

afferent fibers from all parts of the cerebral cortex and from the medial central nucleus of the thalamus, and it provides the main neural input into the basal ganglia (Kemp & Powell, 1970; Kunzle, 1975; 1978; Nauta, 1964; Yeterian & vanHoesen, 1978). Selemon et al (1985) showed that the striatum could be differentiated into specialized functional parts by virtue of the specific array of cortical projections it receives. Thus, widespread areas of the association cortex were shown to extend via "longitudinal bands" into the anterior putamen, as well as to the caudate, whereas, the motor, sensory and premotor cortices project to the putamen. They suggested a functional distinction between an "association neostriatum", which would include the caudate and anterior putamen, and a "motor neostriatum", which would include the posterior putamen.

The neostriatum may be viewed as a well-informed structure receiving abundant pre-processed information about the world. The putamen's role, with its sensorimotor cortical inputs, may be viewed as primarily one of motor processing. The caudate, on the other hand, may pertain to certain types of 'cognitive activity', through which cognitive centers influence motor output, with only a minor involvement with control of movement (Oberg and Divac, 1979).

2. Nigrostriatal afferent system. Disorders of the nigrostriatal pathway are central to the understanding of the pathology of Parkinson's disease. The substantia nigra, the midbrain's largest single nuclear mass, has connections with the corpus striatum and thalamus. It is composed of two parts: (1) the pars compacta, a region of large, pigmented cells, and (2) the pars reticulata, a region poor in cells. The neurons of the pars compacta contain a high

concentration of dopamine, and appear to be the main source of dopamine found in the striatum (Carpenter, 1978).

Nigrostriatal fibers project dorsolaterally over the subthalamic nucleus and cross through the internal capsule, traverse parts of the globus pallidus to terminate in the putamen (receiving fibers from the caudal two-thirds of the substantia nigra) and the caudate nucleus (receiving the medial parts of the nigra fibers) (DeLong and Georgopoulus, 1983).

The nigrostriatal track appears to be part of a "closed feedback loop" (nigro-striato-nigral) which has acquired particular interest because its properties appear to be of crucial physiological, pharmacological, and pathological importance in Parkinson's disease.

Summary. In summary, the neostriatum is the receptor pathway for input originating from all areas of the cortex and is therefore provided with relevant information of activity in secondary association areas, in addition to the information provided by its direct connection to the sensorimotor and premotor cortices. Its efferent project to the pallidium and the zona reticulata portion of the substantia nigra. These anatomical connection provide the pathway for a finely balanced neurochemical functional loop, the disruption of which will cause a loss of the "kinetic melody of movement" (Barbeau, 1972); or, said differently, a loss in the ability to "execute simultaneous or sequential motor programs" (Marsden, 1982).

There has been a controversy over the role that the basal ganglia plays, if any, in human cognition. Improved mental performance observed after successful drug therapy for bradykinesia has led to the hypothesis that there may be a common neurochemical patho-physiology

for both mental and motor symptoms secondary to basal ganglia damage. The mesocortical dopaminergic system has been suggested as being the site responsible for these mental deficits (Delis, Direnfield, Alexander, Kaplan, 1982).

Efferent pathway: the mesocortical dopaminergic system:

The mesocortical dopaminergic system has also been implicated in the cognitive deficits found in Parkinson's disease (Delis et al., 1982). The brain's dopamine has been recently located in the prefrontal cortex (area 9 and 12) (Thierry, et al., 1977). Pathological studies in the brains of normal and Parkinson's patients have revealed that dopaminergic cells are contained in the VTA (Javoy-Agid and Agid, 1980) and that the prefrontal cortex (area 9) of Parkinsonian brains suffer a depletion of 19% of its dopaminergic content (Scatton, 1982).

Appendix 2

Patient	Drug
1	Diazepan, Sinemet, Parlodel
2	Sinemet
3	Bromocriptine
4	Sinemet; Cogentin
5	Sinemet; Symmetrel
6	Diazepan, Sinemet, Parlodel
7	Bromocriptine, Sinemet, Symmetrel
8	Sinemet
9	Sinemet
10	Sinemet; Symmetrel
11	Sinemet; Symmetrel
12	Sinemet

Appendix 1

Brief Summary of Relavant Neuroanatomy

The basal ganglia comprise the following subcortical structures of the telencephalon; the caudate nucleus, the putamen, the globus pallidus, and the amygdaloid nuclear complex (Carpenter, 1978). The caudate and putamen together comprise the neostriatum or striatum; the neostriatum together with the globus pallidus comprise the corpus striatum. Two nuclei which have become unofficial members of the basal ganglia because of their important connections to the neostriatum are the substantia nigra (located in the midbrain (mesencephalon)) and the subthalamic nuclei (located in the diencephalon (FitzGerald, 1985).

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Appendix 2

Patient	Drug
1	Diazepan, Sinemet, Parlodel
2	Sinemet
3	Bromocriptine; Parlodel
4	Sinemet; Cogentin
5	Sinemet; Symmetrel
6	Diazepan, Sinemet, Parlodel
7	Bromocriptine, Sinemet, Symmetrel
8	Sinemet
9	Sinemet
10	Sinemet; Symmetrel
11	Sinemet; Symmetrel
12	Sinemet

