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MEMORY FUNCTIONS IN PATIENTS WITH PARKINSON'S DISEASE

by

MARJATTA HÄMÄLÄ, M.A.

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

Doctor of Philosophy
Department of Psychology

Carleton University

Ottawa, Ontario

April 27, 1990

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ABSTRACT

Memory impairment is frequently reported as being a feature in the profile of cognitive changes in Parkinson's disease, although it is not fully understood exactly which processes are involved. Studies of patients with memory disorders have indicated that memory is not a unitary phenomenon. Instead specific brain regions may be associated with certain aspects of memory functioning. Consequently, it is suggested that deficits in memory functioning in different neurological diseases depend both on etiological factors and on the location of the pathological changes in the brain. Twenty parkinsonian patients and twenty age- and education-matched controls were compared on cognitive and memory tests purported to evaluate those aspects of memory which have been previously associated specifically either with subcortical structures or the frontal lobes.

Results of this study showed that subtle, but qualitatively distinct set of memory alterations in Parkinson's disease may occur even in patients with no gross intellectual impairments. Memory impairments, however, appeared to be more memory-related processing deficits than failure in memory function itself, although overall, Parkinson's patients performed less well than control subjects. Parkinsonian patients had major difficulties in accessing semantic information. In semantic memory tasks this deficit could be seen particularly as an impairment in search of categorical information.

Corresponding deficit also appeared in episodic memory tasks and in some cognitive tasks as a failure in initiation of processing. The degree of processing deficits seemed to depend on the amount of effort the tasks involved. In the situations, in which mental flexibility and effortful processing were needed, obvious difficulties arose. This could be observed in increasing effects of interference in executive tasks (perseverative errors) and in memory tasks (intrusions). In cognitively less demanding situations, in which processing is more automatic, parkinsonian patients performed relatively well even when confronting interference. In the PI-release task they were able to organize semantic information and resist interference (release from PI) almost as well as controls. In procedural memory task, on the other hand, parkinsonian patients were slower than controls to learn the new skill even if they were able to recognize and remember the information well.

In general, the pattern of memory and cognitive alterations was compatible with the pattern seen in other, primarily subcortical diseases. Most clearly, the deficits resembled those described in frontal patients, but did not entail all reported symptoms. These findings indicate that in Parkinson's disease some basal ganglia - frontal lobe connections may be more involved than others and produce characteristic symptoms.

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I INTRODUCTION

1. Motor Symptoms

Parkinson's disease is a neurodegenerative disorder involving primarily the substantia nigra, which forms a part of the basal ganglia. This disorder is characteristically defined by a triad of symptoms, tremor at rest, muscular rigidity and hypokinesia (Adams and Victor, 1989). The latter may include difficulty in the initiation of movements (akinesia) or slowness in their execution (bradykinesia). Different motor symptoms may manifest themselves as difficulties in gait (e.g. march-a-petit pas; unsteady, shuffling walking), postural disturbances (e.g. stooped postures), and hypomimia due to blankness of facial expression and lack of blinking (masked face; Fahn, 1989).

The onset of the disease is gradual and the course is always progressive, although there are large individual differences in appearance, and developmental rate of symptoms (Barbeau, 1986). The disease process can best be described using a 5 point rating scale

developed by Hoehn and Yahr (1967). Patients in Stage I generally have tremor, rigidity and/or motor slowing often on one side of the body. In Stage II, symptoms appear bilaterally with increasing severity, in Stage III postural instability is evident in addition, in Stage IV patients are severely disabled, but can still walk, until in the final stage, Stage V, walking becomes impossible and patients are confined to a wheelchair or bed. All present therapies are effective palliative treatments, none cure the disease.

Difficulties in daily living (e.g. in dressing, eating, and taking care of personal hygiene) caused by motor symptoms are usually the reasons why patients seek medical help. Diagnosis depends entirely on clinical criteria and is based on the thorough evaluation of the patient's symptoms on neurological examination. There is no laboratory test at this time specific enough to confirm or disconfirm the diagnosis (Stern and Lees, 1982).

Parkinson's disease is primarily a disease of middle and old age. Three quarters of all parkinsonian patients develop the disease between the fifth and sixth decade

(Koller et al., 1986). Incidence rates derived from different epidemiological surveys approximate 20 new cases per 100 000 per year (Schoenberg, 1987). After the age of 30-40 years, incidence rates increase with age, but start to decline after the age of 75 (Schoenberg, 1987). The average length of the disease has increased over the years, now being approximately 9 - 14 years. The duration, however, can vary greatly and in individual cases can be much longer (Mayeaux et al., 1981). At the same time, especially with the development of effective symptomatic medication, the mortality rates have decreased as well (Diamond et al., 1987).

James Parkinson was the first to describe the symptoms of the disease named after him (Parkinson, 1817). Although the motor concomitants of the disease are now well understood, causal factors remain elusive. However, the appearance of parkinsonian symptoms as a secondary sequelae after various etiologies, are well documented. Parkinsonian symptoms may appear after a history of encephalitis, as a consequence of a long-term neuroleptic treatment (e.g. dopamine receptor blockers or dopamine storage depletors), and after intoxication with

industrial poisons (e.g. carbon monoxide poisoning or poisoning with some metals; Fahn, 1989). Nevertheless, the majority of parkinsonian patients suffer from the idiopathic variant (Jellinger, 1986). Genetic hypotheses have been considered as a cause for the idiopathic disease, but present evidence is not strong enough to make firm conclusions (Duvoisin, 1986).

Motor symptoms resemble in many ways changes seen in normal aging, and another, unproven assumption has been that the disease arises as a consequence of premature or accelerated aging (Albert, 1978). Recent findings, that some drug abusers develop symptoms similar to those seen in Parkinson's disease after taking synthetic heroin (1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine, i.e. MPTP) intravenously (Stern and Langston, 1985), have led to the third assumption that environmental factors may play an important role (Barbeau et al., 1986). None of these three hypotheses has been confirmed to date: in fact some researchers have gone further and assume that the disease is multifactorial, involving both internal and external factors acting against a background of normal aging and genetic susceptibility (Barbeau et al., 1986).

2. Mental Status

Among the most controversial issues concerning Parkinson's disease has been the question whether the disease causes the appearance of cognitive disability. James Parkinson characterized the disease by its motor symptoms only and stated categorically that "intellect and senses" remain intact (Parkinson, 1817). However, there is increasing evidence that there are indeed changes in mentation, either psychiatrically or cognitively based or both. In his literature review, Boller (1980) concludes that virtually all of the research carried out since 1970, has reported some mental changes in these patients in addition to motor dysfunction and currently, it is generally accepted that cognitive changes among parkinsonian patients occur more often than in the general population (Boller, 1980).

There are several possible explanations why mental changes, especially mild ones, went unnoticed. Before the development of adequate treatment, the more severe motor disturbances associated with the disease tended to overshadow any cognitive deterioration (Albert, 1978).

When the control of motor symptoms improved with medication, the milder cognitive changes emerged more clearly. On the other hand, it is possible that medication itself can have either beneficial or adverse effects in cognitive functions. Recent studies (Mohr et al., 1987, 1989) have shown that slight cognitive improvement may indeed be associated with drug therapy, but these changes may not affect all cognitive functions similarly (Mohr et al., 1989). Whether such treatment is beneficial in some functions but not in others, may depend on the underlying pathology involved in different functions.

Even if the occurrence of mental changes in Parkinson's disease is acknowledged, considerable differences of opinion still exist concerning the incidence, extent, intensity, and specific nature of such changes.

Estimates of actual dementia, the most serious intellectual change, have varied greatly in past studies ranging from under 10 % to over 80 % (Boller, 1980; Marttila and Rinne, 1976; Brown and Marsden, 1984). The wide range depends on the population included, on the

definition of dementia and on the methods used to evaluate mental status (Brown and Marsden, 1984). Inclusive criteria for selecting patients has an effect on the results of epidemiological work. Studies which cover all Parkinson's patients, regardless of the cause of the symptoms, have generally reported higher incidence rates for dementia. Disease which appears after a history of encephalitis leads to dementia more often than the idiopathic form of the disease (Marttila and Rinne, 1976). The lack of universally accepted criterion for dementia classification and the great variation in those used, may also have affected results. Finally, some studies have used only a bedside evaluation of mental changes, instead of thorough assessment of mental capabilities making empirical evaluation difficult (Brown and Marsden, 1984).

According to Brown and Marsden (1984) dementia estimates in past studies are too high. After re-evaluating the estimates taking into consideration only those studies that specify a diagnosis of idiopathic Parkinson's disease and use of special rating scale for dementia (e.g. the "mini mental state examination by

Folstein et al., 1975), they concluded that an average incidence rate of dementia in idiopathic disease is approximately 25 %.

Changes in mood, particularly depression, are often noted in parkinsonian patients (Taylor et al., 1986; Mayeaux et al., 1981, 1983; Gotham et al., 1986), which further complicates the evaluation of dementia in these individuals. Depression may disrupt cognitive functions, especially memory, which of course serves as the criterion measure for dementia. Although some studies have found depression to be related to the level of cognitive impairment (Mayeaux et al., 1981), this relationship is far from simple. Comparison of the parkinsonian patients and those with endogenous depression on certain memory tests has shown that regardless of the severity of depression, Parkinsonians tend to perform better than endogenously depressed subjects (Taylor et al., 1986). It is possible that the quality of depression is different in these two groups. Depressive affect seen in Parkinson's patients may be explainable partly as a reaction to the disabling consequences of chronic disease interacting with changes

in mood state, which is intrinsic to the disease (Taylor et al., 1986).

The fact that dementia does not always go along with Parkinson's disease, has led to speculations that two subgroups of Parkinsonians exist: one with and another without dementia (Lieberman et al., 1979; Boller, 1980; Celesia and Wanamaker, 1972; Garron et al., 1976; Marttila and Rinne, 1976). Attempts have been made to systematically delineate specific characteristics which make some patients more prone to develop dementia than others, but findings have been inconsistent to date.

In fact, certain evidence suggests that instead of two groups defined by the absence or the presence of dementia, there may be a continuum of cognitive deficits in individual patients varying from relatively intact intellectual functioning to severe dementia (Pirozzolo et al., 1982). Furthermore, it seems that nearly all Parkinson's patients show some kind of cognitive deficit compared to age- and education-matched controls (Mohr et al., in Press; Pirozzolo et al., 1982). This view corroborates clinical observations that a number of subtle cognitive changes may occur even in those patients

who are intellectually less impaired (Lees and Smith, 1983). It seems that selective cognitive impairment occurs even in patients with a high premorbid intellectual level, who continue to hold demanding professional positions (Mohr et al., in Press). This issue is of critical importance because with improving medication for motor symptoms and increasing life expectancy, Parkinsonians are able to continue longer in worklife. These individuals thus can best be helped, if the quality of potential cognitive deficits is understood and they can be made aware of specific difficulties they may meet and be advised about possible compensatory strategies.

3. Pathological Changes

Neuroanatomically, the major pathology in Parkinson's disease involves structures of the basal ganglia and their projections. Idiopathic parkinsonism is characterized by cell loss, reactive gliosis, and depigmentation in the substantia nigra, the locus coeruleus, the dorsal nucleus of the vagus and the

substantia innominata (Barbeau, 1986). Although the primary pathology in Parkinson's disease is in subcortical structures, it is possible that the pathological changes extend beyond their limits and can, thereby, cause functional changes similar to those seen in some cortical areas. Several authors (Albert et al., 1974; Albert, 1978; Lees and Smith, 1983; Taylor et al., 1986, 1988) have suggested that particularly the basal ganglia - frontal lobe interactions may be of crucial importance in the pathology of Parkinson's disease. According to this view, the close anatomical and physiological interconnections between the basal ganglia, selected nuclei of the thalamus, and the frontal cortex may lead to lesions anywhere in this system disrupting functions of the entire circuit (Albert, 1978).

The basal ganglia connections were for a long time poorly understood, but during the past decade much new information has been accumulated (Alexander et al., 1986). Earlier work revealed that the basal ganglia receive input from the cortex, thalamus and some brain stem structures and project mainly to the thalamus (Cote, 1982; Grofova, 1979). An even more sophisticated model

has recently been suggested (Alexander et al., 1986). This model forwards the concept that in cortical areas the main basal ganglia outputs are transmitted to at least five restricted portions of the frontal cortex: motor, oculomotor, prefrontal dorsolateral, lateral orbitofrontal, and the anterior cingulate circuits (see Figure 1). At the subcortical level, these circuits involve discriminate, essentially non-overlapping parts of the striatum, globus pallidus and substantia nigra.

In addition to subcortical deficits, various non-specific changes such as Lewy-bodies and different types of senile alterations have also been associated with parkinsonian pathology. Neurofibrillary tangles, senile plaques, and granulovacuolar degeneration have been noted more often in parkinsonian patients than in age-matched controls (Boller et al., 1980; Hakim and Mathieson, 1979). These alterations, however, can also be seen in normally functioning individuals without any other pathological changes (Perry et al., 1978) and it is still uncertain whether they play any important part. Cerebral atrophy is another cortical change which has been observed in some parkinsonian patients (Sroka et al.,

Figure 1

Suggested cortical targets of basal output. Schematic illustration of the five cortical areas that contribute to the "closed loop" portions of the basal-ganglia thalamocortical circuits (Alexander et al., 1986).

ACA: anterior cingulate area; APA: arcuate premotor area, DLC: dorsolateral prefrontal cortex, FEF: frontal eye fields, ITG: inferior temporal gyrus, LOF: lateral orbitofrontal cortex, MC: motor cortex, PPC: posterior parietal cortex, SC: somatosensory cortex, SMA: supplementary motor cortex, STG: superior temporal gyrus

1981; Portin et al., 1982; Schneider et al., 1979), but it is still uncertain whether atrophy is intrinsic to the disease.

Neurochemically, Parkinson's disease has been characterized by a severe deficiency of dopamine levels in the substantia nigra (particularly the pars compacta) related to the neuronal degeneration in this area. Substantia nigra striatal projections also tend to decrease the level of dopamine in the striatum (caudate and putamen) and in the globus pallidus (Agid et al., 1987). When the first parkinsonian symptoms appear, at least 70 % of the nigrostriatal system is already damaged and presynaptic dopaminergic hyperactivity becomes insufficient for maintenance of dopaminergic neural transmission (Agid et al., 1989). Other, but not all dopaminergic pathways in the brain may be involved in the pathology (the hypothalamic, mesolimbic, and mesocortical pathways; Figure 2; Agid et al., 1989). At present, it would seem that the descending dopamine system to the lumbar spinal cord is spared in the disease (Agid et al., 1987).

Figure 2

Schematic representation of the central dopaminergic systems in Parkinson's disease. Broken lines: the nigrostriatal, the mesocorticolimbic and the hypothalamic systems degenerate in Parkinson's disease (Agid et al, 1989).

ACC: nucleus accumbens, CX: prefrontal cortex, CN: caudate nucleus, HIP: hippocampus, HT: hypothalamus, PU: putamen, SNC: substantia nigra, VTA: ventral tegmental area.

In addition to dopamine deficiency, other transmitter abnormalities may also appear in the Central Nervous System (CNS) of affected patients (Agid et al., 1989). Pathological changes have been observed in the locus coeruleus, which provides noradrenergic innervation to the limbic areas of the cortex (Cote, 1982) particularly the frontal cortex (Mohr et al., 1987); in the nucleus basalis of Meynert which provides cholinergic innervation to the frontal cortex and hippocampus (Coyle et al., 1983; Perry et al., 1985); and in serotonergic raphe nuclei, which project to the frontal cortex (Cote, 1982). Disturbances in these transmitter systems, in addition to dopaminergic deficiencies, may well play a significant role in the mechanisms of mental deterioration in Parkinson's disease.

Further support for the involvement of other transmitter systems comes from the contradictory results in some recent regional metabolism and blood flow studies with new brain scanning techniques (single photon emission computed tomography, SPECT and ^{99m}Tc -HM-PAO, ^{99m}Tc -Hexamethylpropyleneamine, as a tracer). Although

nigrostriatal pathology in Parkinson's disease is well established and some studies have demonstrated a significant change in the uptake of HM-PAO in the caudate nucleus (Costa et al., 1988), other reports have not found relevant changes in these subcortical regions with these techniques (Pizzolato et al., 1988).

4. Treatment

After the demonstration of a dopamine deficiency as a primary cause for the appearance of motor symptoms, treatment of Parkinson's disease has targeted this transmitter either with dopamine precursors or dopamine agonists or other pharmacologic mechanisms (e.g. restoration of acetylcholine-dopamine homeostasis with artane). Dopamine precursors (e.g. levodopa) affect the synthesis of dopamine, while dopamine agonists stimulate the function of postsynaptic receptors (Agid et al., 1989).

However, even if the use of palliative treatment has greatly improved the quality of patients' lives by decreasing their motor symptoms, present medication does

not actually arrest the disease. Furthermore, despite the many beneficial effects, dopamine therapy has also some shortcomings, including dyskinesias, fluctuations in efficacy, and exacerbation of confusional states (Bergmann et al., 1986).

During dopamine therapy, many patients experience fluctuations in motor symptoms (rapid changes between akinesia and dyskinesia) when the effect of medication starts to wear off. The reason for these often unexpected changes is not known yet, but it is thought that they start at the stage in which postsynaptic dopamine receptors (specifically D2 receptors) increase in density in certain regions of the striatum (Agid et al., 1989). Motor symptoms clearly vary as a function of the "on"- "off" -states, but only slight changes in cognitive functions can be seen (Mohr et al., 1987, 1989; Delis et al., 1982).

In addition to short term wearing-off effects, it seems that after some years of successful treatment, the beneficial effects of dopaminomimetics often begin to fade (Portin and Rinne, 1980). The reason for this change is not fully understood, but it has been suggested

that the dopamine deficiencies induce hypersensitivity in the dopamine receptors, thereby exacerbating both motor and cognitive symptoms. Another explanation may be that rather than being dopamine induced, exacerbation of some symptoms, especially the cognitive ones, may depend on the appearance of other lesions in the brain (Agid et al., 1989).

