

REGIONAL CEREBRAL BLOOD FLOW AND COGNITION IN
DEMENTIA OF THE ALZHEIMER TYPE

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A Thesis submitted to the University of Glasgow in fulfilment
of the requirements for the degree of Doctor of Philosophy.

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December 1993

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ACKNOWLEDGEMENTS

I would particularly like to thank Dr. Lindsay Wilson for supervising this thesis and for his continual help and encouragement, and the confidence that this has given me.

I would also like to thank Mary-Theresa Hansen, Dr. Jim Patterson and Dr. Dave Wyper for directing and carrying out, the SPECT scanning and for numerous occasions where they provided help and advice.

I wish to thank John McColl for statistical advice and encouragement.

I worked closely with Susan Cameron and Gita Bhutani who contributed a great deal to the project, and without whom, we would not have enjoyed such a positive response from patients and families. I would like to thank them especially.

Several psychiatrists were involved in this work but would like to thank Dr. Susan Logie, Dr. Elizabeth Barron and particularly, Dr. Tony Moffoot, for his enthusiastic approach to the memory clinic.

I would like to thank Gartnavel Royal Hospital Day Units, the patients and their families.

I thank all my family and close friends for providing continual support and encouragement, something which I could not have managed without.

SUMMARY

The studies described in this Thesis were designed to investigate the patterns of cerebral blood flow (CBF) deficits that occur in Dementia of the Alzheimer Type (DAT) and relate them to performance on a variety of cognitive tasks. Previous work investigating the relationship between CBF and cognition in DAT (Bonte et al. 1986; Burns et al., 1989; Hunter et al., 1989) has produced large numbers of non-specific associations which are difficult to interpret. It was hypothesised that more meaningful associations might be produced if the assessment of cognition involved more specific neuropsychological tests. Therefore these studies aimed to investigate the CBF-cognition relationship using a general cognitive test as well as a number of specific neuropsychological tasks. In recent years the focus of research in this field has shifted from the later to the earlier stages of DAT. This shift is reflected here with the investigations of rCBF and cognition not only in a moderate to severe DAT group, but also in a mild and a minimal group.

Using a dedicated neuroimager (SME 810) and the relatively recently developed radiopharmaceutical, ^{99m}Techneium labelled Hexamethyl-propylenamine oxime (HMPAO). Single Photon Emission Computerised Tomography (SPECT) was carried out to measure regional cerebral blood flow in DAT patients and controls. SPECT images were obtained for two slices; a 'standard' slice containing medial and lateral frontal, temporal, posterior temporal, occipital, calcarine, thalamic and basal ganglia regions; and a 'high' slice containing high frontal and parietal regions. Measures of blood flow were obtained and expressed as proportions of calcarine activity for normalisation purposes. The patient populations were recruited from a psychiatric hospital (moderate and severe cases), and from a memory clinic (minimal and

mild cases.) All patients were diagnosed as suffering from DAT according to the CAMDEX diagnostic criteria (Roth, Tym, Mountjoy et al., 1986) and severity was classified according to cognitive performance on the CAMCOG (Roth et al., 1986) a general cognitive assessment procedure.

Further cognitive assessment involved recall and recognition memory performance on a Delayed Recognition Span Task (DRST) (Moss et al., 1986), performance on four established 'Frontal' tasks (word fluency, Wisconsin card sorting task, delayed alternation task, subject ordered pointing task) and performance on a standardised confrontational naming task (Graded Naming Test, McKenna & Warrington 1983). Performance of the DAT patients compared to controls was examined for both the memory and frontal investigations, while performance on the naming task was examined for the presence of highly specific subgroups within the DAT population itself.

SPECT scanning was carried out within four weeks of neuropsychological assessment. Correlational analyses were performed in order to investigate the relationship between cognition and rCBF. In particular, correlations were carried out between CBF and performance on the CAMCOG (and its subscores) , CBF and performance on the Recognition Span Task and CBF and performance on the frontal tasks. The relationship between performance on the naming task and CBF was investigated quite differently. Subgroups of patients were selected on the basis of the types of naming error they made and their CBF patterns were examined to see whether they reflected their particular cognitive impairment.

These studies found that a memory clinic provides a suitable method of recruiting cases of early DAT for research purposes and that the analysis of presenting symptoms may contribute to the difficult task of identifying

very early cases of dementia. The results of the CBF studies support the view that deficits develop very early on in the degenerative process since the minimal group display a clear left temporal deficit. The increased severity of the mild DAT group is reflected in their CBF picture; this group display deficits in much of the cortex as well as the thalamic region. The moderate to severe group also displayed extensive CBF deficits reflecting severe damage to all cortical regions.

The cognitive assessment of the patients with the CAMCOG revealed ceiling and floor effects suggesting that this type of task is more suitable for general cognitive monitoring rather than for the investigation of specific cognitive functions. The Recognition Span task illustrated very early deficits in both recall and recognition and demonstrated that recall scores distinguished the minimal DAT group from the control group. While recall scores drop to floor level by the moderate stage of DAT, performance on the recognition tasks shows that some recognition memory ability remains beyond this point. Performance on the frontal tasks was also shown to be impaired by DAT and related to overall severity. No outliers were found on any of these tasks therefore making it unlikely that a disproportionate frontal deficit exists in these patients. The Wisconsin Card Sorting Test was found to be particularly unsuitable for both the DAT and elderly controls since performance was very poor on this task. Performance on the Graded Naming Test identified three specific subgroups; those with a perceptual deficit, those with a semantic deficit and those with an anomic deficit each deficit reflecting impairment to a different cognitive process.

Relating rCBF and cognition revealed multiple correlations with the CAMCOG. These correlations, while fitting with theories of localisation of function probably simply reflect relationships between overall cognitive impairment and CBF. Correlations between the Delayed Recognition

Span Task and CBF were more interesting since correlations specifically involved temporal and thalamic regions, both of which are known to be involved in memory function. Furthermore, a relationship between frontal CBF and recall was found while no such relationship was found with recognition; perhaps reflecting the differential demands of these two memory processes. Investigating the different CBF patterns produced by each of the three naming subgroups revealed a high degree of concordance between the cognitive impairment and the cortical regions displaying CBF deficits in each group.

These, and other findings, are discussed with reference to several major issues concerning research in this field. Firstly, early CBF changes in DAT, where it was concluded that CBF deficits do appear to develop very early on in the dementia when only very slight memory impairments are present. Secondly, with respect to differential diagnosis and Frontal Lobe Dementia, the findings suggest that neither frontal CBF, or frontal neuropsychological deficits should be used to differentiate between the dementias. Finally, with reference to the use of different methods of cognitive assessment, these studies conclude that specific neuropsychological tasks should be used if meaningful associations between CBF and cognition are to be found.

CHAPTER ONE

INTRODUCTION

Dementia is a recognised degenerative syndrome, which generally occurs in late adulthood, is characterised by intellectual impairment including a breakdown of memory, language, perception, praxis, problem solving and abstract thinking. It can also include disorders of personality, mood and social behaviour. Paranoid symptoms, delusions and aggression may also develop particularly during the later stages. The prevalence of dementia has been estimated to be 5% of those over 65 and 20% of those over 80 (Terry & Katzman, 1983). Jorm, Korten & Henderson (1987) have reported that prevalence rates double with every five years increase in age, in populations over 65. Therefore with the growth of our elderly population, dementia has become one of the most pressing medical problems of the twentieth century and will remain so, well into the twenty-first century.

The last decade has witnessed a growing awareness of the problems associated with dementia. As a result, considerable momentum has gathered behind research focusing on various aspects of dementia. The search for the aetiology of dementia has revealed at least 60 potential causes (Haase, 1977). These include vascular disorders, tumours, infections, toxins, metabolic disorders, neurodegenerative disorders and also HIV (Everall, Luther & Lantos, 1993). However, Alzheimer's Disease (AD) remains the most common single cause of dementia accounting for about 50 to 60 percent of all dementias (Katzman, 1983).

THE NEUROPATHOLOGICAL AND CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE

The first reported case of AD (Alzheimer, 1907) was of the autopsy

findings of a 55 year old woman who had displayed progressive dementia. The results of this study revealed the presence in the cortex of abnormal nerve cells containing tangles of fibres (neurofibrillary tangles) and clusters of degenerating nerve endings (neuritic plaques). During subsequent decades debates continued over the specificity of these neuropathological markers and the relationship between 'presenile' and 'senile' dementia. By the late 1960's, research had reached the conclusion that mental status in life, correlated with neuropathological changes of the type described by Alzheimer, at post mortem (Blessed, Tomlinson & Roth, 1968) and that the neuropathological changes found in 'presenile' and 'senile' AD were identical (Terry, 1964). Therefore Alzheimer's Disease was established as a single disorder of major consequence to both the medical profession and organisations concerned with public health.

To date the accurate diagnosis of Alzheimer's disease remains dependent on neuropathology. At present there is no known antemortem marker for AD and while some work using biopsied material has been done (Neary et al., 1986), it is generally recognised that the lack of available treatment specific to the diagnosis suggests that this level of intervention is unjustified and even unethical. The majority of reports of confirmed AD refer therefore, to work involving post mortem investigations of brain tissue. Whether through biopsy or post mortem investigation, the definitive diagnosis of AD depends on the presence of senile plaques and neurofibrillary tangles in the frontal, temporal and parietal regions of the cortex and in the amygdala, the hippocampal formation, the basal ganglia and the substantia nigra. Khatchachurian (1985) summarised the minimum microscopic criteria necessary to establish or confirm the diagnosis of AD. While it is beyond the scope of this thesis to describe these detailed criteria, the procedure requires firstly, the neuropathological exclusion of other forms of organic dementia (eg. Pick's Disease), subsequently, age-related norms or criteria, for the

presence and density of senile plaques and neurofibrillary tangles are applied.

It is, therefore, clear that short of using biopsies, an antemortem diagnosis of AD can only be one of 'presumed' Alzheimer's disease and that confirmation depends, ultimately, on neuropathological analysis. However, research into Alzheimer's disease must apply some level of antemortem diagnosis in order to classify patients for research purposes. As the clinical diagnosis of Alzheimer's disease is not a definitive diagnosis, but a presumed diagnosis, the use of the term Alzheimer's disease to describe a case of presumed Alzheimer's disease is at least very misleading. It is more accurate to refer to these cases as examples of Dementia of the Alzheimer Type or DAT, since this highlights the fact that the dementia follows the clinical picture associated with AD but that its neuropathological classification remains unconfirmed. The clinical diagnosis of DAT will be discussed in some detail in chapter 2, however it is important to note that this diagnostic procedure involves the consideration of clearly identified inclusion and exclusion criteria in order to ensure the highest possible degree of accuracy and the avoidance of both Type I and Type II errors. For these reasons, the accuracy of the clinical diagnostic procedure is of considerable interest. The only way to evaluate this is to study the concordance between the clinical and neuropathological diagnoses. This can be carried out by multidisciplinary research groups who have both a clinical and a neuropathological component. Examples of such studies have produced levels of concordance ranging from 100% (Morris et al., 1989; Martin et al., 1987) to 68% (Boller et al., 1989). This represents a considerable disparity in diagnostic accuracy and might be explained in terms of variations in the strictness with which one applies the clinical criteria. However, it must be remembered that the neuropathological diagnosis of Alzheimer's Disease is also dependent on criteria. These criteria are subject to variations in levels of adherence and to specific cut-off points, around

which there remains considerable debate, especially with reference to normal limits of senile plaques and neurofibrillary tangles. The work described in this thesis was carried out as part of a multi-disciplinary project and post mortem confirmation of the clinical diagnosis was available where possible. This depended on consent of the families and on whether death had occurred in the patients studied. The level of concordance between clinical and neuropathological diagnosis for the present set of studies is estimated to be 80% based on the neuropathological investigation of 30 cases. Within this thesis, the studies and their findings refer mainly to cases of unconfirmed, or presumed AD, therefore for correctness and to avoid confusion, the term Dementia of the Alzheimer Type (DAT) will be used throughout.

THE AETIOLOGY OF ALZHEIMER'S DISEASE

The aetiology of AD remains unknown although numerous theories have been proposed. The controversial theory of the involvement of aluminium in the development of AD has probably received most attention. While Schneck, Reisberg and Ferris, (1982) among others, have reported abnormally high levels of aluminium in the brain tissue of cases of AD. A genetic factor is also thought to play a part in the development of AD. A familial component for AD has been reported with early onset cases (Whalley et al., 1982) and more recently with later onset cases (Martin et al., 1988), for a review of this area, see Clarke & Goate (1993). Further evidence of a genetic factor in AD has emerged from the link between Down's syndrome and AD. It has found that the few cases of Down's syndrome who have lived beyond the age of forty, show a similar neuropathological picture of plaques, tangles, choline acetyltransferase loss and abnormal amyloid protein to that found in AD (Yates et al., 1980). While evidence of a genetic factor does exist, it has been suggested that this factor interacts with other possible factors such as neurotoxins and infectious agents to produce AD in susceptible individuals (Nalbantoglu, Lacoste-Royal & Gauvreau, 1990). Another

possible risk factor for AD has been shown to be previous serious head injury (Mortimer et al., 1985). Finally, a number of other, less substantiated, risk factors have also been identified. These include malnutrition (Abalon 1984), thyroid disease (Heyman, Wilkinson & Hurwitz, 1983; Heyman, Wilkinson & Stafford, 1984), increased maternal age of mother of AD sufferer (Cohen, Eisdorfer & Leverenz, 1982), and perhaps rather oddly, an excess of AD births during the months January, February and March (Philpot et al., 1989).

THE STAGING OF DEMENTIA OF THE ALZHEIMER TYPE

The very nature of a degenerating clinical syndrome like DAT, leads to the assumption that clearly identifiable stages must exist. Constantinidis (1978) described a four-stage deterioration characterised by a progressive and simultaneous development of aphasia, apraxia and agnosia. This model describes memory impairments as being universal to all stages and not as a discriminating factor between the stages. In contrast, Reisberg, Ferris & Crook (1982) described a stage model with seven stages of decline, in which memory played a prominent discriminating role.

There is general agreement that a common picture of cognitive and behavioural breakdown can be described (Cummings & Benson, 1983; Huppert & Tym, 1986; Bayles & Kaszniak, 1987; Spinnler & Della Sala, 1988). Early on in DAT, a distinctive impairment in recent memory develops, this is sometimes accompanied by a decline in topographical memory resulting in spatial disorientation. Patients might display exaggerated premorbid personality traits as well as signs of irritability, apathy, anxiety and/or hostility. Anomia, both in spontaneous speech and on confrontational naming, is common early on in DAT as are other verbal impairments such as loss of spontaneity. The next stage of DAT would generally be characterised by further development of the memory impairment and therefore more extensive confusion. Apraxia, agnosia

and dysphasia may also develop at this stage together with deficits in calculation and simple problem solving as well as significant disturbances in reasoning ability. This moderate stage of DAT might also be characterised by a prominent apathy, a flattening of affect and possible defective social judgment resulting in antisocial and inappropriate behaviour. The later, or severe stage of DAT reflects the total dependence of the patient on others. By this stage behaviour and cognition have broken down to such a degree that changes in memory and other cognitive functions are hard to identify. Paraphasias, such as echolalia and palilalia and verbal perseverations become common as do babbling and mutism. The patient will display little, if any, premorbid personality traits and will generally suffer from double incontinence by this time. Therefore while stages do exist in DAT and a stage model can be a useful interpretative tool, there is some disagreement as to how best to describe these stages. Perhaps there should not be one single method, instead the most appropriate method might depend on the aims of the study.

The rate of decline in DAT is an area that has not received much attention. This may be because it is difficult to measure decline without making assumptions concerning reference points such as approximate time of onset of the dementia. There are many different dimensions or scales on which to measure decline including cognition, behaviour and rCBF, and here again, the choice of which to use would depend on the demands of the study in question. Spinnler & Della Sala (1988) estimated the average time course of DAT to be 6 to 12 years and it might be reasonable to expect the rate of decline to vary between different points along this time course. While the general description of DAT usually depicts a gradual and continuous decline, there have been reports of a plateau stage (Cummings & Benson, 1983; Katzman, 1985). In a more recent study, Haxby et al. (1992) investigated the rate of cognitive decline in DAT. They found a plateau stage in patients at the

early stage of DAT who had isolated memory impairments. They also reported that once non-memory deficits emerged, the rate of decline increased dramatically and while remaining approximately constant for each patient, varied considerably between patients.

SPECIFIC COGNITIVE DEFICITS ACCOMPANYING DEMENTIA OF THE ALZHEIMER TYPE

The above description of the degenerating process of DAT is a general picture of both the cognitive and behavioural breakdown. Neuropsychological research has also identified specific cognitive deficits accompanying DAT. The most frequently reported cognitive deficit in DAT is the impairment in memory function. This is not a unitary deficit and is reflected in impairments of primary (short-term) memory (Wilson et al., 1983) and secondary (long-term) memory (Wilson et al., 1983; Martin et al., 1985; Becker et al., 1987). Impairments in retention as indicated by increased forgetting rates, have been reported in DAT (Kopleman, 1985; Moss et al., 1986), as have deficits in remote memory (Wilson, Kaszniak & Fox, 1981; Becker & Nebes, 1986; Montaldi & Parkin, 1987). Both recall and recognition memory process have been reported to be impaired in DAT, although they are thought to be differentially damaged at different stages of the disease (Moss et al., 1986; Vitaliano et al., 1984; Welsh et al., 1992). A number of studies have been carried out to investigate the memory breakdown in DAT within the Working Memory model (Baddeley & Hitch, 1974; Baddeley, 1986). These studies have shown that the Central Executive System, responsible for decision making, problem solving and the control and coordination of other working memory components, is impaired in DAT (Morris & Baddeley, 1988; Baddeley, et al., 1991). These authors have interpreted their findings as illustrating impairments in divided attention, holding information in primary memory and retrieving information from semantic memory in DAT. Impairments in selective attention have also been reported by Freed et al., (1989) and by Sahakian et al., (1990).

Sahakian et al., (1990) however, report that the attentional deficit is not found in all DAT patients and their findings suggest it may not be present early on in the degenerative process. However, their earlier work with Parkinson's Dementia patients of very mild severity (Downes et al., 1989), where attentional deficits were found, suggests that the presence of this type of deficit might reflect a particular pattern of neuronal damage rather than the severity of the dementia.

Another area of cognition frequently reported to be impaired in DAT is language. The earliest sign of language impairment in DAT is a naming deficit, or anomia, which is produced on a confrontational naming task. Patients, when shown line drawings of common everyday objects and asked to name them, invariably have difficulty in producing the correct name (Bayles, 1982; Martin et al., 1986; Welsh et al., 1992.) Bayles & Kaszniak, (1987) have focused much research on the breakdown of semantic memory in DAT. The interpretation of the term semantic memory is an open issue, however Bayles and Kaszniak (1987) used the conceptualisation of semantic memory as a "cognitive faculty in which concepts, but not their linguistic representations, are stored." They concluded from their research that DAT patients suffer damage to both the processes and contents of semantic memory, while the mechanical aspects of reading, writing and speaking are relatively spared until quite late on in the dementia. They also report that other areas of language breakdown might include anomia in spontaneous speech, circumlocutory and/or 'empty' speech and a loss of spontaneity.

A third major area of cognitive impairment in DAT is that of constructional apraxia and visuo-spatial skills. Constructional apraxia is most commonly identified in DAT patients through a difficulty on a standard clock drawing task (Villa, Gainotti & De Borris, 1986). Other visuo-spatial skills such as drawing (Moore & Wylie, 1984), facial recognition (Wilson, Kaszniak & Bacon, 1982) and spatial disorientation (Henderson, Mack & Williams,

1989) have been shown to be impaired in DAT and in some cases, were found to be the primary deficit very early on (Martin et al., 1986; Brouwers et al., 1984; Eslinger & Benton, 1983).

While these three areas of cognition have been described separately, it is important to appreciate the difficulty in assessing specific functions due to the complexity of human cognition. It is difficult to measure performance in one cognitive domain without making demands of another domain. For example, the effects of deficits in language and attention are difficult to eliminate from measurements of performance in other cognitive domains such as memory or praxis. An awareness of the complex interrelationship between cognitive domains is particularly pertinent to the study of dementia since, unlike many other clinical syndromes, most areas of cognition are impaired at some point.

So far, this section has described the cognitive picture common to most DAT sufferers, however the literature suggests that a degree of heterogeneity exists within this picture. As Martin et al., (1986) conclude, while DAT may constitute a single neuropathological process, it clearly does not constitute a single neuropsychological syndrome. Kirshner et al., (1984) reported relatively circumscribed word-finding and language deficits in DAT as did Martin et al., (1986). In contrast, deLeon, Portegal & Gurland (1984) reported focal visuo-spatial and constructional abilities similar to those described by Martin et al., (1986). While none of these studies were able to produce neuropathological confirmation of DAT, studies by Podegar & Williams (1984) and Crystal et al., (1982) described focal anomic and focal spatio-constructional deficits respectively in post-mortem confirmed cases of Alzheimer's Disease. These and other findings have provided strong evidence that cognitive subgroups of DAT exist and that they exist independently of severity. While there is a general picture of DAT and evidence of a staging process, reflecting overall cognitive and behavioural severity, it is also

clear that subgroups of patients exist.