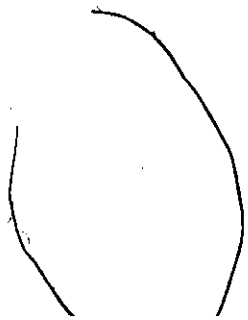
SUMMARY OF CODING FOR TRIALS

APPENDIX 3

Sample printout for one subject

TRIAL #	F/U SET	SIZE	ITEMS	TEST	P/N SET	RESP CODE	VRT (SEC)
1	*	1	Z	Z	P	C	0.460
2	*	3	JZX	F	N	C	0.500
3	*	2	JP	P	P	C	0.680
4	*	3	ZAX	Y	N	C	0.790
5	*	3	AEJ	B	N	C	0.520
6	*	1	E	E	P	C	0.510
7	*	3	VZC	F	N	C	0.590
8	*	2	PV	V	P	C	0.580
9	*	1	J	J	P	C	0.460
10	*	2	EZ	O	N	C	0.520
11	*	1	X	X	P	C	0.500
12	*	3	AZC	F	N	C	0.510
13	*	1	A	O	N	C	0.510
14	*	2	VE	V	P	C	0.770
15	*	2	JP	B	N	C	0.530
16	*	2	XA	Y	N	C	0.590
17	*	2	JV	J	P	C	0.430
18	*	1	J	J	P	C	0.350
19	*	3	EJA	E	P	C	0.760
20	*	3	XCJ	O	N	C	0.800
21	*	3	VZC	D	N	C	0.600
22	*	3	PVJ	O	N	C	0.800
23	*	2	PZ	F	N	C	0.600
24	*	1	V	V	P	C	0.600
25	*	3	ACE	Y	N	C	0.720
26	*	1	C	H	N	C	0.570
27	*	2	XC	X	P	C	0.640
28	*	1	Z	Y	N	C	0.570
29	*	2	XE	F	N	C	0.680
30	*	1	X	F	N	C	0.630
31	*	3	PJC	P	P	C	0.470
32	*	3	VJX	V	P	C	0.590
33	*	2	CV	V	P	C	0.540
34	*	2	EC	W	N	C	0.610
35	*	1	A	O	N	C	0.580
36	*	1	V	V	P	C	0.450
37	*	3	EAV	V	P	C	0.710
38	*	2	PC	H	N	C	0.480
39	*	3	VPX	P	P	I	0.440
40	*	2	VE	E	P	C	0.510
41	*	2	XJ	J	P	C	0.460
42	*	3	XCZ	B	N	C	0.580
43	*	1	J	J	P	C	0.410
44	*	1	V	O	N	C	0.550
45	*	1	V	V	P	C	0.450
46	*	1	E	W	N	C	0.590
47	*	3	EXP	X	P	C	0.750
48	*	1	E	E	P	C	0.340
49	*	2	VE	E	P	C	0.330
50	*	3	XEZ	X	P	C	0.380
51	*	1	C	C	P	C	0.320
52	*	1	Z	Z	P	C	0.380
53	*	2	JC	U	N	C	0.460
54	*	3	EJZ	W	N	C	0.540
55	*	3	ZJE	D	N	C	0.580
56	*	3	PAC	A	P	C	0.570
57	*	2	PA	P	P	C	0.520
58	*	2	VP	V	P	C	0.520
59	*	2	EP	E	P	C	0.490
60	*	1	A	A	P	C	0.480

61	*	2	CX	H	N	C	0.770
62	*	3	CJZ	Y	N	C	0.830
63	*	1	E	E	P	C	0.410
64	*	2	AV	A	P	C	0.650
65	*	1	V	V	P	C	0.380
66	*	3	AZP	U	N	C	0.770
67	*	3	ZCV	O	N	C	0.590
68	*	1	J	J	P	C	0.410
69	*	3	VEC	E	P	C	0.550
70	*	1	C	C	P	C	0.350
71	*	2	JE	O	N	C	0.570
72	*	3	JPV	W	N	C	0.610
73	*	2	JP	J	P	C	0.610
74	*	1	V	B	N	C	0.590
75	*	2	PV	P	P	C	0.530
76	*	3	CJV	V	P	C	0.510
77	*	2	EC	D	N	C	0.520
78	*	1	X	X	P	C	0.420
79	*	1	V	V	P	C	0.400
80	*	1	A	W	N	C	0.420
81	*	2	AX	W	N	C	0.600
82	*	3	JVE	U	N	C	0.660
83	*	2	XE	B	N	C	0.460
84	*	1	A	A	P	C	0.440
85	*	2	ZA	A	P	C	0.660
86	*	3	CPE	Y	N	C	0.760
87	*	3	XJV	D	N	C	0.620
88	*	1	P	O	N	C	0.590
89	*	2	ZC	F	N	C	0.500
90	*	3	VEX	X	P	C	0.630
91	*	3	XVP	X	P	C	0.580
92	*	1	A	U	N	C	0.970
93	*	2	PV	B	N	C	0.500
94	*	1	X	Y	N	C	0.590
95	*	3	PCA	C	P	I	0.570
96	*	3	CEJ	B	N	C	0.560
97	*	2	ZC	H	N	C	0.480
98	*	2	CZ	D	N	C	0.470
99	*	1	X	X	P	C	0.390
100	*	2	XZ	Z	P	C	0.610
101	*	1	C	C	P	C	0.370
102	*	1	A	H	N	C	0.520
103	*	2	PC	H	N	C	0.880
104	*	3	PEV	Y	N	C	0.720
105	*	3	JVC	J	P	C	0.420
106	*	2	VE	F	N	C	0.570
107	*	1	C	H	N	C	0.510
108	*	1	V	V	P	I	0.720
109	*	2	EA	B	N	C	0.570
110	*	3	XPE	E	P	C	0.500
111	*	3	VCP	D	N	C	0.620
112	*	3	EAZ	E	P	C	0.660
113	*	2	VE	V	P	C	0.550
114	*	2	CA	C	P	C	0.500
115	*	1	P	P	P	C	0.390
116	*	3	EAP	Y	N	C	0.660
117	*	1	C	B	N	C	0.550
118	*	2	CA	C	P	C	0.360
119	*	1	P	Y	N	C	0.470
120	*	3	VPZ	P	P	C	0.760
121	*	3	ZEJ	H	N	I	0.650
122	*	3	ZPX	D	N	C	0.570
123	*	1	E	B	N	O	3.150
124	*	2	VJ	V	P	C	0.340
125	*	3	ZXC	Z	P	C	0.580
126	*	3	EZP	H	N	C	0.670