Some earlier studies reported slight improvements in cognitive functions after long term levodopa treatment (Loranger et al., 1972; Bowen, 1976), but these were limited to the performance on relatively simple sensorimotor tasks (Bowen, 1976). However, alternative evidence was presented showing that after a slight initial improvement, cognitive functions in fact start to deteriorate (Portin and Rinne, 1980).

While a multitude of other drugs as well as combination therapies have been used in the palliative treatment of Parkinson's disease (e.g. symmetril, which is thought to affect both dopamine and serotonin systems; PDR, 1982), present therapeutic approaches most commonly include dopaminomimetics and/or anticholinergics. The use of the latter is based on the theory that these drugs

will help to return the disturbed balance between dopamine and acetylcholine in the nigrostriatal area (Stern and Lees, 1982). Anticholinergic medication, however may have some unwanted side-effects on cognition such as reduced efficacy in memory function observed in healthy volunteers with these components (Drachmann and Leavitt, 1974).

II CONCEPTS OF MEMORY

Several approaches have been taken in the attempt to understand memory functioning. Experimental research on normal memory has been of considerable heuristic value for the understanding of amnesic disturbances. Experimental research has concentrated on basic knowledge of the functional systems (i.e. processes involved in acquiring, storing, and recalling information). Various aspects of memory also may be neurochemically distinct (Squire and Cohen, 1984). In the following section, current views of memory functioning and their pathological substrates are outlined.

1. Models of Cognitive Processing in Memory Research in Amnesia

Experimental research pertaining to normal memory functioning employs several models. These have also been found useful in the study of impaired memory due to neurological disturbances, although no one satisfactory model has yet been identified. Their utility rests with

the fact that they offer the degree of specificity required to make fine discriminations among memory impairments in different neurological diseases. Furthermore, these models are based on information processing factors which allow the interpretation of data generated by neurological patients in the wider context of cognitive functioning, such as attentional factors.

The original models of memory function were structural (e.g. Craik, 1984), later ones emphasized more the processes involved in learning and remembering. These models suggest that information passes either in temporal sequences or via parallel processes through different memory stages from modality specific sensory memory to short term memory (immediate memory, primary memory) and long-term memory (recent memory) (e.g. Zechmeister and Nyberg, 1982). Memory stages separately differ primarily according to how information is encoded at acquisition and in the durability of the memory trace (Zechmeister and Nyberg, 1982). Control operations such as attention, rehearsal, and organization are posited to function in the transfer of material from one stage to another. Before remembering can occur, to-be-remembered

material must be properly encoded (trace formation, i.e. the internal process of the nervous system that converts the information about an experienced event, in a particular time, into an engram, or memory trace; Tulving, 1983), stored (the persistence of information over time), and then retrieved (the recovery and utilization of stored information).

Stage models advanced three basic hypotheses to explain memory disturbances: the encoding, consolidation (i.e. storage), and retrieval hypotheses. The encoding deficit hypothesis suggests that a failure to encode new information at the time of input results in a weak memory trace. The storage deficit hypothesis maintains that the memory trace erodes with the passage of time or as a result of other activity (interference) during the retention interval and consequently there is an inability to form new permanent memories. Finally, the retrieval hypothesis attributes amnesia to failure in the capacity to access information at the time of testing (Smith, 1980; Moscovitch, 1982).

The general aim of the earlier models was to break down the cognitive processes involved in memory into

components and to assess their characteristics and interrelations (Craik, 1984). More recent models, in contrast, approach the cognitive system from a more holistic perspective (Craik, 1984). Memory is seen as a continuous system rather than as occurring in stages. Intact memory would thus be an interactive system between encoding and retrieval processes and, consequently, memory deficit must be considered in terms of both of these processes (Schachter and Tulving, 1982).

These models also emphasize the ability of the subject to enhance memorization. Encoding and retrieval are not considered to be passive processes. With respect to encoding, the subject is viewed as actively elaborating the incoming information and relating it to his or her previous knowledge. Elaboration involves different strategies such as rehearsal, organization, imagery, and word meaning. Thus, "good" memorization depends, at least in part, on the subject's own efforts. Finally, such models place memory and learning within a contextual perspective and stress the role of perceptual (Craik and Lockhart, 1972; Jacoby, 1982), and attentional processes (Hasher and Zacks, 1979; Jacoby 1982). In

short, memory is considered in relation to other cognitive functions.

Some models which include attention as an explanatory factor, have assumed that an individual has a limited amount of attentional capacity and cognitive operations differ due to the degree of attention required (Hasher and Zacks, 1979). Accordingly, automatic processes represent one end of the continuum and in that they demand limited involvement of the attentional mechanism, and therefore, do not interfere with other cognitive activities to any great extent (Hasher and Zacks, 1979). At the other end of the continuum are effortful processes, which require more attentional capacity, and therefore, compete with other cognitive operations. Unlike automatic processes (i.e. spatial and temporal mechanisms in evaluating the frequency of occurrence), effortful processes (i.e. elaborative mnemonic activities) are intentional in the sense that a person must be aware of the learning experience. Accordingly, when attentional capacities are limited due to depression, high levels of arousal, or old age, more effortful processing suffers (Hasher and Zacks, 1979).

Tulving (1972) first suggested that memory can be conceptualized as two distinct systems, the episodic and semantic. Semantic memory is purported to involve the more cognitive aspects of memory such as knowledge of general facts, concepts, relations, and rules. It is also thought to include the internal lexicon (i.e. the conceptual lexicon for words) deemed necessary for efficient use of language (Moscovitch, 1979). Examples of the quality of semantic memory are such information as knowing the capital of Canada, the rules of how to behave in a restaurant, or the meaning of a word (Baddley, 1982). Semantic memory is usually measured using tasks that require acquired knowledge (i.e. information), vocabulary tasks which require use of lexicon (i.e. word recognition based on the ability to define words) or word fluency tasks which evaluate the availability of the words to their user (i.e. the access to semantic knowledge). Episodic memory, on the other hand, includes memory for events and personal experiences such as remembering meeting an old friend or remembering what was

eaten at breakfast (Baddley, 1982) and is measured with recall and recognition of both verbal and nonverbal material.

The basic difference between episodic and semantic memories is that while the former covers autobiographical information associated with specific events of episodes which provided that information (temporal relations of events), semantic memory combines new information with that already stored and thus allows the interpretation of incoming information (Zola-Morgan et al., 1983). Access to the structures of semantic memory is necessary for memorization of new information and semantic information grows through episodic experiences (Schachter and Tulving, 1982; Baddley, 1982). Episodic memory consumes attention (i.e. is more dependent on such factors as physical context, subjective state, and cognitive operations performed), while semantic memory seems to be less dependent on attention, to be more automatic (i.e. more independent of how the individual feels, and what he/she does, or did, about this information in any

previous context) (Kinsbourne and Wood, 1982). Accessing information from semantic memory would thus be generally automatic.

Retrieval of distant (remote) memories is a special case of long-term retrieval. This becomes evident especially in the study of amnesia. Amnesic patients may have difficulties in remembering events occurring prior to brain injury (retrograde amnesia) and for events occurring after the injury (anterograde amnesia). Although generally these concepts have not been considered in connection with the semantic-episodic distinction, it has been suggested that distant memories are normally retrieved primarily from semantic memory though they were originally part of episodic memory (Cermak, 1984). Accordingly, normal remote recall for distant decades would rely on semantic memory while more recent decades would tend to be retrieved from episodic memory.

The most recent addition to the concepts of memory are "declarative" and "procedural" memory. This distinction is based on the assumption that these two systems process two kinds of knowledge: knowing "that"

and knowing "how". Declarative knowledge represents facts, while procedural knowledge is described as a system of rules and methods of actions (Cohen and Squire, 1980). These concepts were born from the need to explain skill learning especially in cases of anterograde amnesia associated with hippocampal damage (case H.M.) and medial thalamic damage (Cohen and Squire, 1980). According to this approach, in learning a particular task, performance is first more dependent on attention-demanding declarative knowledge, but later, with practice, the process becomes less attention consuming and can be performed using procedural knowledge. Procedural knowledge consists of "cognitive skills" which include procedures and operations that are used to perceive and encode information, formulate rules and solve problems (Schachter and Tulving, 1983).

There have been several slightly different conceptualizations of procedural memory in the literature. Some authors include procedural memory as a part of semantic memory (e.g. Weingartner et al., 1984), while others have used procedural memory as an independent memory system (Cohen and Squire, 1980).

Semantic memory and episodic memory can be considered as both being substrates of declarative memory. Procedural memory and declarative memory would consequently be separate systems controlled by different areas of the brain (Cohen and Squire, 1980).

In summary, experimental research pertaining to normal memory function employs several cognitive models. Although there is no one simple model accepted by everyone, many have been adopted in neuropsychological approaches to memory research and have been found useful in describing the behavioral dissociations in the study of amnesia. Thus, for example, although experimental memory research with normals has not yet confirmed whether the episodic and semantic systems represent two functionally and structurally dissociable entities, most investigators accept this distinction in terms of the different types of information they process (Baddley, 1982; Moscovitch, 1979; Anderson and Ross, 1980; Tulving, 1983; Weingartner et al., 1984; Cohen and Squire, 1980). Conceptualizing memory within this framework in neurological diseases, seems appropriate because it

provides an opportunity to look at memory functions as a part of a wider cognitive impairment. Furthermore, studies of memory functions in amnesia strongly suggest that episodic and semantic memory may be differentially affected (Schachter and Tulving, 1982; Butters et al., 1983).

2. Neurological Substrates of Memory Disorders

The areas in the brain most frequently associated with memory functioning are the temporal lobes and surrounding structures. The four major areas involved are the hippocampal areas within the temporal lobes, the fornix, the mamillary bodies and the thalamus. They all form part of the limbic system and are interconnected (Parkin, 1984). Damage to those structures, whether it is caused by trauma, vascular incident, tumor, or other neurological disease, leads to amnesia with defective learning and retention of day-to-day events while leaving general cognitive functions, language and social skills relatively unimpaired.

Previously, primary amnesias were studied as a unitary disorder regardless of the location of pathology as long as it was anywhere in a circuit that included the hippocampal areas, fornix and mamillary bodies (Squire and Cohen, 1984). Evidence is increasing, however, which indicates that although all amnesic patients have a basic common deficit in their memory, there may be differences in some features of memory deficit as a function of the brain site involved (Parkin, 1984; Kinsbourne and Wood, 1975; Squire and Cohen, 1984). Consequently, different etiologies of amnesia may be expected to produce distinct amnesic syndromes depending on brain structures implicated (Squire and Cohen, 1984).

Those diseases in which the main lesions are in the limbic-diencephalic areas involving the dorsomedial nucleus of the thalamus and the mamillary bodies may form one group (Parkin, 1984). Damage to these structures seems to produce a deficit in the ability to acquire new information and to remember it even if the other cognitive abilities, immediate memory (measured by digit span) and semantic memory, are intact. Retrograde amnesia extends to cover many decades before the onset of

the injury, although it may be temporally graded (i.e. greatest in the recent time periods and smaller in more remote time periods; Cohen and Squire, 1981). The most common reason for damage to these areas is the alcoholic Korsakoff syndrome, but other cases with different etiology (e.g. penetrating brain injury) have also been reported (Squire, 1981).

The other areas associated with specific types of amnesia are the medial temporal lobes including the hippocampus, amygdala, and uncus. These areas are most commonly involved in the amnesic syndrome after herpes encephalitis and after temporal lobectomies carried out for the treatment of epilepsy (Parkin, 1984). In these patients the memory deficit also includes immediate memory and their retrograde amnesia is relatively brief before the onset of the injury (Cohen and Squire, 1981). The most important difference between diencephalic patients and temporal lobe patients is that in the former certain features resemble those seen after damage to the frontal lobes. This has been suggested to be particularly true in Korsakoff's disease. Consequent to temporal lobe damage, deficits of this kind are not seen

(Butters, 1974, 1979; Moscovitch, 1982; Squire, 1982; Butters et al., 1983; Cohen, 1984; Squire et al., 1984; Parkin, 1984; Table 1).

Frontal lesions have been associated with several memory problems. Affected patients seem to be unable to use memories that are stored rather than having impairments in learning and remembering new information. It has been proposed that frontal lobe patients have difficulties in maintaining new information in memory while working with it (Fuster, 1980). This creates problems in utilizing the relevant cues from the ongoing situation and leads to loss of relevant information. One feature of the memory deficit concerns the ability to plan encoding and retrieval strategies effectively enough (Moscovitch, 1982). These difficulties in more elaborative processing may be related to some more general impairment such as deficiency in an active, intensive element of cognitive function that is essential for pursuing prospective goals (Fuster, 1980). Shifting sets as a result of continuous perseverative intrusions

SUMMARY OF MAJOR FINDINGS IN AMNESIADiencephalic amnesia

General intellectual level relatively intact (Butters, 1979).

Language functions not impaired (Parkin, 1984).

Semantic memory not impaired (Schachter and Tulving, 1982; Weingartner, et al., 1983).

No deficit in skill learning (Martone et al., 1984).

Forget new material rapidly in front of distraction (the Brown Peterson task), but in other short term tasks forgetting rate is normal (Squire et al., 1984).

Variety of frontal lobe symptoms

Deficit in the Wisconsin Card Sorting Test (Moscovitch, 1982)

Sensitivity to interference. Performance improves, when interference is reduced (Butters et al., 1983). Intrusions (Butters, 1984) and perseverative errors (Parkin, 1984).

No release from proactive interference (Moscovitch, 1982).

Deficit in memory for temporal order (Cohen and Squire, 1984).

Lack of insight to their memory problems and confabulation (Parkin, 1984).

Temporal amnesia

General intellectual level relatively intact (Butters, 1979).

Language functions not impaired (Parkin, 1984).

Semantic memory not impaired (Schachter and Tulving, 1982; Weingartner, et al., 1983).

No deficit in skill learning (Martone et al., 1984).

Forget new material in short term memory tasks, but not selectively in front of distraction (Squire et al., 1984).

No deficit in frontal lobe tasks

Normal performance in the Wisconsin Card Sorting Test (Butters, 1974)

No sensitivity to interference (Butters et al., 1983).

Release from proactive interference (Moscovitch, 1982).

No deficit in memory for temporal order (Cohen and Squire, 1984).

Less confabulation and good insight to their memory problems (Parkin, 1984).

is a cognitive deficit most commonly associated with frontal lobe injury, especially with dorsolateral lesions (Milner, 1964; Drewe, 1974). Such patients seem to be incapable of changing response sets according to varying environmental requirements (Stuss and Benson, 1984).

The other features causing forgetting after frontal lobe lesions is increased sensitivity to interference (Butters, 1979, Moscovitch, 1982). Other deficits include rapid forgetting from short-term memory (Stuss and Benson, 1984), rigidity in appreciating temporal relations (Moscovitch, 1982), and difficulties in judging item frequency (Albert and Kaplan, 1980).

Previously, the basal ganglia structures were mainly associated with sensorimotor functions (Marsden, 1982). Recently, however, evidence has accumulated showing that in addition to motor functions these subcortical structures may also be involved in cognition (Mayes, 1988; Cools et al., 1984; Mortimer et al., 1982; Divac and Oberg, 1979, Teuber, 1976). Injury to these brain structures seems to produce characteristic cognitive deficits including impairment in arousal, attention, mood, motivation, certain aspects of language, memory,

abstraction, and visuospatial skills (Cummings and Benson, 1983). Memory deficits associated with subcortical lesions have been reported to include forgetfulness characterized by difficulty in spontaneously retrieving information and by slowness of thought processes (Albert, 1978; Cummings and Benson, 1983). Procedural memory has also been associated with a system which includes the basal ganglia structures (Martone et al., 1984).

In summary, the anatomical sites involved in learning and memory are not clearly circumscribed, but there is growing evidence from behavioral studies with human amnesia that features of memory deficits may differ according to location of the damaged area. Thus, lesions to diencephalic areas of the brain and temporal cortex may lead to memory deficits with specific features. Other areas of the brain which may be associated with specific kinds of memory deficits are the frontal areas and the basal ganglia.

III REVIEW OF COGNITIVE CHANGES IN PARKINSON'S DISEASE

1. General Cognitive Impairment vs. Specific Deficits

Several neuropsychological studies with unselected parkinsonian patients have shown a slight generalized intellectual decline, although most tend to still perform within the normal range (Loranger et al., 1972; Reitan and Boll, 1971; Pirozzolo et al., 1983). Such studies have mostly used as an assessment technique psychometric tests like the Wechsler Intelligence Tests (1956, 1981; Bowen, 1976; Loranger et al., 1972) or the Halstead Reitan Battery (Reitan and Boll, 1971; Pirozzolo et al., 1983). Their findings, however, may be confounded by the fact that general intellectual measures include tests which require motor abilities. Deficits in these measures could therefore reflect motor disability rather than intellectual dysfunction. In fact, there are findings, which show that mean Wechsler performance IQs are lower than verbal IQs in Parkinson's patients (Loranger et al., 1972).

Rather than general intellectual impairment, some studies have described impairment in specific areas of cognitive functioning. The most consistent findings concern visuospatial cognition. Deficits have been reported in visuoperceptual functions (Villardita et al., 1982; Boller et al., 1984; Sahakian et al., 1988), in visuospatial functions such as the integration of the object in spatial framework or the execution of mental operations involving spatial concepts (Sahakian et al., 1988; Hovestadt et al., 1987; Boller et al., 1984; Mortimer et al., 1982; Danta and Hilton, 1975; Bentin et al., 1981), spatial orientation (e.g. walking a route guided by a visual map; Bowen et al., 1972), perceptual motor tasks (Loranger et al., 1972; Pirozzolo et al., 1983) or planning motor behaviour (Flowers, 1978; Sharpe et al., 1983). In most of the aforementioned studies, tasks had motor components as well as a visuospatial requirements and it is difficult to differentiate which of these two components are more involved in observed deficits. Nevertheless, some recent work has demonstrated that visuoperceptive and/or visuospatial deficits are not demonstrable when motor impairment is controlled (Della-

Sala et al., 1986; Brown and Marsden, 1986; Girotti et al., 1988).