THE ASSESSMENT OF GENERAL COGNITIVE PERFORMANCE IN DEMENTIA OF THE ALZHEIMER TYPE

The study of cognition in DAT involves two levels of investigation. Firstly, the investigation into specific cognitive deficits as described in the previous section. The second level of investigation involves the assessment of general cognitive performance which is commonly used as a method of rating the severity of the dementia. The Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975) has been one of the most commonly used assessment general cognitive assessment tools. This test comprises 30 questions concerning orientation, memory, language and praxis and takes only a few minutes to administer. Despite the brevity of this test, Galasko et al., (1990) have attempted to produce a shortened version. This study concluded however, that further language assessment was necessary if the MMSE was to be a valuable tool in the identification of dementia. Another study (Dick et al., 1984) found that further assessment of both language and visuo-spatial function might improve its value in differentiating focal versus diffuse hemisphere disease. These studies provide examples of an area of confusion concerning the cognitive assessment of neurological patients. Depending on the aims of the investigation, a short test like the MMSE might be appropriate, however, to expect such a test to differentiate focal and diffuse brain damage is unrealistic. Therefore, if the aims of an assessment involve more than obtaining a global cognitive picture, a test like the MMSE would not be suitable; specific neuropsychological assessment tools should be used instead. It was the lack of specificity of the MMSE that led to the development of the Cambridge Cognitive Examination (CAMCOG) as a subcomponent of the CAMDEX (Roth et al., 1986). The CAMCOG is described in chapter 2, however, while it measures performance in a number of cognitive domains it is also

restricted in its ability to identify specific cognitive deficits. These 'clinico-cognitive' tests are useful research tools in the rating of severity of dementia, perhaps more so than some of the clinical rating scales. This type of rating scale, for example, the Global Deterioration Scale (Reisberg et al., 1982), or the Clinical Dementia Rating scale (Berg, 1988) rely on a degree of subjective interpretation in terms of the presence or absence of cognitive impairments. Moreover, this type of scale refers mostly to the patient's ability to perform everyday activities, rather than to performance within specific cognitive domains. Therefore while these different methods of assessing the general cognitive performance of a patient are valid, their application within research must depend on the aims of the research in question.

FUNCTIONAL NEUROIMAGING

Advances in technology allow us, through neuroimaging, to examine the extent, location and nature of brain lesions in vivo. The last decade has witnessed considerable developments in the field of functional neuroimaging, and in its application to the investigation of clinical disorders.

The brain is an obligate glucose user and must metabolise this aerobically, but has no stores of glycogen. Therefore since all the glucose and oxygen come directly from the blood, measures of regional Cerebral Blood Flow (rCBF) reflect levels of brain activity. Earlier methods of rCBF measurement in clinical studies, used the ^{133}Xe clearance technique. When a freely diffusible tracer, which does not become bound, is introduced as an instantaneous bolus, equilibrium of tracer concentrations between blood and brain is soon established and the rate at which the tracer is subsequently washed out, gives a measure of cerebral blood flow. Therefore, after an intra-carotid injection of ^{133}Xe , the instantaneous arrival and subsequent clearance of tracer can be

measured by multiple external scintillation detectors, each measuring the activity in a different brain region. The rate of disappearance of ^{133}Xe from each region is proportional to the level of perfusion in that region and absolute flow values can be calculated from the exponential clearance curves. The invasiveness of the intra-carotid injection technique seriously limits its clinical usefulness and led to the development of methods in which ^{133}Xe could be administered intravenously or by inhalation. The number of detectors positioned over each hemisphere is variable, but commonly 16 detectors are positioned over each side of the head, allowing regional information to be obtained (Risberg et al., 1983). Resolution is limited by the radiation dose given to the patient (which determines count rates at each detector), the amount of scatter (which is relatively high), and the time available for imaging which is limited when dynamic (eg. wash-out) methods are used. This is a planar or 2-dimensional technique and therefore cortical perfusion values dominate the information obtained.

In contrast to the ^{133}Xe method, Single Photon Emission Computed Tomography (SPECT) produces 3-dimensional information about brain function. SPECT involves the intravenous administration of a radiopharmaceutical labelled with a gamma emitting isotope. The gamma counts emitted from the brain are then detected by a gamma camera and images of cortical and subcortical slices are constructed from these counts reflecting regional cerebral blood flow and therefore, brain activity. Data is acquired at equally-spaced orientations around the brain and then 'reconstructed' to form tomographic images representing a plane, usually transverse, in the subject's brain. One advantage of this technique in comparison with the ^{133}Xe technique is that the data obtained is 3-dimensional and therefore provides more accurate positional information, allowing for better localisation of lesions. A further advantage of SPECT is that the contrast in the images it produces is much higher since the effect of the underlying and overlying tissues is

greatly reduced. However one disadvantage of the SPECT technique is that it produces relative and not absolute values of blood flow. The SPECT technique and radiopharmaceutical used in the studies featured in this thesis will be described in more detail in chapter 3 as will the methods adopted to overcome the lack of absolute blood flow values.

Positron Emission Tomography (PET), also produces tomographic images reflecting the concentration of radioactive tracers in the brain. In this neuroimaging technique images reflect the function of the brain in terms of glucose metabolism, oxygen uptake or other functional parameters, depending on the particular technique used. In this way, the measurement of brain function made by PET imaging is more directly related to brain activity than that made by SPECT imaging. However, while PET might provide a more direct indication of brain function, both these techniques have the potential to investigate endogenous biochemical activity as well as responses to drug administration. Another area of neuroimaging where both these techniques have considerable potential, is the imaging of activation trials. Functional neuroimaging can be carried out during the administration of a cognitive or behavioural task, thereby providing images of the "activated brain". While most researchers recognise the advantages of PET over SPECT, the availability of PET scanners is restricted on the basis of cost, since a cyclotron is required as part of the equipment. Few medical centres therefore, have a PET scanner, while SPECT scanning is slowly becoming a routine part of many neurological and psychiatric investigations and as a result, an increasing number of these scanners are becoming available. Another reason why SPECT imaging is more readily available is that the equipment does not have to be dedicated to brain imaging. Rotating gamma cameras for example, can be used to image any part of the body and as a result, have a greater level of applicability and therefore become a more cost effective piece of equipment.

REGIONAL CEREBRAL BLOOD FLOW IN
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During the last decade, when the technological developments mentioned above, were made, there was also a rapidly growing awareness of the malignancy and prevalence of DAT and consequently, its recognition as a major scientific challenge. This combination led to numerous studies investigating rCBF in DAT (Bonte et al., 1986; Johnson et al., 1985; Risberg, 1985; Gemmell et al., 1984; Neary et al., 1987). Several general conclusions can be drawn from reviewing these earlier studies. Firstly, a considerable degree of heterogeneity exists in the CBF deficits accompanying DAT. The areas of cortex reported to show deficits included the frontal and temporal regions (Bonte et al., 1986; Johnson et al., 1985;), the posterior temporal regions (Johnson et al., 1985;) and the parietal regions (Risberg 1985; Gemmell et al., 1984; Bonte et al., 1986; Johnson 1985; Neary et al., 1987;). The only cortical region thought to be relatively spared in DAT was the occipital cortex (Risberg, 1985). Therefore while most areas of cortex have at some stage been reported to be affected, the differing patterns of CBF deficit reported by each study highlights this heterogeneity. A second conclusion that can be drawn from the early studies, which is also related to the issue of heterogeneity, is that the severity of the DAT population under investigation may affect the findings. Different patterns of blood flow deficit, may to a certain extent, reflect different levels of severity of the disease, therefore adding to the heterogeneous picture. The third conclusion, also related to the issue of heterogeneity, is that considering the diagnostic difficulties mentioned earlier, some of the heterogeneity might reflect problems of differential diagnosis and therefore rather than imaging DAT, several of the earlier studies may have been imaging a sample of mixed dementias. Finally, despite the heterogeneity often reported, there is one feature common to most studies; this is the reduction of blood flow in parietal regions. The frequency with which this deficit was reported, led Holman

to conclude in his George Taplin Memorial Lecture (1986), that reduced parietal blood flow was the hallmark of DAT.

The focus of most subsequent CBF research in DAT can be related to the conclusions outlined above. For example, recent research has attempted to identify CBF changes accompanying the early stages of DAT (Perani et al., 1988;). However few studies have attempted to investigate the "preclinical" stages. Reed et al., (1989) studied rCBF in early DAT cases with isolated memory problems but they were not "preclinical". In a PET study, Haxby and his colleagues (Haxby et al., 1986) had concluded that metabolic abnormalities might precede clinical symptomatology (ie. cognitive deficits). In contrast, Reed's study (1989), concludes that memory impairments might precede the onset of CBF deficits in the temporal and parietal regions and that a lack of temporal and parietal deficits in CBF does not discount DAT. Considering the relationship between brain metabolism and blood flow, outlined in the previous section, a possible explanation of these apparently contrasting results could be that metabolic abnormalities precede CBF changes. Recent studies have also addressed the issue of differential diagnosis (Cohen et al., 1986; Costa et al., 1988; Battistin et al., 1990) although the value of SPECT as a diagnostic tool remains unclear. The focus of some CBF studies has been to identify the CBF patterns characteristic other (non-Alzheimer) dementias, especially those which are not distinguishable from DAT in vivo (Neary et al., 1987; Elfgren et al., 1991). An ambitious study by Holman and his colleagues (Holman et al., 1992) has identified a number of CBF patterns found, with differing frequency, in DAT. While this and other studies may contribute to the DAT picture, the power of SPECT in the differential diagnosis of dementia probably remains limited, at present, to that of the casting vote. In other words, when no other information (clinical or physiological), answers the diagnostic question, SPECT may have a potential diagnostic role. For example, SPECT might either refute DAT on the basis of no posterior

CBF deficits, or accept DAT on the basis of the presence of these deficits.

CEREBRAL BLOOD FLOW AND COGNITION IN DEMENTIA OF THE ALZHEIMER TYPE

Following the initial efforts to investigate CBF patterns in DAT it became clear that combining CBF and cognition might aid the investigation of severity, differential diagnosis and heterogeneity. Many studies were carried out to investigate the first two of these issues. It was clearly established that increased severity of dementia, measured in terms of overall cognitive performance on a rating scale, correlated with the extent of CBF deficits (Hagberg & Ingvar, 1976; Duara et al., 1984)). In terms of differential diagnosis, the investigation becomes considerably more complex. Since the clinical methods of differential diagnosis involve some form of cognitive assessment, extreme care must be taken to avoid circular arguments. For example, in differentiating DAT from Multi-Infarct Dementia, the Hachinski scale (1983) is administered which distinguishes these two populations on many factors including the identification of focal neurological deficits (which manifest themselves cognitively). Therefore, attempts to use cognition and blood flow to distinguish the two groups would simply reflect the presence of the focal deficits, already identified on the Hachinski Scale. Work focussing on this issue should concentrate on those dementias where neuropathological confirmation is required. The investigation of heterogeneity by combining neuroimaging and cognition has led to the identification of specific subgroups. Martin et al. (1986) identified marked individual differences regarding word-finding and visuo-spatial abilities in DAT patients. They found that while some patients displayed equal ability in these two cognitive domains, others displayed specific impairments in one or other of the domains which were not simply a reflection of disease severity. These subgroups were investigated further by measuring glucose metabolism using PET. The study showed that while overall metabolic rates were equal, the impaired word-finding group had a reduced

metabolic rate in the left temporal region and the impaired visuo-spatial group had a reduced metabolic rate in the right temporal and parietal regions. By following-up the patients over time, they also found that initial subgroup membership was predictive of the subsequent pattern of deterioration. Similar studies have been carried out using PET and have provided further evidence of subgroups and differing patterns of deterioration (Grady et al., 1988). A similar study using CBF and SPECT has also been reported (Burns et al., 1989) however, the assessment of cognitive deficits was not carried out using a neuropsychological test battery as used by Martin et al., (1986) or Grady et al., (1988). Burns' study (1989) used a general assessment procedure designed for the severity rating of dementia. It is possible that the failure to identify subgroups similar to those described by Martin et al., (1986) and Grady et al., (1988) reflects a failure to use specific neuropsychological assessments.

RESEARCH AIMS

The research described in this Thesis was designed to carry out two general aims:

- 1) To investigate and define the patterns of regional Cerebral Blood Flow deficit that accompany Dementia of the Alzheimer Type.
- 2) To investigate the relationship between regional Cerebral Blood Flow and cognition in Dementia of the Alzheimer Type.

CHAPTER TWO

RECRUITMENT AND DIAGNOSIS OF A SUITABLE PATIENT POPULATION

Since the recruitment and diagnosis of a suitable study population is fraught with confounding problems and issues and may therefore prove much more problematic than originally foreseen, this chapter will deal with three important issues which are often the cause of problems for those researching DAT:

1. The identification of dementia.
2. The classification of Dementia of the Alzheimer Type.
3. The recruitment of a suitable patient population.

This chapter will start by considering these three issues in some detail before describing the diagnostic procedure adopted for the studies included in this thesis. Finally it will describe both the procedure and results of an experimental recruitment method focusing on the need to gather cases of very early DAT.

1. THE IDENTIFICATION OF DEMENTIA

The identification of dementia in a person must constitute the very first stage in the procedure of classifying a case of DAT. It is an issue which should be dealt with quite separately from that of the diagnosis of DAT. Unfortunately however, these issues are frequently confused and what should be a clear distinction between the psychological identification of dementia and the medical classification of its type is often blurred. For example, while neuropsychological assessment can strongly aid the

former it cannot as yet be used for the latter (which relies entirely on medical exclusion). In this sense, therefore, publications whose titles suggest that their or others' findings provide a neuropsychological contribution to the diagnosis of DAT or dementia (Huff et al.,1989) might contribute to the confusion because the issue of diagnosis in DAT, while being problematic, makes the assumption that dementia has been identified and merely assesses its severity as part of the diagnostic procedure. This blurring of terms can be particularly damaging because it allows the unwary to minimise the problems associated with the identification of dementia itself by seeing it as purely a small subcomponent of diagnosis. This is seen particularly in the development of some clinico-cognitive tools (Berg et al., 1982). While at the later stages, the identification of dementia is generally quite clear and straightforward, earlier stages are not so easily identified

for the following reasons:

- a) The presence of mild cognitive problems or deficits can be caused by conditions and factors other than dementia.
- b) The definition of a mild cognitive deficit is highly subjective, dependent on many factors and difficult to measure.
- c) Non-disease related, age-associated cognitive deficits are not uncommon in the elderly population and therefore further complicate the identification of dementia.

To date, the majority of DAT research has concerned patients suffering from the later stages of the disease (moderate and severe cases) mainly because these patients are by this stage registered with some community or health organisation and therefore constitute a readily available population allowing one to avoid to a large degree, the serious problems outlined above. More recently however, clinical, neuropsychological and

some neuroimaging research has moved its focus to the earlier stages of the disease process, (Berg, 1988; Storandt & Hill, 1989; Prohovnik et al., 1988; Reed et al., 1989; Perani et al., 1988). This shift in emphasis is partly due to the fact that the study of earlier cases may be more informative clinically, more interesting and challenging neuropsychologically and more productive in terms of future pharmacological treatment. The group of studies described here involve patients of all severities, however, particular studies were designed to address DAT at particular stages and this change in focus from the later to the earlier stages is reflected here.

2. ISSUES IN THE DIAGNOSIS OF DAT

The diagnosis of DAT is a complex procedure and must be clearly differentiated from the diagnosis of Alzheimer's Disease which remains dependent on post mortem neuropathological findings. Since at present there is no known in vivo indicator of AD, all diagnoses prior to post mortem can only be of presumed AD and therefore referred to as cases of Dementia of the Alzheimer Type. This diagnostic procedure is based on the exclusion of other possible causes of dementia and for this reason is long and costly in comparison to many other psychiatric diagnoses. In order to ensure that this procedure is carried out in a systematic and standardised fashion, a set of inclusion and exclusion criteria are required. Various research and health related organisations worldwide have developed sets of such criteria which, in general, correspond well to each other.

The NINCDS-ADRDA criteria developed by McKhann et al., (1984) is probably the most widely used diagnostic tool in the USA while the

CAMDEX developed by Roth et al., in 1986 is possibly the most frequently referred to procedure in the UK. Other sets of criteria have been developed by the Medical Research Council and there also exist standard DSM III diagnostic guidelines (American Psychiatric Association, 1980). The diagnostic procedure adopted for the present studies will be described below but first I will identify potential problems inherent in any system of diagnosis of DAT.

Apart from the fore mentioned problem of the identification of dementia which is itself an inclusion criterion for DAT there are other important factors which add to the complexity of this diagnostic decision making process. The process can be time consuming and costly and even then the diagnosis remains one of DAT and not AD. As Levy (1982) points out in a discussion on recruitment for therapeutic trials, it is not atypical to have to screen ten cases of dementia to produce one suitable case of DAT. This obviously is not because it is rare as it is the most common form of dementia, rather it is because there are many exclusion criteria and depending on the strictness with which these criteria are applied one may have more or less success at recruiting a study population. Having said that, there is however little scope to ignore the diagnostic criteria. One such area is that of physical illness which, in an aging population, is not uncommon. The exclusion of cases with illnesses or history of illnesses such as cancer can greatly reduce the potential study population as can exclusion of cases with impaired sight or hearing. At this point any research project must decide how strict to be with such criteria and this should depend on the aims and objectives of the research in hand and should be described in published work. Another area where exclusion may not be straightforward is that of alcohol use. Alcoholic dementia involves very high levels of alcohol intake and exists as a disorder in its own right and as such will be

discussed later, however, lower levels of alcohol intake would also be grounds for exclusion from a DAT population. The difficulty lies in assessing both the individual levels of alcohol use, which are frequently underestimated by those interviewed, and the level at which this may become a confounding factor in the diagnostic process. Again, the importance placed on alcohol intake and the efforts made to assess it must be determined by the aims and objectives of the research .

The above are examples of factors which are thought in some way to affect human cognitive performance and as such are identified as exclusion criteria. There exists another area of exclusion which is more clear cut and easily identifiable; this is the area of the differential diagnosis of dementia. As mentioned in the introduction many causes of dementia exist however, there are several commonly recognised alternative causes of cognitive impairment and dementia, each of which can be determined by laboratory tests, scans, and histories:

a) **Multi-Infarct Dementia.** This is generally caused by high blood pressure and can be identified using a combination of the Hachinski score and CT scans. It is common in the elderly and often occurs in conjunction with DAT. If it occurs on its own it can be relatively easily distinguishable from DAT since the onset and development of cognitive change is generally acute and stepwise in contrast to the more insidious onset and gradual development of DAT. If it occurs together with DAT its presence is often difficult to detect but may be identified through CT scans.

b) **Pseudo-Dementia.** This form of dementia as its name suggests, resembles dementia in behaviour and cognition but is generally considered to be non-organic and caused by the presence of

depression. It is also not uncommon in the elderly and can be identified through interviews with the patient and informant. Other forms of Pseudo-dementia also exist (Hysterical dementia, Simulated dementia) however, Depressive Pseudo-dementia is the most common.

c) Alcoholic Dementia. This form of dementia develops as a result of years of alcohol abuse. It should be distinguished from the Wernicke-Korsakoff syndrome (WKS) in that a Wernicke Encephalopathy is not thought to occur. The onset of cognitive change is insidious and results in a more global deficit typical of dementia rather than the amnesia associated with WKS. An alcoholic aetiology is identified through interviews with the patient and informant.

d) Pernicious Anaemia. This B12 deficiency has been associated with the development of progressive dementia and laboratory tests can easily identify the deficiency.

e) Megaloblastic Anaemia. This results from a deficiency in Folic Acid and reports have pointed to an association between folic acid deficiency and organic psychiatric illness including impairment of memory and dementia. This deficiency can also be detected by laboratory tests.

f) Normal Pressure Hydrocephalus. This is an enlarging of the ventricles despite normal ventricular pressure and in the absence of proportionate atrophy in the sulci and gyri. It is known to produce symptoms similar to dementia including forgetfulness and a general intellectual impairment. It can be detected primarily through a CT scan and subsequently through pressure monitoring.

While the above are all alternative causes of dementia and cognitive

impairment there are several other forms of dementia which may display similar patterns of deterioration to that of DAT but have distinct pathophysiological diagnoses of their own. Unlike a) to f) above, these dementias cannot yet be distinguished from DAT in vivo and rely solely on post mortem pathology for their differential identification. In some cases their very existence as distinct from AD remains unclear. A number of interesting questions derive from this issue whose answers may lie to some extent, in combined neuropsychological and neuroimaging investigations. For this reason these alternative forms of dementia are worthy of some detailed description and discussion.

a) Pick's Disease (PD). This form of dementia like AD, depends ultimately on post mortem investigations to confirm its diagnosis. The neuropathological identification of PD contrasts with AD in its absence of plaques and tangles and the presence of 'Pick' and 'Hirano' bodies together with mid-cortical layers taking on a spongy appearance while the neurons display a swollen or 'balloon' shape and extensive demyelination of the white matter. PD is also characterised by a clear shrinkage of the frontal and temporal lobes accompanying a mild general atrophy which may also affect the Basal Ganglia and Thalamus. The parietal and occipital regions are rarely affected by this disease. Interestingly, Neumann and Cohn (1967) proposed the possible existence of a second form of PD which they termed Pick's Disease Type II or Progressive Subcortical Gliosis and is characterised by pronounced and severe subcortical gliosis with little if any affect on the cortex itself. Any cortical changes accompanying this alternative form of PD were described as producing shrunken rather than swollen cortical neurons.

From a clinical and behavioural perspective, PD is an early onset dementia peaking between 50 and 60 years of age. The most distinctive

feature is reported to be changes indicative of frontal lobe damage such as alterations in character and social behaviour, early on in the dementing process with the later development of memory and other intellectual deficits. Little work has focussed on the psychological profile of PD and neuroimaging studies have rarely concerned themselves with it. EEG findings are generally normal (Johannesson et al., 1979) and do not reflect the predominant frontal characteristics of PD. In contrast the CT scan of a typical case displays substantial atrophy to the frontal and temporal regions with enlargement of the frontal horns. The posterior regions are not significantly affected.

b) Frontal Lobe Dementia (FLD). Recently the most important issue concerning frontal lobe involvement in DAT has been the identification of a new form of dementia, namely Frontal Lobe Dementia (FLD) (Brun, 1987). As with AD and PD, FLD is dependent on post mortem investigations to confirm its existence. Histopathologically, it is characterised by predominantly frontal change as opposed to the more posterior change normally associated with DAT and is differentiated from DAT and Pick's disease by a lack of plaques and tangles and Pick cells, respectively. While FLD itself, is characterised by spongiform changes and astrocytic gliosis, these degenerative changes in FLD have so far been described as nonspecific (Gustafson, Brun & Risberg, 1990). Measurements of rCBF in suspected FLD cases indicate abnormal flow patterns and focally reduced rCBF in the frontal regions. Clinically, FLD patients like PD patients have been reported to have normal EEGs and tend to present with early emotional and personality changes while memory and spatial functions have been found to be relatively spared (Gustafson, 1987). Two recent studies have investigated the psychometric characteristics of FLD in patients whose diagnosis was confirmed at post-mortem. They found a lack of consistency in the

psychometric performance of their patients while both describe emotional and personality problems interfering with test administration (Johanson & Hagberg, 1989; Knopman, et al.,1990). Knopman et al (1990) have demonstrated impairments on frontal tests such as word fluency, mazes, trail-making and recency memory. There is not, however, at present, any established differential psychometric profile of FLD.