127	*	2	ZX	Z	P	C	0.730
128	*	1	J	J	P	C	0.430
129	*	1	X	X	P	C	0.430
130	*	2	JX	J	P	C	0.390
131	*	1	E	E	P	C	0.410
132	*	2	PC	P	P	C	0.520
133	*	2	EC	U	N	C	0.620
134	*	1	E	Y	N	C	0.580
135	*	3	VZE	O	N	C	0.490
136	*	1	P	U	N	C	0.510
137	*	2	JE	F	N	C	0.620
138	*	1	J	O	N	I	0.970
139	*	3	XZJ	U	N	C	0.650
140	*	3	JCE	D	N	C	0.630
141	*	3	ZJX	O	N	C	0.680
142	*	2	ZP	F	N	C	0.990
143	*	1	X	X	P	C	0.360
144	*	2	EX	O	N	C	0.540
145	*	2	CP	C	P	C	0.640
146	*	1	X	D	N	C	0.520
147	*	2	PJ	D	N	C	0.580
148	*	1	V	V	P	C	0.590
149	*	3	XJC	B	N	C	0.620
150	*	3	JAC	J	P	C	0.440
151	*	2	XV	V	P	I	0.460
152	*	3	AEJ	J	P	I	0.510
153	*	1	A	A	P	I	0.440
154	*	2	PX	H	N	I	0.820
155	*	2	JP	Y	N	I	0.650
156	*	2	AX	A	P	I	0.610
157	*	2	PE	W	N	I	0.760
158	*	1	X	D	N	O	0.060
159	*	3	JCE	Y	N	I	0.720
160	*	1	Z	U	N	I	0.510
161	*	3	JCP	P	P	I	0.680
162	*	1	C	C	P	I	0.410
163	*	1.	Z	Z	P	I	0.440
164	*	3	PEJ	O	N	O	0.590
165	*	3	EAX	E	P	I	0.460

VRT FOR EACH MEMORY LOAD SIZE

POSITIVE PROBES

F SET				U SET			
1	2	3	4	1	2	3	4
0.460	0.680	0.760	0.000	0.000	0.000	0.000	0.000
0.510	0.580	0.470	0.000	0.000	0.000	0.000	0.000
0.460	0.770	0.590	0.000	0.000	0.000	0.000	0.000
0.500	0.430	0.710	0.000	0.000	0.000	0.000	0.000
0.350	0.640	0.440	0.000	0.000	0.000	0.000	0.000
0.600	0.540	0.750	0.000	0.000	0.000	0.000	0.000
0.450	0.510	0.380	0.000	0.000	0.000	0.000	0.000
0.410	0.460	0.570	0.000	0.000	0.000	0.000	0.000
0.450	0.330	0.550	0.000	0.000	0.000	0.000	0.000
0.340	0.520	0.510	0.000	0.000	0.000	0.000	0.000
0.320	0.520	0.630	0.000	0.000	0.000	0.000	0.000
0.380	0.490	0.580	0.000	0.000	0.000	0.000	0.000
0.480	0.650	0.570	0.000	0.000	0.000	0.000	0.000
0.410	0.610	0.420	0.000	0.000	0.000	0.000	0.000
0.380	0.530	0.500	0.000	0.000	0.000	0.000	0.000
0.410	0.660	0.660	0.000	0.000	0.000	0.000	0.000
0.350	0.610	0.760	0.000	0.000	0.000	0.000	0.000
0.420	0.550	0.580	0.000	0.000	0.000	0.000	0.000
0.400	0.500	0.440	0.000	0.000	0.000	0.000	0.000
0.440	0.360	0.510	0.000	0.000	0.000	0.000	0.000
0.390	0.340	0.680	0.000	0.000	0.000	0.000	0.000
0.370	0.730	0.460	0.000	0.000	0.000	0.000	0.000
0.720	0.390	0.000	0.000	0.000	0.000	0.000	0.000
0.390	0.520	0.000	0.000	0.000	0.000	0.000	0.000
0.430	0.640	0.000	0.000	0.000	0.000	0.000	0.000
0.430	0.460	0.000	0.000	0.000	0.000	0.000	0.000
0.410	0.610	0.000	0.000	0.000	0.000	0.000	0.000
0.360	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.590	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.440	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.410	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0.440	0.000	0.000	0.000	0.000	0.000	0.000	0.000

VRT FOR EACH MEMORY LOAD SIZE

NEGATIVE PROBES

F SET				U SET			
1	2	3	4	1	2	3	4
0.510	0.520	0.500	0.000	0.000	0.000	0.000	0.000
0.570	0.530	0.790	0.000	0.000	0.000	0.000	0.000
0.570	0.590	0.520	0.000	0.000	0.000	0.000	0.000
0.630	0.600	0.590	0.000	0.000	0.000	0.000	0.000
0.580	0.680	0.510	0.000	0.000	0.000	0.000	0.000
0.550	0.610	0.800	0.000	0.000	0.000	0.000	0.000
0.590	0.480	0.600	0.000	0.000	0.000	0.000	0.000
0.590	0.460	0.800	0.000	0.000	0.000	0.000	0.000
0.420	0.770	0.720	0.000	0.000	0.000	0.000	0.000
0.590	0.570	0.580	0.000	0.000	0.000	0.000	0.000
0.970	0.520	0.540	0.000	0.000	0.000	0.000	0.000
0.590	0.600	0.580	0.000	0.000	0.000	0.000	0.000
0.520	0.460	0.830	0.000	0.000	0.000	0.000	0.000
0.510	0.500	0.770	0.000	0.000	0.000	0.000	0.000
0.550	0.500	0.590	0.000	0.000	0.000	0.000	0.000
0.470	0.480	0.610	0.000	0.000	0.000	0.000	0.000
3.150	0.470	0.660	0.000	0.000	0.000	0.000	0.000
0.580	0.880	0.760	0.000	0.000	0.000	0.000	0.000
0.510	0.570	0.620	0.000	0.000	0.000	0.000	0.000
0.970	0.570	0.560	0.000	0.000	0.000	0.000	0.000
0.520	0.620	0.720	0.000	0.000	0.000	0.000	0.000
0.060	0.620	0.620	0.000	0.000	0.000	0.000	0.000
0.510	0.990	0.660	0.000	0.000	0.000	0.000	0.000
0.000	0.540	0.650	0.000	0.000	0.000	0.000	0.000
0.000	0.580	0.570	0.000	0.000	0.000	0.000	0.000
0.000	0.820	0.670	0.000	0.000	0.000	0.000	0.000
0.000	0.650	0.490	0.000	0.000	0.000	0.000	0.000
0.000	0.760	0.650	0.000	0.000	0.000	0.000	0.000
0.000	0.000	0.630	0.000	0.000	0.000	0.000	0.000
0.000	0.000	0.680	0.000	0.000	0.000	0.000	0.000
0.000	0.000	0.620	0.000	0.000	0.000	0.000	0.000
0.000	0.000	0.720	0.000	0.000	0.000	0.000	0.000
0.000	0.000	0.590	0.000	0.000	0.000	0.000	0.000

Appendix 4a

In this test, I will be using the television screen in front of you. On it will be displayed some letters of the alphabet being presented one at a time. Let me show you the letters. Watch the TV screen and read aloud the letters being displayed.