Memory dysfunction is another consistent finding in Parkinson's disease. Mnemonic deficits have been reported even in those parkinsonians who show otherwise little intellectual dysfunction (Bowen, 1976; Mayeaux et al., 1984; Pirozzolo et al., 1983; Tweedy et al., 1982). It seems that patients can be deficient on some subtests of the Wechsler Memory Scale, while retaining normal overall Memory Quotient levels compared to controls matched for age and Verbal IQ performance (WAIS) (Bowen, 1976). Furthermore, impairment in episodic memory has been reported even in select parkinsonian patients who were able to continue working in highly demanding senior level professional positions (Mohr et al., in Press).

In summary, some findings show that a slight decline in general cognitive level can occur in patients with Parkinson's disease even if these patients cannot be considered as demented using strict criteria. The most commonly described specific deficits have been in visuoperceptual areas, especially in visuospatial

functioning, and in memory and in certain tasks involving tracking and sequencing.

2. Specific Features of Memory Deficit

Many earlier studies concerning memory functions in Parkinson's disease only demonstrated the existence (or nonexistence) of memory deficit in a quantitative way, but did not attempt a qualitative explanation of the ways in which memory is impaired. During recent years, however, data have accumulated which allow consideration of the qualitative features of memory functions.

Episodic Memory

In the realm of episodic memory, short-term retention has been found generally to be intact in Parkinson's disease (Reitan and Boll, 1971; Bowen, 1976; Bentin et al., 1981; Pirozzolo et al., 1983). Short-term retention in these studies has been evaluated by digit span on the assumption that it is the purest measure of immediate memory (Waugh and Norman, 1965). Digit span

requires that information is accessible only briefly and does not involve any active manipulation of information before retrieval (Kinsbourne and Wood, 1975).

In long term retention, amnesia research has long attempted to find a locus of deficit in the memory system. Usually a memory deficit has been considered to reflect a disorder in some particular stage of information processing, such as acquisition, storage, and/or retrieval (e.g. Moscovitch, 1982). Tasks of recall and recognition have been most commonly used in these studies. Based on earlier studies of memory (Ebbinghaus, 1885) it has been claimed, that memory tasks differ in the extent to which they involve retrieval processes. Successful performance on recognition tasks require fewer retrieval operations than performance on recall tasks. Furthermore, recognition does not require any manipulation of material in the memory situation while recall demands that a subject participates more actively in order to remember (Flowers et al., 1984).

There is some indication that, in contrast to items which involve recall of material, parkinsonian patients are less impaired on tasks which require recognition.

Several studies have not found any impairment in visual recognition tasks including facial recognition (Lees and Smith, 1983) or pictures of common objects or abstract pictures (Flowers et al., 1984; Mohr et al., in Press). Parkinsonian patients seem also to perform as well as controls both in immediate retention of pictorial material and in retention after a delay (Flowers et al., 1984). Furthermore, according to some observations, performance in nonverbal memory tests does not correlate with age, motor disability, or duration of the disease (Flowers et al., 1984).

Similar findings have been reported in verbal recognition tasks (Lees and Smith, 1982; Tweedy et al., 1982), although some deficits have also been reported (Tweedy et al., 1982; Sahakian et al., 1988). Parkinsonian patients seem also to be able to use cues to improve their performance even in free recall tasks (Tweedy et al., 1982). Cued recall as well as recognition are assumed to minimize the retrieval requirements of the task and impaired recall relative to spared recognition have been interpreted as a deficit in retrieval processes.

While recognition of material seems to remain relatively intact in Parkinson's disease, several studies have reported impairment on recall tasks which involve both verbal and visual material (Weingartner et al., 1984; Caltagirone et al., 1985; Mohr et al., in Press). Deficits in the recall of visual material may also be independent of the patients' visuoconstructional abilities (Caltagirone et al., 1985), although the relationship between visuospatial impairment and recall of visual material seems still to be uncertain. Some researchers have reported difficulties both in complex visuospatial functions as well as in visual memory tasks (e.g. Mohr et al., in Press).

One possible explanation of the underlying mechanism of memory deficit in patients with Parkinson's disease is that they are sensitive to the disruptive effects of interference. Consequently, they are unable to select information from episodic memory due to the interference from inappropriate memories (Tweedy et al., 1982). Interference phenomena can originate either because memory traces cannot be suppressed and thereby intrude ("disinhibition" hypothesis) or there is an alteration in

trace strength which gives rise to a higher intrusion rate (Weiskrantz and Warrington, 1975). In behaviour, the deficit can be seen in the amount of information a person repeats from information learned earlier (e.g. response perseveration in list learning).

The most common paradigm used to measure interference from information learned earlier (proactive interference) is the Brown-Peterson paradigm or the distractor task (Peterson and Peterson, 1959). This task involves presenting a sequence of three items (either consonants, words, or simple visual patterns) and requiring subjects to retain the items over a period of time (60 seconds generally), during which they are prevented from rehearsing by being given a secondary task such as counting backwards. With respect to normal memory, it has been found that when rehearsal is prevented, information is rapidly forgotten due to decay of the memory traces.

Forgetting in the Brown-Peterson task can also occur due to interference from information learned earlier. If the words on successive trials are related to each other (i.e. from the same conceptual category), some of the

forgetting occurs because of the confusion between the items presented in an earlier trial. In normal subjects, memory performance deteriorates when information is continuously presented from the same conceptual category on successive trials because of the interference from the earlier trials (proactive interference). When the category on successive trials is changed, for example if animal names are substituted for names of professions, there is a marked increase in memory performance because of the interference is minimized (release from proactive interference, Wickens, 1970)

Although immediate recall on a Brown-Peterson task with words appears intact, parkinsonian patients show a more rapid loss of information than controls when rehearsal is prevented by a distractor task (Tweedy et al., 1982). Furthermore, patients seem not to benefit when the number of intrusion material is decreased. It is possible, then, that the memory deficit stems from the fact that appropriate memory traces are weak (Baddley, 1982). The results of error analysis were not totally supportive of the interference hypothesis. If interference is the problem in memory, intrusion errors

(i.e. words from previous trials) should be increased. Patients with Parkinson's disease did make more intrusion errors than pure omissions, but the number of intrusions overall was not very high.

Mechanism of the memory deficit in Parkinson's disease may also be related to encoding processes, i.e. patients cannot remember adequately because they are unable to encode information distinctively enough. Attentional requirements of the tasks (Hasher and Zacks, 1979) have been used as an explanatory factor on the suggestion that while parkinsonian patients can process information which requires little cognitive capacity (i.e. information which can be processed automatically), they have difficulties engaging in elaborative processing because of the attentional requirements involved (Weingartner et al., 1984). Tasks which are supposed to evaluate automatic processing include frequency monitoring of repeated unrelated words (the subject were required to judge how often the repeated word had been presented) and learning of unrelated words and pictures which involve identification of the modality in which the stimulus has been presented (pictures and words). Tasks

that can be performed quickly, effortlessly, and relatively autonomously are generally considered to be automatic (Hasher and Zacks, 1979). Effortful processing is measured with tasks that require more than automatic cognitive operations such as memorizing related words, free recall of words, pictures and events, and serial learning of unrelated words (Weingartner et al., 1984).

It has been shown that even unmedicated parkinsonian patients with mild to moderate disease were able to learn and remember information that can be processed automatically, but had difficulties in those tasks which demand more attention, compared to controls (Weingartner et al., 1984). Patients' performance was worst on serial learning, which was the most demanding of the tests used. Accordingly, cognitive deficits in Parkinson's disease can thus appear even in patients in the early stages of the disease.

While the observed memory deficits in Parkinson's disease may be attributable to interruption of specific processes in retention, it has also been suggested that some more general deficit in information processing might be responsible for their memory impairment. One such

proposal has been that Parkinson's patients process information slower than generally would be expected (Wilson et al., 1980; Rafal et al., 1984). The term "bradyphrenia" has been applied to slowed information processing in Parkinson's disease. A deficit in speed of processing has been thought to be of the same origin as the motor slowing due to a deficient initiation of movements (bradykinesia). The suggestion has been that the same mechanisms in the subcortical structures would be involved both in motor and mental slowing. If speed of processing were a relevant variable, rate of processing should particularly affect performance on those tasks which demand organization, rehearsal, and more elaborative processing and be less involved in recognition and cued recall (Salthouse, 1980).

Several studies have used Sternberg's memory task (Sternberg, 1966) to evaluate the speed of information processing. In this task a subject is asked to decide as quickly as possible, whether the presented item is a member of a memory set. The task allows measurement of rate of processing (length of time elapsing between presentation of the item and initiation of a response)

due to the independent assessment of the accessing process and a measurement of accuracy of recall (a number of correctly identified probes).

Results with Sternberg's task have not fully confirmed the slowing hypothesis as being analogous to bradykinesia (slowing of motor functions). Some studies have not found any relationship between slowing of processes evaluated by Sternberg's task and bradykinesia (Rafal et al., 1984). Furthermore, slowing of cognitive processes has often been claimed as a reason for the memory deficit in elderly people (Craik, 1977). There are findings which show that only older parkinsonian patients access the information in Sternberg's task at a slower rate than normal age-matched controls (Wilson et al., 1980).

Some studies have evaluated retrograde memory in Parkinson's disease, although retrograde-anterograde concepts are less obvious with respect to advancing neurological illnesses, because the onset of underlying pathology cannot be identified exactly in time. This is true especially in Parkinson's disease in which the onset is often insidious and difficult to define. On the basis

of clinical data it has been generally assumed that memory for remote events is relatively intact in Parkinson's disease, but studies carried out so far, have demonstrated a decline in the ability to remember distant events whether they include personal information or autobiographical data (Warburton, 1967), events, or persons well-known from the past (Freedman et al., 1984; Sagar et al., 1988).

Amnesia research has shown that duration of retrograde amnesia can vary (Albert et al., 1981; Cohen and Squire, 1981). Retrograde amnesia can involve a temporal gradient with relative sparing of more remote memories or it can show no temporal gradient with equal loss of memories for all periods of distant past (Wilson et al., 1981). In Parkinson's disease the existence of the temporal gradients seems to depend on the degree of intellectual impairment (Freedman et al., 1984). Some studies have shown that on tests which evaluate temporal gradient formally (the Famous Faces Test developed by Albert et al., 1979) all parkinsonian patients performed less well than controls overall, but only demented parkinsonian patients had an impairment which was equal

for all time periods tested (i.e. no temporal gradient was found). Thus, although general intellectual decline alone cannot explain the retrograde memory deficit in Parkinson's disease, a temporal gradient may be related to severity of dementia (Freedman et al., 1984; Sagar et al., 1988).

Evaluation of remote memories raises the question as to whether the method used in these studies measures impairment in remote episodic memory or impairment in remote semantic memory. Successful performance on the Famous Faces Test also requires general knowledge which depends on free access to information assumed to be stored in semantic memory (Zola-Morgan et al., 1983).

To summarize, judging from previous studies, it appears that memory deficits in the realm of episodic memory in less impaired parkinsonian patients do not involve all areas of memory functions in all patients. Usually in short-term retention, immediate memory is at least less impaired than the other aspects of memory. In long-term retention, while there seems to be an impairment in recall of information both for verbal and

visual material, recognition of information is not affected (Table 2). Deficit in recall appears to concern also remote events, but it may be that those patients who are intellectually less affected, remember more recent events less well than more distant ones (temporal gradient). When the dementing process advances, remote memories seem to get lost as well.

Several explanations of the underlying mechanism of the memory deficits in Parkinson's disease have been presented. Both retrieval and encoding hypotheses have gained some support. The findings that parkinsonian patients fail to show a normal release from proactive interference in the Brown-Peterson task may implicate that the patients are impaired in their ability to retrieve information from memory because they are sensitive to effects of interference. Instead of retrieval, attentional deficits emphasize encoding processes as a functional cause for the memory deficit. When a situation requires that patients use cognitive capacity actively, they seem to have difficulties, while on the other hand, in those memory situations which require only automatic cognitive processes without active

TABLE 2

SUMMARY OF FINDINGS IN EPISODIC MEMORY IN PARKINSON'S DISEASE

Task	Purpose	Investigator	No. of patients	Age (Mean)	Deficit
<u>Short-term Memory Span</u>	Immediate memory (assessment of the information that can be held in memory)	Pirozzolo et al, 1983	60	62.7	Deficit, but less than in the other tests
		Reitan and Boll, 1977	25	50.9	
<u>Long-term Memory Recognition</u>	Visual, abstracts - immediate - delayed	Flowers et al, 1984	54	62.8	No deficit No deficit
	Visual, faces	Benin et al, 1981 Less and Smith, 1983	32 30	62.4 59.4	Deficit No deficit
	Words	Lees and Smith, 1983	30	59.4	No deficit
	Forced-Choice	Tweedy et al, 1982	35	69.2	No deficit
	Synonyms	Tweedy et al, 1982	35	69.2	Deficit, but less than in recall
					54

TABLE 2 (cont'd)

Task	Purpose	Investigator	No. of patients	Age (Mean)	Deficit
Recall	Repetition	Tweedy et al, 1982	35	69.2	Deficit, but less than in recall
	Unrelated words and pictures	Weingartner et al, 1984	6	65.5	Deficit
	Unrelated words and visual memory for designs	Caligiore et al, 1984	57	61.3	Deficit
	Related words	Weingartner et al, 1984	6	65.5	Deficit
	Cued recall	Tweedy et al, 1982	35	69.5	Helps, but not to the normal level
Frequency monitoring Brown-Peterson (categories)	Serial learning	Weingartner et al, 1984	6	65.5	Deficit
	Automatic processes	Weingartner et al, 1984	6	65.5	No deficit
	Rate of forgetting	Tweedy et al, 1982	35	69.5	Deficit
	Interference	Tweedy et al, 1982	35	69.5	Deficit

TABLE 2 (cont'd)

Task	Purpose	Investigator	No. of patients	Age (Mean)	Deficit
Sternberg's memory scanning	Rate of information processing	Wilson et al, 1982	20	Old 69.4 Young 58.1	Old ones deficit in the rate of processing but not the young ones No deficit
		Rafal et al, 1984			
Retrograde amnesia	Personal information Temporal gradient	Warburton, 1967	140		Deficit
		Freedman et al, 1984	22 8 demented	64.5	No temporal gradient Temporal gradient
			14 nondemented	63.5	

involvement on the part of the subject, they function normally. Some patients, especially older ones, seem also to process information at a slower rate than generally would be expected, which may affect performance in those memory tasks which demand more effortful processing. It may well be that several factors contribute to the memory deficit seen in Parkinson's patients.

Semantic Memory

Semantic memory is often evaluated by examining patients' vocabulary skills and information stored during their life-time. The vocabulary tests used are, in a way, the equivalent of recognition tasks in the realm of episodic memory. Successful performance on vocabulary tasks requires word recognition based on the ability to define words (Albert, 1980). The other more complex task used to assess semantic memory is a test of verbal fluency in which a subject generates as many words as possible beginning with a given letter or belonging to a given category (e.g. animals). Compared to vocabulary

tests, which require only the definition of a word, verbal fluency is a purely spontaneous phenomenon, which involves the active use of words retrieval of information. Verbal fluency tasks might in fact measure access to the semantic memory rather than semantic storage (Weingartner et al., 1983).

Although verbal fluency is generally thought of as a test of semantic memory (Baddley, 1982; Weingartner et al., 1983), interpretation may be confounded by the fact that these tasks are also used in aphasic studies as a measure of reduced verbal abilities rather than a measure of memory deficit. Some authors, however, maintain that performance in object-naming tasks can be dissociated (Benson, 1979). Impairment in verbal fluency tasks may, accordingly be more related to the failure of semantic retrieval mechanisms (Baddley, 1982). Performance in verbal fluency tasks can also be impaired without necessarily involving damage in central language areas. Patients with frontal lobe damage, even without the involvement of Broca's area, for example, often have a

decrease in the spontaneity of speech (Stuss and Benson, 1983), which may be associated with memory problems (Fuster, 1980).

Although not surprisingly, parkinsonian patients often have problems with their expressive speech even in the beginning of the disease (Streifel and Hoffman, 1984), language deficits have not been generally reported in this disorder. Even those patients who have developed dementia, seem to preserve their language abilities (Mayeaux et al., 1981; Bayles and Tomoeda, 1983). Spared language and general intellectual functioning in verbal area, suggest that semantic memory store is intact. Parkinsonian patients seem to be able to perform at nearly normal levels on tasks that require acquired, well-practiced information (e.g. in the information subtest of the WAIS) and on vocabulary tests (Loranger et al., 1972; Pirozzolo et al., 1983; Bentin et al., 1981).

Several researchers have demonstrated a deficit in the ability to generate words in Parkinson's patients and clinically these patients often complain of difficulties in expressing themselves fluently because they cannot access the words automatically (Lees and Smith, 1983;

Caltagirone et al., 1985; Matison et al., 1982). Controversial results have been reported, however, as to whether there is a differential deficit in generating words and in generating category names. Some findings show that parkinsonian patients may be more impaired in tasks requiring naming words from a semantic category, but not in tasks which involve words that begin with specific letters (Matison et al., 1982). These two tasks differ qualitatively (Rosen, 1980). The former demands that subjects produce words from restricted categories, the latter that they must use larger, unfocused categories. The fact that parkinsonian patients may have more difficulties in a semantic task than in a task producing words from letters, is also significant because generating words from the semantic categories is generally assumed to be easier than producing words beginning with given letter (Schaie, 1980). Furthermore, impairment in category naming seems to be significantly correlated with disease severity, especially with bradykinesia (Matison et al., 1982).

Even if there is no evidence of the aphasic-type of language impairment in Parkinson's disease, some studies

have reported mild naming deficits even in those patients who had no difficulty with vocabulary tasks. Patients were also helped by cuing, which indicates that the word itself was not lost from memory. Thus this deficit could be part of a semantic retrieval deficit (i.e. they have difficulties in accessing semantic information) rather than an aphasic disturbance (Matison et al., 1982). It is reminiscent of the difficulties which sometimes can be seen in normal memory. The "tip-of-the-tongue" phenomenon refers to a failure to recall a specific word even though the individual has the feeling that he is about to retrieve it. Minimal cuing is generally needed to produce the correct word (Zechmeister and Nyberg, 1982).