Some studies have sought to differentially diagnose FLD on the basis of in vivo investigations such as clinical presentation and neuroimaging techniques (Neary, et al., 1988; Jagust et al., 1989). Neary et al(1988) reported evidence on 7 cases of a presumed frontal lobe dementia using SPECT as well as clinical and neuropsychological histories. The SPECT findings clearly indicated greater frontal blood flow deficits than normally expected in DAT. The neuropsychological assessment of these patients included the use of tasks generally regarded as sensitive to frontal lobe function (eg verbal fluency and the Wisconsin Card Sorting Task) and the results revealed deficits, although it is important to note that these deficits were not related to the severity of the disease. Moreover, the study clearly demonstrated that the FLD patients, despite their orientation in space and time, performed poorly on other memory tests. In both studies mentioned above, the sample sizes were small (7 and 5 respectively) and the diagnosis remains to be confirmed histopathologically. While both Brun (1987) and Neary et al., (1988) conclude that FLD is likely to make up between 10 - 20% of organic dementias, Brun (1987) has stressed it may be unwise to diagnose FLD on purely clinical grounds due to strong evidence of heterogeneity within the dementias.

3. RECRUITMENT OF A SUITABLE RESEARCH POPULATION

The method of recruiting a suitable population must be guided by the aims of the research project in question. For example, different methods

of recruitment should be adopted for the collection of patients of differing severity, likewise as mentioned earlier, the strictness to which some of the exclusion criteria are met (eg. physical illness, impaired sight or hearing) must depend on the needs and limitations of the project. The recruitment of most DAT populations to date has been through the use of some form of psychogeriatric service; either hospital day units or long-stay wards. This technique is ideal for projects wishing to investigate the latter stages of DAT (eg. combined imaging and post mortem studies) but not so for projects aiming to investigate the earlier stages of DAT. Since the intention of this thesis has been to study the CBF patterns that accompany the earliest stages of DAT and relate these to both general and specific measures of neuropsychology, it became clear early on that these studies required the use of patients in the earlier stages of the disease where their cognitive abilities still allowed them to perform adequately on neuropsychological tests. This requirement became clear after the completion of the work described in chapter 4. Therefore while initial work involved moderate and severe cases of DAT recruited from a hospital population, much of this thesis focuses on patients suffering from minimal or mild DAT. The recruitment of these two groups involved the setting up of a Memory Clinic which is described later in this chapter.

THE DIAGNOSIS OF DAT

The Cambridge Diagnostic Examination for the Elderly (CAMDEX) (Roth et al., 1986) is a psychiatric tool which ensures that the diagnosis of DAT is carried out in a strict and standardised fashion. The CAMDEX criteria for the diagnosis of DAT are outlined below.

1. GRADUAL ONSET AND PROGRESSION OF DEMENTIA
2. EXCLUSION OF SECONDARY AND REVERSIBLE DEMENTIAS
3. EXCLUSION OF A VASCULAR AETIOLOGY
4. EVIDENCE OF ATROPHY

Information concerning these inclusion and exclusion criteria is obtained by administering the CAMDEX which consists of eight subcomponents each of which must be completed before a diagnostic decision is taken .

- | | |
|-------------------------|-------------------------------|
| 1. DEMOGRAPHIC DETAILS | 2. PSYCHIATRIC INTERVIEW |
| 3. COGNITIVE ASSESSMENT | 4. INTERVIEWER'S OBSERVATIONS |
| 5. PHYSICAL EXAMINATION | 6. LABORATORY INVESTIGATIONS |
| 7. MEDICATION | 8. RELATIVE INTERVIEW |

Most of the above is sufficiently self explanatory for the purposes of this thesis. Apart from standard laboratory tests, all patients also received CT scans, EEG and ECG measurements as well as chest X-rays. These, together with the physical examination and the interviews, all serve to fulfil criteria 2, 3 and 4. The first criterion, the presence of dementia, is established using the CAMCOG which is a general but relatively thorough cognitive assessment test. The CAMCOG takes about half an hour to administer and covers the following eight areas of cognition:

- | | |
|--------------------------------|--------------------------|
| 1. ORIENTATION (max = 10) | 2. LANGUAGE (max = 30) |
| 3. ATTENTION (max = 7) | 4. PRAXIS (max = 12) |
| 5. MEMORY (max = 27) | 6. CALCULATION (max = 2) |
| 7. ABSTRACT THINKING (max = 8) | 8. PERCEPTION (max = 11) |

An overall cognitive score can be obtained (max.=107) or alternatively, the CAMCOG can be broken down into its eight component scores.

The CAMDEX (Roth et al.,) 1986 recommends a cut-off of 80 on the CAMCOG, describing anyone scoring below 80 as suffering from a cognitive impairment and those scoring 80 and above as 'normal'. While some form of cut-off is needed for the identification of dementia for diagnostic purposes it is clear that this strict delineation between 'normal aging' and dementia can lead to a dangerous oversimplification of this distinction. Use of 'clinico-cognitive' tools such as the CAMCOG, MMSE (Folstein et al. 1975) and the Dementia Rating Scale (Mattis et al.,1976) are very useful for rating severity and for identifying clear-cut cases of dementia but they are not so useful and in fact, may even be a hindrance in the identification of earlier cases of dementia where scores approach cut-off. In the final section of this chapter, ways will be suggested in which dementia might be identified early on, independently of any cognitive tests.

RATING THE SEVERITY OF DEMENTIA

As with any degenerating disease, the severity or stage of the disease is crucial both in the design of a study and in the publication of findings. Unfortunately until recently, the severity of a DAT population was rarely reported in publications, this may have been for two reasons. Firstly, there was a lack of awareness of the importance of information regarding severity; and secondly, the majority of DAT patients would have been at the later stages of the disease. Now that the focus has changed to the earlier stages of dementia it is necessary to describe the severity of a population in terms of both clinical and cognitive deficits. For the purpose of the studies described in this thesis, the principal clinical characteristics of the four major stages of dementia included the following:

Minimal Dementia: A limited and varied impairment in new learning and recall. An increased tendency to lose and misplace possessions. The possibility of occasional errors related to work or housework. Self-care, emotional life and usually orientation remain preserved. Accurate insight into cognitive problems. No objective cognitive deficit is required for classification at this level.

Mild Dementia: A clear but sometimes intermittent, impairment in learning, recall, reasoning and problem solving. Orientation is impaired and inconsistent. A slight degeneration of Knowledge (especially of prominent people and important events). Increased errors related to daily living. Inappropriate conduct may be reported as might be impaired self-care and emotional responsiveness though they may remain preserved at this stage. Varied insight into cognitive and behavioural problems.

Moderate Dementia: A severe impairment in all the cognitive domains mentioned above. Language is notably effected and may be unclear or incoherent. Unable to function independently in daily tasks including shopping, cooking and housework, dressing and eating may also be affected. Self-care is seriously deteriorated and intermittent incontinence will have developed. Minimal insight will exist.

Severe Dementia: A complete inability to store or recall new information, islands of memory may exist. Complete inability in reasoning and problem solving. Speech and comprehension markedly impaired and in some cases can be absent. All indices of orientation are severely impaired. Incapable of independent existence as self-care is non-existent and the patient is unable to dress, wash, feed or look after self. Failure to recognise close relatives and even own mirror image. Emotional poverty

and apathy as well as variable double incontinence. No insight exists at this stage.

A patient once identified as suffering from DAT, would be classified according to severity using the guidelines described above. For research purposes, a severity rating was also attributed to each patient according to their score on the CAMCOG. For the remainder of this thesis therefore, levels of severity are derived directly from the CAMCOG scores.

<u>LEVEL OF SEVERITY</u>	<u>CAMCOG SCORE</u>
Minimal	75-106
Mild	50-74
Moderate	25-49
Severe	<25

RECRUITMENT BY MEMORY CLINIC: AN EXPERIMENTAL DESIGN

At present, the earliest identifiable stage of DAT is that at which the patients themselves, or their relatives become aware that "something is wrong". Therefore the task of identifying very early cases should perhaps focus as much on the subjective reports of potential patients and relatives as on the cognitive screening tools, which may prove to be more useful in rating severity once the dementia has been established. Being a progressive disorder, the staging of DAT has been the primary focus of many studies (Reisberg et al., 1982; Constantinidis 1978; Berg, 1988). While some of these studies tackle the issue of the early detection of a dementia they rarely deal with the distinction between dementia and normal aging, although some do propose cut-off scores on cognitive scales for this purpose. In my experience, however, the dementia has to

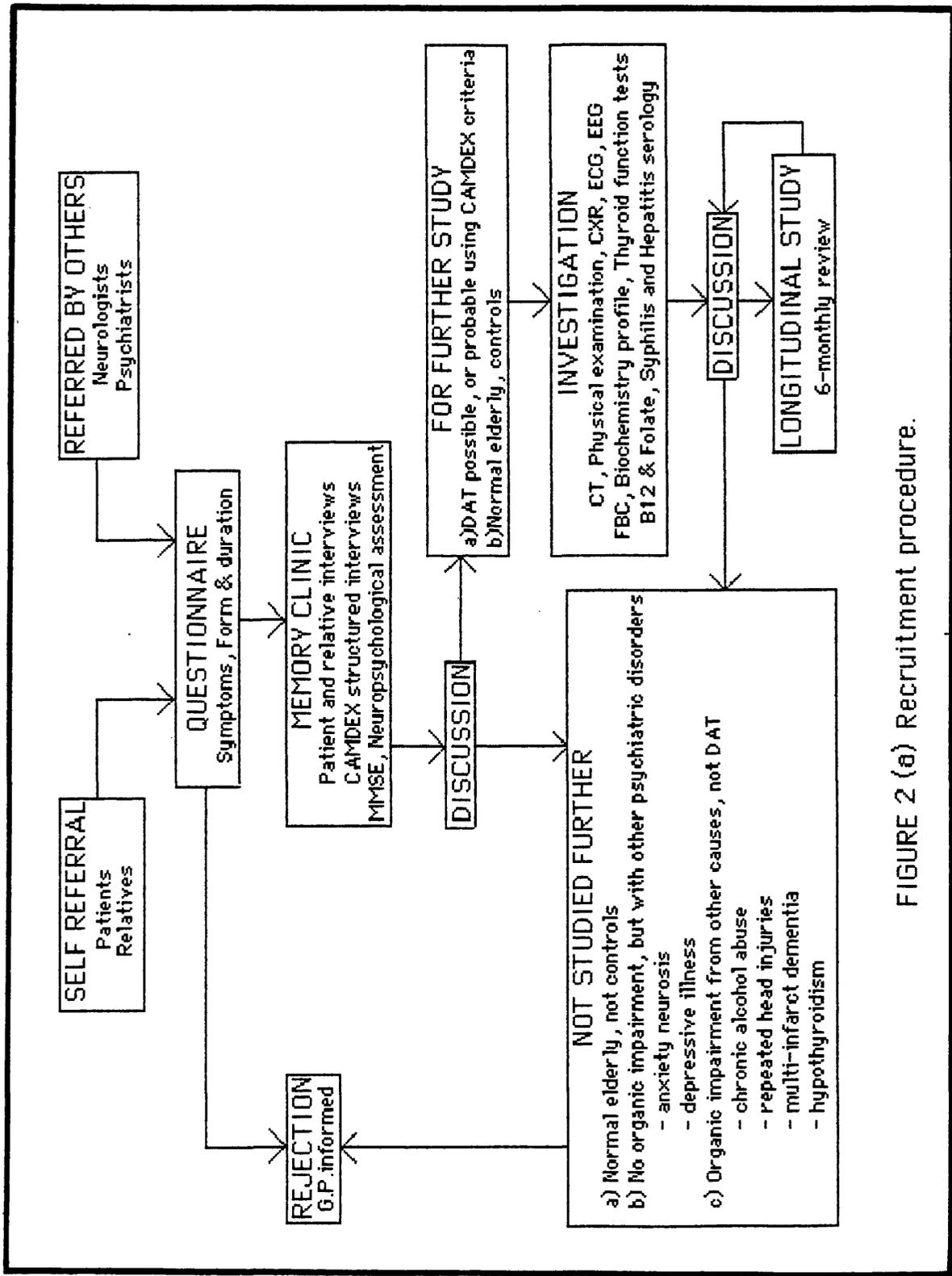


FIGURE 2 (a) Recruitment procedure.

have progressed considerably before failures on such tests (eg. MMSE, CAMCOG) can be reliable indicators of dementia. Some researchers have used subjective reports of cognitive deficits to identify the early stages of DAT; Berg (1988) developed a scale incorporating a "questionable" dementia stage. However, problems arise when attempting to categorise patients as "questionable" since this category requires the presence of "benign" forgetfulness, the identification of which, in itself is a formidable task, and its meaning in terms of memory deficit is far from clear.

In order to tackle both the problem of the recruitment of large numbers, and the identification of the very earliest stage of dementia, a memory clinic was introduced. The aims, apart from recruiting cases for research, were to estimate the value of a memory clinic in aiding the recruitment of cases of DAT, and to investigate the potential of subjective reports in differentiating dementia from normal aging.

RECRUITMENT PROCEDURE

The recruitment procedure as described below is illustrated in Figure 2(a). The majority of cases were self-referrals (97%), following the placement of an advertisement in the Glasgow press and leafletting of public libraries. The others were referred from general practitioners and psychiatrists or from self help groups such as Alzheimer's Scotland. A preliminary screening questionnaire was devised to enable the screening of the 438 replies received, in order to reject cases where the presenting complaint was clearly not of progressive cognitive impairment. The questionnaire gave an outline of symptoms and medical history of the applicants, and simple information concerning the form and duration of the complaint. The questionnaire was administered over the

telephone by either the psychiatrist or the psychologist in the team. The results were reviewed with the aim of selecting cases of organic mental disease for the memory clinic.

Those selected for the memory clinic were asked to attend with their spouse, or a close relative or friend. The patients and relatives were interviewed by the psychiatrist and psychologist to obtain a history of the complaints. The structured patient and informant interviews from the CAMDEX, together with the MMSE (Folstein et al., 1975) were administered. Brief neuropsychological assessment was made using subtests of the WMS-R (Psychological Corporation, 1987). The findings were evaluated by the psychiatrist and psychologist, and patients were categorised initially into two groups:

GROUP 1: FOR FURTHER STUDY

- a) those in whom a diagnosis of DAT seemed possible or probable, using the operational diagnostic criteria described earlier.
- b) those whom we considered to be normal who agreed to act as controls.

GROUP 2 : NOT FOR FURTHER STUDY

- a) the normals who did not wish to be controls
- b) those with no evidence of organic mental impairment but with other psychiatric disorders which would explain their subjective complaints, e.g. depressive illness, anxiety neurosis
- c) those with organic mental impairment from other causes, not DAT, e.g. chronic alcohol abuse, repeated head injuries.

The second stage of assessment for those with a possible or probable diagnosis of DAT was a CT scan; physical examination and blood

	DAT	NORMAL	ANXIETY	ALCOHOL	DEPRESSION	OTHER
NO. OF CASES	34	24	26	7	3	6

TABLE 2.1 DIAGNOSIS OF FIRST 100 MEMORY CLINIC ATTENDERS

SEVERITY	N	AGE		ESTIMATED DURATION
		Mean	Range	(Months)
Minimal	25	67.2	45-82	12-36
Mild	7	69.6	56-82	24-36
Moderate	2	70.0	66-74	18-84

TABLE 2.2 CHARACTERISTICS OF DAT GROUP

	N	AGE	MMSE		CAMCOG	
		mean	mean	range	mean	range
DAT PATIENTS	25	67.2	27.4	24-30	94.5	88-103
CONTROLS	16	64	29.8	28-30	100.8	97-104

TABLE 2.3 MINIMAL DAT GROUP CHARACTERISTICS

sampling for laboratory investigations. Those acting as controls received a CT scan.

RESULTS

The distribution of diagnoses of the first 100 people attending the Memory Clinic (screened from the original 438 applicants), is shown in table 2.1. As the table illustrates, the largest proportion of diagnoses were of probable DAT (34%), the second largest group were found to be suffering from anxiety neurosis (generally chronic and mild) (26%), while the third largest group were of normal elderly (24%).

A breakdown of the DAT cases by clinical severity using the CAMDEX (table 2.2) shows that by far the largest proportion of cases were suffering from minimal dementia (74%) , the other cases were classified as mild (20%) or moderate (6%). Table 2.3 describes the minimally demented and normal controls in terms of age, and general cognitive performance on the CAMCOG and MMSE. As the ranges of scores in table 2.3 confirm, mental status scores alone are not sufficient to distinguish minimal dementia from normal aging. When compared across large groups, the difference in scores may be found to be statistically significant, as they were found to be in this study using a Mann-Whitney U-test, ($U=36$, $p<0.01$). However when dealing with cases on an individual basis, the range of scores obtained by individuals in each group does not permit their differentiation in this way.

Frequency of presenting Symptoms

Having diagnosed these cases of DAT according to the CAMDEX, the cases of minimal DAT (N=25) and normal elderly (N=24) were examined further and any information regarding presenting symptoms was extracted from the interviews. Although this information was both

PRESENTING SYMPTOMS	DESCRIPTION
1 MEMORY (MEM)	Subjective complaints of memory failure, affecting either, or both of, recent and remote memory.
2 NAMES (NAME)	Difficulty with placing names to faces.
3 WORDS (WORD)	Difficulty with word finding.
4 CONCENTRATION (CONC)	Reported impairment of concentration.
5 THOUGHT (THO)	Disruption in the normal continuity of thought processes; commonly reported is the sensation of being oblivious to their own thoughts, often described as distressing blanks.
6 DISORGANISATION (ORG)	The report of disorganisation in the day-to-day running of affairs. This is reported especially by those who are working; in some cases this has led to premature retirement.
7 PERSONALITY (PERS)	The report of a personality change. In most cases this is reported by the relative and is said to be hard to define. A common example is that the patient "is no longer the same person" followed by the description of a string of incidents illustrating uncharacteristic behaviour.
8 LOST (LOST)	The report of transient feelings of being lost in familiar surroundings.

FIGURE 2 (b) DESCRIPTION OF PRESENTING SYMPTOMS.

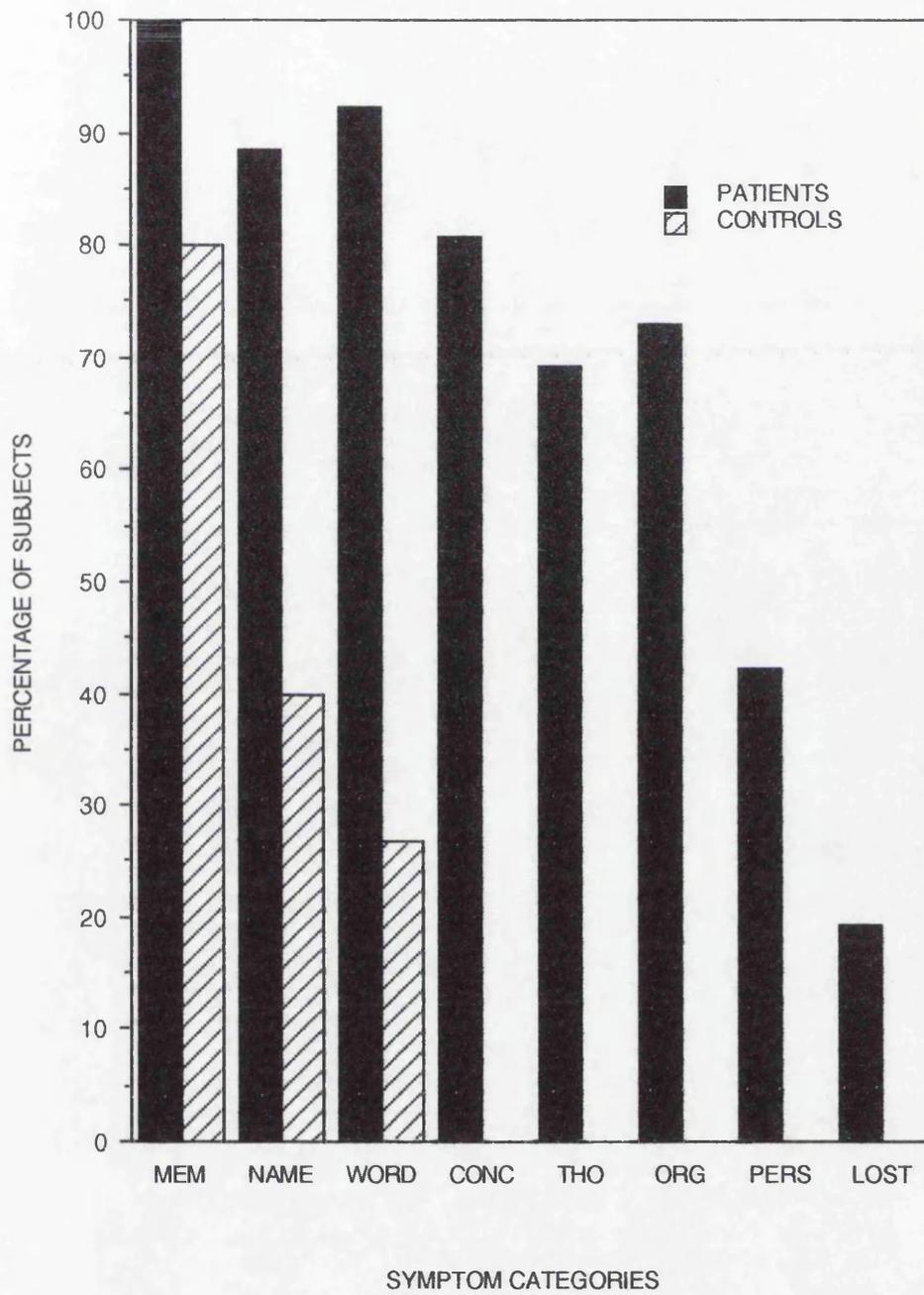


FIGURE 2(c) INCIDENCE OF PRESENTING SYMPTOMS IN PATIENTS AND CONTROLS

unprompted and spontaneous we found that it fell into the 8 categories described in Figure 2(b). The graph in figure 2(c) shows the incidence of these symptoms in each group. These results clearly illustrate a distinction between cases of normal aging and cases of minimal dementia. The former report only symptoms 1-3 (memory, naming and word-finding); while the latter not only report these symptoms, but also symptoms 5-8 (concentration, thought, disorganisation, personality and lost).