Present letters: A, V, P, C, X, E, Z, J, U, B, W, D, Y, F, O, U.

Very good. When we begin the task, you will see on the screen either one, two or three letters. The letters will be presented one at a time. There will never be more than three letters being displayed for you to learn. Your task is to remember these letters.

You will be wearing these headphones. After the last letter to be learned has been presented (remember, it can be either one, two or three letters), you will hear a "tone". This sound tells you that a letter will be displayed on the screen. Your task is to tell me as quickly as possible whether that letter is one you have learned. If it is, you will say the word 'yes' as quickly as possible; and if it is not, you will answer with the word "no", again as quickly as possible.

Let me go over these instructions again before we do a practice trial.
First, you will see either one, two or three letters being displayed one at a time. You will learn these in silence. Then you will hear a sound coming from these headphones you will be wearing. This tells you that a test is coming. After the sound, a letter will appear on the screen. Your task is to tell me, as quickly as you can, with only the use of the words "yes" or "no" whether this letter was part of the letters you learned prior to the tone. After you have answered, you can forget the letters because I will give you others.

Let's do a practice trial. Put these headphones on your head and watch the screen. Tell me when you are ready to start by saying the word "Go" in the microphone.

Do not forget to give your answer -'yes' or 'no' as quickly as possible.

Appendix 4b

Dans cette t^ache, nous allons nous sevîr du téléviseur placé devant vous. Vous verrez apparaitre à l'écran des lettres de l'alphabet qui vous seront présentés une à la fois. Je vais maintenant vous montrer ces lettres. Regardez l'écran et lisez les lettres à haute voix à mesure qu'elles apparaissent.

Lettres présentées: A, V, P, Ç, X, E, Z, J, U, B, W, D, Y, F, O, U.

Très bien. Maintenant, lorsque nous commencerons la t^ache, vous verrez sur l'écran soit une, deux, ou trois lettres. Les lettres seront présentées une à la fois. Vous n'aurez jamais plus de trois lettres à apprendre. Votre t^ache est d'apprendre cette ou ces lettres.

Vous proterez ces écouteurs. Lorsque la dernière lettre sera présentée, (souvenez-vous, vous aurez une, deux ou trois lettres à apprendre) vous entendrez un son. Ce son vous indique qu'une lettre apparaitra sur l'écran. Votre t^ache est de me dire aussi vite que possible si cette lettre en est une que vous avez appris. Si elle l'est, vous direz "oui" aussi vite que possible; et si elle ne l'est pas, vous direz "non" aussi vite que possible.

Je vous répète les instructions une ature fois avant de vous donner quelques essais de pratique. D'abord, vous verrez soit une, deux ou trois lettres, qui vous seront présentées une à la fois. Vous les apprendrez en silence. Ensuite, vous entendrez un son provenant des écouteurs que vous porterez. Ce son vous informe qu'un test suit. Après le son, une seule lettre apparaitra sur l'écran. Votre t^ache est de me dire, aussi vite que possible, et seulement en utilisant les mots "oui" ou "non", si cette lettre en est une que vous avez appris. Lorsque vous aurez émis votre réponse, vous pourrez oublier ces lettres parce que je vous en donnerez de nouvelle.

Maintenant, faisons quelques essaies. Placez ces écouteurs sur votre t^ete et regardez l'écran attentivement. Informez-moi que vous ^etes pr^et(e), en utilisant le microphone devant vous, avec les mots "allez-y").

N'oubliez pas qu'il est important que vous répondiez avec les mots oui ou non aussi vite que possible.

APPENDIX 5a

Pool of words for the memory test

CATEGORY	WORD	CLUSTER
FRUIT	orange	8
	banana	8
	cherry	8
	peach	8
	pear	8
	lemon	8
	apple	8
	berry	8
ANIMALS	mouse	7
	camel	7
	skunk	7
	snake	7
	beaver	8
	moose	8
	horse	8
	tiger	8
FLOWERS	daisy	8
	orchid	8
	tulip	8
	violet	7
	poppy	-
	crocus	-
	lillies	-
	zinnia	-

MUSICAL INSTRUMENT	flute	8
	piano	8
	violin	8
	cymbal	7
	fiddle	7
	guitar	-
	organ	-
	trumpet	8
FURNITURE	broom	7
	bucket	7
	carpet	7
	kettle	7
	chair	8
	cradle	8
	pulpit	7
	stool	7
OCCUPATION	priest	8
	nurse	8
	lawyer	8
	coach	6
	judge	6
	banker	7
	dentist	7

Appendix 5b

Serie de mots a apprendre pour le test de memoire

CATEGORIE	MOTS	FREQUENCES
FRUIT	ananas	6
	banane	30
	cerise	6
	peche	47
	citron	104
	fraise	11
	prune	2
	raisin	12
ANIMAL	lievre	42
	cheval	67
	dinde	6
	singe	48
	agneau	101
	pivoine	11
	glaieul	144
	zinnia	28
FLEUR	tulipe	22
	muguet	3
	lilas	5
	jasmin	1
	pensee	85
	pivoine	-
	glaieul	-
	zinnia	-

INSTRUMENT DE MUSIQUE	guitare	11
	cymbale	2
	harpe	-
	orgue	4
	violon	7
	tambour	20
	flute	4
	piano	32
OBJET MENAGER	lavabo	5
	lustre	2
	poele	73
	radio	5
	lavabo	5
	lustre	2
	poele	73
	radio	5
OCCUPATION	pilote	9
	commis	2
	police	78
	mineur	2
	pilote	9
	commis	2
	police	78
	mineur	2