In summary, although structures of semantic memory in parkinsonian patients seem to remain relatively intact, there are controversial findings as to whether these patients have difficulties in accessing the information in semantic structures. There are some indications, that a deficit in verbal fluency is selective (Table 3), and is revealed only in those

TABLE 3

SUMMARY IN FINDINGS IN SEMANTIC MEMORY IN PARKINSON'S DISEASE

Task	Purpose	Investigator	No. of patients	Age (Mean)	Deficit
Information	Acquired knowledge	Loranger et al, 1972	63		No deficit
		Pirozzolo et al, 1983	60	62.7	Mild deficit
Vocabulary	Semantic recognition based on word definition	Loranger et al, 1972	63		No deficit
		Pirozzolo, et al, 1972	60	62.7	Mild deficit
Verbal fluency Letters	Semantic retrieval Retrieval from general categories	Matisson et al, 1982	22	62.3	No deficit
		Weingartner et al, 1984	6	65.5	No deficit
		Lees and Smith, 1983	30	59.4	Mild deficit due to perseveration

TABLE 3 (cont'd)

Task	Purpose	Investigator	No. of patients	Age (Mean)	Deficit
Categories	Semantic relationships, retrieval from restricted categories	Matison et al, 1982	22	62.3	Deficit
		Weingartner et al, 1984	6	65.5	No deficit

situations in which patients must choose information required from restricted categories.

This means that patients are incapable of utilizing all the semantic relationships and of shifting cognitive strategies in a systematic way. Difficulties in accessing information in semantic memory may form a part of the memory problem in Parkinson's disease and if this is indeed so, may be related to other putative cognitive deficits of the disease.

IV ORIGIN OF COGNITIVE CHANGES IN PARKINSON'S DISEASE

The most controversial issue in Parkinson's disease has been the origin of the cognitive impairment. The argument has concentrated on the issue of whether cognitive changes seen in the disease are mediated by the same subcortical structures that are responsible for the motor symptoms or whether they may in fact be mediated cortically. A third hypothesis has been that pathological changes in subcortical structures disturb the connections between subcortical and cortical structures and cause some cognitive changes, which generally have been associated with frontal lobe dysfunction.

Approximately a decade and a half ago it was first suggested that the pathological changes in subcortical and cortical structures of the brain lead to different, identifiable patterns of cognitive symptoms (Albert et al., 1974). The controversial terms "cortical" and "subcortical" dementias were introduced. Traditionally, subcortical areas, especially the basal ganglia structures, had not been associated with cognitive

functions (Alexander et al., 1986). Although it is now widely accepted that neurological diseases leading to degenerative cognitive deterioration may differ both anatomically and neuropsychologically, data accumulated during the past ten years have challenged these concepts of dementias. Even if the primary pathology is in different areas, cognitive deficit may involve both subcortical and cortical structures and/or their connections.

1. Subcortical Involvement in Cognitive Deficits

The typical behavioral pattern in subcortical dementias has been characterized comprising some changes in memory and cognition, emotional or personality alterations (apathy and depression), and slowness in mental processes (Albert, 1978). Memory deficits in subcortical dementias have been said to include forgetfulness characterized by difficulty in spontaneously retrieving information. There seems to be

no impairment in central language abilities, although some less severe speech problems can be noticed (Albert, 1978; Cummings and Benson, 1983).

Lesions of the basal ganglia are found in a variety of motor disturbances other than Parkinson's disease including Huntington's disease, supranuclear palsy, Wilson's disease, and thalamic dementia. All of these diseases have pathological changes that include primarily, but not exclusively, the thalamus, basal ganglia, and related brain stem nuclei (Cummings and Benson, 1984) and all of them lead to cognitive deficits of various degrees. Depending on the underlying pathologies, different kinds of motor abnormalities such disorders of muscle tone, postural reflexes, and involuntary movements (dyskinesias) are associated with most subcortical dementias (Cummings and Benson, 1983).

If all neurobehavioral changes in Parkinson's disease are considered, many symptoms resemble those seen in subcortical dementias. Generally, aphasia (Bayles and Tomoeda, 1983) and apraxia is not included among the

symptoms in Parkinson's disease and as was mentioned previously, changes in mood, particularly depression, often accompanies the disease.

From the perspective of subcortical dementias, memory failure in Huntington's disease has been studied most and some of the features of cognitive deficits in that disorder resemble those seen in Parkinson's disease. Rather than being a general decline in all intellectual abilities, intellectual deterioration in Huntington's disease involves a slow, gradual, and selective loss of mental abilities, especially in the early stages of the disease (Butters et al., 1978; Josiassen et al., 1982; Wexler, 1979). The most common finding with respect to intellectual functioning has been that verbal abilities are more preserved than are performance skills (Taylor and Hansotia, 1983; Josiassen et al., 1982; Fedio et al., 1979). Specific deficits on various tasks which require perception, visuospatial or visumotor integration, utilization of directional cues and difficulties in concept formation and problem solving have been reported (Fedio et al., 1979; Taylor and Hansotia, 1983).

As in Parkinson's disease, immediate memory evaluated by the digit span, remains relatively intact in Huntington's disease and the performance on the Brown-Peterson task has been found to be unimpaired when there is no delay (Caine et al., 1977; Butters et al., 1978). Abnormally quick forgetting follows, however, even after short delay periods when auditory word or consonant trigrams or visual trigrams are used as stimulus material (Caine et al., 1977; Butters et al., 1978). Furthermore, in both diseases, the recall of both verbal and visual information seems to be more affected than the recognition of such material although to a certain extent recognition also is impaired (Caine et al., 1977; Martone et al., 1984; Butters et al., 1975; Biber et al., 1981). It has been demonstrated that Huntington's patients can be helped to overcome their difficulties in recognition of pictorial stimuli by providing them with verbal labels and mediators at the time of testing (Biber et al., 1981).

Similar to Parkinson's disease, the hypothesis that specific memory problems arise because of the sensitivity to the interference effects, has also been studied in

Huntington's disease. Huntington's patients have been found to be impaired in the condition of high proactive interference (Butters et al., 1976). It seems, however, that the interference effects alone cannot explain the memory deficits in Huntington's disease, because no improvement in performance was observed when interference was decreased (i.e. there were no differences between the massed and spaced trials; Butters et al., 1976). The analysis of errors further supports this interpretation. Patients made more errors of omission than intrusions from previous lists (Meudell et al., 1978). Furthermore, recently it has been demonstrated that effects of interference do not affect long-term retention (Wilson et al., 1987). Huntington's patients showed a normal sensitivity to proactive interference, although a build up of interference and an expected release following a shift in semantic category did not seem to occur to the same degree as in controls (Wilson et al., 1987). The pattern of intrusion errors in recall was also normal.

As in patients with Parkinson's disease, the semantic memory store seems to be relatively intact in Huntington's disease. No impairment has been reported in

acquired knowledge and vocabulary (Weingartner et al., 1979; Caine et al., 1977) and the performance in picture naming appears to be unaffected even in the later stages of the disease (Butters et al., 1978; Bayles and Tomoeda, 1983). Access to semantic memory, however may show some deficit from the early stages of the disease and in contrast to parkinsonian patients, decreased fluency has been found both in word generation from letters (Josiassen et al., 1982; Butters, 1976) and in a semantic category task (Wilson et al., 1987). Although these difficulties appear in the early stages of the disease, they do not increase further in the more advanced stages (Butters, 1976).

Procedural memory has not been well studied in Parkinson's disease, but this kind of memory seems to suffer in Huntington's disease (Martone et al., 1984) and moreover, a deficit in procedural memory may be specific to basal ganglia lesions. When the performance of Huntington's patients was compared to that of Korsakoff's patients and normal controls on a Mirror Reading Task (i.e. the ability to learn reading the words which appear as mirror images of themselves) (Cohen and Squire, 1980),

it was found that patients with Huntington's disease learn and retain this skill at lower rates than controls or Korsakoff's patients (Martone et al., 1984). In spite of their difficulties in learning, Huntington's patients, however, seemed to be as capable as controls in recognizing the words repeated to them over the trials. Patients with Korsakoff's disease, on the other hand, could not identify those words as repeated even if they improved their performance over the trials.

The observation that patients with Korsakoff's disease and those with Huntington's disease acquire mirror reading skills differently, seems to provide evidence for different memory systems which would operate independently of each other (Cohen, 1984). Declarative memory (i.e. remembering information that depends on the ability to recall the specific content of the task) appears to depend on the integrity of the medial temporal and diencephalic brain regions which are damaged in amnesia, while procedural memory is maintained independently of these regions (Squire et al., 1984). Successful performance in procedural memory, on the other hand, may rely on intact basal ganglia function and

consequently, be selectively impaired in subcortical disease.

In summary, when patients with Parkinson's and Huntington's disease are compared, some similarities in clinical features are clearly evident. As far as memory functions are concerned, there are indications that some similar aspects can be found both in semantic and episodic memory impairment. Accessing semantic information may be partially responsible for the memory disorder in both diseases and in episodic memory both patient groups perform better in recognition than in recall and have shown sensitivity to interference effects in short-term retention. It seems, however, that although Huntington's patients have slight difficulties in long-term retention, they still show normal sensitivity to proactive interference. In Parkinson's disease this has not been studied to date. Huntington's patients seem also impaired on procedural (rule-based) memory, and it has been suggested that this deficit may be specific to subcortical areas. If procedural memory is indeed functionally related to subcortical structures,

impairment in this domain should be ascertainable in Parkinson's patients.

2. Frontal Connections in Parkinson's Disease

In some subcortical diseases, including Parkinson's disease, elucidation of the quality of cognitive deficits becomes more complicated because of the multitude of cortical connections of the subcortical structures. Several researchers have suggested that the origin of some cognitive deficits may be either the frontal cortex or basal ganglia-frontal lobe interactions (Albert et al., 1974; Albert, 1978; D'Antona et al., 1985; Lees and Smith, 1983; Taylor et al., 1986, 1988).

Behavioral changes after frontal lobe lesions include emotional or personality changes, lack of spontaneity and initiation of behaviour, slowing of mental processes, forgetfulness or specific disorders affecting memory, reduced verbal fluency and articulatory weaknesses (Albert et al., 1974; Stuss and Benson, 1984). Often specific deficits in cognitive functions appear even if the performance in general intelligence tests

remains at the normal level. It has been suggested that the major role of the frontal cortex in cognitive functioning is the temporal organization of behaviour by means of three basic factors: preparatory set in planning, provisional memory, and suppression of interference (Fuster, 1980).

Some features of the cognitive deficit in Parkinson's disease resemble those seen after certain types of frontal lobe damage. Parkinsonian and frontal patients seem to have similar deficits in spatial orientation and some motor activities. They both have shown abnormal responses in the setting of the visual vertical under condition of body tilt (an Aubert phenomenon) (Bowen, 1976) and they both have exhibited similar inability to plan motor activities (Sharpe et al., 1983; Flowers, 1978).

Impairment in shifting sets as a result of continuous perseverative intrusions is a cognitive deficit most commonly associated with frontal lobe lesions, especially with dorsolateral frontal lesions (Robinson et al., 1986; Taylor et al., 1988; Milner, 1964; Drewe, 1974). In tests such as the Wisconsin Card

Sorting Test, which require that subjects repeatedly change their principal line of reasoning to solve problems, frontal patients often indicate that although they realize the conceptual requirements of the task they are unable to use this information to guide their actions (Lees and Smith, 1983). If the patients, however, are warned to expect the shift, their performance improves (Teuber, 1969). In patients with Parkinson's disease, similar deficits in shifting concepts seem to appear quite early on in the disease process (Lees and Smith, 1983).

Although there are no studies which directly compare the quality of the memory deficit in parkinsonian and frontal lobe patients, there seems to be similarities in some aspects of memory impairment. As in Parkinson's disease, frontal patients seem to be unable to use memories that are stored rather than having an impairment in learning and remembering and according to recent finding they also appear to have a relative sparing of recognition (Grafman et al., in Press; cited in Mayes, 1988) and in cued recall (Jetter, 1986) vis a vis impaired recall of information. Furthermore, a deficit

in recall may be specific to dorsolateral frontal lesions, since no memory deficits were seen in orbitofrontal patients (Grafman et al., in Press; cited in Mayes, 1988). It has also been demonstrated that both parkinsonian and frontal patients may have difficulties in effortful processing (Weingartner et al., 1983; Mayes, 1988), in sequencing of events (Taylor et al., 1988; Moscovitch, 1982) and in recency discriminations (Sagar et al., 1988; Milner et al., 1985).

Several authors have investigated the vulnerability of frontal patients to proactive interference (Stuss et al., 1982; Moscovitch, 1982). Sensitivity to interference effects has been demonstrated in short-term retention (the Brown Peterson) with bilateral orbitofrontal damage after surgery without any severe impairment in general memory tests (Stuss et al., 1982). Moreover, similar deficits have been demonstrated in long-term retention (Moscovitch and Milner, 1982). Patients with frontal damage seemed to be unable to improve their performance when interference was decreased (the release trial) and furthermore, these same patients also had difficulties in the Wisconsin Card Sorting Test

(Moscovitch, 1982). Recent findings have also shown that only those frontal patients who had a memory deficit on the Wechsler Memory Scale showed no release effect (Freedman et al., 1986).

A decrease in verbal fluency has been a commonly reported finding in frontal patients (Milner and Petrides, 1984; Perret, 1974; Benton, 1968), which indicates that these patients may have difficulties in retrieving information from semantic memory. It is still uncertain, though, whether deficit in verbal fluency concerns all frontal patients equally. It seems, that there may be functional differences between orbitofrontal and dorsolateral frontal regions in this regard. Patients with dorsolateral damage appear to be unable to reproduce words starting with specific letters while patients with orbitofrontal lesions seem to have no difficulties in this task (Stuss and Benson, 1984).

In summary, neuroanatomical evidence, supported by neuropsychological findings, suggests that some cognitive deficits in Parkinson's disease may be due to a combination of subcortical and cortical damage.

Particularly an interaction between the frontal cortex and the subcortical striatal structures may have some functional importance. In recent years evidence has accumulated showing that several cognitive and memory deficits seen in Parkinson's disease resemble those seen after frontal lobe lesions. With respect to memory, frontal lobe damage seems to lead to some kind of processing deficit which then impairs recall of material both from episodic and semantic memory. It is not known, however, how extensive these symptoms are and to what extent they affect memory performance in Parkinson's patients.

The suggestion that there are anatomical differences between the orbitofrontal and dorsolateral areas of the frontal cortex (Alexander et al., 1986), may indicate that there are functional differences between these two areas as well. Contrary to earlier opinions that the prefrontal cortex forms a functionally homogeneous unit, several authors (Fuster, 1980; Stern, 1983; Divac and Oberg, 1979) have suggested that different parts of the frontal cortex may mediate some separable but

interrelated cognitive and emotional functions. The orbitofrontal cortex with connections to the diencephalic areas would be responsible for more emotional aspects of behaviour and the regulation of ongoing behaviour while the dorsolateral regions would be more involved in the control and integration of the more cognitive-perceptual aspect of the behaviour (Rosvold, 1972; Fuster, 1980).

In animal studies with primates, unique patterns of deficits have been associated with lesions of the different areas of the frontal cortex (Divac and Oberg, 1979). Furthermore, deficits equivalent to orbitofrontal and dorsolateral lesions have also been found after lesions to those striatal areas which are connected with the respective frontal areas (Divac and Oberg, 1979; Stern, 1983; Fuster, 1980; Table 4). These findings have emphasized the possibility of the functional importance of the basal ganglia-frontal lobe interactions. Functional differences between various areas of the striatum and their cortical connections may not concern only the frontal cortex but other areas of the brain as well. It has been suggested that the anterior striatal region and prefrontal cortex are important for early

TABLE 4

DIFFERENTIAL EFFECTS OF THE BASAL GANGLIA SYSTEMS IN
ANIMAL STUDIES (Stern, 1983; Oberg and Divac, 1979;
Fuster, 1980)

Lesion	Connection to basal ganglia	Affected Tasks
Orbito- frontal cortex	Ventrolateral head of the caudate	Object reversals Go - No go tasks
Dorso- lateral frontal cortex	Anterolateral head of the caudate	Delayed responses Delayed spatial alterations Prisma adaptation
Infero- temporal	Tail of the caudate Medial globus pallidus	Visual discriminations

consolidation of memory and/or preparation to respond on the basis of recent memory, while posterior striatum and the temporal cortex are more important for perceptual processes (Oberg and Divac, 1979).

Functional differences between dorsolateral and orbitofrontal areas, however are still controversial. On the basis of studies with primates, it has been maintained that the ventral and medial frontal cortex are particularly involved in the suppression of interfering tendencies while the dorsolateral frontal areas are primarily involved in tasks that require the integration of spatially and temporally discontinuous elements of cognition (Fuster, 1980). In human studies, sensitivity to interference effects has been found in all frontal patients regardless of the location of the lesion (Stuss and Benson, 1983; Moscovitch, 1982), although some studies have demonstrated that the dorsolateral frontal areas may be more involved than the others (Milner, 1964). It is also possible that interference evaluated with different measures is not the same. Thus, although leucotomized orbitofrontal patients seemed to have difficulties in the Wisconsin Card Sorting Test, they had

no difficulties in the Stroop Test, which evaluates the degree of interference between two competing stimuli (Stuss et al., 1981)..

It still must be delineated whether some features of the memory deficits in Parkinson's disease have any connections with the assumed functional differences between different areas of the frontal lobes. Furthermore, it must be noted that subcortical structures may also have other frontal lobe projections such as the anterior cingulate circuit (Alexander et al., 1986) which may be involved in cognition as well. Any functional significance, however, remains unclear.

3. Cortical Involvement in Cognitive deficits in Parkinson's Disease

Alzheimer's disease is a progressive neurodegenerative disorder that involves primarily association cortices and hippocampus (Mohr and Chase, in Press). Because of the involvement of cortical areas, in addition to severe memory deficit, apnasic problems, agnosia, apraxia and visuospatial deficits are included

as symptoms in this illness (e.g. Martin et al., 1967). Several researchers have suggested that those Parkinson's patients who have dementia, have coincidental Alzheimer's disease (Boller et al., 1980; Lieberman et al., 1979; Hakim and Mathieson, 1979). Consequently, the pattern of cognitive deterioration in Parkinson's disease would be indistinguishable from dementia seen in Alzheimer's disease with deficits in almost all areas of intellectual functioning, but especially memory problems. The more recent view is that for unknown reasons, patients with Parkinson's and Alzheimer's disease are more susceptible to developing symptoms of both diseases (Jellinger, 1987).