DISCUSSION

The results of this study have clearly shown that a memory clinic is an efficient method of recruiting cases of early dementia. As the results illustrate, one in every three cases who actually attended the memory clinic (following the telephone questionnaire), were suffering from DAT according to the CAMDEX operational diagnostic criteria. Of those diagnosed as suffering from DAT, 74% were at the very early stage described as minimal dementia. At this stage in many cases, the dementia is merely a suspicion in the mind of the patient or his family and the memory clinic presents the first opportunity for these fears to be expressed. The use of memory clinics to recruit for research purposes might receive criticism on the basis that it offers nothing to the patient in terms of treatment. However, throughout our assessments we made a point of full and frank discussion of our findings and their implications with our patients and their relatives. This also included a detailed explanation of the requirements of the research project and the present lack of possible treatment. We provided advice on management and support in each individual case, which we have found boosts the morale of sufferers and carers alike. We encouraged contact with local self help organisations, and on occasion have been instrumental in hastening day

and holiday relief care.

The accurate differentiation between dementia and normal aging is crucial to the efficiency of large research programmes investigating DAT. The diagnostic procedure for DAT is expensive and time consuming and without a sensitive method of distinguishing dementia from normal aging much money and time could be wasted on attempting to diagnose cases who are in fact not dementing. While some cognitive screening tests are possibly sensitive to early deterioration, they are less able to detect it in particularly intelligent people and do not allow for healthy low achievers. Furthermore a one-off test cannot consider the event of change in a person's ability and so again, the boundary between normal elderly and early dementia is extremely blurred. These results suggest that the identification of the earliest stages of dementia should be carried out using structured information supplied by the patient and informant regarding the cognitive changes they have noticed during daily life. From the results, we observe a clear difference in the form and frequency of presenting symptoms between the dementing (subsequently diagnosed as probable DAT,) and the normal elderly. Complaints of memory, placing names to faces, and word-finding difficulty are common to both groups, whereas impairment of concentration, disruption of normal thought processes, disorganisation, personality change and transiently feeling lost in familiar surroundings are found only in those with DAT (minimal). Consequently, it might be hypothesised that the use of criteria based on the aggregation of presenting symptoms may be crucial in differentiating cases of very early dementia from cases of normal aging. To date, 15 of the 25 cases we categorised as minimal DAT have shown clear, objective signs of further deterioration and a much greater proportion of the DAT group compared to the normal elderly group, have shown CT abnormalities.

CHAPTER THREE

SPECT NEUROIMAGING PROCEDURE

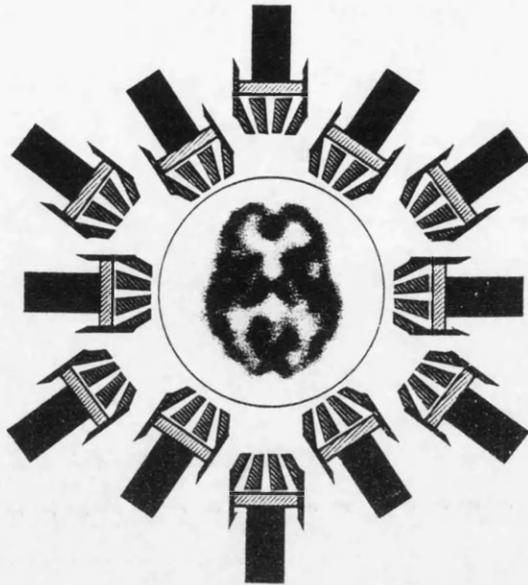
This chapter will describe the neuroimaging technique used for these studies. Results from Single Photon Computerised Emission Tomography (SPECT), as with most forms of neuroimaging, are subject to variation dependent on both the equipment used and procedure adopted. However, another significant source of variation when using SPECT is that of data quantitation and interpretation. Therefore this chapter will not only describe equipment and procedure but will also describe and discuss quantitation techniques.

EQUIPMENT

Neuroimager

Neuroimaging was carried out using an SME 810 Tomograph (Strichman Medical Equipment). This machine is a dedicated neuroimager and therefore is purpose built for brain scanning unlike a rotating gamma camera used by many centres, which is designed to image many different parts of the body. There are a number of advantages to using a dedicated neuroimager, particularly its sensitivity and efficiency since it is capable of collecting data simultaneously from many points around the brain, therefore making full use of the radiation emitted. The SME 810 imager uses the Harvard multi-detector scanning design utilising 12 sets of sodium iodine scintillation detectors with focussing collimators, arranged at 30 degree intervals around the field of view (figure 3(a)). Each detector scans both tangentially and radially to the field of view resulting in relatively uniform spatial resolution, sensitivity and slice thickness throughout the slice.

SME 810 SPECT Scanner



Detector movement

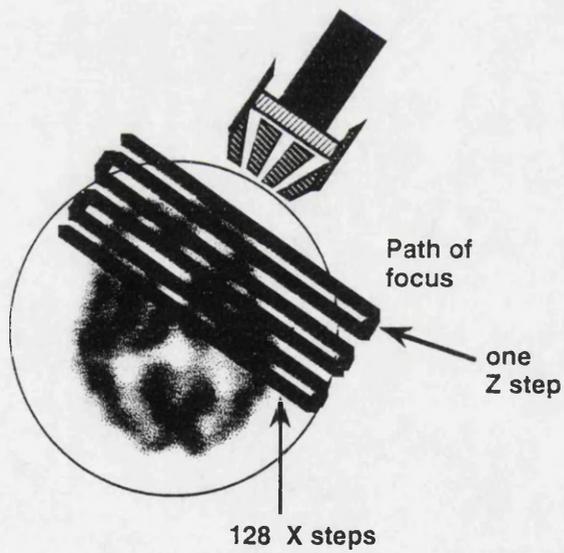


Figure 3(a) SME 810 collimator system: layout of 12 detectors (above) and pattern of detector movement (below).

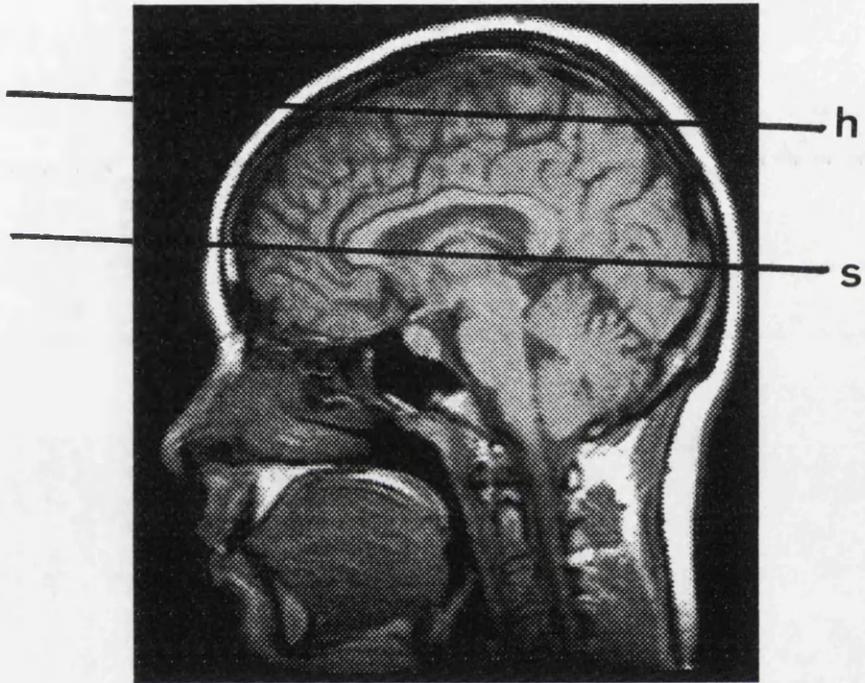


Figure 3(b) Sagittal section displaying orientation and height of brain slices

Radiopharmaceutical

The radiopharmaceutical used, (Ceretek, Amersham International plc, UK Product Licence No PL0221/0091) was prepared by adding 1200 MBq of 99m-Techneium pertechnetate in 5 ml saline to the freeze-dried mixture of the ligand Hexamethyl-propylenamine oxime (HMPAO). HMPAO is readily removed from the blood during its first pass through the brain (Andersen et al., 1988) therefore reducing redistribution almost to zero. Thereafter a fast decomposition of the molecule takes place causing entrapment in the brain and producing a distribution which reflects regional cerebral blood flow (Neirinckx et al., 1987).

PROCEDURE

Patients were seated in a quiet room with their eyes closed while a 500 MBq dose of Ceretek was injected intravenously using a cannula. Imaging was carried out 5 minutes to 1 hour post injection. The patients lay unrestrained on the imager couch during the scanning session which lasted 25 minutes. In this time, 5 slices 12mm thick, were obtained in a plane parallel to the orbito-meatal line and at positions 30, 40, 50, 60 and 70mm superior to this line. The 5 acquired images were compared with the anatomical patterns presented in a typical brain atlas for the purpose of defining two particular anatomical levels and for the identification of different brain regions (figure 3b). The lower of the two slices the STANDARD slice (s), (most usually at OM + 40,) was defined by the presence of the basal ganglia, thalamus and occipital cortex and by the absence of cerebellum and is displayed in figure 3(c). The HIGH slice (h), (usually OM + 70) lay immediately superior to the corpus callosum, and typically appeared as an elliptical ring of high activity in the cortex with a further line of high activity running continuously anterior to posterior representing cortex on each side of the inter-hemispheric fissure, figure 3(d).

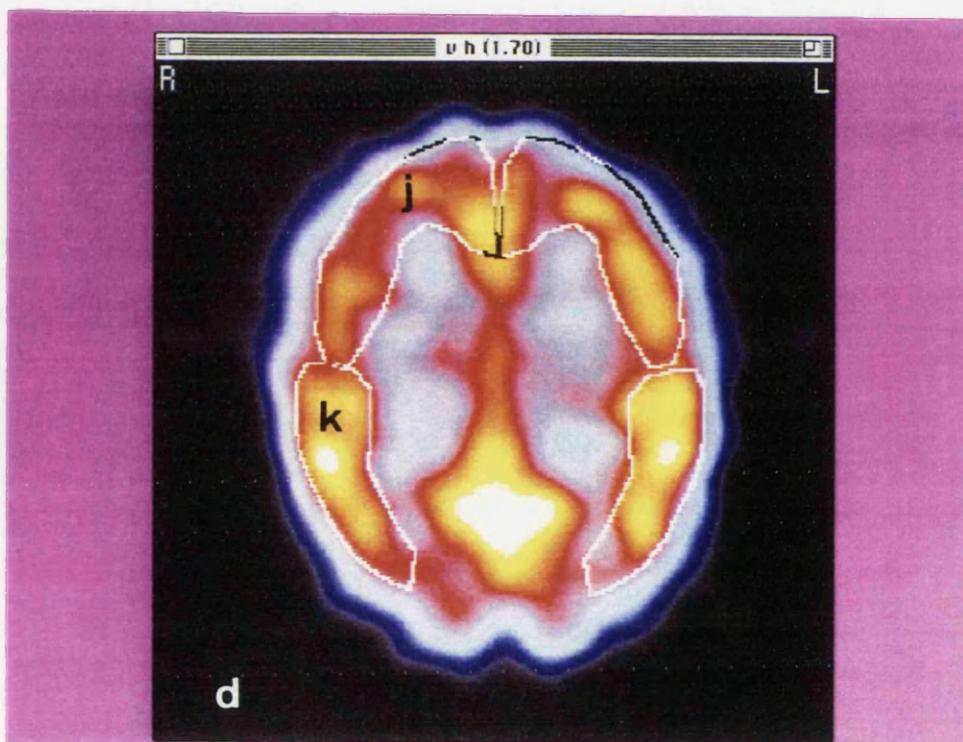
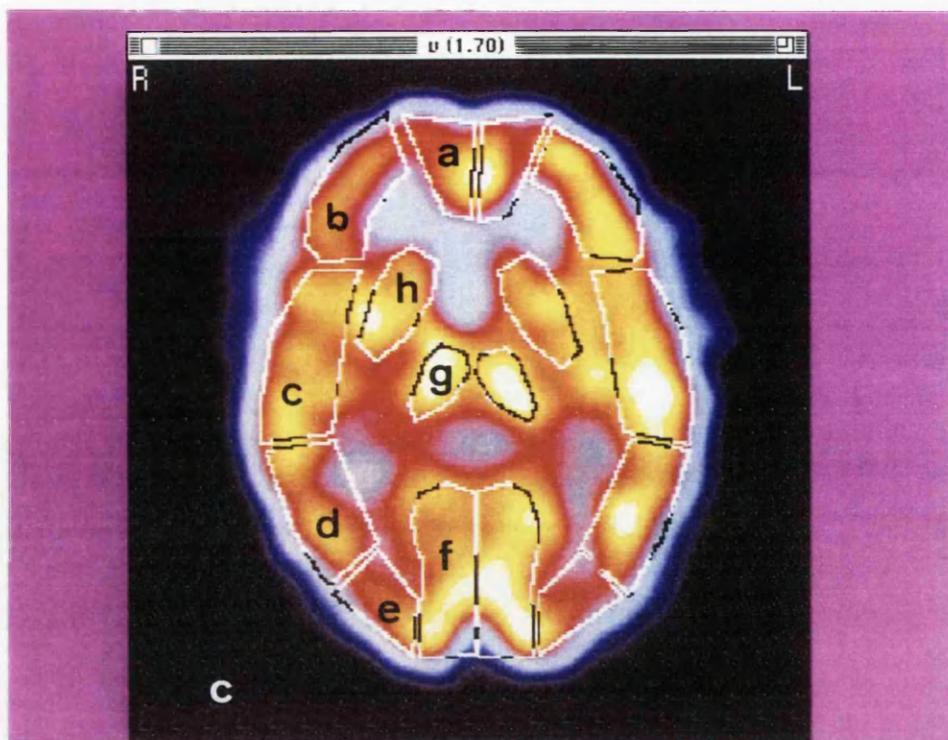


Figure 3 (c) and (d). ROI's in the standard slice (c) and in the high slice (d).

REGIONS OF INTEREST

The issues of selection and definition of regions of interest (ROI) are critical to this form of investigation. The selection of which ROI's to identify and quantify depends on a combination of the aims of the research and the constraints (eg. resolution) of the equipment. Having selected the ROI's for investigation, the actual identification and definition of ROI's can be problematic. Different research groups use different techniques each one aiming to minimise potential inter- and intraobserver variability. Costa et al., (1988) for example, use a technique involving the selection of regular constant shapes as ROI's while Hellman et al., (1989) have developed a semiautomated method of generating ROI's encompassing the whole cortex.

For these studies, ROI's were identified and defined using an anatomical atlas. Then using the scanner's computer system, 20 ROI's outlining different brain regions were drawn onto the slices. 16 ROI's (8 on each side) were drawn on the standard slice (Figure 3c) and 4 on the high slice (Figure 3d) with a separate outline encompassing the whole cerebral activity in each slice. Corresponding right and left regions were symmetrically identical. The ROI boundaries were drawn along the outside surfaces of the brain and internally followed the division between cortex and white matter. On the standard slice the 8 regions were described as lateral frontal (a), medial frontal (b), temporal (c), posterior temporal (d), occipital (e), calcarine (f), thalamic (g) and basal ganglia (h); with high frontal (j) and parietal (k) on the high slice. The number of ROI's used in each study depending on the neuroimaging protocol at the time. Therefore, any changes in the regions investigated will be specified in the methods section of each study.

QUANTITATION

The quantitation of CBF data is complicated by the fact that SPECT does not produce absolute values but relative values of blood flow. For any group data to be meaningful therefore, it has to be normalised in some way in order to remove intersubject variability. Normalisation involves expressing the CBF value in any ROI as a proportion of CBF in another brain area, used as a reference area, resulting in a ratio of brain activity. Normalised data can then be grouped and analysed without intersubject variability affecting the results. However, selecting a brain area to act as the reference area is not straightforward and depends on several factors:

- 1) The likelihood that the region is relatively unaffected by whatever disease process or brain trauma is being investigated.
- 2) The pertinence of the region to the aims and hypotheses of the research since the reference area cannot be used in any subsequent analysis because it cannot be normalised itself.
- 3) The normalisation region must be readily imaged taking into consideration limitations of resolution and definition.

The cerebellum, which has been used as the normalisation region, in other studies (Burns et al., 1989; Holman et al., 1992), was not used here for two reasons. Firstly, using a dedicated neuro section scanner, a single image can be obtained within three minutes. This facility for rapid data collection provides a distinct advantage over the gamma camera in studies of dementia, since refusal rates can be high with this patient population. Since the images used to extract cortical data cannot include the cerebellum, additional slice images would be required, thus significantly increasing the imaging time and thereby prejudicing our very low refusal rate of 2%. Moreover, the elderly population is subject to

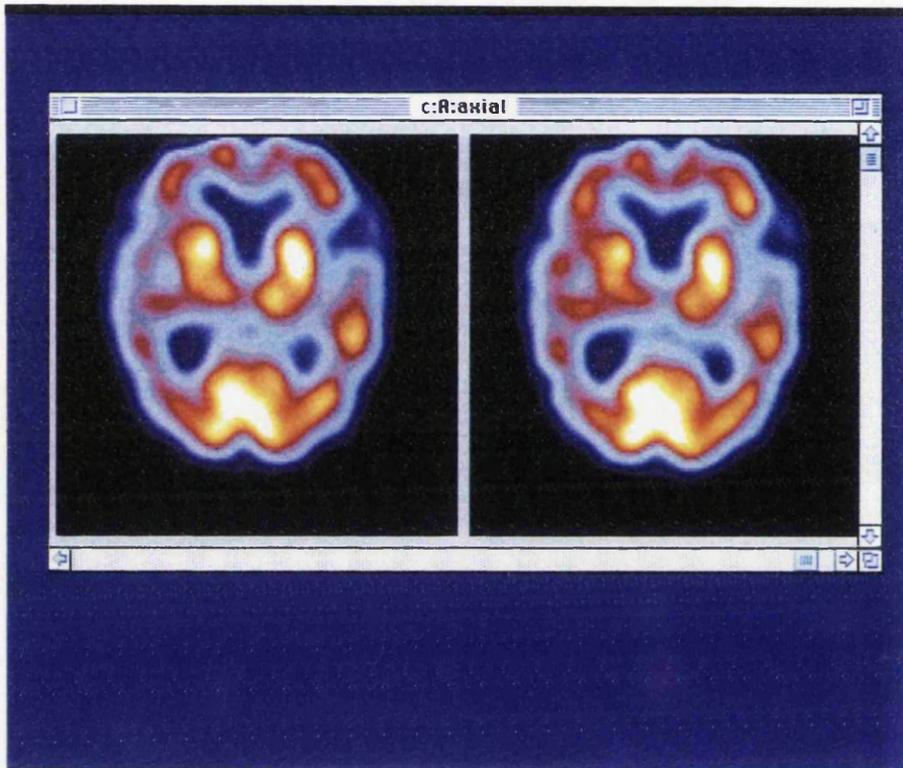


Figure 3 (e) Relative sparing of occipital and calcarine regions in a case of DAT confirmed at postmortem.

suffering from disorders which result in a curving of the spine, this leads to considerable difficulties in positioning patients for imaging of middle and lower brain regions. The second reason for not adopting the cerebellum for normalisation is that cerebellar blood flow may be affected by crossed cerebellar diaschisis resulting from damage to the cortico-ponto-cerebellar system (Baron et al., 1980). Finally, recent work by Pupi et al., (1991) reports a high degree of variance in cerebellar CBF in DAT and they urge caution with its use as a reference area.

A region thought to be relatively unaffected by DAT is the calcarine region. Risberg (1985) described a sparing of this area in a group of DAT patients compared to controls. This finding has received support from more recent studies by Duara et al., (1986) and Pupi et al., (1991). Furthermore, preliminary work carried out with the patients used in these studies supports this finding (Montaldi et al., 1990). As the the SPECT scan in Figure 3(e) illustrates; despite reduced blood flow in much of the cortex, the occipital and calcarine regions remain relatively unaffected in a case of DAT, neuropathologically confirmed at post mortem.

For each region therefore, the area and mean number of counts per pixel were measured and expressed as a proportion of the activity in the calcarine region, producing an ROI/calcarine activity ratio.

CHAPTER FOUR

REGIONAL CEREBRAL BLOOD FLOW AND COGNITIVE PERFORMANCE IN DEMENTIA OF THE ALZHEIMER TYPE

INTRODUCTION

As described in the previous chapter, the developments in functional neuroimaging, together with the growing awareness of the challenge that Alzheimer's Disease presented, led many research groups to investigate blood flow and metabolism deficits in DAT. The results of these earlier studies led to the conclusion that while there was evidence of a pattern of deficit common to DAT, there was also evidence of considerable heterogeneity. The parietal cortex was most frequently reported to show deficits in DAT (Risberg, 1985; Frackowiak et al., 1981; Bonte et al., 1986; Holman, 1986) however, deficits were also reported in the posterior temporal and frontal regions (Bonte et al., 1986; Johnson et al., 1985). Frackowiak et al., (1981) found that on the whole, metabolic deficits were particularly marked in posterior regions, however, the more severely demented patients also displayed frontal metabolic abnormalities. Neary et al., (1986) reported that parietal and temporal CBF deficits found in DAT were consistent with neuropsychological impairments reported in the same population. More recently, Burns et al., (1989) and Hunter et al., (1989) investigated CBF patterns and their relationship to cognition in a more systematic manner. Their approach involved correlating CBF and cognitive performance on the CAMCOG (Roth et al., 1986). Both these studies illustrated posterior blood flow deficits in the DAT patients and these deficits correlated highly with numerous measures of cognitive function.