APPENDIX 6a

Words for the free and cued recall task

CATEGORY	WORD	CLUSTER
FRUIT	orange	8
	banana	8
	cherry	8
	peach	8
ANIMALS	beaver	8
	moose	8
	horse	8
	tiger	8
FLOWERS	daisy	8
	orchid	8
	tulip	8
	violet	7
MUSICAL INSTRUMENT	flute	8
	piano	8
	violin	8
	cymbal	7
FURNITURE	chair	8
	cradle	8
	pulpit	7
	stool	7
OCCUPATION	priest	8
	nurse	8
	lawyer	8
	dancer	7

APPENDIX 6b

Mots pour le rappel libre et avec indice

CATEGORIE	MOTS	FREQUENCES
FRUIT	ananas	6
	banane	30
	cerise	6
	peche	47
ANIMAL	lievre	42
	cheval	67
	dinde	6
	singe	48
FLEUR	tulipe	22
	muguet	3
	lilas	5
	jasmin	1
INSTRUMENT DE MUSIQUE	violon	7
	tambour	20
	flute	4
	piano	32
OBJET MENAGER	lavabo	5
	lustre	2
	poele	73
	radio	5
OCCUPATION	pilote	9
	commis	2
	police	78
	mineur	2

APPENDIX 7a

Distractors for the recognition test

CATEGORY	WORD	CLUSTER
FRUIT	pear	8
	lemon	8
	apple	8
	berry	8
ANIMALS	mouse	7
	camel	7
	skunk	7
	snake	7
FLOWERS	poppy	-
	crocus	-
	lillies	-
	zinnia	-
MUSICAL INSTRUMENT	fiddle	7
	guitar	-
	organ	-
	trumpet	8
FURNITURE	broom	7
	bucket	7
	carpet	7
	kettle	7
OCCUPATION	coach	6
	judge	6
	banker	7
	dentist	7

Appendix 7b

Distracteurs pour le test de reconnaissance

CATEGORY	WORD	CLUSTER
FRUIT	citron	104
	fraise	11
	prune	2
	raisin	12
ANIMAL	agneau	101
	pivoine	11
	glaieul	144
	zinnia	28
FLEUR	pensee	85
	pivoine	-
	glaieul	-
	zinnia	-
INSTRUMENT DE MUSIQUE	guitare	11
	cymbale	2
	harpe	-
	orgue	4
OBJETS MENAGER	poelon	1
	chaise	385
	tapis	44
	table	245
OCCUPATION	avocat	105
	clerc	3
	soldat	170
	pretre	288

APPENDIX 8a

Randomization of Words Within List 1

1	2	3	4	5	6	7	8
cherry	cherry	tiger	tiger	banana	chair	tiger	peach
horse	banana	peach	orange	tiger	tiger	pulpit	cradle
peach	horse	chair	moose	chair	pulpit	chair	horse
tiger	chair	banana	peach	orange	peach	peach	stool
banana	orange	horse	beaver	horse	beaver	beaver	orange
chair	beaver	cherry	chair	pulpit	banana	banana	banana
stool	pulpit	moose	cradle	beaver	orange	orange	moose
cradle	cradle	stool	horse	peach	cradle	cradle	chair
pulpit	stool	orange	stool	cradle	moose	moose	pulpit
beaver	peach	cradle	cherry	moose	cherry	stool	cherry
moose	tiger	beaver	banana	stool	stool	horse	tiger
orange	moose	pulpit	pulpit	cherry	horse	cherry	beaver

9	10	11	12	13	14	15	16
chair	banana	chair	beaver	moose	tiger	cherry	banana
moose	cradle	tiger	banana	cradle	beaver	stool	pulpit
cherry	pulpit	cherry	cradle	cherry	moose	cradle	moose
horse	stool	pulpit	orange	pulpit	peach	chair	peach
orange	horse	banana	cherry	banana	stool	orange	banana
stool	peach	peach	stool	peach	horse	moose	cradle
tiger	moose	moose	tiger	stool	cherry	pulpit	horse
pulpit	chair	stool	moose	tiger	pulpit	tiger	chair
cradle	cherry	horse	horse	beaver	banana	beaver	cherry
peach	orange	orange	chair	orange	chair	banana	stool
banana	tiger	beaver	peach	chair	cradle	horse	orange
beaver	beaver	cradle	pulpit	horse	orange	peach	tiger

17	18	19	20
banana	pulpit	stool	orange
pulpit	cradle	horse	cradle
beaver	peach	cradle	tiger
cherry	horse	peach	stool
moose	cherry	banana	chair
chair	beaver	tiger	beaver
horse	tiger	beaver	horse
tiger	orange	moose	banana
orange	moose	cherry	moose
stool	banana	orange	pulpit
cradle	stool	pulpit	peach
peach	chair	chair	cherry

APPENDIX 8b

Randomization of Words (French List) Within List 1

1	2	3	4	5	6	7	8
cerise	cerise	radio	radio	banane	lievre	radio	peche
poele	banane	peche	ananas	radio	radio	dinde	cheval
peche	poele	lievre	poele	lievre	dinde	lievre	poele
radio	lievre	banane	peche	ananas	peche	peche	singe
banane	ananas	poele	lavabo	poele	lavabo	lavabo	ananas
lievre	lavabo	cerise	lievre	dinde	banane	banane	banane
singe	dinde	lustre	cheval	lavabo	ananas	ananas	lustre
cheval	cheval	singe	poele	peche	cheval	cheval	lievre
dinde	singe	ananas	singe	cheval	lustre	lustre	dinde
lavabo	peche	cheval	cerise	lustre	cerise	poele	cerise
lustre	radio	lavabo	banane	singe	singe	singe	radio
ananas	lustre	dinde	dinde	cerise	poele	cerise	lavabo

9	10	11	12	13	14	15	16
lievre	banane	lievre	lavabo	lustre	radio	cerise	singe
lustre	cheval	radio	banane	cheval	lavabo	singe	cheval
cerise	dinde	cerise	cheval	cerise	lustre	cheval	lustre
poele	singe	dinde	ananas	dinde	peche	lievre	ananas
ananas	poele	banane	cerise	banane	singe	ananas	dinde
singe	peche	peche	singe	peche	poele	lustre	poele
radio	lustre	lustre	radio	singe	cerise	dinde	lavabo
dinde	lievre	singe	lustre	radio	dinde	radio	cerise
cheval	cerise	poele	poele	lavabo	banane	lavabo	poele
peche	ananas	ananas	lievre	ananas	lievre	banane	lievre
banane	radio	lavabo	peche	lievre	cheval	poele	banane
lavabo	lavabo	cheval	dinde	poele	ananas	peche	radio