Some neuropathological findings in Parkinson's disease seem to support the notion of cortical involvement, but it is yet uncertain whether cortical changes are in any way related to cognitive impairment. Cortical atrophy, while present, has not been correlated to cognitive or personality features (Schneider et al., 1979). This is particularly true when the effects of age are controlled (Sroka et al., 1981). Furthermore, two primary CT-scan measures of cerebral atrophy, enlarged

impaired in at least one group of patients belonging to the subcortical dementias, namely Huntington's disease. Accordingly, it was suggested that procedural memory may be associated with the basal ganglia structures. If this were indeed the case, procedural memory should also evidence impairment in Parkinson's disease.

In line of the aforementioned considerations, the following hypotheses were tested:

Rather than being impaired in the accuracy of memory in general, it was expected that patients with Parkinson's disease might experience specific deficits in

- a) accessing information from the semantic network and/or
- b) handling interference and/or
- c) learning procedural information

These specific characteristics in cognitive functioning were expected to be evident independent of the general intellectual level of the patients.

2. Methods

Subjects

2

ventricles and widened sulci, relate differently to mental changes. Enlarged ventricles, if any, evidently demonstrate a stronger relationship to cognitive deterioration in Parkinson's disease than do widened sulci (Portin et al., 1982). This would indicate that degeneration of subcortical structures may be relevant to cognitive impairment.

Although senile alterations intrinsic to Alzheimer's disease have been reported more often in parkinsonian patients than in age-matched controls (Boller et al., 1980; Hakim and Mathieson, 1979), these changes seem not to be related to cognitive deterioration and can be seen both in demented and nondemented parkinsonians (Perry et al., 1983, 1985).

Both in Parkinson's and Alzheimer's disease it has been claimed that cholinergic systems (i.e. nucleus basalis of Meynert or its projections to the cortex and to the hippocampus) can be involved (Coyle et al., 1983; Perry et al., 1985; Ruberg et al., 1982; Agid, 1986). The connection between the mental deterioration and the cholinergic deficiency, however, is not clear. Some researchers have not found any differences in the

severity of the nucleus basalis dysfunction between demented and nondemented Parkinsonians (Whitehouse et al., 1983). Some others, on the other hand, have reported that even if cholinergic abnormalities may occur in those patients who have no gross mental changes, the degeneration of cholinergic neurons creating pathological cortical changes may be related to declining cognitive functioning (Perry et al., 1985).

The comparison studies with Parkinson's and Alzheimer's patients are fraught with difficulties because of the need to control the degree of cognitive involvement in individual patients. The diagnosis of Alzheimer's disease is based on clinical criteria and is tenuous especially at the early stages of the disease. In Parkinson's disease, on the other hand, only those patients can be included who in fact evidence matched involvement of neurocognitive function. Comparison studies between Alzheimer's patients and demented parkinsonians should, however, give some information about the possible continuity of the cognitive deficit in Parkinson's disease (Caltagirone et al., 1989).

While in Parkinson's disease severe memory deficits seem to develop relatively slowly, a deterioration of memory functioning in Alzheimer's disease is a hallmark of the disease even in the early stages and it seems that most aspects of episodic memory are gradually affected (Weingartner et al., 1981; Wilson et al., 1982). Both storage of semantic information as well as access to such information are affected, especially in the later stages of the disease (Weingartner et al., 1983; Rosen, 1980). In contrast to Parkinson's disease, the deficit in verbal fluency in Alzheimer's disease seems to develop differently. While patients with mild dementia of Alzheimer's type seem to be impaired on both tasks of verbal fluency, their generation of words from a restricted category (animals) is superior to retrieval of words starting with specific letter (Rosen, 1980). As the disease progresses, however, Alzheimer's patients become equally impaired in both tasks (Rosen, 1980; Weingartner et al., 1981). In addition to retrieval, verbal fluency tasks also require intact language functions and, in the early stages of the disease, word-finding difficulties in Alzheimer's disease seem to be

more related to memory disturbances and only in the later stages language involvement becomes more profound (Wilson et al., 1981; Weingartner et al., 1981). In Parkinson's disease semantic memory seems to be selectively preserved throughout the disease, although retrieval of semantic information may be affected.

Compared to parkinsonian patients, some recent findings have shown that even when cognitive level is controlled, the profiles of demented Alzheimer's and Parkinson's patients may differ (Mohr et al., in Press; Litvan et al., in Press; Caltagirone et al., 1989; Pillon et al., 1989). While Alzheimer's patients perform worse in verbal memory tasks, parkinsonian patients appear to have selective difficulties in the tasks which are considered to be sensitive to the effects of frontal lobe damage (Litvan et al., in Press; Caltagirone et al., 1989; Pillon et al., 1989). Confirmation for this hypothesis was seen in demented parkinsonian patients differing in visuospatial processing; specifically Parkinson's patients may be more affected on visuospatial tasks involving abstraction from an incomplete stimulus and visuospatial reasoning (Mohr et al., in Press).

In summary, it appears that cognitive and memory deficits in Parkinson's disease can appear as a combination of subcortical and cortical lesions rather than resulting from lesions restricted to one or the other of these areas. In recent years evidence has accumulated showing that some selective, distinct frontal-type cognitive and memory deficits can be seen even in those parkinsonian patients who develop dementia. These deficits differentiate them from Alzheimer's disease. Behavioral symptoms in Parkinson's disease seem to resemble those seen in other subcortical diseases and in respect to memory there are some indications that similar processes may be involved. Further data, however, are needed to determine whether parkinsonian patients have deficits in those areas such as procedural memory which have been claimed to be specifically linked to basal ganglia structures.

V PRESENT STUDY

1. Rationale and Hypotheses

Although memory seems to be adversely affected in Parkinson's disease, it is not fully understood in which specific processes the impairment occurs.

Recent research has shown that amnesia may not be a unitary phenomenon, but differential aspects of memory functioning may be lost in different neurological diseases while others may be spared. Both etiological factors and the location of the damage in the brain seem to define the specific features of memory deficit in the various disorders.

The purpose of this study was to examine more closely memory functioning in patients with Parkinson's disease within the framework of recent theoretical concepts of research in amnesia in general. In Parkinson's disease, the primary pathological damage is in the subcortical structures, but there is ample evidence that changes may also affect the frontal lobes via their extensive connections with subcortical

structures. Consequently, it could be expected that both of these areas add specific features to the memory disturbance in Parkinsonism. It was assumed that memory failure in Parkinson's disease may involve some features similar to those seen in other subcortical dementias and others, which resemble those seen after frontal lobe lesions. Studies of patients with memory disorders have indicated that a memory deficit in different neurological diseases may be the result of a certain combination of several damaged areas of the brain rather than having its origin in just one particular locus.

Previous studies have shown some features in cognitive deficits of parkinsonian patients which resemble those seen after frontal lobe damage. These deficits may in fact be casually related to the memory problems the parkinsonian patients experience. Memory deficit both in parkinsonian and frontal patients may, then, be a consequence of a processing deficit rather than being a selective failure of memory as it is the case in amnesia. Frequently reported features in episodic memory in frontal lobe patients have included their sensitivity to interference effects. This can be

seen in those patients' inability to use semantic information in an appropriate way. They are unable to maintain new information because of interference from previously learned materials (i.e. proactive interference). They also tend to perseverate their responses which leads to poor performance in memory tasks. Difficulty in accessing semantic structures of memory as shown in decreased verbal fluency (Weingartner et al., 1983; Baddley, 1982), is another feature often associated with frontal lobe lesions. Based on this, it seems plausible that patients with Parkinson's disease may experience similar difficulties as a part of their memory problem.

Problems in overall memory functions in subcortical dementias have been reported to include forgetfulness and a disturbance in the ability to initiate retrieval of information even if it still can be learned (Benson, 1984). Recent research with Korsakoff's and Huntington's patients have introduced certain new perspectives (Martone et al., 1984). It was ascertained that procedural memory (cognitive operations required to accomplish skill tasks) was preserved in amnesia but

impaired in at least one group of patients belonging to the subcortical dementias, namely Huntington's disease. Accordingly, it was suggested that procedural memory may be associated with the basal ganglia structures. If this were indeed the case, procedural memory should also evidence impairment in Parkinson's disease.

In line of the aforementioned considerations, the following hypotheses were tested:

Rather than being impaired in the accuracy of memory in general, it was expected that patients with Parkinson's disease might experience specific deficits in

- a) accessing information from the semantic network and/or
- b) handling interference and/or
- c) learning procedural information

These specific characteristics in cognitive functioning were expected to be evident independent of the general intellectual level of the patients.

2. Methods

Subjects

Twenty patients with idiopathic Parkinson's disease were drawn from a pool of patients seen at the Parkinson's Clinic of the Ottawa Civic Hospital. All patients underwent an extensive neurological exam and were diagnosed on the basis of presence of at least two of the three cardinal features of Parkinson's disease (bradykinesia, resting tremor and rigidity) and the absence of any known cause of secondary Parkinsonism. All patients were outpatients who came regularly to the clinic for examination. The patients were selected by excluding those, who based on the evaluation of the neurologist had developed dementia. Participation in the research was voluntary. All patients gave informed consent.

Parkinsonian symptoms had been present on the average for 5.3 years with a standard deviation of 3.7 and a range of 1 - 11 years. All patients evidenced mild to moderate parkinsonian symptoms (1 to 3 on the Hoehn and Yahr Scale), with one patient in stage 1, 12 in stage 2, and 7 in stage 3 while treated with previously established optimal levels of antiparkinsonian

medication. One was treated with Symmetrel only, with a daily dose of 100 mg; four were on Sinemet only, low doses of 325 + 96 mg (range 200 to 400 mg); 12 received Sinemet in daily doses of 669 + 344 mg (range 300 to 1250 mg) and additionally either Bromocriptine, with daily doses of 23,5 + 14 mg (range 7.5 to 45 mg) and/or on Symmetrel, 175 + 50 mg per day (range 100 - 200 mg), with one patient receiving additionally 5 mg of Pergolide daily. Two patients remained untended throughout the study since their motor symptoms resulted in no significant functional interference in their daily lives. None of the treated individuals experienced significant adverse medication effects at the time of the testing.

Twenty patients matched for age, sex and education (Table 5), who were seen for lower backache complaints, served as controls. These individuals were chosen over healthy volunteers to have available subjects suffering from a physical complaint. None of the controls received any centrally active drugs at the time of testing.

Depression was assessed using Beck's self-rating depression inventory (BDI, 1961). A BDI score of 10 or more is considered to reflect significant depression

TABLE 5
AGE AND EDUCATION, BY GROUP AND SEX

Group/Sex	Number subjects	Age in years			Education in years		
		Mean	Range	SD	Mean	Range	SD
Parkinsons							
Males	14	57.7	46-71	8.1	11.9	6-19	3.0
Females	6	66.8	49-71	9.0	11.3	7-16	2.9
Whole group	20	60.5	46-71	9.2	11.8	6-19	2.9
Controls							
Males	14	58.4	46-73	8.6	14.4	8-19	3.0
Females	6	65.2	58-70	4.4	9.7	4-15	3.7
Whole group	20	60.4	46-73	8.1	13.0	4-19	3.8

(Mayeaux et al., 1981). Thirty per cent of the Parkinson's patients (six) and forty per cent of the controls (eight) evidenced such a BDI score overall. The mean depression score was slightly higher for the controls ($X = 9.25$) than for the Parkinson's patients ($X = 8$), but the difference between the groups was not significant ($F(1,38) = .30, p > .05$).

Procedures

The following neuropsychological and psychological parameters served as outcome measures.

General Cognitive Functions

Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981).

The WAIS-R is a standardized psychometric test of general intelligence. The test yields three intelligence quotients: Verbal IQ, Performance IQ and Full Scale IQ. The verbal subtests Information, Vocabulary, Comprehension, and Similarities require retrieval from

previously acquired knowledge. Digit Span measures immediate memory and performance on the Arithmetic task reflects the ability to numerically manipulate acquired knowledge. Performance subtests mainly require perceptual analysis, organization, and acquisition of new unfamiliar material. Digit Symbol evaluates specifically visual-spatial perception and visual scanning speed and Block Design examines visuo-constructional skills.

Halstead Reitan Battery (Modified by Trites, 1980).

The Halstead Reitan Battery is a standardized psychometric test originally designed for an assessment of neuropsychological impairment in brain injured patients. The subtests are mainly nonverbal and require adaptive abilities rather than previously learned information. The following subtests from the battery were carried out:

Finger Tapping measures psychomotor speed and coordination. This test consists of a tapping key with a device for recording the number of taps. There are five 10-second trials for each hand with brief rest periods

between trials. The score is the mean of the five 10-second trials for each hand. This test has been previously used as an index of bradykinesia (Matthews and Haaland, 1979).

Seashore Rhythm Test measures auditory perception of nonverbal stimuli and also requires attention. Subjects make a same-different differentiation between 30 pairs of rhythmic patterns presented by a tape recorder. The score analyzed is the overall number of incorrect answers.

Speech Perception Test measures perception of verbal material through auditory and visual channels and also requires attention. Subjects underline on an answer sheet one of the four nonsense syllables that most clearly correspond to the word presented by a tape recorder. Altogether there are 60 items. The score analyzed is the number of incorrect answers.

Aphasia Screening Test (a modification of the Halstead-Wepman Test) evaluates expressive and receptive linguistic abilities related to both spoken and written language. Scores vary from 0 to 3 depending on how perfect the answer is.

Sensory deficit is a sensory examination that tests for finger agnosia, skin writing recognition, and sensory perception in the tactile, auditory, and visual modalities. The score is a summary value (from 1 to 3) derived from the number of errors obtained on different tasks.

Trail Making Test evaluates visual-spatial perception. It requires speed and, in the second part of the test, shifting conceptual sets. In part A, subjects must connect 25 consecutively numbered circles distributed on a sheet of paper in a random order. In part B, half the circles are numbered and half are lettered and the subject must connect circles alternating between number and letter sequences. The score is the time spent to connect the circles.

Grip Strength measures motor proficiency. The average force in kilograms is recorded for two trials with each hand using a dynamometer.

Grooved Pegboard measures motor proficiency by evaluating finger dexterity and motor speed. Subjects must insert as rapidly as possible slotted pegs in the holes on the pegboard. The time required to place 25 pegs is recorded

for each hand.

A rating of general adequacy of activities on cerebral integrity is provided by the Impairment Index, which is derived from the results of first six tests. Each of these measures has a cut-off point between normal and impairment levels (Finger Tapping with dominant hand 50 or more; Speech Perception 8 and up; Rhythm discrimination 6 and up; Sensory deficit 1 and up; Aphasia Screening 1 and up; Trail Making Test 12 and down). Values of the Impairment Index can vary from 0.0 to 1.0.

Episodic Memory

Wechsler Memory Scale (WMS, Wechsler, 1945).

The WMS is a standardized measure of general level of memory functions. The Scale yields a Memory Quotient (MQ) based on subtests of Personal and Current Information, Orientation, Mental Control, Logical Memory, Memory Span, Visual Reproduction, and Associate Learning.

Randt Memory Test (a standardized version by Randt and Brown, 1983).

The Randt Memory Test is comprised of seven individual modules which measure both verbal and nonverbal recall and recognition memory with distractors in rote, associative, and incidental situations. Some subscales utilize a selective reminder technique (in different trials only those stimuli are repeated which a subject does not remember from the previous trial) to control overlearning of stimulus material. The test allows for the evaluation of acquisition of information and delayed recall separately. Delayed recall is evaluated twice: during the test session and 24 hours later (next day). The test was designed for the older population. Accordingly, although comprehensive, the testing time is only 20-25 minutes to avoid fatigue effects. The test yields three summary scores: an acquisition and a delayed recall and a global memory index.

Semantic Memory

The Controlled Word Association Task (Benton, 1968).

requires that a subject name as quickly as possible words starting with certain letters (F,A,S) and category names (animals and vegetables) in a restricted time (60 seconds per letter or category). In addition to counting the number of produced words (total number of acceptable words from successive presentation of three letters or two categories), perseverative errors (same word repeated) are counted.

The Sentence Completion Task (Kleiman, 1980, 1983).

consist of 42 highly structured sentence frames with the final word deleted. The subject's task is to give the word that would best complete the sentence. All sentence frames used have a single, generally agreed upon, best completion such as: "Some say that a dog is a man's best ----". The test requires a search of semantic memory for the information needed. The number of errors is recorded.

Interference Effects

Release from proactive interference (a version of Wickens's PI-release technique modified by Winocur, Kinsbourne and Moscovich, 1981) is a method used to evaluate interference effects in memory. In this version, lists of words are drawn from a same or different semantic category and presented to subjects without a distractor task between the list presentation and recall. Earlier studies have shown that this version is sensitive in amnesics, patients with frontal lesion and in revealing age-related changes (Winocur et al., 1981).

The words in different lists belong to one of the four taxonomic categories - sports, professions, body parts, and clothing chosen from the lists by Battig and Montague (1968). Words are printed in large letters and presented by a Kodak Carousel slide projector against a white background approximately 5 feet (1.8 m) from the subject. The end of each list is signified by a blank slide and the experimenter's instruction to report the words. No limit is placed on the amount of time required to read words aloud (requiring visual, articulatory, and acoustic encoding) to avoid complications due to

inattention or modality-specific memory problems (Baddley, 1982).

The test is presented in three different parts. In the first part (no shift condition), five successive lists of nine familiar words from the same category are presented only once. Subjects are instructed to recall each list immediately following the presentation. In the second part (shift condition), the fifth and ninth list start a new category, and are from a different category than the previous lists. In the third part (contextual shift condition), the fifth list in addition to being from a different category, is also printed in a different colour than the first four lists (red letters on green base in contrast to black letters on white base). Such a contextual shift makes a new category list more discriminable from previous lists (Moscovitch and Winocur, 1982). In order to avoid learning effects, the presentation order of the three parts of the tests was randomly changed over the testing sessions.