The present study provided a preliminary investigation into the rCBF

deficits accompanying DAT and their relationship with cognitive performance. The aims were three-fold; firstly to standardise the imaging procedure described in the previous chapter. Using a new dedicated tomographic brain scanner, a recently developed radiopharmaceutical and a novel quantitation technique, this study attempted to replicate previously established findings. Secondly, to identify those cortical regions where blood flow is particularly reduced in this Alzheimer population. Finally, to make an initial investigation into the relationship between cognitive performance and cortical blood flow in DAT using an extensive but non-specific, cognitive assessment procedure of the type frequently adopted for the psychiatric monitoring of dementia.

METHODS AND PROCEDURE

Patient population

All patients used in this study were recruited from Gartnavel Royal Hospital Psychogeriatric Day Units catering for patients suffering from dementia in its later stages. These patients were no longer capable of looking after themselves and attended the hospital as outpatients although many were awaiting a bed on the long term wards.

A group of 26 patients (17 females) diagnosed as suffering from dementia of the Alzheimer type (DAT) were studied (table 4.1). Diagnosis was carried out using the standard inclusion and exclusion criteria as described earlier (ch.2). The mean age of the group was 76 years (54-79). The severity of the patients' dementia was predominantly moderate to severe as reflected by the CAMCOG and MMSE scores shown in table 4.1.

Control population

A group of 10 normal elderly volunteers (8 females) recruited from local social centres were screened before entry into this control group. All volunteers reported themselves to be healthy and suffering from no significant cognitive problems, this was confirmed by formal assessment on the CAMCOG. The mean age of the group was 71 years , ranging from 50 to 80 .

TABLE 4.1 Patient and Control characteristics

	N	AGE		MMSE		CAMCOG	
		Mean	Range	Mean	S.D.	Mean	S.D.
DAT	26	76	54-90	9.6	5.5	35.0	19.7
NC	10	71	50-80	28.0	1.8	94.8	6.6

Regions of interest

The method of identifying ROI's is described in chapter 3. For the purpose of this study 12 ROI's were selected. These regions were left and right: Frontal, temporal, posterior temporal, occipital (including calcarine), high frontal and parietal. SPECT scanning was carried out as described in chapter 3 and CBF values were calculated and expressed as ROI/occipital ratios.

Cognitive Assessment Procedure

A problem encountered by most studies investigating diseases involving progressive cognitive deterioration, is that a general cognitive assessment tool is required that is capable of monitoring cognitive degeneration from the earliest to the most severe stages of the disease. There are three principal reasons for this requirement; firstly, the study of dementia requires the parallel study of the normal processes of aging whether this be incidental or intrinsic to the study itself. In this way, the study of the cognitive deterioration accompanying dementia must bear in mind the cognitive deterioration that accompanies normal healthy aging. Therefore as mentioned earlier in chapter 2, a problem that often arises is the need to distinguish between the normal elderly and the demented and the only established way at present to do this, is to use general cognitive screening tests with cut-off levels below which an abnormal cognitive deficit may be presumed. Secondly, the

degenerative nature of the disease requires that one can compare changes in a single patient's performance over time. Thirdly the need to be able to measure and report the severity of patient populations on a continuous scale to ensure both a well designed study and accurate reporting of findings. The cognitive assessment tool used in these studies is the CAMCOG which forms the cognitive assessment section of the CAMDEX (Roth et al., 1986). The CAMCOG is a short mental status examination similar to, but more extensive than, the widely used MMSE (Folstein et al. 1975) which is included within its design. In this way both a CAMCOG and an MMSE score can be obtained through the administration of a single test.

The CAMCOG, which is described more fully in chapter 2, can either provide a single total score of overall cognitive performance for any of the three purposes outlined above, or it can be broken down into subscores to suit the requirements of the investigation. For the specific purpose of this study an overall score of cognitive performance was used to describe the patient population while specific subscores were extracted for the correlational analysis of cognition and rCBF. The three broad cognitive domains of particular interest within the context of DAT are memory, language and praxis since they are all known to be affected by the disease. Furthermore they constitute the largest subcomponents of the CAMCOG and for these reasons were selected for the correlational analysis. Administration of the CAMCOG takes approximately half an hour and was carried out within 2 weeks of SPECT scanning.

ANALYSIS AND RESULTS

Cerebral Blood Flow patterns

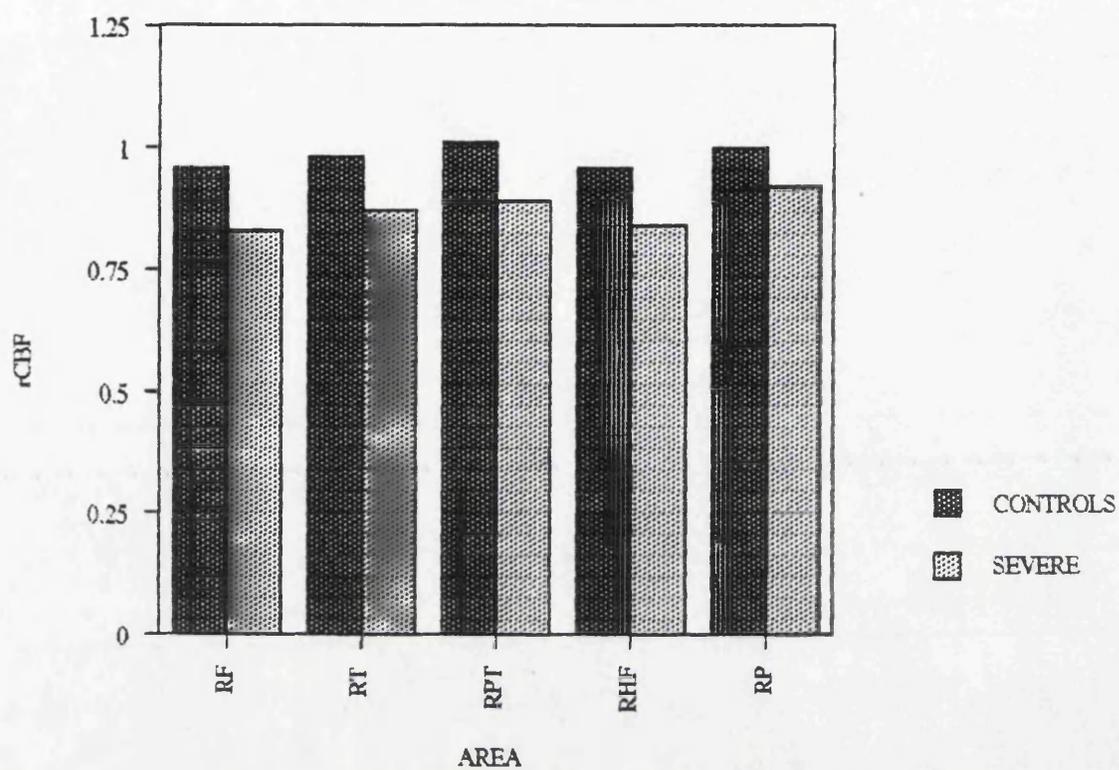
The data analysis was designed to compare rCBF in the DAT group to

ROIs	DAT Mean	SD	Controls Mean	SD	p value
LPT	0.90	0.12	1.07	0.06	<0.0001**
RPT	0.89	0.11	1.01	0.08	0.0006**
LT	0.84	0.12	0.98	0.09	0.0007**
LP	0.93	0.10	1.04	0.08	0.0012**
RF	0.83	0.10	0.96	0.10	0.0016**
LF	0.82	0.12	0.94	0.09	0.0023**
RP	0.92	0.11	1.00	0.07	0.0055*
RT	0.87	0.11	0.98	0.11	0.0090*
RHF	0.84	0.14	0.96	0.11	0.0090*
LHF	0.85	0.14	0.96	0.11	0.0115*

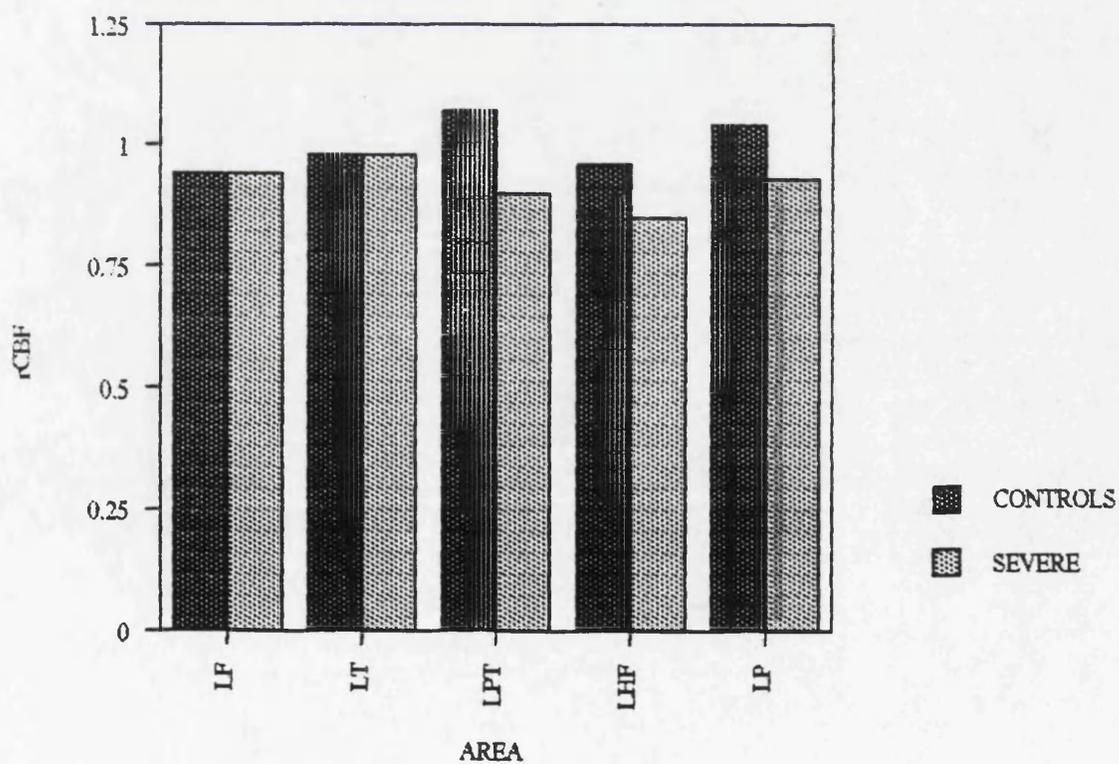
*significant at an individual 5% level

**significant at an overall 5% level

TABLE 4.2 CBF deficits in moderate to severe DAT patients compared to Controls

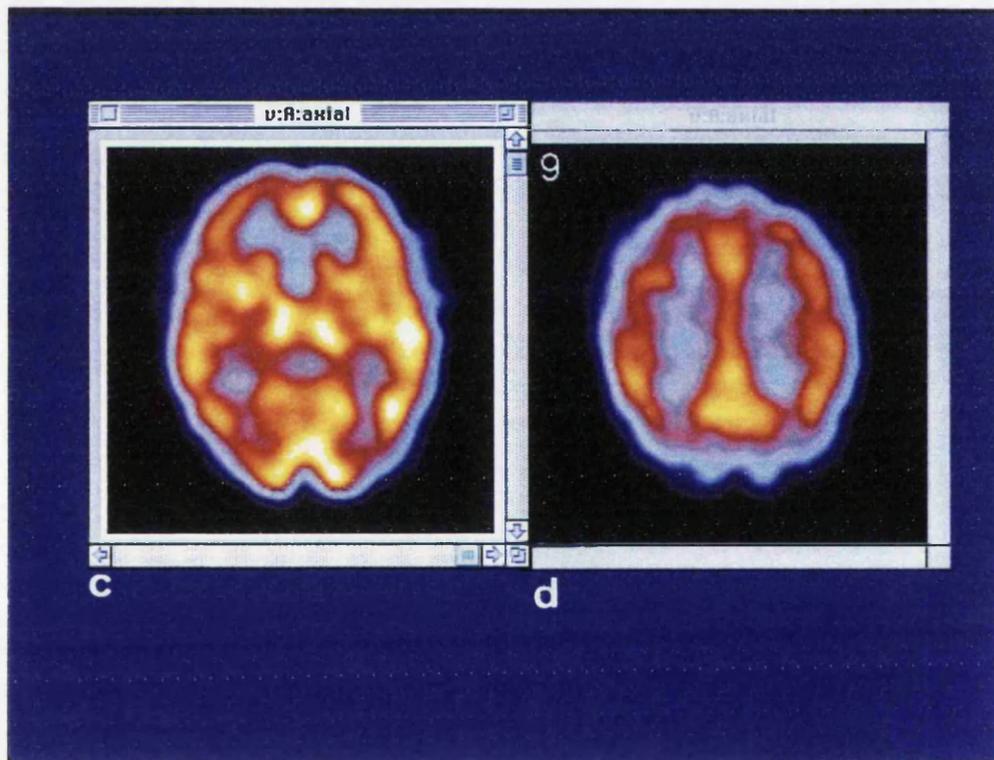
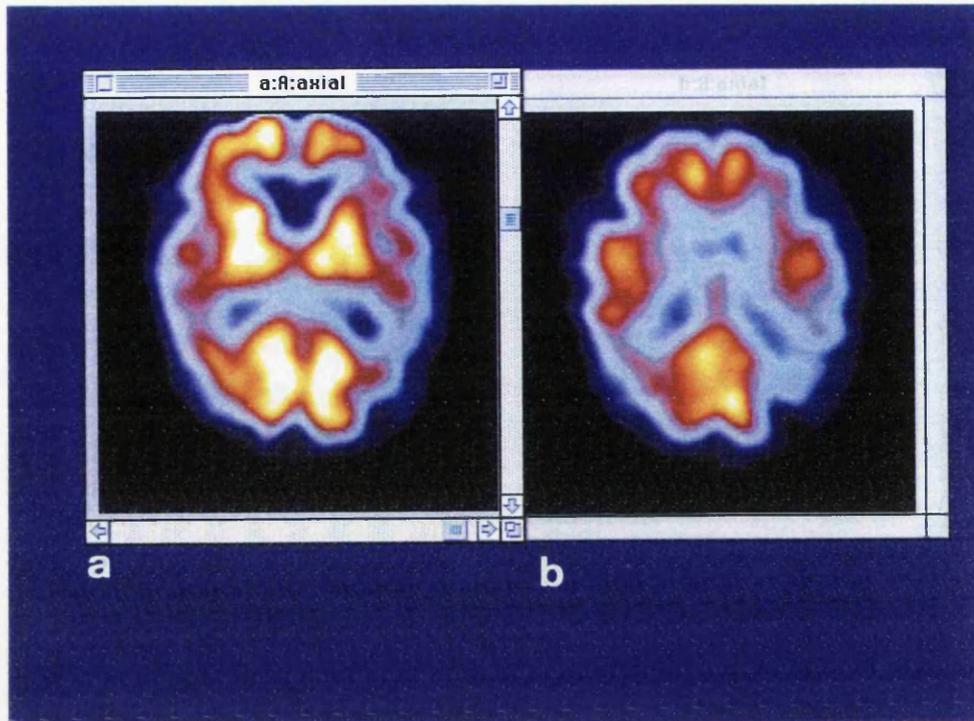


rCBF values in right sided ROIs of severe DAT patients and Controls



rCBF values in left sided ROIs of severe DAT patients and Controls

FIGURE 4(e)



Figures 4. (a)-(d) Posterior temporal (a) and parietal (b) CBF deficits in a confirmed case of DAT and compared to a control (c) and (d).

that of controls. To do this, two sample t-tests were used to compare the ROI/occipital ratios for each ROI across the two groups.

The results of this study are illustrated in Table 4.2. As the p-values clearly show there is strong evidence of reduced blood flow in all cortical regions of interest. A Bonferroni correction was applied at this point, since all ROI's were found to be significant. The function of this correction procedure is to reduce the possibility of chance significance. A number of ROI's displayed particularly strong evidence of blood flow deficits since significance was still obtained at an overall 5% level when applying a Bonferroni correction. These regions included the left and right posterior-temporal, the left temporal, the left parietal and both the right and left frontal regions. The remaining four regions also showed blood flow deficits however their significance did not withstand the Bonferroni correction and was therefore limited to an individual 5% level. These findings are also clearly illustrated in the SPECT images displayed in figures 4 (a)-(d). Reduced blood flow is particularly evident in the posterior temporal and parietal regions of a case of DAT whose diagnosis was confirmed at post mortem (4(a) and (b)), in comparison to blood flow in a healthy control (4(c) and (d)).

CBF and Cognition

This stage of the analysis investigated the association between rCBF data and cognitive performance in the DAT group. The strength of these associations was measured using Spearman's rank correlation coefficient.

Numerous associations were found between rCBF and cognitive performance, and figure 4(f) includes correlations where significance was obtained at an individual 1% level and also the numerous less

ROI	CAMCOG	MEMORY	LANGUAGE	PRAXIS	MMSE
RF	0.37 *	0.21	0.38 *	0.51 *	0.47 *
LF	0.34 *	0.13	0.39 *	0.45 *	0.47 *
RT	0.47 *	0.20	0.41 *	0.42 *	0.46 *
LT	0.57 **	0.30	0.63 **	0.45 *	0.49 *
RPT	0.69 **	0.40 *	0.62 **	0.68 **	0.59 **
LPT	0.72 **	0.39 *	0.74 **	0.68 **	0.75 **
RHF	0.33	0.26	0.28	0.46 *	0.36 *
LHF	0.25	0.17	0.24	0.38 *	0.36 *
RP	0.68 **	0.47 *	0.55 *	0.70 **	0.47 *
LP	0.64 **	0.41 *	0.66 **	0.61 **	0.53 *

* Significant at individual 5% level

**Significant at individual 1% level

FIGURE 4 (f) Associations between CBF and CAMCOG scores

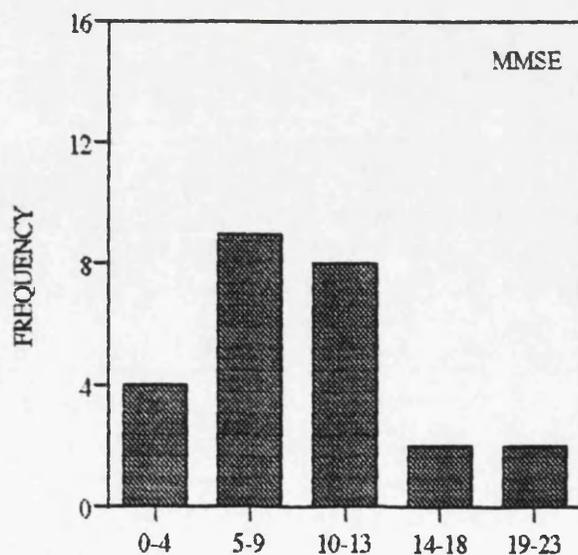
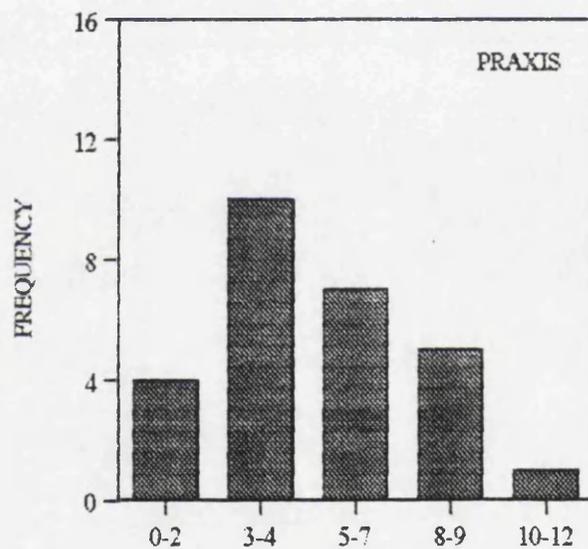
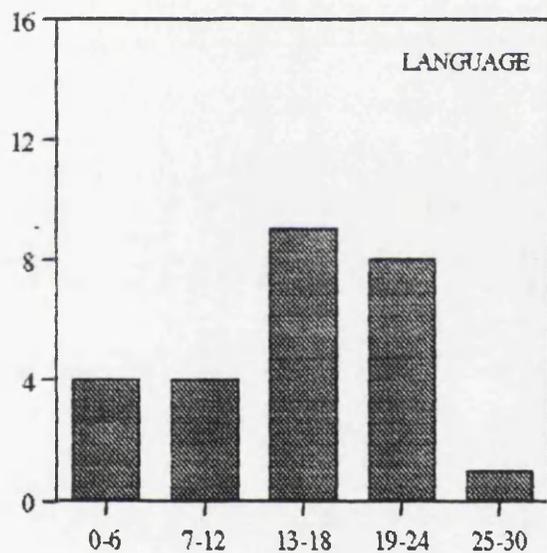
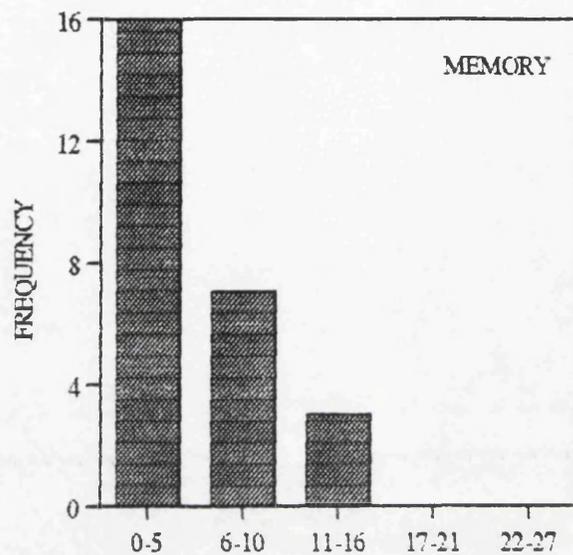
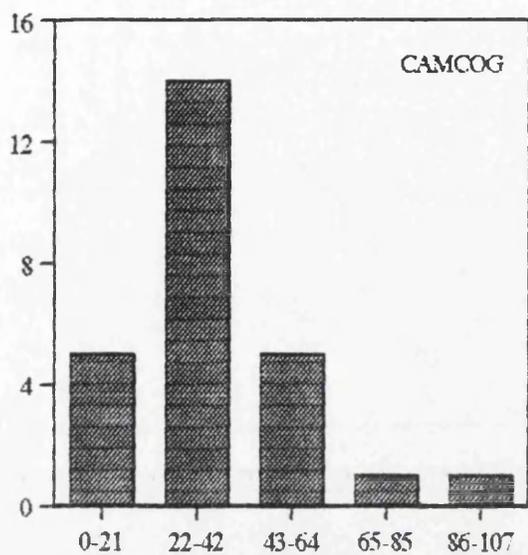


FIGURE 4g Distribution of CAMCOG scores for moderate to severe DAT patients

significant associations where significance was at a 5% level. As the table clearly displays multiple correlations resulted from this analysis. However, despite the large number of strongly significant correlations, there were surprisingly no such correlations between rCBF and performance on the memory component. This lack of strong correlations with memory was investigated further by analysing CAMCOG total, and subscore distributions. As figure 4(g) illustrates, the total score, and language and praxis scores all show a broad distribution. The memory scores however show no such distribution, displaying instead a marked floor-effect. Since correlational analysis requires a reasonable distribution of scores to produce meaningful results, the absence of correlations with memory may be interpreted as reflecting this floor-effect.