17	18	19	20
dinde	lustre	banane	dinde
lustre	singe	dinde	cheval
banane	poele	lavabo	peche
lavabo	peche	cerise	poele
poele	banane	lustre	cerise
ananas	dinde	lievre	lavabo
cerise	radio	poele	radio
radio	lievre	radio	ananas
lievre	cerise	ananas	lustre
singe	lavabo	singe	banane
peche	ananas	cheval	singe
cheval	cheval	peche	lievre

APPENDIX 9b

Randomization of Words Within List 2

A	B	C	D	E	F	G	H
violet	violet	daisy	daisy	lawyer	orchid	daisy	dancer
nurse	lawyer	dancer	tulip	daisy	daisy	cymbal	flute
dancer	nurse	orchid	priest	orchid	cymbal	orchid	nurse
daisy	orchid	lawyer	dancer	tulip	dancer	dancer	piano
lawyer	tulip	nurse	violin	nurse	violin	violin	tulip
orchid	violin	violet	orchid	cymbal	lawyer	lawyer	lawyer
piano	cymbal	priest	flute	violin	tulip	tulip	priest
flute	flute	piano	nurse	dancer	flute	flute	orchid
violin	piano	tulip	piano	flute	priest	priest	cymbal
priest	dancer	flute	violet	priest	violet	nurse	violet
tulip	daisy	violin	lawyer	piano	piano	piano	daisy
cymbal	priest	cymbal	cymbal	violet	nurse	violet	violin

I	J	K	L	M	N	O	P
orchid	lawyer	orchid	violin	priest	daisy	violet	piano
priest	flute	daisy	lawyer	flute	violin	piano	flute
violet	cymbal	violet	flute	violet	priest	flute	priest
nurse	piano	cymbal	tulip	cymbal	dancer	orchid	tulip
tulip	nurse	lawyer	violet	lawyer	piano	tulip	cymbal
piano	dancer	dancer	piano	dancer	nurse	daisy	nurse
daisy	priest	priest	daisy	piano	violet	priest	violin
cymbal	orchid	piano	priest	daisy	cymbal	cymbal	violet
flute	violet	nurse	nurse	violin	lawyer	violin	dancer
dancer	tulip	tulip	orchid	tulip	orchid	lawyer	orchid
lawyer	daisy	violin	dancer	orchid	flute	nurse	lawyer
violin	violin	flute	cymbal	nurse	tulip	dancer	daisy

Q	R	S	T
cymbal	priest	lawyer	cymbal
priest	piano	cymbal	flute
lawyer	nurse	violin	dancer
violin	dancer	priest	nurse
nurse	lawyer	orchid	violet
tulip	cymbal	nurse	violin
violet	daisy	daisy	daisy
daisy	orchid	tulip	tulip
orchid	violet	piano	priest
piano	violin	fluce	lawyer
dancer	tulip	dancer	piano
flute	flute	violet	orchid

APPENDIX 9b

Randomization of Words (French) Within List 2

A	B	C	D	E	F	G	H
lilas	lilas	mineur	mineur	muguet	violon	mineur	jasmin
police	muguet	jasmin	tulipe	mineur	mineur	flute	tambour
jasmin	police	violon	commis	violon	flute	violon	police
mineur	violon	muguet	jasmin	tulipe	jasmin	jasmin	piano
muguet	tulipe	police	pilote	police	pilote	pilote	tulipe
violon	pilote	lilas	violon	flute	muguet	muguet	muguet
piano	flute	commis	tambour	pilote	tulipe	tulipe	commis
tambour	tambour	piano	police	jasmin	tambour	tambour	violon
flute	piano	tulipe	piano	muguet	commis	commis	flute
pilote	jasmin	tambour	lilas	commis	lilas	police	lilas
commis	mineur	pilote	muguet	piano	piano	piano	mineur
tulipe	commis	flute	flute	lilas	police	lilas	pilote

I	J	K	L	M	N	O	P
violon	muguet	violon	pilote	commis	mineur	lilas	piano
commis	tambour	mineur	muguet	tambour	pilote	piano	tambour
lilas	flute	lilas	tambour	lilas	commis	tambour	commis
police	piano	flute	tulipe	flute	jasmin	violon	tulipe
tulipe	police	muguet	lilas	muguet	piano	tulipe	flute
piano	jasmin	jasmin	piano	jasmin	police	commis	police
mineur	commis	commis	mineur	piano	lilas	flute	pilote
flute	violon	piano	commis	mineur	flute	mineur	lilas
tambour	lilas	police	police	pilote	muguet	pilote	jasmin
jasmin	tulipe	tulipe	violon	tulipe	violon	muguet	violon
muguet	mineur	pilote	jasmin	violon	tambour	police	muguet
pilote	pilote	tambour	flute	police	tulipe	jasmin	mineur

Q	R	S	T
flute	commis	muguet	flute
commis	piano	flute	tambour
jasmin	police	pilote	jasmin
pilote	jasmin	lilas	police
police	muguet	commis	lilas
tulipe	flute	violon	pilote
lilas	mineur	police	mineur
mineur	violon	mineur	tulipe
violon	lilas	tulipe	commis
piano	pilote	piano	muguet
muguet	tulipe	tambour	piano
tambour	tambour	jasmin	violon

APPENDIX 10

Order of List Presentation for the PD Group

Subject	List Order	Organisation Within List
1	1-2	1-A
2	2-1	B-2
3	1-2	3-C
4	2-1	D-4
5	1-2	5-E
6	2-1	F-6
7	1-2	7-G
8	2-1	H-8
9	1-2	9-I
10	2-1	J-10
11	1-2	11-K
12	2-1	L-12
13	1-2	13-M
14	2-1	N-14
15	1-2	15-O
16	2-1	P-16
17	1-2	17-Q
18	2-1	R-18
19	1-2	19-S
20	2-1	T-20