The number of words in each part are recorded. The error analysis comprises three types of errors: intrusions (the number of words recalled from previous

lists), perseverations (the number of words repeated within the list), and semantic errors (the number of words recalled which were semantically related to the content of the list but which had not been included).

The Stroop Test (a standardized version by Golden, 1978) consists of three parts which are presented in the same sequence to all subjects: one in which colour names (in black ink) are read, one in which randomly ordered colored figures (three blue, red or green X's) are named, and one (the interference sheet) in which the name of the colors are printed in ink of a different colour. In this third part, the subject is required to call out the colour of the ink rather than to read the printed word (e.g. blue is printed either green or red but never in blue). The time allowed for each sheet is 45 seconds. In order to perform the last portion of the test quickly and accurately, the subject must be able to categorize the separate features of the stimuli into colour and verbal content, suppress the latter category, and respond only in accordance with the former. The interference effect in the last part of the test is supposed to occur

as a result of interference in verbal processing. The Stroop stimuli activate an automatic verbal processing response which interferes with the consciously instructed colour naming (Golden, 1978).

The test yields three basic scores (the number of items read in 45 seconds in each sheet): the words score, the colour score, the colour-word score. The latter is used as an interference score. Errors are not counted, because they are corrected, and result in a lower overall score, since the subject is made to repeat the item.

Wisconsin Card Sorting Test (Grant and Berg, 1948) consists of four-stimulus cards each of which is unique in terms of its colour (options), shape (options), and number of items (options). The response cards comprise two sets of 64 cards with all combinations of colour, shape and number. The subject is required to place each response card below a stimulus card in the position he/she thinks it fits best. The subject must first match for colour and then, after ten correct responses, switch without warning to shape and subsequently to number. The

subject must detect the shift from the fact that the experimenter has changed the system of calling "rights" and "wrongs". No other cues are given at any stage. The procedure is continued until the subject has successfully completed six sorting categories (colour, form, number, colour, form, number), or until all 128 cards have been placed. The test measures the ability to identify new concepts and to shift sets. It requires a subject to suppress previously correct responses and produce new one.

Assessment of the overall proficiency of the test is judged by the number of categories achieved (concept formation requiring the subject to make use of positive and negative feedback for problem-solving strategies) and the number of errors made. Analysis of errors include perseverative errors (the inability to suppress ongoing activity despite environmental feedback that is no longer appropriate) and nonperseverative errors. An error is scored perseverative if it followed the category concept which was correct for the immediately preceeding category. All other errors are scored as nonperseverative.

Procedural Memory

Mirror Reading Task (Martone et al., 1984) is a pattern-analyzing task that involves both skill learning (procedural knowledge) and verbal recognition (declarative knowledge). In this task subjects are required to read blocks of word triads that appear as mirror images. Three blocks of 20 triads are presented to each subject on three testing sessions (60 word triads in each session). Ten word triads are unique to each block, and ten word triads are common to all blocks across each three sessions. Thus, with the exception of the first block of the first test session, when all of the triads are new to the subjects, half of the triads within a particular test block have been seen previously and half have not. The order of presentation of the unique and repeated triads were randomized on each block of 20 triads.

Immediately after the third test block on session three, a recognition memory test for the words used during the mirror reading task, are administered. The

subjects are shown a list of 60 type written words: 30 from the mirror reading task, 15 repeated and 15 unique. The remaining 30 words are distractor items that have not appeared in the mirror reading task.

At the beginning of each learning session, subjects are told that they will see slides, each with three words and that the words will appear printed in mirror image. They are told that their task is to read each word aloud as quickly as possible in any order they like, but reading each of them from right to left. No practice trials are given. If subjects do not recognize the word, they are told to report it letter by letter. Subjects are also told when the words or syllables have been read incorrectly. The time to read all three words is measured with a digital stopwatch and recorded for each test triad. If a word triad cannot be read within 120 seconds (maximum time scored), the remaining unsolved words on that slide are read to the subject.

The ability of the subjects to acquire the skill (procedural memory) is evaluated by the mean time needed to read the unique, mirror reflected words. Normal learning of the procedure is reflected by a decrease in

the reading time of the unique word triads. The ability of the subjects to recognize verbal materials (i.e. declarative information) is assessed in two ways: 1) by any differences between the mirror-reading of unique and repeated words and 2) by administering a verbal recognition test following the last trial of mirror reading task. Normal subjects are expected to read the repeated words faster than unique words and they should be able to identify on the recognition task the words used on the mirror reading task.

Tests were administered in the individual sessions at the Royal Ottawa Hospital. Total testing time was approximately 6-9 hours. For most subjects, this was spread over 2-3 days. Furthermore, because the tests were quite demanding and required sustained concentration, the subjects were allowed to have rest periods on demand at appropriate times. Although the neuropsychological battery was comprehensive, all subjects included in the study, completed the testing.

The order of presentation of the tests was varied randomly over the three parts of the release from

proactive interference test and amongst the three parts of the mirror reading task.

Statistical Analyses

Results were assessed statistically using multivariate analysis of variance procedures. Analyses of covariance were carried out when appropriate. The PI-release tasks and the Mirror Reading Task were analyzed by analyses of variance with repeated measures. Correlational methods were used to evaluate the relationships between the memory tasks and the functional motor manifestations of the disease (Hoehn and Yahr scores).

VI RESULTS

1. General Neuropsychological Evaluation

Significant differences emerged between patient and control groups in overall performance on the Wechsler Adult Intelligence Scale - Revised (Full Scale IQ mean $\pm$ SD of 102.8 $\pm$ 10.7, Parkinson's, 112.3 $\pm$ 11.8, controls; $F(1,38) = 7.20$, $p < .01$); nevertheless, patients with Parkinson's disease functioned at a low normal level. Of importance was the fact that there was no significant difference between the two groups in the Verbal IQ 106.5 $\pm$ 12.3, Parkinsonians, 111.0 $\pm$ 12.5 controls; ($F(1,38) = 1.32$, $p > .05$) nor on any of the verbal subtests. There were significant differences both in the Performance IQ 97.2 $\pm$ 10.2 Parkinson's patients, 112.6 $\pm$ 10.7 controls; ($F(1,38) = 21.96$, $p < .001$) and on all the individual performance subtests. The results of the overall MANOVA are summarized in Figure 3 and the results of the individual subtests of the WAIS-R in Table 6.

Figure 3

SUMMARY OF OVERALL MANOVA

MANOVA

($F = 2,30, p < .04$)

TABLE 6
MEANS AND STANDARD DEVIATIONS OF WAIS-R
SCORES FOR TWO GROUPS

Subtests	<u>Parkinson's</u>		<u>Controls</u>		<u>Significance</u> (at $p < .05$)
	Mean	SD	Mean	SD	
Verbal IQ	106.5	12.3	111.0	12.5	n.s.
Performance IQ	97.2	10.2	112.6	10.7	< .001)
Full Scale IQ	102.8	10.7	112.3	11.8	< .01
Information ^{x)}	10.9	1.8	11.6	2.8	n.s.
Comprehension	11.1	2.7	11.2	1.5	n.s.
Arithmetic	10.6	3.1	11.5	3.3	n.s.
Similarities	8.5	3.4	10.0	3.0	n.s.
Sigit Span	9.0	2.7	10.6	2.6	n.s.
Vocabulary	10.9	2.2	11.1	2.5	n.s.
Digit Symbol	6.1	1.6	7.8	1.8	< .003
Picture Completion	7.8	2.2	9.7	2.4	< .01
Block Design	7.5	2.1	10.4	3.1	< .002
Picture Arrangement	6.8	1.8	9.5	2.2	< .001
Object Assembly	6.7	1.9	8.9	1.9	< .001

x) = values in subtests are in scaled scores

In the Halstead Reitan Battery there were significant difference between patients and controls in the Impairment Index ($F(1.38) = 5.46, p < .03$; Table 7). Except for Grip Strength and Finger Tapping with the nondominant hand, the performance of the Parkinson's patients was worse than that of controls in all tasks assessing motor functions. This was especially so in those which required speed, in addition to motor efficiency (Finger Tapping with dominant hand, $p < .04$; Trail Making Test, $p < .01$; Pegboard $p < .001$). Those tests which evaluate purely sensory functions, were not affected (Speech Perception, Seashore Rhythm Test, Aphasia Test, or combined evaluation of a sensory deficit).

2. Episodic Memory

On the Wechsler Memory Scale, performance of parkinsonian patients was consistent with that demonstrated on the WAIS-R (Table 8). Level of performance on this test was in the normal range (Mean MQ = 110.6, SD = 17.5). The control group, on the other

**MEANS AND STANDARD DEVIATIONS OF THE TESTS
EVALUATING THE BASIC COGNITIVE FUNCTIONS IN
PARKINSON'S PATIENTS (N=19) AND CONTROLS (N=14)**

Variables	<u>Parkinson's disease</u>		<u>Controls</u>		Significance (at $p < .05$)
	Mean	SD	Mean	SD	
Finger Tapping, dominant ¹⁾	39.16	9.40	45.78	7.50	.04
Finger Tapping, nondominant ¹⁾	38.84	8.62	43.43	6.93	n.s.
Speech Perception ²⁾	5.47	4.22	3.86	2.98	n.s.
Rhythm discrimination ²⁾	4.53	3.45	4.43	3.13	n.s.
Sensory Deficit ³⁾	1.53	1.12	1.00	1.24	n.s.
Trails, A+B ⁴⁾	11.37	3.40	14.57	3.37	.01
Pegboard, dominant ⁵⁾	130.84	58.82	65.86	9.91	.001
Pegboard, nondominant ⁵⁾	133.84	52.00	70.50	11.29	.001
Dynamometer, right ⁶⁾	29.58	9.22	39.46	10.39	n.s.
Dynamometer, left ⁶⁾	28.73	9.22	29.35	10.29	n.s.
Impairment Index	0.49	0.23	0.32	0.22	.03

- 1) average number of taps per 10 seconds
- 2) adjusted error score
- 3) combination score from visual, auditory, and tactile perception
- 4) adjusted time score for forms A+B combined
- 5) time
- 6) kilograms

TABLE 8
PERFORMANCE OF PARKINSON'S PATIENTS (N=18)
AND CONTROLS (N=20) ON THE WECHSLER MEMORY
SCALE

Subtests	<u>Parkinson's</u>		<u>Controls</u>		<u>Significance</u> (at $p < .05$)
	Mean	SD	Mean	SD	
Memory Quotient	110.6	17.5	122.0	18.3	.05
Information	5.3	0.6	5.1	0.8	n.s.
Orientation	5.0	0.0	5.0	0.0	n.s.
Mental Control	6.5	2.1	7.9	2.0	.05
Memory Passages	7.7	2.6	9.5	2.9	n.s.
Digit Span	10.9	1.8	12.1	2.5	n.s.
Visual Production	7.5	3.1	9.9	2.6	.01
Associative Learning	13.8	3.0	13.6	3.6	n.s.

hand, had a mean MQ of 122 and a standard deviation of 18.3 and the difference between the groups was statistically significant ($F(1,38) = 4.31, p < .05$). Parkinsonians performed consistently worse than normals on several subtests of the Wechsler Memory Scale, namely on Mental Control ($F(1,36) = 4.06, p < .05$), and visuospatial memory (Visual Reproduction: $F(1,36) = 6.72, p < .01$). The difference in Memory Passages (meaningful verbal memory) did not quite achieve statistical significance ($F(1,36) = 3.83, p < .06$).

A comparison between the WAIS-R IQ:s and the Wechsler Memory Scale MQ:s revealed that both groups had higher MQ:s than IQ:s. In order to further control the effects of the general intellectual level on memory performance, an analysis of variance was carried out with the WAIS-R Verbal IQ as a covariate. The difference between the groups continued to be significant ($F(1,37) = 4.05, p < .05$), but the value of covariate was also highly significant ($F(1,37) = 9.90, p < .003$).

Performance of the patients with Parkinson's disease was lower than that of the controls on all parts of the Randt Memory test, although there were no significant

differences in the Memory Index ($F(1,37) = 3.36, p > .05$) or in the Delayed Recall ($F(1,37) = 1.74, p > .05$; Table 9). On the Acquisition Part of the test performance groups performed was consistently different from each other ($F(1,37) = 4.32, p < .05$).

3. Semantic Memory

In both verbal fluency tasks, the FAS and the Category Naming, controls produced more correct words than did patients with Parkinson's disease, but the difference between groups was significant only in the Category Naming ($F(1,38) = 8.50, p < .006$), not in FAS ($F(1,38) = 3.42, p > .05$; Table 10).

An examination of perseverations summarized in Table 11, revealed that the parkinsonian patients made slightly more perseverations than did the controls on both tasks. The mean for FAS was 1.36 and for Categories 1.42 in the control group and 1.68 and 1.42 respectively in the Parkinson's group.

TABLE 9

PERFORMANCE OF THE GROUPS ON THE RANDT MEMORY TEST

	<u>Parkinson's patients</u>		<u>Controls</u>		<u>Significance</u>
	Mean	SD	Mean	SD	(at p < .05)
Randt					
Acquisition	100.95	22.84	114.70	18.34	.05
Delayed Recall	99.42	17.40	106.66	16.86	n.s.
Memory Index	100.00	21.94	111.85	18.34	n.s.

TABLE 10

PERFORMANCE OF PARKINSON'S PATIENTS AND CONTROLS
ON TESTS OF VERBAL FLUENCY

	<u>Parkinson's patients</u>		<u>Controls</u>		<u>Significance</u> (at $p < .05$)
	Mean	SD	Mean	SD	
FAS					
Mean of the letters	13.26	3.40	15.45	4.05	n.s.
Categories:					
Mean of the words	15.42	2.88	18.45	3.64	.006
Sentence Completion					
Errors	5.84	2.72	3.95	2.11	.02

TABLE 11

PERSEVERATIONS IN NAMING CATEGORIES AND FAS

Controls							
	<u>Animals</u>	<u>Vegetables</u>	<u>Total</u>	<u>E</u>	<u>A</u>	<u>S</u>	<u>Total</u>
1.	-	-	-	1	1	-	2
2.	-	-	-	-	1	-	1
3.	1	-	1	-	2	-	2
4.	3	-	3	2	1	-	3
5.	1	-	1	-	-	1	1
6.	-	-	-	2	-	-	2
7.	2	-	2	-	3	-	3
8.	-	1	1	-	-	1	1
9.	-	1	1	-	-	1	1
10.	-	-	-	-	-	-	-
11.	-	1	1	1	-	-	1
12.	-	-	-	1	-	3	4
13.	-	-	-	-	-	-	-
14.	-	-	-	-	-	-	-
15.	1	1	2	-	-	-	-
16.	1	2	3	1	-	1	2
17.	1	1	2	-	-	-	-
18.	-	1	1	1	1	-	2
19.	-	1	1	-	1	-	1
20.	1	-	1	1	-	-	1
Mean	.55	.45	1.00	.50	.50	.35	1.35
Total	11	9	20	10	10	7	27

TABLE 11 (Continued)

PERSEVERATIONS IN NAMING CATEGORIES AND FAS

Parkinson's							
	<u>Animals</u>	<u>Vegetables</u>	<u>Total</u>	<u>E</u>	<u>A</u>	<u>S</u>	<u>Total</u>
1.	-	-	-	-	1	-	1
2.	1	2	3	1	1	-	2
3.	1	2	3	-	-	-	-
4.	-	-	-	-	-	-	-
5.	-	4	4	1	1	-	2
6.	-	-	-	-	-	-	-
7.	1	2	3	1	-	-	-
8.	1	-	1	2	-	2	4
9.	1	-	1	4	1	2	7
10.	-	1	1	1	-	2	3
11.	-	-	-	-	-	-	-
12.	1	5	6	1	1	-	2
13.	1	-	1	2	-	-	2
14.	1	-	1	-	-	1	1
15.	1	-	1	-	-	-	-
16.	-	-	-	2	2	-	4
17.	-	-	-	-	-	-	-
18.	1	1	2	-	1	-	1
19. Missing							
20.	-	-	-	1	-	1	2
Mean	.52	.89	1.42	.84	.42	.42	1.68
Total	10	17	27	16	8	8	31

On the sentence completion test, patients with Parkinson's disease also made more errors than did controls ($F(1,38) = 6.03, p < .02$). There were no differences, however, in the quality of errors. Almost all were semantically and logically related to the context of the sentence.

4. Interference Effects

On the Stroop Test, words were read significantly slower by the patients with Parkinson's disease than by controls ($F(1,38) = 4.31, p < .05$; Table 12). However, there were no differences between the groups in colour naming ($F(1,38) = 2.56, p > .05$) or in colour-word naming ($F(1,38) = 0.81, p > .05$). The latter most strongly evaluates interference effects.

TABLE 12
PERFORMANCE OF THE GROUPS ON THE STROOP TEST

	<u>Parkinson's patients</u>		<u>Controls</u>		<u>Significance</u> (at $p < .05$)
	Mean	SD	Mean	SD	
Word	90.20	14.81	100.25	15.77	.05
Color	57.60	13.33	64.30	13.17	n.s.
Color-Word	31.00	8.93	33.17	10.29	n.s.

On the Wisconsin Card Sorting Test, there were no differences between the groups in number of categories completed ($F(1,38) = 1.89, p > .05$). The results are shown in Table 13. Although the majority of the controls completed all categories, there were six persons who completed less than three categories. However, while 12 (60 %) of the controls finished the test (reached 6 categories), only 7 (35 %) of the Parkinson's patients achieved completion.

Analysis of errors showed that in addition to producing significantly more errors overall ($F(1,38) = 4.21, p < .05$), patients with Parkinson's disease also made considerably more perseverative errors ($F(1,38) = 10.98, p < .002$) than controls. There were no significant differences between groups in the number of nonperseverative errors ($F(1,38) = 1.33, p > .05$). The separate analysis of errors was performed only on those patients and controls, who failed to finish the test. This analysis showed that the parkinsonian patient produced markedly more perseverative errors than controls (Mann-Whitney U, 2-tail test, $U = 15,0, Z = -2.69, p < .007$).