DISCUSSION

Patterns of rCBF

Using this technique the study provides strong evidence of the involvement of the posterior temporal regions in Alzheimer's disease. There are a numerous reports of similar posterior temporal and parietal deficits evident from SPECT and PET studies (Frackowiak et al., 1981; Bonte et al., 1986; Johnson et al., 1985; Risberg, 1985; Gemmell et al., 1984). The well documented reduction in parietal blood flow in Alzheimer's disease has received further support from this study. However while parietal blood flow is significantly reduced in this patient population, (especially in the left hemisphere), these results suggest that there is an even greater involvement of both the left and right posterior temporal regions in this disease.

The involvement of the frontal lobes in Alzheimer's disease provokes considerable debate. There is no doubt that in many cases of DAT, a degree of frontal pathology exists (Grady et al., 1988; Foster et al., 1984; Bonte et al., 1986). However some researchers have separated patients with frontal damage and labelled them as 'frontal dementias' or possible Pick's disease (Neary et al., 1987). The results of this study identify an unambiguous frontal component in DAT since the rCBF deficits were highly significant in both the left and right frontal regions of a population showing no disproportionate frontal signs clinically. Foster et al., (1984) suggest that anterior changes occur late on in the disease process, and this suggestion is supported by these findings, since the majority of the patients were moderately to severely demented. This does not, of course, exclude the possibility that minimal or mild cases of DAT could also display some frontal rCBF deficits.

Since all ten cortical regions of interest showed a statistically significant reduction in blood flow in the Alzheimer group, it might be considered that this global effect challenges the proposition that certain regions are affected at different stages of the disease process. However as noted earlier, the patient population used in this study comprised predominantly moderately to severely demented people, which would be expected to be accompanied by diffuse rather than asymmetrical or focal cortical degeneration.

Patterns of CBF and cognitive performance

While a number of the highly significant correlations, ranging from 0.57 to 0.74, between rCBF and cognitive performance, fit well with current theories of cortical organisation and cognitive function, there are two problems which make interpretation of results particularly difficult. The first problem is that of multiple correlations. Apart from the thirteen very highly significant correlations, numerous less significant associations were also found. This multiplicity of correlations prevents the drawing of firm conclusions about the specific relationship between rCBF deficits and cognition in this population. The second problem is that in spite of the strength of some of the correlations and the extensively reported memory deficit accompanying DAT, no such correlations between rCBF and memory performance on the CAMCOG were obtained.

There are two alternative explanations for these problems which may be taken into account in the design of future studies. The first of these is that the CAMCOG and other cognitive screening tests may be inappropriate tools for this form of investigation. Due to the requirements of "brief" cognitive screening tests, such procedures are, by nature non-specific and the subtests may frequently overlap in the cognitive domains they are assessing. Therefore while this type of assessment tool is ideal for providing a general cognitive picture, much

greater task specificity is required if meaningful correlations are to be sought. The inappropriate use of the CAMCOG could therefore be responsible for the excessive number of correlations found in this and other studies (Burns et al., 1989; Hunter et al., 1989). Interestingly enough, this lack of task specificity may also account for the failure to find correlations between rCBF and memory. The non-specific nature of screening tests greatly reduces their sensitivity and capacity to identify subtle differences in cognitive performance between patients. This situation is clearly illustrated here by the floor-effect found with the memory component of the CAMCOG (Fig. 4(g)). Despite evidence for differential memory deficits in dementia (Bayles & Kaszniak, 1987); memory on this test can only be expressed as one single score since any further breakdown would produce meaninglessly small scores. Again, while these subcomponents adequately assess memory for screening procedures, they are far too generalised (eg. they measure almost exclusively verbal memory), for use in correlational studies of this form. Therefore the first explanation of these results hypothesises that without the use of specific tasks, floor-effects or similar confounding features will prevent both an accurate analysis and a useful interpretation of results. In view of this, the use of this type of tool to provide evidence of meaningful subgroups (Burns et al., 1989) particularly for studies of the heterogeneity of Alzheimer's disease is questionable and highly inadvisable.

The second explanation for these results could be the nature of the patients who are typically in the later stage of the disease. As with the reductions in blood flow, the cognitive impairments resulting from the later stages of the disease are diffuse and appear to affect nearly every cognitive domain; multiple correlations may therefore be expected. Unfortunately reports of similar studies also producing multiple correlations (Burns et al., 1989; Hunter et al., 1989) do not describe the severity of the population under investigation so comparisons cannot be

made. As far as the floor effect on memory is concerned, it could be argued from this point of view, that it has resulted solely from the severe nature of the patient population. Adopting specific cognitive tasks and using patients of varying degrees of dementia may allow us to investigate more specific relationships between rCBF and cognition whilst avoiding the problem of multiple correlations which swamp any specific effects.

In conclusion, this study has illustrated rCBF deficits, using HMPAO and SPECT, in a moderate to severely demented population suffering from DAT. In particular, the posterior temporal regions have been identified as those showing the largest blood flow deficits however at this late stage of the disease, blood flow deficits have been found in all areas of the cortex. The results of the investigation into the relationship between cognitive performance and CBF patterns are particularly difficult to interpret. This difficulty may in part, be due to the severity of the DAT population. Furthermore, non-specific tools such as the CAMCOG can produce results which are difficult to interpret and which may lead to oversimplistic and inaccurate conclusions.

CHAPTER FIVE

rCBF DEFICITS ACCOMPANYING THE EARLY STAGES OF DAT AND THEIR RELATIONSHIP TO COGNITION

INTRODUCTION

Following the widespread application of SPECT techniques to the investigation of DAT, numerous studies have been carried out with the primary aim of identifying patterns of rCBF characteristic of DAT (Battistin et al., 1990; Bonte et al., 1986; Hunter et al., 1989;). The majority of these studies have focussed on the investigation of DAT in its more advanced stages since this is an identified, and readily accessible population. Apart from a relative sparing of the occipital lobes (Riesberg 1985, Pupi et al., 1991), cerebral blood flow deficits present at this moderate to severe stage of the disease have been shown to span most of the cortex but particularly frequently reported, are temporal and parietal deficits as reviewed by Holman (1986).

By investigating the earlier stages of DAT on the other hand, we might provide CBF information which would contribute to the understanding of the preclinical neurophysiological changes occurring in DAT and of particular importance, how these early CBF patterns differ from those accompanying other forms of dementia. As chapter 2 describes, there are many different aetiologies of dementia and numerous SPECT studies have been carried out with the principal aim of contributing to the difficult task of differentiating between the dementias (Neary et al., 1987; Costa et al., 1988). However many of these studies have involved patients whose dementia has progressed well beyond the early stages and in a few studies the patient groups differ significantly in terms of their dementia severity (Battistin et al., 1990) and therefore any CBF differences may

simply be a result of these severity differences. As memory is generally reported to be the first cognitive domain to be affected by DAT (Grady et al., 1988), CBF investigations involving patients suffering from memory deficits alone, would provide the closest approximation to preclinical information. Haxby et al., (1986), concluded that in a small group of such DAT patients, underlying neocortical metabolic changes in the frontal, lateral temporal and parietal regions were already occurring. Holman et al., (1992) carried out an extensive study attempting to determine the predictive value of a number of CBF patterns in identifying DAT. Unfortunately, while the authors report that all 132 patients were attending a unit for the evaluation of memory loss and other cognitive problems, they fail to report any information concerning the severity of dementia. While it is possible that they have studied some very early cases whose specific CBF patterns would be of particular interest, the probable mix of severity questions any conclusions they make. However, their investigations conclude that bilateral temporo-parietal deficits are highly predictive of DAT. This extensive piece of research will be referred to in greater detail in the discussion section of this chapter.

In CBF and metabolism research, much emphasis has been placed on the involvement of the posterior cortex in DAT, so much so, that it has sometimes been referred to as a posterior dementia (Holman, 1986). This, together with the emerging literature concerning the identification of a Frontal Lobe Dementia (FLD) (Neary et al., 1987), has perhaps prematurely, led people to believe that frontal signs and a frontal pathology are very rare in DAT and could even be used as an exclusion criterion within the differential diagnosis procedure. Considerable evidence suggests that a frontal CBF component does accompany DAT, (Waldemar et al., 1991; Montaldi et al., 1990; Haxby et al., 1988; Perani et al., 1988; Johnson et al., 1988; Bonte et al., 1986), however it is unclear at what stage of the degenerative process this may develop. Moreover, since a form of FLD clearly exists from a neuropathological viewpoint

(see chapter 2) and given the difficulties inherent within differential diagnosis, it is extremely difficult if not impossible, to be sure what proportion of any dementia population is in fact FLD. Brun (1987) and Neary et al., (1988) suggest that 10-20% of any organic dementia population are cases of FLD. It appears to be clear however, that the frontal cortex is also implicated in the neuropathological breakdown accompanying DAT.

One reasonable hypothesis which would accommodate the various findings might be that the posterior component of the disease develops early on in the degenerative process while a frontal component may develop to a greater or lesser degree, later on in the process. Of the few studies to date that address early DAT, several suggest that CBF deficits start in the temporal region of the cortex (Jagust et al.,1991; Reischies et al.,1987; Costa et al., 1988) extending subsequently to the posterior temporal and parietal regions (Costa et al.,1989). Therefore we might hypothesise that a common pattern of neurophysiological breakdown does exist in DAT starting with the temporal regions, moving on to the parietal areas and then during the latest stages of the degenerative process, a frontal component develops. It may be that a common pattern does exist and that conflicting results concerning this pattern may in fact be a reflection of differing disease severity and diagnostic accuracy.

One aim therefore, of the present study, was to investigate rCBF patterns in very early DAT. Patients displaying little if any objective evidence of dementia but reporting subjective symptomatology characteristic of DAT, especially memory loss, were studied. In particular, this study questions whether rCBF changes are already occurring at this minimal stage of the degenerative process, and if so in which cortical regions. The study also investigates rCBF deficits developing in the subsequent stage of DAT where the cognitive signs are clearly measurable while the overall

dementia is still classified as mild. Finally the specific relationship between cognitive breakdown and neurophysiological degeneration at these very early stages in the dementia process is examined.

METHODS

Patient population

The majority of patients used in this study were recruited through a memory clinic specialising in the early detection of DAT. The 42 patients were diagnosed as suffering from DAT according to the guidelines of the CAMDEX (see chapter 2). Patients fell into two groups according to the cognitive severity of their dementia as measured by the CAMCOG (Roth et al. 1986) and the MMSE (Folstein et al. 1975). As illustrated in Table 5.1, 24 patients showed signs of minimal dementia scoring 75-104 on the CAMCOG and 24-30 on the MMSE and 18 patients displayed mild dementia scoring 50-74 on the CAMCOG and 15-23 on the MMSE. All patients lived in the community and many of the minimal group were still partially employed (see Minimal Dementia: chapter 2).

Control population

Two groups of normal healthy controls were used for this study since the mean age of the minimal and mild DAT group differed considerably (Table 5.1); each control group was therefore age-matched with its respective patient group. All were voluntary controls recruited from the community who reported and displayed no cognitive deterioration as reflected by their mean CAMCOG and MMSE scores (Table 5.1). Sex ratios varied but this was not considered to be important since CBF differences related to gender have not been found.

	N	AGE		MMSE		CAMCOG	
		mean	range	mean	SD	mean	SD
Minimal DAT	24	67.4	45-82	26	2.9	90.3	8.8
Controls (min)	29	68.4	49-86	29.1	1.4	98.9	4.8
Mild DAT	18	75	51-89	18.2	2.6	60.8	7.1
Controls (mild)	20	73.4	64-86	28.9	1.6	97.6	5.5

Table 5.1 Characteristics of the minimal and mild DAT groups and the age-matched control groups

Neuroimaging

Scanning was carried out as described in chapter 3. Normalised CBF values were obtained for 16 regions of interest, using the calcarine cortex as the reference area for normalisation. Subsequent to the work described in the previous chapter, the neuroimaging protocol was altered. The occipital region was divided into two parts; a calcarine and an occipital region, to allow for the measurement of occipital flow in DAT. Normalised CBF values were obtained for the following regions in both the left and right hemispheres:

Medial Frontal
Lateral Frontal
High Frontal
Temporal
Posterior Temporal
Parietal
occipital
Thalamus
Basal Ganglia

Cognitive Assessment

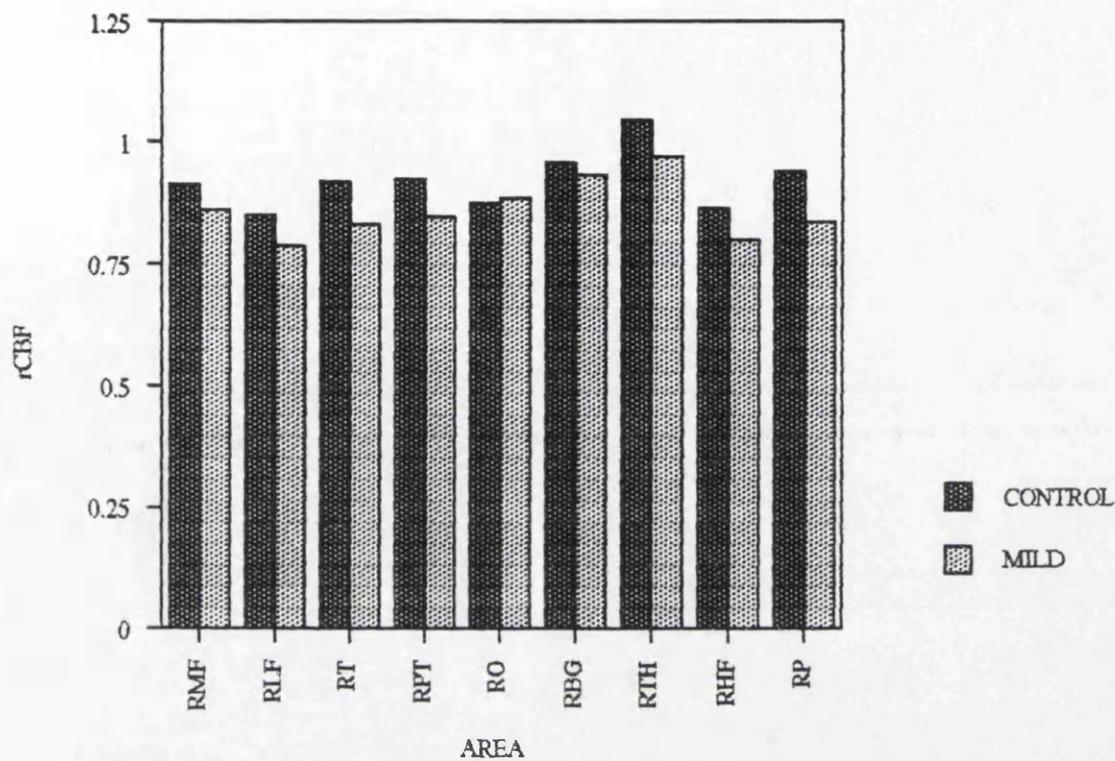
Cognitive assessment was carried out using the CAMCOG as described in chapter 2. Measures of overall cognitive performance, language, memory and praxis were obtained for each subject. Cognitive assessment was carried out within 2 weeks of scanning.

ROIs	Minimal DAT Mean	DAT SD	Controls Mean	SD	p value
LP	0.83	0.08	0.88	0.14	0.047
LT	0.89	0.06	0.93	0.06	0.009

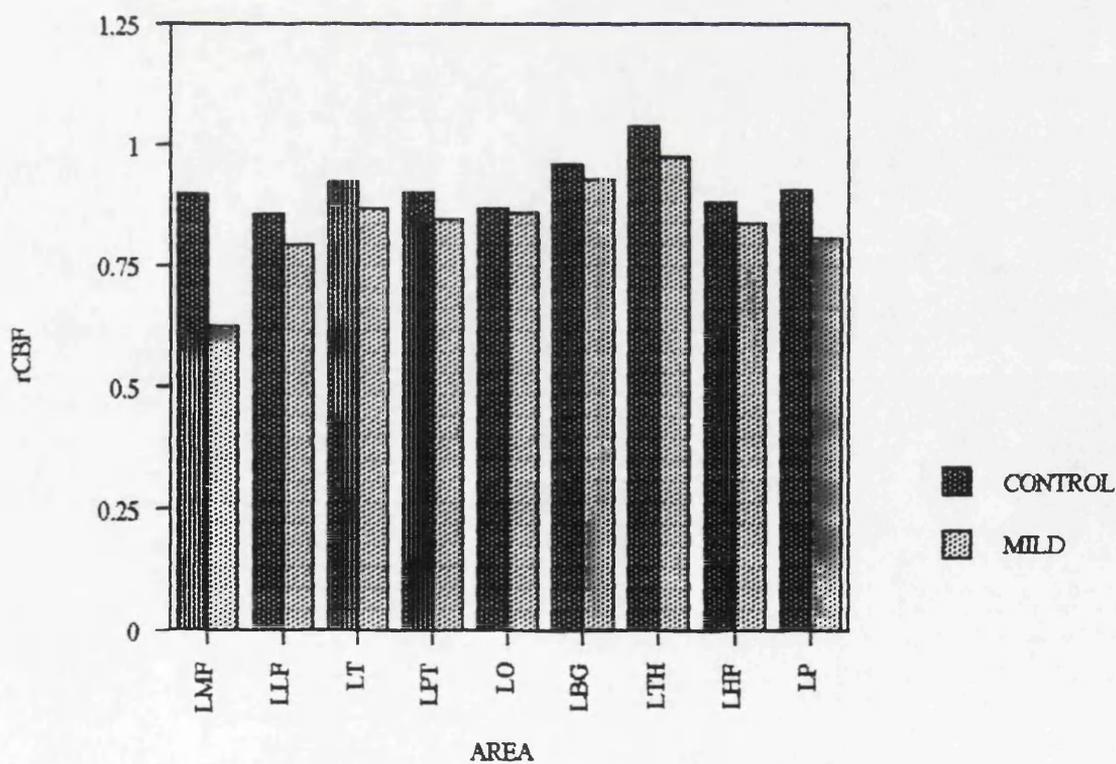
TABLE 5.2 CBF deficits in minimal DAT patients compared to Controls

ROIs	Mild DAT Mean	DAT SD	Controls Mean	SD	p value
RTH	0.97	0.06	1.04	0.08	0.001
RT	0.83	0.09	0.92	0.07	0.001
RLF	0.78	0.09	0.85	0.08	0.010
RPT	0.85	0.12	0.92	0.05	0.010
LPT	0.84	0.07	0.90	0.05	0.006
LMF	0.82	0.10	0.90	0.08	0.009
RMF	0.86	0.11	0.91	0.09	0.050
LTH	0.97	0.09	1.04	0.09	0.015
LT	0.87	0.08	0.92	0.07	0.020
LLF	0.79	0.09	0.86	0.08	0.015