* CODE: List 1: numerical
List 2: alphabetical

APPENDIX 11

Order of List Presentation for the SDAT Group

Subject	List Order	Organisation Within List
1	2-1	T-20
2	1-2	19-S
3	2-1	R-18
4	1-2	17-Q
5	2-1	P-16
6	1-2	15-O
7	2-1	N-14
8	1-2	13-M
9	2-1	L-12
10	1-2	11-K
11	2-1	J-10
12	1-2	9-I
13	2-1	H-8
14	1-2	7-G
15	2-1	F-6
16	1-2	5-E
17	2-1	D-4
18	1-2	3-C
19	2-1	B-2
20	1-2	1-A

APPENDIX 12

Order of List Presentation for the NC Group

Subject	List Order	Organisation Within List
1	1-2	12-L
2	2-1	M-13
3	1-2	14-N
4	2-1	O-15
5	1-2	16-P
6	2-1	Q-17
7	1-2	18-R
8	2-1	S-19
9	1-2	20-T
10	2-1	A-1
11	1-2	2-B
12	2-1	C-3
13	1-2	4-D
14	2-1	E-5
15	1-2	6-F
16	2-1	G-7
17	1-2	8-H
18	2-1	I-9
19	1-2	10-J
20	2-1	K-11

APPENDIX 13a

Instructions: Memory Paradigm

Condition A

Learning Phase

I am going to give you a list of words that I want you to learn. The words are going to be projected one at a time on the wall infront of you. I want you to read each word aloud as it appears. I also want you to remember the words because after they have been all presented I will ask you to recall them. Now, watch carefully and learn the following words.

Recall Phase

Turn the sheet in front of you and write on the blank lines as many of the words as you can remember. Write the words in any order.

or

I will write for you all the words that you can remember. Tell me the words you can recall in any order.

(Please take a few more seconds and see if you can remember more words.)

Then,

You will notice that some words are printed on it. These words represent the categories to which the words you have learned belong. Go over each of these and see if you can remember the words you have just learned. Write all the words you can remember including those you have already written

(Please take a few more seconds to recall.)

or

I will write for you all the words that you can recall.

Then,

Here is a list of words. I want you to read each of the words and underline those that were in the list you learned.

Condition B

Learning phase

I am going to give you a new list of words that I want you to learn. This time, the presentation of the words will be different from the other. I will tell you before hand the categories to which belong the words you are to learn, that is how the words may be grouped together. For example, if I tell you that the words to learn belong to the category "game" the words could be card, bingo, etc.

Now I will present you the list of words. Pay attention and learn them because you will have to recall the words when I am finished. Again, I want you to read each word aloud as it is projected. All the words you will learn fit into one of the three following categories: _____, _____, _____. Here is a sheet with the three categories. If during the presentation you forget what they are, you can check on the sheet.

Recall Phase

Same as for first presentation

Appendix 13b

Instructions française pour le test de mémoire

Condition A

Phase d'apprentissage

Je vais vous présenter une liste de mots que vous devrez apprendre. Les mots seront projetés un à la fois sur le mur en face de vous. Je veux que vous lisiez chaque mot à haute voix à mesure qu'ils apparaissent sur le mur. Je veux aussi que vous appreniez ces mots parce que je vais vous demander de vous les rappeler. Maintenant, portez attention et apprenez les mots suivants.

Phase de rappel

Tournez la feuille de réponse qui est placée devant vous et écrivez sur les lignes autant de mots que vous pouvez vous rappeler. Ecrivez les dans n'importe quel ordre.

(Prenez un peu plus de temps).

ou

Je vais écrire pour vous les mots dont vous pouvez vous rappeler. Dites les moi dans n'importe quel ordre.

Ensuite,

Passez à la feuille suivante placée devant vous. Vous noterez que certains mots sont imprimés sur la feuille. Ces mots représentent les catégories auquelles appartiennent les mots que vous avez appris. Lisez ces mots et essayez de vous souvenir des mots que vous venez d'apprendre.

(Prenez un peu plus de temps).

Encore un fois je vais écrire les mots pour vous.

Condition B

Voici une nouvelle liste de mots que vous devez apprendre. Cette fois-ci, la présentation des mots sera différente de la précédente. Je vais vous dire avant de commencer les catégories auquelles appartiennent les mots à apprendre. Par exemple, si je dis que les mots à apprendre appartiennent à la catégorie "jeu", les mots pourraient être carte, bingo, etc. Voici la liste de mots. Portez attention et apprenez les parce que vous devrez vous les rappeler. Encore une fois, je vous demande de lire chaque mot à haute voix. Tous les mots que vous apprendrez font parties des catégories suivantes: , , et . Voici une carte avec les trois catégories. Vous pourrez la consulter si vous oubliez ces mots lors de la préentation.

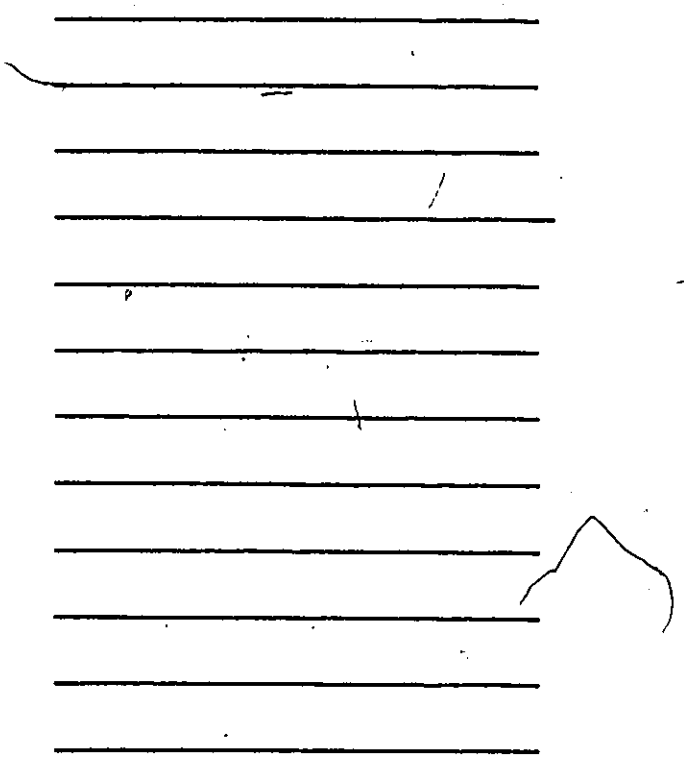
Phase de rapel:

Suivre les instructions pour Condition A

Reconnaissance (pour Condition A et B)

Voici une liste de mots. Je veux que vous lisiez chacun des mots et que vous soulignez ceux qui etaient sur la liste apprise.