TABLE 13
PERFORMANCE OF THE GROUPS ON THE WISCONSIN
CARD SORTING TEST

	<u>Parkinson's patients</u>		<u>Controls</u>		<u>Significance</u>
	Mean	SD	Mean	SD	(at $p < .05$)
Concepts	3.70	1.98	4.55	1.93	n.s.
<u>Errors</u>					
Total	45.15	24.20	28.90	22.40	.05
Perseverative	21.80	14.04	9.90	7.79	.002
Nonperseverative	23.35	15.92	19.00	16.46	n.s.

The effects of interference in memory tests were assessed in the PI-release paradigm. Three Group x Trials analyses of variance were carried out. Results are summarized in Figures 4, 5 and 6. The first part of the test compared the performance of the Parkinson's patients and controls on the no-shift condition in which all five lists consisted of words in the same category. The results showed that both groups demonstrated a progressive decline in the number of words correctly recalled over Lists 1 - 5. Analysis of variance revealed that the main effect of trials was not significant ($F(1,36) = 1.37, p > .05$).

Against expectation, there were no significant differences between groups in the category shift condition ($F(1,36) = 2.10, p > .05$). Both groups showed similar improvement in recall on Trial 5 (the trial with the category shift). List 5 recall by both groups in the category shift condition was as good as their earlier recall of List 1.

In the condition in which the contextual cues were used, the analysis of variance revealed a significant effect of trials ($F(1,36) = 5.54, p < .02$). The group x

FIGURE 4

**PERFORMANCE ON PARKINSON'S AND CONTROL GROUPS ON THE PROACTIVE
INTERFERENCE TASK WITHOUT A CATEGORY SHIFT**

FIGURE 5

**PERFORMANCE ON PARKINSON'S AND CONTROL GROUPS ON THE PROACTIVE
INTERFERENCE TASK WITH A CATEGORY SHIFT**

PERFORMANCE ON PARKINSON'S AND CONTROL GROUPS ON THE PROACTIVE TASK
WITH A CATEGORY AND CONTEXTUAL SHIFT

trials interaction, however, failed to reach significance, which shows that both groups improved their recall on trial 5 with the category change. Subsequent analysis showed that the contextual cuing was, however, more effective in Parkinson's patients than in controls. The difference between trial 5 in the shift condition and trial 5 in the contextual shift condition was not significant in controls ($t = 1.15, p > .05$) while Parkinson's patients recalled significantly more words in the contextual shift condition than in the shift condition ($t = 2.19, p < .05$).

Three types of the errors were recorded: response intrusions (words that appeared in preceding lists), semantic errors (semantically related words that were repeated within the list), and perseverations (words that were repeated within the list). The error patterns are shown in Table 14. Although the difference in recall between the groups was not significant, patients with Parkinson's disease made significantly more intrusion errors than controls in the no-shift condition ($F(1,38) = 6.61, p < .01$) and in the shift condition ($F(1,38) = 5.14, p < .03$). There were no differences between the

TABLE 14

**MEAN NUMBER OF INTRUSION, SEMANTIC, AND PERSEVERATION ERRORS
FOR PARKINSON'S PATIENTS AND CONTROLS IN ALL THREE CONDITIONS OF THE PROACTIVE
INTERFERENCE TASK**

<u>Condition and group</u>	<u>Response intrusion errors</u> Mean (Trials 1-5)	<u>Semantic errors</u> Mean (Trials 1-5)	<u>Perseverations</u> Mean (Trials 1-5)
<u>No shift</u>			
Parkinson's Controls	5.85 3.40	1.05 0.30	1.95 0.85
	(Trials 1-9)	(Trials 1-9)	(Trials 1-9)
<u>Shift</u>			
Parkinson's Controls	7.85 3.70	2.05 0.95	4.15 1.45
	(Trials 1-5)	(Trials 1-5)	(Trials 1-5)
<u>Contextual</u>			
Parkinson's Controls	3.35 2.00	1.85 0.95	1.80 0.70
			134

groups in number of intrusions in the contextual condition ($F(1,38) = 3.10, p > .05$). Furthermore, Parkinsonians made also more perseverative errors than controls in all conditions (no shift: $F(1,38) = 5.38, p < .03$; shift: $F(1,38) = 9.44, p < .004$; contextual: $F(1,38) = 5.94, p < .02$). The difference in the number of semantic errors was significant only in the no shift condition ($F(1,38) = 4.02, p < .05$).

5. Procedural Memory

The results of the Mirror Reading Test were analyzed with Groups $\times$ Trials $\times$ Sessions $\times$ Conditions analysis of variance (Figures 7 and 8). Figure 7 and 8 show the mean reading time for the repeated and unique words for the two groups across the three test sessions. The analysis of variance yielded significant group ($F(1,36) = 10.25, p < .003$), condition (repeated vs. unique) ($F(1,36) = 152.86, p < .001$), session ($F(2, 75) = 93.52, p < .001$), and block ($F(2,72) = 78.17, p < .001$) effects. A number of significant first and second-order interactions were also obtained including Group $\times$ Session ($F(2, 72) = 7.10,$

FIGURE 7

PERFORMANCE OF GROUPS ON MIRROR READING OF REPEATED WORD TRIADS. MEAN TIME TO READ WORD TRIAD IS SHOWN FOR EACH BLOCK ON ALL THREE TESTS SESSIONS.

FIGURE 8

PERFORMANCE OF GROUPS ON MIRROR READING OF UNIQUE WORD TRIADS.
MEAN TIME TO READ WORD TRIAD IS SHOWN FOR EACH BLOCK ON ALL THREE TEST
SESSIONS.

$p < .002$), Condition $\times$ Session ($F(2,72) = 11.74$, $p < .001$), Group $\times$ Block ($F(2,72) = 4.05$, $p < .02$), Condition $\times$ Block ($F(2,72) = 31.05$, $p < .001$), Session $\times$ Block ($F(4,144) = 25.30$, $p < .001$), and Condition $\times$ Session $\times$ Block ($F(4,144) = 6.60$, $p < .001$) interactions.

The significant group effect indicates that Parkinson's patients were overall slower at mirror reading than controls. The significant condition, session, and block effects demonstrate that this difference remains over the sessions and between the test blocks within each session, both for unique and repeated words.

Inspection of figure 7 and 8 suggest that patients with Parkinson's disease were able to learn the mirror reading skill as well as controls. This was indicated by the apparent decreased reading times from session one to session three and within each session from block one to block three for both unique and repeated words. Furthermore, the words in the repeated condition were read at a faster speed than those in the unique condition by the subjects in both groups. The Group $\times$ Condition interaction only approached significance ($p < .06$). There seems, however, to be a slight difference between

the groups in repeated and unique words over the blocks and sessions as shown in Figures 9, 10, 11 and 12. In the repeated word condition, between sessions two and three and between blocks two and three within each session, parkinsonian patients appear to approach the performance of the controls. In the unique word condition, however, only a slight improvement can be noticed between blocks two and three and between sessions two and three parkinsonian patients even show a small increase in reading time.

Because patients with Parkinson's disease were impaired in several perceptual tasks, an analysis of variance was performed on the mean reading time using the WAIS-R performance IQ as a covariate. This analysis yielded practically the same results as the analysis without a covariate.

The results of the word recognition test administered after the last trial of the Mirror Reading Task, showed that the recognition memory for both repeated ($F(1,36) = 3.14, p < .05$) and unique words ($F(1,36) = 0.06, p > .05$) did not differ significantly from that of controls.

FIGURE 9

PERFORMANCE OF GROUPS ON MIRROR READING OF REPEATED WORD TRIADS.
MEAN TIME TO READ WORD TRIAD IS SHOWN FOR THREE TEST BLOCKS.

FIGURE 10

PERFORMANCE OF GROUPS ON MIRROR READING OF UNIQUE WORD TRIADS.
MEAN TIME TO READ WORD TRIAD IS SHOWN FOR THREE TEST BLOCKS.

FIGURE 11

PERFORMANCE OF GROUPS ON MIRROR READING OF REPEATED WORD TRIADS.
MEAN TIME TO READ WORD TRIAD IS SHOWN FOR THREE TEST SESSIONS.

FIGURE 12

PERFORMANCE OF GROUPS ON MIRROR READING OF UNIQUE WORD TRIADS.
MEAN TIME TO READ WORD TRIAD IS SHOWN FOR THREE TEST SESSIONS.

6. Correlational Analysis

Planned correlational analysis was performed between the disease duration and disease severity (the Hoehn Yahr stages) and different measures of memory and cognition and between the different frontal lobe measures. To minimize chance findings due to such factors as selection and sample size, it was established that a correlation was considered meaningful only when the level of significance for these specific correlations exceeded .01 and a correlation itself exceeded .50.

With these strict criteria, duration of the disease was significantly associated with all three semantic tasks (FAS: $r = .62$, $p < .002$; Category Naming: $r = .50$, $p < .002$; Sentence Completion: $r = .51$, $p < .01$). Duration was also related to the appearance of errors in the PI-release task (intrusions: $r = .52$, $p < .01$; semantic errors: $r = .53$, $p < .008$; perseverations: $r = .71$, $p < .001$). None of these behavioral measures were related to the severity of the disease, although the correlations to the Category Naming and to the errors in the PI-release task approached significance. None of the cognitive and memory measures were associated with the

depression inventory.

Correlational analysis between different frontal lobe tests revealed that the release trial in the PI-task was related to the Category Naming ($r = .58$, $p < .005$) and to the perseveration errors in the Wisconsin Card Sorting Test ($r = -.54$, $p < .007$) and to the Stroop interference task ($r = .50$, $p < .01$).

In summary,

1) Patients with Parkinson's disease performed worse than controls in overall intellectual ability (Full Scale IQ) and on the performance portion of the WAIS-R, but not on verbal IQ. The analysis of individual subtests indicated that differences between the groups in all performance subtests were significant while all of the verbal subtests were performed comparatively by Parkinsonians and controls.

2) Patients with Parkinson's disease performed worse than the controls on those subtests of the Halstead Reitan Battery involving motor performance. No significant differences between groups were evident on

sensory examination.

3) There was a significant difference between the groups in the Wechsler Memory Scale MQ, but the Parkinsonians, nevertheless, performed within the normal range.

Performance on the Wechsler Memory Scale subtests

(Mental Control and Visual Production) classified patients as being significantly lower functioning than controls. The difference between the groups in the subtest of the Memory Passages approached statistical significance.

4) On the Randt Memory Test, the only significant difference between the groups was in the acquisition part of the test. Neither the delayed test section nor the Memory Index revealed differences.

5) Measures which evaluate accessing semantic memory, demonstrated significant differences between the groups only in the Category Naming and in the Sentence Completion test, but not on the FAS word fluency. Patients with Parkinson's disease made slightly more perseverative errors than controls.

- 6) The Stroop performance revealed significant differences only in the first part (reading speed). Neither colour reading or colour-word reading indicated differential performance.
- 7) In the Wisconsin Card Sorting Test, patients with Parkinson's disease made more errors, particularly perseverative errors, than controls.
- 8) Patients with Parkinson's disease showed a normal pattern of proactive interference in the non shift condition demonstrated by a steady decrease of recall, but also showed a normal release from proactive interference in two experimental conditions (the shift condition and the contextual shift condition). Parkinson's patients, however, remembered altogether fewer words than controls. In the contextual shift condition, they improved their performance more than controls. The number of errors, particularly perseverative errors, was significantly higher in the Parkinson's than in the control group.

9) In the mirror reading task, patients with Parkinson's disease were slower overall in learning the skill compared with controls in both the repeated and in the unique condition. Both groups improved their performance at the same rate in repeated presentation of words within blocks and from session to session. There were no significant differences between groups in the recognition test carried out with the words learned during the mirror reading task.

10) Duration of the disease was related to all semantic memory tasks and to the appearance of errors in the PI-release task. Severity of the disease was not associated with these behavioural measures. The PI-release task was correlated to two semantic tasks and to perseverative errors in the Wisconsin Card Sorting Test as well as to the Stroop interference task.

VII DISCUSSION

The main objective in the study was to examine memory and cognitive processes in a group of Parkinson's patients without gross mental deterioration by comparing their performance with controls. A model which involves episodic, semantic, and procedural memories was considered as an appropriate framework for revealing deficits in specific aspects of memory in these patients. The pathological changes in Parkinson's disease would suggest that these alterations may involve features from the subcortical and frontal areas. Accordingly, it was hypothesized that even if the memory in general was not severely affected parkinsonian patients, like those with frontal lobe damage, would be sensitive to interference effects evaluated by the PI-release task, the Wisconsin Card Sorting Task, and the Stroop task. Furthermore, it was expected that they would have difficulties in accessing semantic memory measured by verbal fluency tasks. An impairment in procedural memory assessed by the Mirror Reading task was also

difficulties accessing it immediately after learning. Similar findings have been reported in patients with Huntington's disease (Caine et al., 1977).

The problem of inconsistent retrieval in Parkinson's patients may lie partly in their difficulty of initiating action in an appropriate way. In the Randt Test, different modules of information (personal knowledge, span, word list, associative learning, short story, and picture recognition) are presented one after another in sequence. Consequently, changing from one module of information to another may confuse the patients and affect their immediate performance although they are able to register the necessary information and recall it later. This kind of a deficit in sequential planning may also be a sign of frontal impairment in Parkinson's disease.

The results of the Mental Control subtest of the Wechsler Memory Scale and the Stroop Test lend further support to the activation hypothesis. The Mental Control subtest consists of tasks such as counting backwards from twenty to one, reporting the alphabet,

motor speed. These findings emphasize the fact, that parkinsonian patients continue to have problems in basic adaptive abilities even when medicated at optimum levels. Conversely, clear sensory deficits were not found in these patients.

Altogether, these findings emphasize the importance of careful analysis of the quality and extent of cognitive deficits in parkinsonian patients. Some decline may occur in tasks involving at least some visuospatial and visuomotor components even when the verbal abilities in general remain relatively intact. The interpretation of these deficits, however, remains controversial. According to recent findings, motor components rather than visuospatial elements of the tasks may be more important in successful performance of some subtests of the WAIS-R (the Block Design and the Object Assembly) in parkinsonian patients (Gairotti et al., 1988). Thus, although an impairment in these tasks affects the global evaluation of intelligence, deficient performance only in these tasks cannot be considered as presenting a true, generalized dementia.

Accessing semantic memory. While the semantic memory store itself (Information, Vocabulary) was not impaired in parkinsonian patients, they had difficulties in accessing such information. Three procedures were used to evaluate the facility of subjects in accessing semantic memory: two word generation tasks and a sentence completion task. Compared to controls, patients with Parkinson's disease showed a decrease in verbal fluency in a semantic task (Category Naming). The difference in a phoneme task (FAS) was not statistically reliable. This confirms previous findings indicating that parkinsonian patients have more difficulties in naming words from a more restricted, abstract semantic category than producing words from larger, unfocused categories (Matison et al., 1982). In the latter task, the use of phonemic cues obviously facilitates the search for semantic information (Butters et al., 1987). All semantic memory tasks were associated with duration of motor symptoms, but not with gross motor symptom severity

(Hoehn Yahr stages). It must be noted, however, that the Hoehn Yahr scale is quite a crude measure of the motor symptoms of the disease. Only category naming was correlated with the perseverative errors in the Wisconsin Card Sorting Test.

In general, the deficit in category generation appears to be mild in Parkinson's patients. According to standardized norms (Borod et al., 1980), the average number of animal names produced in one minute for the normal population is 22.5. Parkinsonian patients in this study produced 15 names on average. Further support for the existence of a semantic retrieval deficit in patients with Parkinson's disease comes from the results of the sentence completion test, in which patients had more difficulties than controls. Successful performance in this test requires, in addition to language abilities, retrieval from previous knowledge. A language deficit does not explain the difficulties Parkinson's patients had in this test because they had no problems in the Aphasia Screening Test nor the verbal subtests of the WAIS-R.

Neuroanatomically, the impairments in well-established semantic memories have been associated generally with damage to the parieto-temporal regions of the brain (Mayes, 1988). Recently, however, it has been suggested that storage and retrieval of word names may involve the circuit that involves the left temporal cortex, frontal cortex, and basal ganglia with major storage sites in the left temporal cortex (Mayes, 1988). This assumption would explain the selectivity and the degree of accessing deficit in Parkinson's disease: primary pathological changes are in basal ganglia and their frontal lobe connections, while the temporal cortex is less affected, if at all. Correlations between the Category Naming and some frontal tasks such as the PI-release task and perseverative errors in the Wisconsin Card Sorting Task support the view that the basal ganglia - frontal lobe connectivity may be specifically involved in the retrieval deficit.

Evaluation of episodic memory. The overall accuracy of memory in parkinsonian patients was affected (the

Wechsler Memory Scale and the Randt Memory Test), but relatively mildly so. In spite of the group differences in memory measures, parkinsonian patients continued to perform within the normal range. On the other hand, good verbal abilities may help the patients in verbal memory tasks. Also in amnesia studies it has been found that relatively intelligent amnesics can perform better on some verbal tasks (e.g. in the verbal items of the Wechsler Memory Scale) than less impaired amnesics of lower intelligence (Parkin, 1984). Parkinsonians in this study, however, continued to recall less efficiently even when the effects of verbal cognitive level was controlled using verbal IQ of the WAIS-R as a covariate.

In addition to impairment in overall memory, the results on episodic memory tasks also showed that memory failure in Parkinson's patients appears particularly in the beginning of the task. Given time, they were capable of performing at a level comparable to that of the controls. These difficulties appeared clearly in the Randt Memory

Task, in which both immediate memory and delayed memory can be evaluated. Parkinsonians performed poorly on the immediate recall condition, but were able to remember information as effectively as controls even

after a delay of 24 hours. The reason for these difficulties cannot be either in the deficient initial registration of the information as evidenced by the performance of the patients in the delayed recall or in short-term memory as such because these patients were as capable as the controls in the Digit Span task, which evaluates immediate memory. Furthermore, deficits in the short-term memory generally have been associated with damage to parietotemporal-occipital association cortex, which according to current knowledge is not involved in Parkinson's disease. Rather, the impairment in this part of the test may indicate that Parkinson's patients have difficulties in consistently retrieving stored information. In other words, the information is clearly in memory as evidenced by delayed recall, but reasons for that will be discussed later, parkinsonian patients have

difficulties accessing it immediately after learning. Similar findings have been reported in patients with Huntington's disease (Caine et al., 1977).