TABLE 5.3 CBF deficits in mild DAT patients compared to Controls

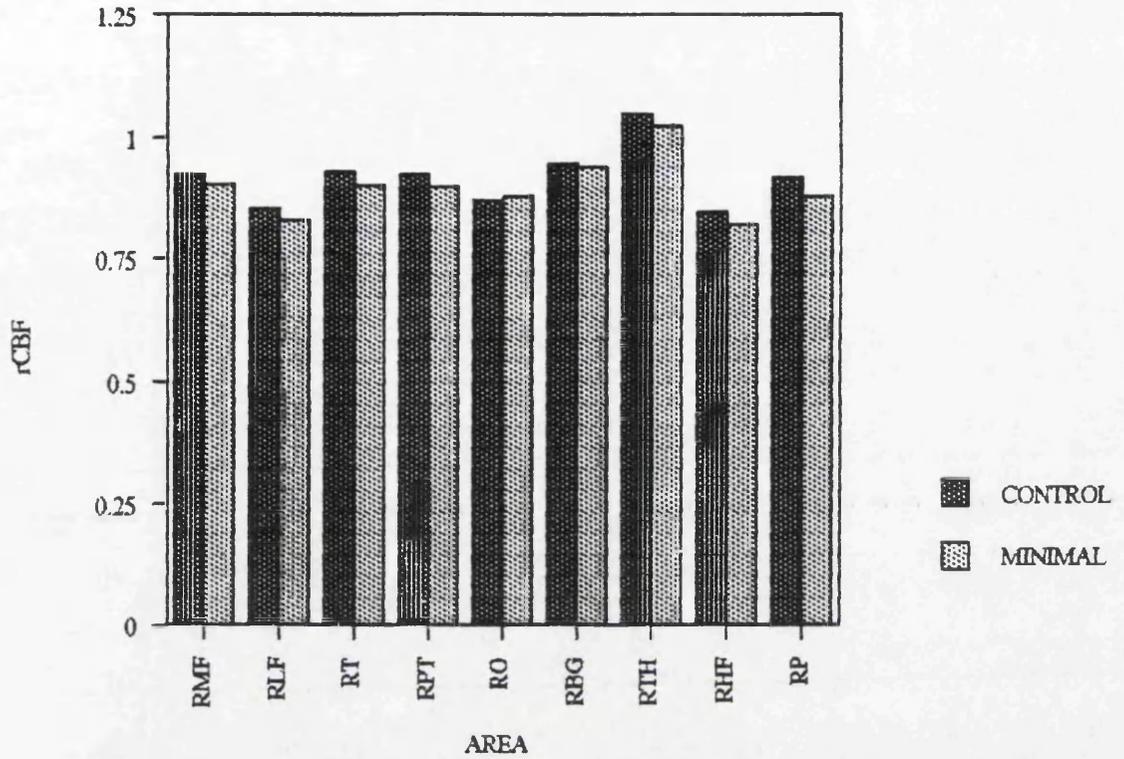


rCBF values in right sided ROIs of mild DAT patients and Controls

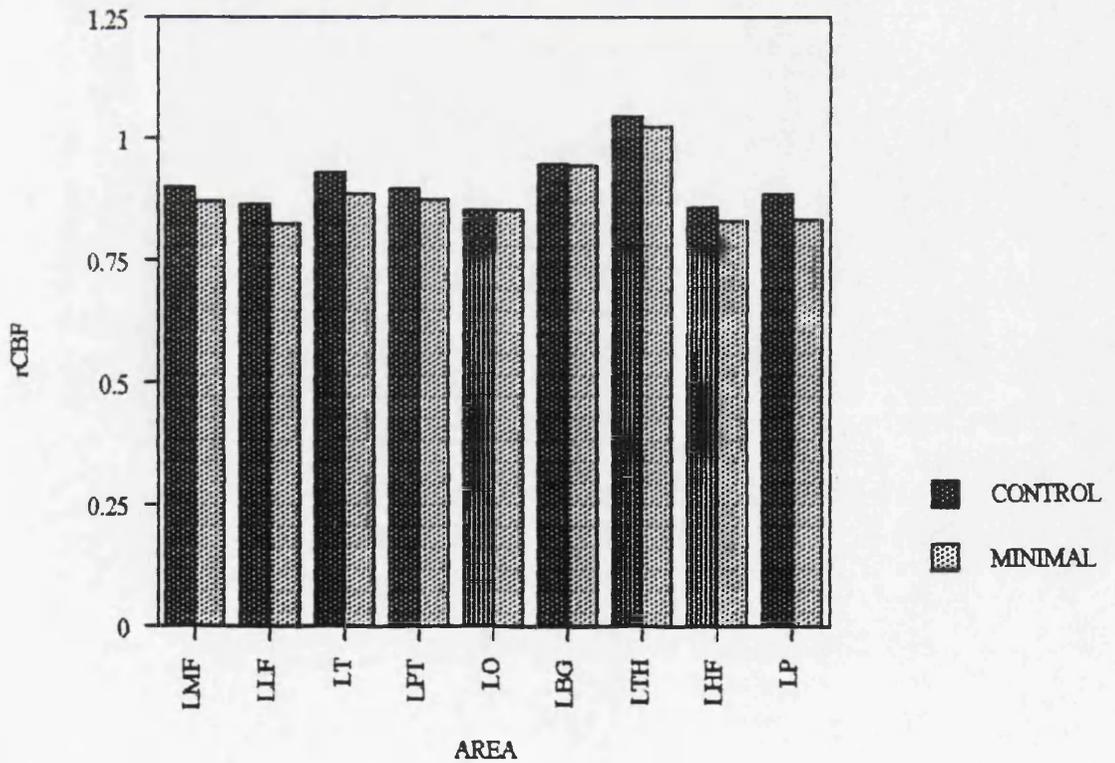


rCBF values in left sided ROIs of mild DAT patients and controls

FIGURE 5(b)



rCBF values in right sided ROIs of minimal DAT patients and Controls



rCBF values in left sided ROIs of minimal DAT patients and Controls

FIGURE 5(a)

RESULTS

Analysis of CBF deficits

Analysis was designed to compare the levels and patterns of rCBF between the two patient groups and their respective controls. Both pairs of groups were compared across each region individually in terms of the mean normalised flow, using independent t-tests.

Table 5.2 describes the data obtained from the minimal group in terms of group means, standard deviations and p-values. Significant CBF deficits were found in the left temporal and parietal regions. Table 5.3 shows the data obtained from the mild group in terms of group means, standard deviations and p-values. Significant CBF deficits were found in both the left and right medial frontal, lateral frontal, temporal, posterior temporal and thalamic regions. The CBF data in the minimal and mild DAT groups is also displayed in the graphs in figure 5(a) and (b) respectively.

Analysis of CBF and Cognition in DAT

The results of the CAMCOG assessment are described in table 5.4 for each patient group (including data from the previous chapter for comparison), displaying both means and ranges. In order to analyse the relationship between CBF patterns and cognitive performance the association between the 18 regions of interest and four measures of cognition were analysed using Spearman's Rank correlation coefficient. The results of this analysis, which made use only of DAT data, are presented in **figure 5d**.

While a number of correlations resulted from the analysis, most were relatively weak in terms of the correlation coefficient value (r). Of those 11 correlations where $r > 0.4$, more than 10 were correlations involving right

SUBJECT GROUP	n	CAMCOG		MMSE		Memory		Language		Praxis	
		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Controls	29	98.9 (4.8)	85-105	29.1(1.4)	26-30	23.6(1.7)	18-26	28.4 (1.6)	23-30	11.6 (.8)	9-12
Minimals	24	90.3 (8.8)	75-103	26.0 (2.9)	20-30	20.0 (4.8)	8-25	26.9 (1.7)	25-30	11.3 (.9)	9-12
Controls	20	97.9 (5.5)	85-105	28.9(1.6)	26-30	23.4(1.8)	18-26	28.3 (1.6)	26-30	11.6 (.8)	9-12
Milds	18	60.8 (7.1)	51-74	18.2 (2.6)	13-22	10.0 (4.3)	3-18	22.4 (2.5)	17-27	8.6 (1.7)	6-12

TABLE 5.4 CAMCOG scores for minimal and mild DAT patients and Controls

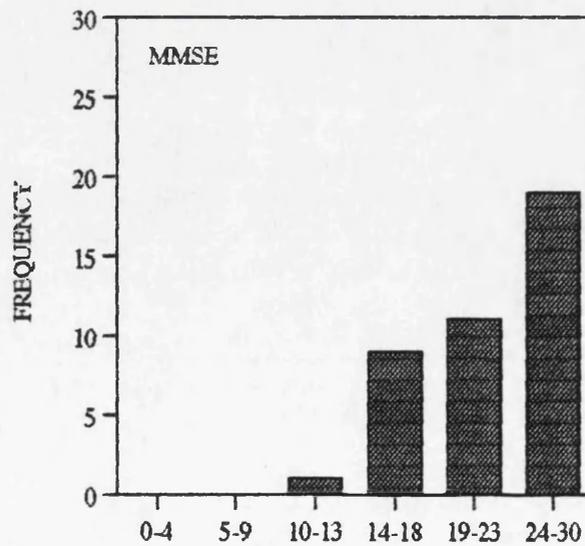
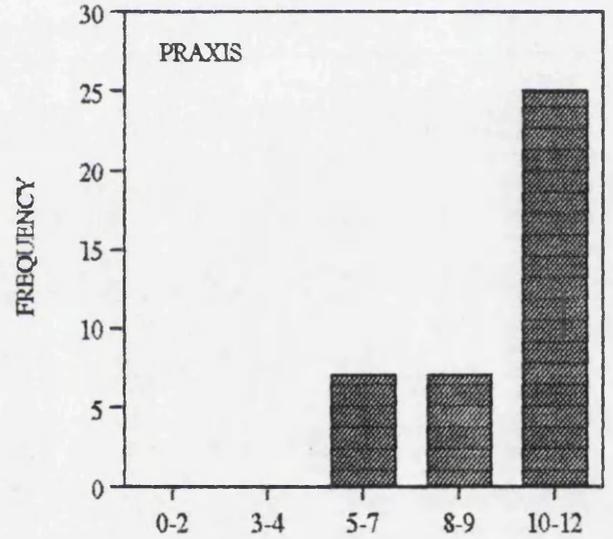
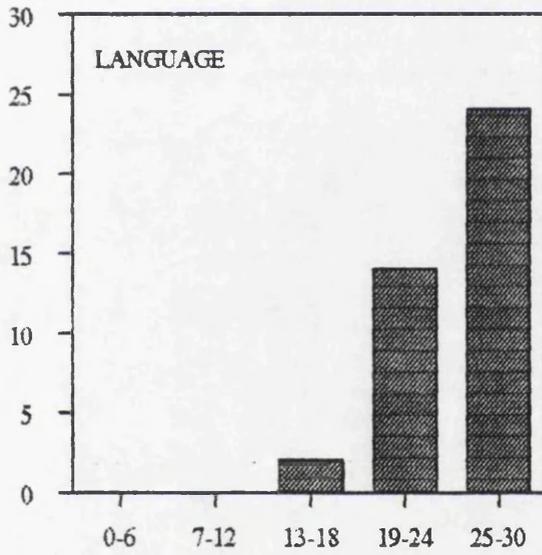
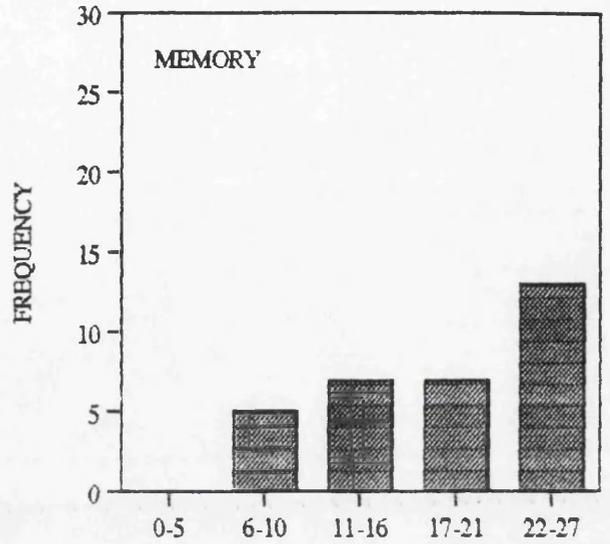
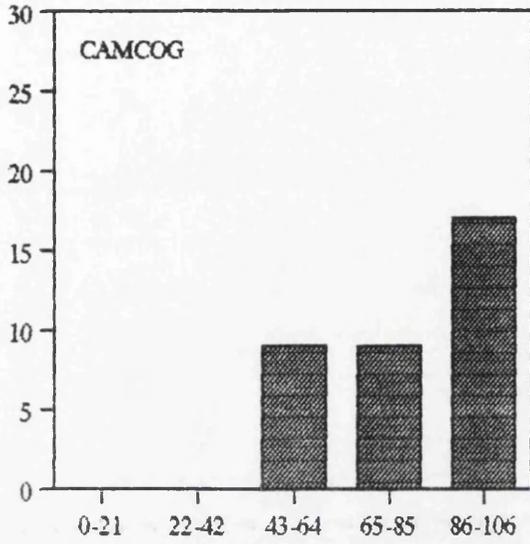


FIGURE 5(c) Distribution of CAMCOG scores for minimal and mild DAT patients

ROI	CAMCOG	MEMORY	LANGUAGE	PRAXIS	MMSE
LMF	0.26*	0.3*			0.29*
RMF	0.25*	0.29*			0.29*
LLF					
RLF					
RHF	0.41**	0.4**	0.35**	0.28*	0.43**
LHF	0.24*	0.26*			0.26*
RT	0.46++	0.39**	0.42**	0.33*	0.44**
LT					
RPT	0.26*				0.32*
LPT	0.29*			0.29*	0.33*
RP	0.48**	0.45**	0.37**	0.35**	0.5+
LP	0.37**	0.34**	0.29*	0.26*	0.4**
FO					
LO					
RTH	0.33*	0.32*	0.34**	0.25*	0.3*
LTH	0.33*	0.31*	0.3*		0.34*
RBG					
LBG					

- * Significant at individual 5% level
- ** Significant at individual 1% level
- ++ Significant at individual 0.1% level

FIGURE 5 (d) Associations between CBF and CAMCOG scores

hemisphere regions, and of those, 6 involved overall cognitive performance (total CAMCOG or MMSE). The remaining 4 correlations involved more specific cognitive domains; correlations were found between right parietal and temporal CBF and language performance, right parietal CBF and memory and right parietal and praxis. One other correlation involved the left parietal region and overall cognition as measured by the MMSE.

DISCUSSION

This study investigates the rCBF deficits accompanying the early stages of DAT. These results suggest that using this technique, CBF deficits might be detectable in the earliest stages of DAT. At the minimal stage of the disease the most significant region of reduced blood flow is the left temporal region. There is also a deficit in the left parietal region, however this deficit must be interpreted cautiously as it only just reached significance. Interestingly, these are the only two ROI's found to be affected by the disease process at the earliest stage of the disease. While these findings are both consistent with previous results of posterior deficits, the temporal CBF deficit which is not always reported in DAT, is particularly interesting and supports recent findings with very early cases (Jagust et al., 1991). Moreover the temporal deficit is perhaps not surprising since at this stage of dementia the most common form of cognitive impairment is one of memory loss and much of memory function is thought to depend on intact temporal structures (see Mayes 1988, for a review). While it may also appear interesting that these deficits are specific to the left hemisphere, this might not be a characteristic of the degenerating process of DAT itself, but rather a result of a selection bias. Since language functions (including verbal memory) are particularly dependent on the left hemisphere, it may be that those patients at the early stage of DAT who have left-sided damage are

identified more frequently than patients with early right-sided damage in whom the cognitive symptoms are less obvious.

By the mild stage of the disease this study shows, as would be expected, that the CBF deficits have spread over a much larger area of cortex. At the mild stage CBF deficits are found to extend over the whole of the temporal lobes, the thalamic region and interestingly, much of the frontal cortex excluding the premotor regions. It may be surprising that the parietal regions, normally the site of major damage in DAT, seem relatively unaffected at this stage. However, this result may be a reflection of disease severity since the results of the investigation described in the previous chapter displayed unambiguous parietal CBF deficits in moderate and severe patients using the same technique. The role of the parietal deficit as the hallmark of DAT (Holman, 1986) may be less clear-cut than once thought. Holman's recent work (Holman et al., 1992) investigated the CBF patterns of 132 patients with cognitive abnormalities aiming to measure the relative probability of a diagnosis of DAT for each of the following seven rCBF patterns:

- 1 Normal
- 2 Bilateral posterior temporal and/or parietal deficit (82%).
- 3 Bilateral posterior temporal and/or parietal deficits with additional deficits (77%).
- 4 Unilateral posterior temporal and/or parietal deficits with or without additional deficits (57%).
- 5 Frontal cortex deficits only (43%).
- 6 Other large (>7cm) defects
- 7 Multiple small(<7cm) cortical defects

The predictive value of each pattern, described in brackets, reflects the frequency with which each pattern occurred in DAT and is expressed as

a percentage of all patients with that particular CBF pattern. Diagnosis of each patient was carried out independently by a psychiatrist and while the majority of patients were diagnosed as DAT, twelve other diagnostic categories, including Parkinson's dementia, Vascular dementia and HIV related dementia were also used. Holman, who classified the SPECT scans into the above 7 categories was blind to the diagnostic decision. It is particularly interesting to note that they do not refer to parietal deficits alone but refer instead to posterior temporal and/or parietal deficits, thus implying that both these regions are both frequently affected by DAT. This issue points to the fact that there may exist considerable variability between research groups as to what they consider to be 'parietal'. Depending on the height of the parietal slice, the area of cortex classified as parietal can vary from the low temporo-parieto-occipital lobule to the high motor area. Therefore interpretations of posterior-temporal and parietal deficits should be aware of such variability. Holman's group (1992) conclude that both patterns 2 and 3 are highly predictive of DAT but that patterns 4 and 5 are not predictive at all. In the light of these findings it is perhaps not surprising that while no strongly significant parietal deficits were found in the present study, there were clear posterior temporal deficits in the mild DAT group. The reason for a lack of parietal deficits in the present study might be explained by the fact that as figure 3 (b) in chapter 3 illustrates, the parietal regions used here are relatively high up and may approach the motor cortex which is considered to be relatively spared in DAT. Work by both Haxby et al., (1986) and more recently by Reed et al., (1989) has identified cases of early DAT where measurements of metabolism and CBF have not revealed deficits in either the temporal or the parietal regions. While the obvious question here is whether the cases they refer to are actual cases of DAT or perhaps examples of another form of dementia, it is clear that the value of using posterior deficits as the hallmark of DAT remains debatable.

Holman's work found that of those patients diagnosed as suffering from vascular dementia (eg MID), only 27% displayed the bilateral deficits described in 2 and 3 above thereby concluding that CBF patterns of this type can contribute substantially to the differential diagnosis of dementia. While this is undoubtedly the case, care must be taken in the interpretation of this argument since as mentioned earlier, Holman et al. provide no indication as to the severity of the cognitive deficits or dementia of their patient population. This is a considerable 'oversight' on the part of Holman and his co-workers as it clouds interpretation of these very interesting findings. For example, patterns of unilateral CBF deficits were interpreted as non predictive of DAT although unilateral deficits have been reported in cases of DAT (Waldemar et al., 1991; Lowenstein et al., 1991; Cardebat et al., 1991), particularly at an early stage, and the results presented in this chapter add further support. It is therefore possible that some of the patients displaying unilateral deficits in Holman's study, were suffering from a milder degree of DAT than those with bilateral CBF deficits rather than a different form of dementia.

Frontal CBF deficits in DAT

It is pertinent here, to refer once again to the recent work of Holman et al., (1992), whose findings include the diagnosis of DAT in 43% of those with isolated frontal CBF deficits. They conclude that this particular CBF pattern is not predictive of DAT and while this may be an accurate conclusion to draw from their study, it is crucial to note that 43% of the patients with this pattern of CBF deficit received a diagnosis of DAT. Holman et al., (1992) do not refer to the existence of FLD as described by either Neary et al., (1988) or by Brun (1987), and while it is difficult to differentiate these dementias on clinical grounds, there is a reasonable chance that a small proportion of these 'frontal' DAT cases are examples of FLD. However, Holman's findings (1992) strengthen the argument that DAT has a frontal component and therefore evidence of a frontal

pathology, either from neuroimaging or neuropsychology, should not be used to exclude the diagnosis of DAT. In particular, Haxby et al., (1988) identified reductions in metabolism in the premotor cortex (high frontal) of moderate and severe cases of DAT, the mild group on the other hand, displayed no premotor deficit, but only temporo-parietal deficits. These findings therefore support the view that the frontal lobes are only affected in the later stages of the disease. In contrast, the findings of the present study do not support this view since both left and right lateral and medial frontal regions show CBF deficits at the mild stage of DAT. The high frontal region contains the premotor area and CBF in the high frontal region remains normal in the mild group while the results presented in the previous chapter illustrates significant CBF deficits in this region in moderate to severe cases of DAT. Therefore, while there remains some question as to the early involvement of the medial and lateral frontal regions in DAT, there is agreement that the premotor, or high frontal regions are affected in the later stages of DAT. The relative involvement of the frontal cortex in DAT compared to other more traditionally "anterior" dementias such as Pick's Disease and FLD may only be determined once in vivo neurophysiological tests for the differential diagnosis of dementia are developed. However, accepting that there is a frontal component in DAT, we may ask whether the inconsistent findings of frontal CBF deficits reflects variations in the severity of the disease. Alternatively they could reflect the presence of a 'frontal' DAT subgroup who suffer a disproportionate deficit in frontal CBF and corresponding neuropsychology while fulfilling all the diagnostic requirements for DAT. This possibility will be investigated and discussed further in chapter 7.

Patterns of CBF and cognition

Following the floor effect and multiple correlations that were described in the previous chapter, this investigation aimed to question whether the use of general cognitive tests could be justified in this type of study if the patients involved were only minimally or mildly impaired. Examining

table 5.4 illustrates that the patients used in this study are mildly impaired in contrast to those featured in the previous chapter.

Focussing now on the associations between rCBF and cognition for these patient groups, it is clear from figure 5(d), that a number of correlations resulted from the analysis. The first feature to point out is the lack of strong correlations between rCBF and praxis in contrast with the previous study where praxis was found to correlate with CBF in all ROI's. The explanation for this might be similar to the problem with the memory subtest encountered in the previous chapter. The praxis subtest of the CAMCOG is a particularly easy section of the test, therefore while the moderate and severe groups displayed a reasonable distribution of scores in the previous chapter, the minimal and mild group in this study did not. This resulted in a ceiling effect in the praxis scores in this study comparable to the floor effect in memory performance reported in the previous chapter. This lack of a distribution of praxis scores will have undoubtedly reduced the chance of producing correlations with rCBF.

Another feature of figure 5(d) is the number of correlations involving overall cognitive performance as displayed by both the CAMCOG (total score) and the MMSE. These correlations presumably reflect the frequently reported relationship between overall dementia severity and reductions in CBF (Hunter et al., 1989; Burns et al., 1989)). Results from the previous study relating cognition and CBF in a moderate to severe DAT population, show correlations between CBF and MMSE scores in all ROI's and with CAMCOG (total score) in all but 2 ROI's. Moreover, the strongest of these correlations involved those ROI's showing the greatest reductions in CBF. In this study on the other hand, while measures of overall cognitive performance do correlate with CBF in a number of ROI's, this correlation is found much less frequently. One important point to make before comparing these results to those of the previous chapter, is that the design of this study involved the analysis of CBF in a larger

number of regions than the previous study, therefore the potential for multiple correlations is even greater. It appears from the comparison of these two sets of results that the relationship between CBF and cognition changes as the disease progresses. Therefore while cognitive performance is related to CBF in early DAT the pattern of this relationship is qualitatively different to that found in the much later stages of the disease. A possible reason for this is that at the earlier stage of dementia, patients might be able to adapt to some of the cognitive problems they encounter. For example, in the earliest stages of dementia when memory is considered to be the principal area of deficit and the cortical regions involved in its function might be damaged, general intellectual function remains intact and can be used by the sufferer to aid in memory performance, through the application of mnemonics perhaps. It is therefore conceivable that at the earlier or mild, stages of DAT degeneration, the neuropsychology and neurophysiology may not reflect each other in the same way that they might later on in the process.