APPENDIX 14

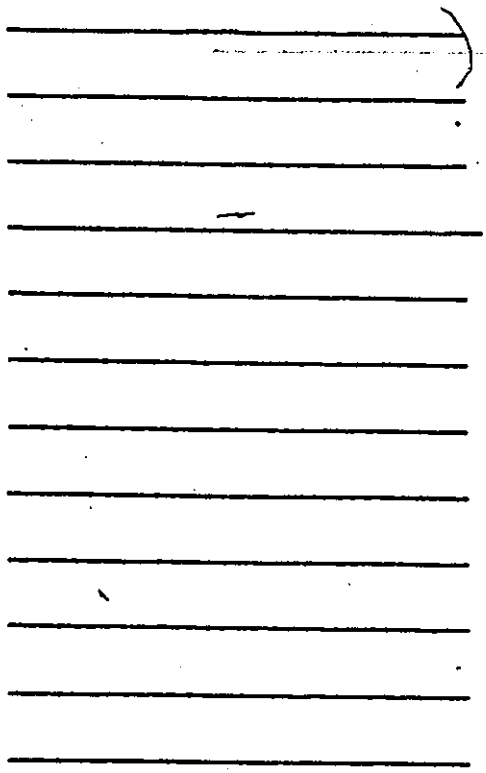


APPENDIX 15a

FRUIT

ANIMAL

FURNITURE



APPENDIX 15b

FLOWER

MUSICAL INSTRUMENT

OCCUPATION

APPENDIX 16a

FRUIT

OBJET DE MAISON

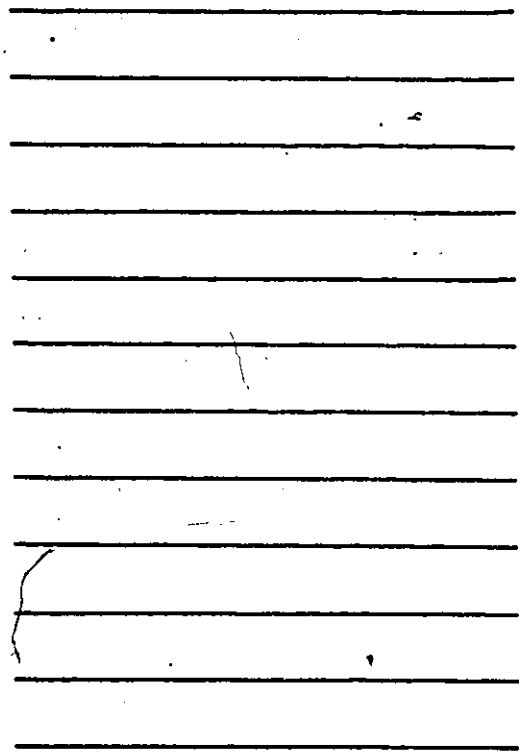
ANIMAL

APPENDIX 16b

FLEUR

INSTRUMENT DE MUSIQUE

OCCUPATION



APPENDIX 17a

Please underline the words that you remember to be from the list you have just learned

---

ORCHID

PIANO

CROCUS

PRIEST

DENTIST

GUITAR

NURSE

POPPY

BANKER

TULIP

CYMBAL

FIDDLE

VIOLET

ZINNIA

ORGAN

LILLIES

FLUTE

TRUMPET

DAISY

VIOLIN

JUDGE

LAWYER

COACH

DANCER

APPENDIX 17b

Please underline the words that you rememember to be from the list you have just learned

---

BANANA

CRADLE

LEMON

BEAVER

SNAKE

BUCKET

MOOSE

PEAR

SKUNK

CHERRY

STOOL

BROOM

PEACH

BERRY

CARPET

APPLE

CHAIR

KETTLE

ORANGE

PULPIT

CAMEL

HORSE

MOUSE

TIGER

APPENDIX 18a

Veuillez souligner les mots dont vous vous souvenez avoir appris dans la première liste

---

MUGUET

TAMBOUR

PIVOINE

PILOTE

PRETRE

CYMBALE

COMMIS

PENSEE

SOLDAT

LILAS

PIANO

GUITARE

JASMIN

ZINNIA

HARPE

VIOLON

ORGUE

TULIPE

FLUTE

COCHON

CLERC

POLICE

AVOCAT

MINEUR

GLAIEUL

APPENDIX 18b

Veuillez souligner les mots dont vous vous souvenez avoir appris dans la première liste

BANANE

LUSTRE

FRAISE

LIEVRE

LAPIN

CHAISE

CHEVAL

CITRON

POULE

CERISE

RADIO

POELON

PECHE

RAISIN

TAPIS

PRUNE

LAVABO

TABLE

ANANAS

COCHON

POELE

AGNEAU

SINGE

DINDE

APPENDIX 19a

FLOWER

MUSICAL INSTRUMENT

OCCUPATION

APPENDIX 19b

FRUIT

ANIMAL

FURNITURE

APPENDIX 20a

FLEUR

INSTRUMENT DE

MUSIQUE

OCCUPATION

FRUIT

ANIMAL

OBJET DE MAISON

APPENDIX 21

Recall positive increment from free recall to cued recall

$$\frac{\text{\# of correct words gained from FR to Cr}}{\text{\# of words missed at FR}} \times 100$$

Recall negative increment from free recall to cued recall

$$\frac{\text{\# of correct words lost from FR to CR}}{\text{\# of words recalled in FR}} \times 100$$

APPENDIX 22

Recognition discriminability and response bias (nonparametric).

Discriminability = [1 - (Misses + False Alarms) / 44] X 100%

Response biais = (Misses - False Alarms) / (Misses + False Alarms)

Note: A value of "1" is substituded for an obtained zero value for Misses and/or False Alarms to avoid division by zero.

From Delis, Kramer & Ober, 1985 (Preliminary Manual)