The problem of inconsistent retrieval in Parkinson's patients may lie partly in their difficulty of initiating action in an appropriate way. In the Randt Test, different modules of information (personal knowledge, span, word list, associative learning, short story, and picture recognition) are presented one after another in sequence. Consequently, changing from one module of information to another may confuse the patients and affect their immediate performance although they are able to register the necessary information and recall it later. This kind of a deficit in sequential planning may also be a sign of frontal impairment in Parkinson's disease.

The results of the Mental Control subtest of the Wechsler Memory Scale and the Stroop Test lend further support to the activation hypothesis. The Mental Control subtest consists of tasks such as counting backwards from twenty to one, reporting the alphabet,

and counting by three's. These tasks are easy for persons with normal intellectual functioning, but successful performance requires immediate responses with concentration and therefore, is difficult for parkinsonians. On the Stroop Test, Parkinson's patients had difficulties in the first part of the test which simply required that a person reads as quickly as possible words printed on paper. The reading speed of the patients was significantly slower than that of the controls, although in the subsequent parts of the test, there were no significant differences between groups.

General activation problems have been interpreted in previous studies in two ways (Sagar et al., 1988). They may be caused by the slowing of thought processes as a part of bradyphrenia. None of the measures showing deficits in the beginning of the test, however, were associated with the severity of duration of the disease. Alternatively, but probably not exclusively so, activation problems could reflect hypofrontality. The deficit seems to involve only activation of cognitive processes: despite the

difficulties in immediate recall, patients were able to recall the same information relatively well later on.

Another area of memory functioning in which Parkinson's patients had difficulties, was the recall of visual material evaluated by the reproduction of geometric figures from memory (the Visual Reproduction subtest of the Wechsler Memory Scale). Unfortunately, this test is not free from the confounding factors of visuospatial and visuomotor abilities and present results may therefore reflect deficits in those functions in addition to visual memory functions per se.

Interference effects. Three different tests were used to evaluate different aspects of interference effects: The Stroop Test, the Wisconsin Card Sorting Test, and the PI-release task. All three of these tasks have been previously used to evaluate the possibility of increased susceptibility to interference in frontal patients and evidence has been presented that at least the performance on the Wisconsin Card Sorting Test and

failure to release in PI release task are related. Furthermore, impairment in these tasks have been used as evidence of the memory-related role of the frontal lobes. These deficits also have been associated with the appearance of the frontal-type symptoms in Korsakoff's amnesics. In Parkinson's patients these three tests produced varied results.

The Wisconsin Card Sorting Test requires both the ability to sort (i.e. concept formation) and the ability to inhibit a previously established response pattern. Only some of the parkinsonian patients (65 %) seemed to have problems in concept formation. On the other hand, patients demonstrated strong perseveration tendencies as a sign of their difficulties in shifting categories. It is to be noted, that there were some methodological problems in reporting the number of errors in the test, which may have affected the results to some extent. Testing was interrupted when a person had reached six categories. Thus, the number of cards each group received was not the same for all. Because concept formation was better in the control group, the number of errors in

this group may be a little less than if the test would have been completed (128 cards presented for all). Further analysis with only those who failed to finish the test, however, revealed that even then parkinsonian patients continued to produce more perseverative errors than controls.

The appearance of perseveration errors in the Wisconsin Card Sorting Test in parkinsonian patients seems to be one of the most consistent findings in the cognitive profile of these patients and has been repeatedly reported in previous studies. In frontal patients, the impairment demonstrated in this test has generally been interpreted as an expression of a deficit in executive functions. According to this view, frontal lesions impair the elaborative and planned processing of information and consequently, may cause a memory disorder which has similar features as organic amnesia (Mayes, 1988).

In the PI-release task, patients with Parkinson's disease showed a normal build-up of interference and a normal release from PI-effect on presentation of the category list. Compared to the controls, however,

they recalled slightly fewer words in all conditions and therefore, they also improved their performance more than controls when salient environmental cues were added to the task. This shows that they were able to utilize contextual cues in an appropriate way. The processes necessary for release from PI are supposed to be automatic in the sense that shifting does not require any conscious attention (Moscovitch and Winocur, 1983). There are previous findings showing that the memory failure in Parkinson's disease is not in automatic processing (Weingartner et al, 1983).

In previous studies (Tweedy et al., 1982) it has been shown that parkinsonian patients fail to release in the short-term retention in the Brown-Peterson task with distractors. Distractor taskd require that a person processes two different set of information simultaneously, and this may be more difficult for parkinsonian patients, because it demands more active participation. Similar findings have been reported in patients with Huntington's disease (Butters, 1976). Failure seems to be test specific since it supposedly

does not occur in the version similar to that used in this study (Wilson et al., 1987).

The Stroop Test, which evaluates interference effects in the context of two competing categories within a single stimulus did not show any abnormal interference effects in parkinsonian patients. In this respect parkinsonian patients in this study differed from frontal patients, who also in this situation have shown difficulties (Perrett, 1974). There is, however, some evidence that the Stroop-type interference may not be similar to that seen in the Wisconsin Card Sorting Test. Recently, it has been demonstrated that parkinsonian patients showed only slight difficulties in the simple Stroop Test, but their performance was considerably impaired, when they had to change the principle (from colour of the word to name of the word) during the reading (Brown and Marsden, 1988). This situation is more similar to that seen in the Wisconsin Card Sorting Test.

If the hypothesis of the appearance of frontal lobe signs in Parkinson's disease were indeed correct, there should have been an impairment on tasks which

are sensitive to interference effects. The finding that only one of the three interference tasks was affected, is not, however, entirely contradictory to the frontal lobe hypothesis.

One explanation could be that these tasks evaluate different functions, which are not all impaired in Parkinson's disease. It has been suggested that frontal lobe damage produces two types of erroneous behaviour: perseverations due to interference seen in difficulties in more complex problem solving tasks and distractibility or "stimulus-boundedness" which can be seen in those tasks which require inhibition of irrelevant factors and these factors instead of relevant ones start guiding the behaviour (Shallice, 1982). Difficulties in the problem solving tasks such as the Wisconsin Card Sorting Test can best be characterized as an inability in abandoning a behaviour even when it is no longer adequate in achieving the goal. The vulnerability of the frontal patients to interference has also been attributed to a general inertia of cognitive processes causing the patient to persevere

instead of moving to another item (Moscovitch, 1982). Rather than requiring problem solving, the inhibition tasks such as some verbal fluency tasks (e.g. the letter generation) and the Stroop Task require suppression of the most available responses (Laine, 1982). In frontal lobe patients it has been shown that performance in the Stroop Test and in word production starting with a given letter are related. The common factor in both of these tests is that they both demand the suppression of the usual habit of using words according to their meaning and instead act either according to colour as in the Stroop or concentrating on the initial letter as in the FAS task (Perrett, 1974). Category naming does not belong to this group because in this task inhibition of the semantic meaning of the word is not required. Actually the meaning is the fact what the subject is looking for (Perret, 1974).

Parkinson's patients seem to have the greatest and most consistent difficulties in those situations in which they must change the strategy when circumstances change: they start perseverating their

answers. On the other hand, in inhibition tasks such as in the Stroop and in the word production task (FAS), their performance appears to be comparable to that of controls. These results also give support to the interpretation that parkinsonian patients are deficient in more effortful processes. Inhibition tasks are more automatic than problem-solving tasks (Shallice, 1982).

The appearance of intrusion and perseverative errors in memory task such as PI-release creates problems in this interpretation. These kind of errors have generally been explained as an abnormal facilitation of memory traces (Weiskrantz and Warrington, 1982), i.e. traces cannot be suppressed and thereby they intrude. In Parkinson's patients, however, the appearance of perseverative errors may be more related to their difficulties in handling semantic information rather than to memory as such. Intrusion errors are typical also for frontal patients (Kapur, 1987) and for Korsakoff's patients (Kinsbourne and Winocur, 1975). Interestingly, also in frontal patients susceptibility to intrusion errors has been

interpreted differently from other interference effects. It has been suggested that intrusions can be a result of the patients' inability to identify the temporal order in which items were presented rather than being a deficit in recognizing the items (Mayes, 1988). Furthermore, it seems that even in frontal patients all interference tasks may not deteriorate simultaneously (Stuss et al., 1983; Kapur, 1987), indicating that different characteristics of interference may be involved in these tasks. Likewise in Korsakoff's disease, memory failure and intrusion errors have not always correlated, which further supports the assumption that different processes may be involved (Kinsbourne and Winocur, 1975).

The specific deficits seen in Parkinson's disease in different tasks may originate also from the fact that frontal cortex is not functionally unitary. In frontal lobe patients, it has been maintained that lesions to dorsolateral regions rather than orbitofrontal areas are associated with recall problems and with the temporal organization of events (Mayes, 1988). Both patient groups have a deficit in

executive tasks, but the mechanism by which this deficit arises may differ. Patients with dorsolateral damage are more likely than orbitofrontal patients to perseverate their responses in the situations characterized by changing demands (Milner, 1964; Mayes, 1988), while in similar situations, patients with orbitofrontal lesions seem to be unable to maintain extended sequence of correct behavior (Stuss and Benson, 1982). Generally it is thought, that dorsolateral areas are more essential to the generation of word lists than orbitofrontal ones (Stuss and Benson, 1983; Milner, 1964), but the task specificity has not yet been established.

Nevertheless, there is an anatomical basis for the appearance of differential frontal symptoms in Parkinson's disease. There are several distinct subcortical frontal circuits connecting different parts of the caudate, substantia nigra and the globus pallidus to various frontal areas. Although at least five such circuits have been differentiated anatomically, any functional specificity is still poorly understood. Neurochemically both the

nigrostriatal and the mesocorticolimbic dopaminergic systems may be involved in the appearance of the frontal lobe symptoms in Parkinson's disease. Two mechanisms by which dopamine depletion may affect cognitive functioning have been suggested. One plausible mechanism is a depletion of dopamine in the mesocorticolimbic system, which projects primarily to medial frontal areas and another via one or both of the orbitofrontal and dorsolateral prefrontal circuits (Gotham et al., 1988). To date little is known, however, of the relative dopamine depletion in these separate circuits either at the level of the basal ganglia or the frontal cortex in Parkinson's disease (Gotham et al., 1988).

Affected connections must not necessarily be dopaminergic. Other neurotransmitter systems, particularly noradrenergic and cholinergic systems may be implicated as well (Agid et al., 1987). Involvement of the noradrenergic system may play a role in the pathology of Korsakoff's patients and these patients also may have cognitive and memory deficits which resemble those seen

in frontal lobe patients. Frontal involvement in Korsakoff's patients, however, seems to be more widespread than in parkinsonian patients: they fail to release from proactive interference and they also have a deficit in the Wisconsin Card Sorting Test imposed on their severe memory deficit. Differences can arise from the fact that the noradrenergic pathways may not be uniformly affected in Parkinson's disease (Agid et al., 1987). It still must be proved, however, whether the noradrenergic system is related to any of these deficits.

Assessment of procedural memory Although Parkinson's patients required much more time overall to learn the new skill (words written in reversed letters) than did the controls, there was no differential slowing at the rate of learning in nonrepeated and repeated items. This means that in addition of being slower in their ability to acquire the rules and procedures for reading mirror-reversed text, parkinsonian patients were also unable to improve their performance when they had an opportunity to utilize their memory for the specific words (repeated words). Their

performance on the recognition test both for unique and repeated words, however, was equal to that of controls.

A previous study with Huntington's disease has shown that these patients learned unique words slower than repeated words, and there were differences at the rate they learned the skill from trial to trial. Thus, if the basal ganglia structures are indeed involved in learning of skills (i.e. procedural memory), some areas of the basal ganglia are more sensitive to this kind of deficit. Compared to subjects in this study, Huntington's patients in this previous study had more severe overall memory deficit.

The slowness of patients with Parkinson's disease in the mirror reading task may also be related to their perseverative tendencies mentioned previously and thus be relevant to the frontal hypothesis. The requirements of the task in mirror reading are qualitatively different from those used in verbal and visual memory tasks. Instead of trying to remember the exact stimulus given, a person must try to remember the rule and act according to that rule. In

the test situations, most of the patients with Parkinson's disease themselves were surprised at their difficulties. They also seemed to be fully aware of having seen a particular letter previously even if they could not read the word. Furthermore, they repeated the letter time after time wrong way similar to what they had done on the previous trials even after mentioning having seen it before. They seemed to remember the perceptual aspect of the words but still were unable to apply the rules involved without a considerable delay. Similar behavioral features have been described in frontal patients as well (Milner, 1976). In addition, the acquisition of a skill in the beginning requires more effortful processes than in the later stages when it has been automatized.

In this study, as in most clinical work, selection of statistical methods for evaluation of results is of importance because of the small sample size and the large number of variables to be accounted for. In the present study, multivariate analyses of

variance procedures generally were used to assess the results in order to control the experimentwise error rate. Only in the PI-release task and in the Mirror reading task was analysis of variance with repeated measures used. Furthermore, a strict conservative approach was applied for the correlational analysis so as to minimize chance findings. An implication of this approach of accepting reliably the group differences would weaken levels of significance in that some small but real differences may have gone undetected due to limited power. Further research in the future in memory changes associated with Parkinson's disease should be useful in identifying such differences.

Another aspect of statistical analysis which becomes a point of consideration in interpretation of the results, is the magnitude of the experimental effects. Some of the observed differences were numerically small, although statistically significant, and it can be questioned how much of the overall variability really can be attributed to them. One example of this point is the interpretation that

differential deficits may be involved in accessing semantic memory based on the small but significant differences between two fluency measures (the FAS and the Category Naming). However, the interpretation that there indeed are differential effects is based not only on the statistical results but also on theoretical consideration and on the pattern of other findings in the study.

A related issue of concern in these measures that emerge from the conservative approach adopted is that in absolute value the difference between the two measures of fluency was small (3.12 words produced in the Category Naming vs. 2.19 words produced in the FAS). This weakens the interpretation of differential effects. This is a problem common to much clinical research. Future studies must be directed towards clarifying whether or not the apparent differential effects reported here are in fact reliable. Similar caution must be applied also to the interpretation that parkinsonian patients had activation problems based on the group differences found in the beginning phases of some tasks.

VIII CONCLUSIONS

The findings of this study further support the view that the cognitive and memory deficits seen in Parkinson's disease result from the combination of pathological areas affected by the disease: subcortical structures and their frontal connections. Qualitatively, memory impairment appears to express itself more as a memory-related processing deficit often seen after frontal lobe damage rather than as an actual failure in remembering. In essence, observed symptoms in memory and cognition are consistent with the pattern of features included in the definition of subcortical dementias. It is debatable, however, whether observed changes indicate true dementia in these patients. Although they showed difficulties in their ability to handle nonverbal information in addition to deficient memory functioning, their verbal abilities were comparable to those seen in their control group.

Memory impairment in subcortical dementias has not been defined accurately. Generally the term

"forgetfulness" has been used (Benson, 1983). This implies that the deficit may not be so much in the inability to learn the new material as in the difficulty in initiating the retrieval of stored memories (Benson, 1983). In this study parkinsonian patients showed such difficulties in retrieval from both semantic and episodic memory. Accessing semantic memory, was not normal, but the degree of impairment, however, seemed to depend on the requirements of the search strategies: the more cognitively complex the search, the less successful the search. Consequently, in the verbal fluency tasks, when patients could choose their responses freely (automatically) from broader category information (e.g. letter task), they experienced less difficulties than when they had to select answers from restricted categories (e.g. animal names). The latter task requires search through conceptual categories. Deficient access to semantic information may also explain the difficulties these patients experienced in initiation of episodic memories. Dilatory initiation did not always produce the total loss of memory

traces, but rather caused inconsistent recall of information.

Difficulties in processing semantic information may also lead to abnormal persistence of information and, at least partly, explain the uncommonly high amount of intrusion errors in some memory tasks and the perseverative errors in executive tasks. As in the case of accessing semantic information, tendency to persevere could be seen more clearly when effortful processing and planning of action were needed. At the cognitive level, parkinsonian patients showed severe difficulties in handling interference in the face of changing demands. Inability to access properly semantic information could be seen also in the PI-release task. Intrusion errors may appear, because patients are unable to differentiate between old and new material. Such discrimination requires efficient access to semantic information. On the other hand, parkinsonian patients were capable of remembering information relatively well in the PI-release task even when confronting interference. They developed the expected PI-effect (recall decreased in

first four lists) and showed a resulting release when the category was changed. Because release from PI is supposed to be automatic, this further supports the interpretation that parkinsonian patients are able to use semantic information in an appropriate way when effortful processing is not involved.

Previously it has been shown, that procedural memory is specifically impaired in subcortical dementias (e.g. in Huntington's disease). Parkinson's patients in this study were slower than controls at learning a new skill in the mirror reading task, but they were equally impaired both on repeated and nonrepeated items. Although patients with Parkinson's disease were able to recognize the words as repeated, they were unable to overcome their difficulties in acquiring the rules and procedures necessary in learning to read mirror-reversed text. One explanation for the slower learning may be the fact, that in learning a new skill, performance is in the beginning more dependent on attention-demanding effortful processing which suffers in Parkinson's disease.

Most clearly, the deficits in Parkinson's disease resembled those described in frontal patients, but symptoms seen here did not entail all those associated with frontal lesions. Thus, parkinsonian patients showed a selective impairment on some tasks sensitive to frontal dysfunction with relatively normal performance on other tasks. Recent neurochemical and neuroanatomical facts have indicated that the frontal lobes may contain several areas which are functionally dissociable and it may be that some basal ganglia - frontal lobe connections are more involved in Parkinson's disease than others and produce some characteristic symptoms. These findings are still inconclusive, but they may well give some insight for further specification of the "frontal syndrome" in Parkinson's disease.

Altogether, evidence presented here shows that using available models of memory as a framework, it is possible to improve the understanding of the nature of memory functions in neurological diseases. Recent models of amnesia have tried to integrate the

knowledge of different aspects of memory functions with the current neuroanatomical and neurobehavioural information allowing a broader and at the same time more exact view to underlying mechanisms of the cognitive and memory deficits in these diseases. This information is necessary for treatment and management of these patients.

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