The language subcomponent of the CAMCOG produces a similar pattern of correlations to that produced by the overall CAMCOG and MMSE scores. This is interesting since while profound language deficits can occur at the earlier stages of DAT, they are not common. It is very likely that this similarity in results in comparison to those produced with the memory or praxis subcomponents reflects the language bias of both the MMSE and the CAMCOG. This is a common problem in the use of general cognitive assessment tests and is a factor that should be considered when designing this type of correlational study.

These results on the whole, suggest that correlations with the subcomponent scores offer little more than that obtained from correlations with overall scores. This reflects an issue raised in the previous chapter, namely the lack of specificity of general cognitive tests designed for clinical use. While the MMSE is a very short mental status

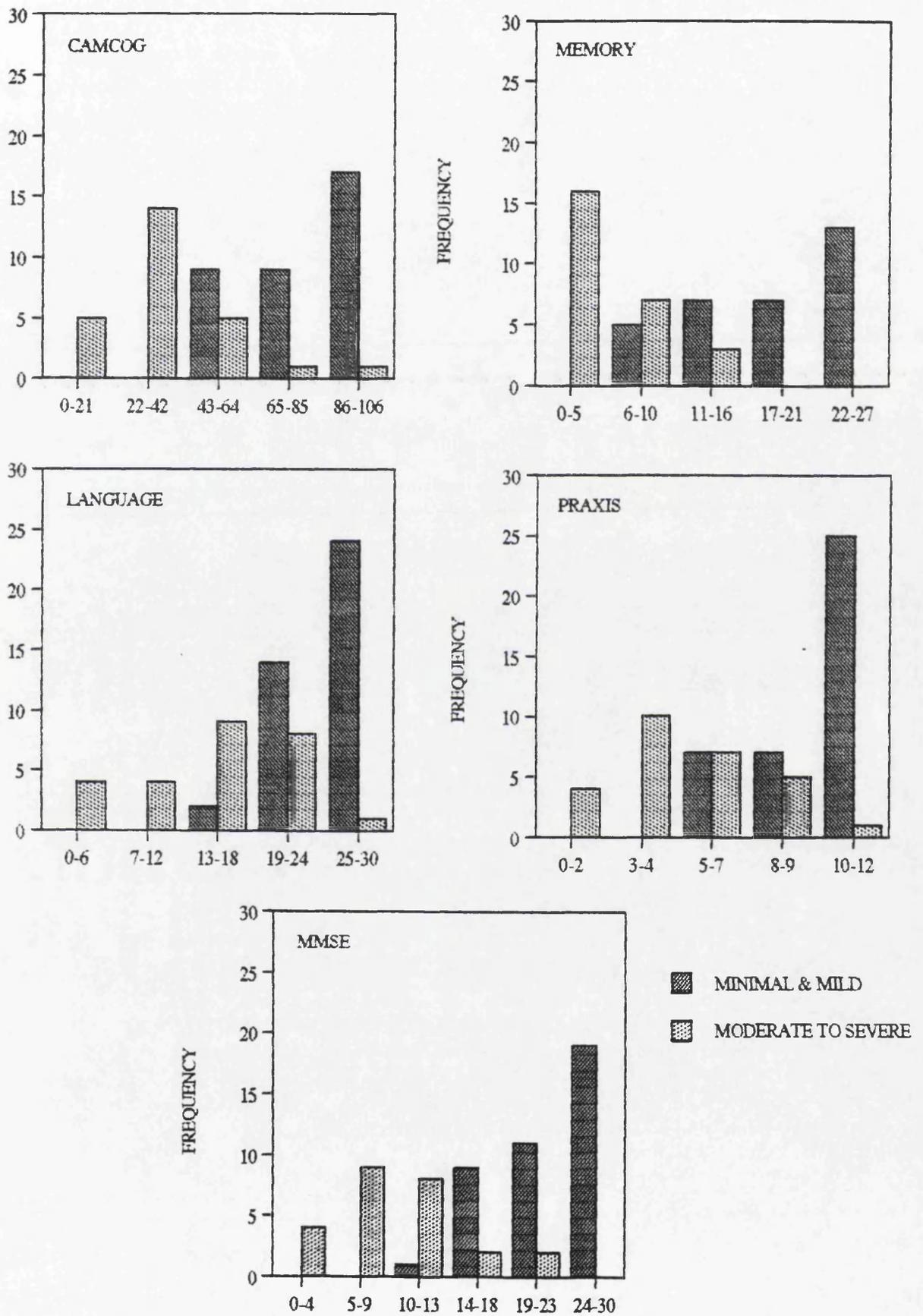


FIGURE 5(e) Distribution of CAMCOG scores for both DAT populations

test designed simply to provide a single measure of mental status, the CAMCOG has been designed for more extensive use. It was designed for the purpose of characterising the cognitive deficits of dementia and as such it is a useful test. However it has also been used by some researchers to differentiate between cognitive subgroups of patients. Burns et al., (1989) used the CAMCOG to identify two groups of DAT patients, one with aphasia and or apraxia and one without. He then compared rCBF between these two groups and found that patients with aphasia and or apraxia had reduced CBF in the lateral temporal and posterior parietal regions in comparison with the other group. Unfortunately, Burns and his colleagues do not provide overall CAMCOG scores so that general differences between the groups can be examined. It is very likely that the differences in rCBF between these two groups is a result of differing dementia severity. This is for two reasons; firstly, patients who display low scores on the parietal and or language subcomponent of the CAMCOG are generally more severely demented, as can be seen by comparing the distribution scores in figure 5(e). Secondly, the regions involved in the correlation reported by Burns et al., (1989) were two of the three regions found to differentiate DAT and controls in the same study. These regions might therefore be expected to show strongly significant deficits when the most severe patients are selected. Finally, Burns et al. describe their work as having correlated rCBF with "discrete neuropsychological functions." This is an example of where the misuse of the CAMCOG and tests like it can be very risky. One major problem with general tests is that they do not measure "discrete neuropsychological functions" although the use of the terms 'memory', 'language' and 'praxis' might suggest otherwise. Moreover, it might be argued that "discrete neuropsychological functions" do not in fact exist since neuropsychological functions are interdependent. On the other hand, clearly defined neuropsychological functions might be a more accurate term. Whatever term is used, the CAMCOG and other procedures like it are not designed for, or capable of, differentiating

between specific cognitive subgroups in DAT. Burns' correlational results are much like the ones presented in the previous chapter. In conclusion, therefore, while the correlations fit with theories of localisation of function, the correlations with the subscores (language, memory, praxis) do not offer any additional information over and above that provided by the overall scores. The results of such studies highlight the need to use highly specific cognitive tests in order to measure particular neuropsychological functions.

CHAPTER SIX

RECOGNITION AND RECALL MEMORY IN DAT AND THEIR RELATIONSHIP TO CBF PATTERNS

INTRODUCTION

For research purposes, assessing the severity of DAT is almost as important as the identification of the dementia itself. In recent years both these tasks have been carried out in terms of cognitive decline (Huppert and Tym, 1986). The sensitive and consistent identification of minimal and mild DAT is fundamental to the comprehension of the processes of cognitive decline which accompany DAT, the identification of cognitive subgroups and the effective administration of pharmacological intervention. Given this, together with the prominence of early memory impairments in DAT, it is clear that the assessment of the nature and progression of memory impairment in early DAT is of considerable importance.

There certainly is no shortage of memory tests, some of which may even be sufficiently sensitive to detect the often subtle memory deficits of early DAT. However, as Salmon et al., (1989) note they are often inadequate for discriminating between different dementias and particularly pertinent to this study, between the different stages of any single form of dementia such as DAT. This point was also discussed by Albert and Moss (1984) who further noted that any investigation of memory deficits in a progressive dementia must take into account the methodological limitations imposed by other cognitive defects that may be present. For example DAT patients often show early defects in confrontational naming which may confound or significantly interact with performance on specific memory tasks. They further stress that even quite minimally demented

patients may be perseverative, circumstantial and stimulus-bound and these tendencies may produce test responses that do not accurately reflect the patients' true ability. The complexity of instructions and required responses in any memory task may also distort patients' performance.

In response to these factors Moss and Albert (1986) developed a Delayed Recognition Span Test (DRST), the basis of which was a test originally designed for non-human primates (Rehbein, 1985). The DRST has several features which make it particularly suitable for use with a demented population: The task instructions and the response required are easily understood and simple yet the task permits detailed tracking and quantification of memory ability. The subjects are not openly confronted with their failures and are therefore less likely to become discouraged or un-cooperative. Moreover, the task has a game-like quality making it appealing and non-threatening. The subjects' recognition span may be compared for different classes of stimuli (eg. spatial, verbal, facial) within the same paradigm. Furthermore, the design of the task allows for two measures of verbal recall; one immediate and one delayed which can potentially provide information concerning forgetting rates.

The original study carried out by Moss et al., (1986) administered this task to four different subject groups; a DAT group, a Huntington's Disease group, a Korsakoff group and an elderly control group. Recognition memory was measured for five classes of stimuli (verbal, spatial, facial, colour and pattern) and recall memory for verbal material (immediate and delayed). The principal findings of this study which are pertinent to the present study are that the DAT group (like the Korsakoff group) was significantly impaired on all five stimulus conditions with the verbal and spatial conditions equally impaired while the facial condition showed a significantly greater degree of impairment. Also of interest is

the finding that while all patient groups displayed impaired recall for verbal material in the first recall trial (immediate), the DAT group suffered a disproportionate loss of information between immediate and delayed recall thus suggesting a particularly rapid rate of forgetting may accompany this disease. More recently, Salmon and his colleagues (1988) carried out a similar study but this time they focused more specifically on DAT including both a mild and a moderate group as well as the controls. Their results not only confirmed those of Moss and Albert but extended them to show that the DRST was sensitive enough to discriminate between the memory deficits accompanying the different stages of the dementia and conclude that the task is ideal for the longitudinal assessment of dementia. Briefly, the results showed that for both verbal recall and overall recognition span significant differences in performance were found between controls, milds and moderates. They then selected the least demented (n=7) from the mild group and analysed their data separately. They found that for this post hoc group overall recognition performance was significantly lower than for the controls, likewise, this group showed significantly lower recall and a **high** rate of forgetting than the controls. However no evidence was found that this test could distinguish the least demented from the remaining mild group in any of the recognition or recall conditions.

The aims of the present study are firstly to replicate the findings of Moss et al., (1986) with respect to DAT in general. Secondly, following Salmon's work (1989), this study should provide more detailed information on the effects of the progression of the dementia on performance on this specific memory task. Thirdly, by including a minimal group (described in detail in chapter 2), this study attempts to investigate the very earliest memory deficits that accompany DAT. Finally, by combining this data with CBF data obtained within a month of task administration, the relationship between specific components of memory (recognition, recall and forgetting rate) and regional cerebral blood flow

GROUP	n	AGE Mean (SD)	CAMCOG Mean (SD)	MMSE Mean (SD)
Control	14	74.4 (6.51)	94.6 (6.64)	27.5 (1.65)
Minimal	12	71.1 (7.76)	88.5 (9.24)	25.9 (3.50)
Mild	10	77.8 (11.41)	63.0 (8.50)	17.8 (3.55)
Moderate	7	76.6 (3.91)	38.0 (3.74)	10.4 (2.41)

TABLE 6.1 Patient and Control Characteristics

patterns will be investigated.

METHODS

Subjects

This study used 43 subjects of whom 14 were normal controls. The remaining 29 were patients suffering from DAT; minimal (N=12), mild (N=10) and moderate (N=7). All patients were diagnosed using the CAMDEX, the diagnostic procedure and severity group classification are described in detail in chapter 2. Table 6.1 displays details of the subjects used in this study.

Apparatus

Testing was performed on a white testing board (46 x 61cm) on which were displayed 30 black dots arranged in five rows of six dots (figure 6(a)), each dot surrounded by a metal washer. The dots provided targets upon which the stimuli could be placed. The stimulus material was mounted on black wooden circular disks, 5.8cm in diameter and fixed to the base of each disk was a strip of magnetic material allowing the disks to grip tightly to the target. The reason for this is that the board must be removed from view of the subject during the addition of each stimulus and while the original design of Moss et al., (1986) used another technique to achieve this, pilot testing suggested the above to be the simplest method.

While Moss and Albert used five different stimulus conditions (Verbal, Spatial, Colour, Pattern and Facial), for this study only three stimulus conditions were used; Verbal, Spatial and Facial. The reason for this was that with respect to early DAT, verbal and spatial memory are of particular interest. Furthermore, the verbal condition allows for a comparison between recall and recognition and measurements of forgetting rates.

The facial (or configurational) condition on the other hand, might provide a good contrast, and was the condition which displayed most impairment in the study by Moss et al., (1986).

The spatial stimuli consisted simply of 16 black disks while the verbal stimuli were constructed by mounting one of 16 selected five-letter words on each disk. These words were low imagery, high frequency nouns and verbs (eg. START, TODAY) each of which had been printed in uppercase, white helvetica (6mm). For the Facial condition, 16 faces were selected from a military academy year book, photographed and mounted, each on an individual black disk. Moss and Albert had used a military year book since clothing, hair length and general expression were similar and therefore the main source of variation between the stimuli remained the configuration to each individual's features.

Procedure

The subjects were tested individually in a quiet room and were seated opposite the experimenter with the test board situated between them on a low table. In order that the positioning of each new disk be achieved out of view of the subject, the experimenter would raise the side of the board nearest the subject until the board faced the experimenter. Apart from this, the testing procedures followed those of Moss et al., (1986) except that while they carried out five trials of each condition and Salmon et al., (1989) carried out two, for this study, three trials for the spatial, verbal and facial conditions were carried out, in that order.

Spatial condition The subject's attention was directed to the board and the experimenter explained that a disk would be placed on one of the target dots and that after a few seconds the board would be hidden from view and another disk would be added. Following this, the board would be returned to view and the subject would be requested to identify

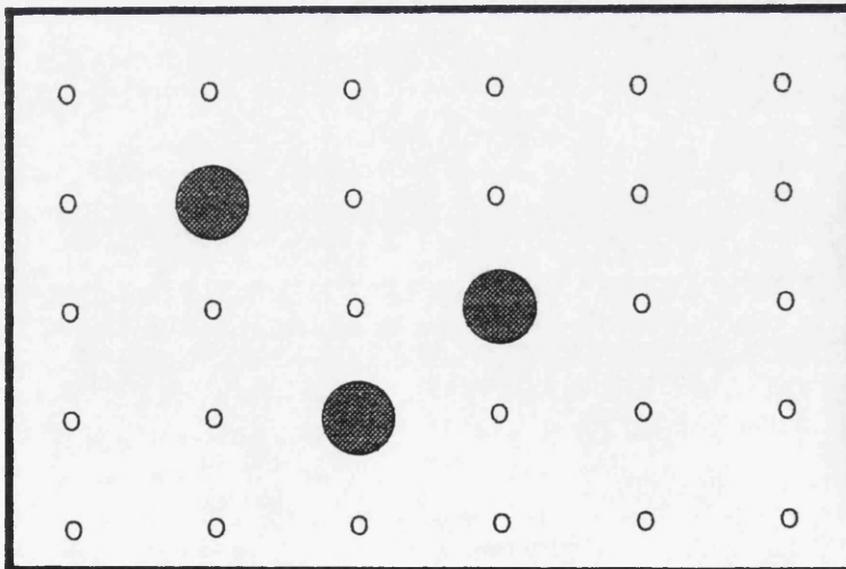
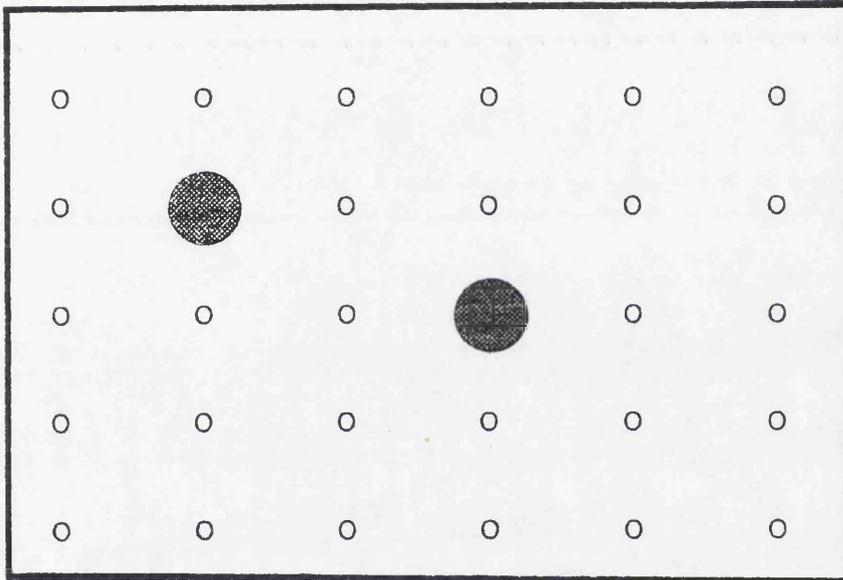
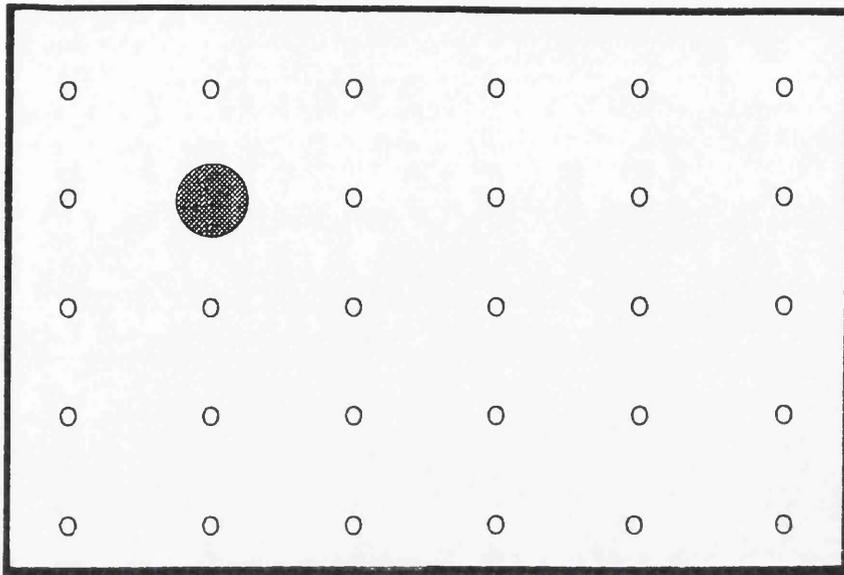


Figure 6(a) Examples of the procedure used in the DRST

which was the 'new' disk. Once these instructions had been clearly explained and the subject showed they had understood by completing a practice trial the test began with the placing of the first disk. Following 15s the board was hidden, the second disk added, and following a 10s delay was revealed again. The subject was allowed 10s to make a decision and if unsure then they were encouraged to make a guess. There then followed a 5s period when the subject was instructed to study the disks on the board before it was again hidden from view for the addition of the third disk (see figure 6(a)). For each of the three trials, this procedure was repeated 16 times or discontinued after the first error. A spatial recognition span score was obtained by averaging the scores over the three trials. Figure 6(a) illustrates an example of this procedure.

Verbal condition The basic procedure for administering the verbal condition was the same as that for the spatial condition with four exceptions. Firstly, prior to starting the recognition span procedure the experimenter displayed all 16 stimuli on the board and requested that the subject read each word in turn. This was to ensure that any subsequent difficulty in recognition could not be due to misperception of the stimuli themselves. Secondly, each time a new disk is added to the board, the other disks are moved randomly around the board to eliminate spatial cues. The experimenter informed the subjects of this and explained the reason for it. Thirdly, no discontinuation was carried out; the procedure was continued for all 16 stimuli irrespective of failures. Finally, on completion of each trial and following a 15s delay, the subject was asked to recall as many as possible of the words that had featured on the board. The subject was then engaged in conversation for a further 2 minutes after which they were again asked to attempt to recall the words. Approximately 1 minute was allowed for each attempt at recall. A verbal recognition span score was obtained by averaging the score over the three trials while only one measure of each of the immediate and delayed recall was obtained.

Facial condition The facial recognition procedure was identical to the verbal except that like the spatial condition there was no initial exposure to the stimuli, each trial was discontinued after the first error and there was no recall procedure. Again, a facial recognition span score was obtained by taking the average over the three trials.

RESULTS

Recognition span

The first area of investigation is that of the effect of severity on performance in the three different recognition conditions, this data is displayed in table 6.2 and illustrated in the graph in Figure 6(b). The graphs suggest that DAT results in impaired performance on recognition tasks and that dementia severity effects performance on all three tasks. In order to investigate the strength of these effects, a one-way Anova was carried out for each condition the results of which are displayed in table 6.3.

The effect of severity on recognition span This analysis produced a significant effect of severity on performance of both the spatial and verbal tasks. The graph illustrates this effect and suggests that the largest loss in both verbal and spatial recognition memory occurs between the minimal and mild stages of the disease with perhaps a slightly greater loss in verbal than spatial recognition. Since the results do not clearly indicate that the minimal group perform significantly worse than the controls and since this distinction is important, a post hoc t-test was carried out. The results produced no significant difference between controls and minimal groups on the recognition tasks, however the graph does suggest a trend in that direction. In contrast, although both the mild and

GROUP	Verbal Mean (SD)	Spatial Mean (SD)	Facial Mean (SD)	Recall1 Mean (SD)	Recall 2 Mean (SD)
Control	9.19 (3.42)	7.84 (3.04)	6.17 (2.99)	8.50 (2.07)	6.86 (2.45)
Minimal	8.01 (2.71)	6.53 (3.00)	5.21 (1.52)	6.92 (2.71)	4.50 (2.61)
Mild	3.94 (1.44)	4.00 (1.12)	2.63 (0.99)	3.50 (1.35)	1.90 (1.45)
Moderate	3.53 (1.28)	3.10 (1.23)	2.04 (0.59)	1.14 (1.46)	0 (0)

TABLE 6.2 Recognition Span scores and Verbal Recall scores for DAT patients and Controls

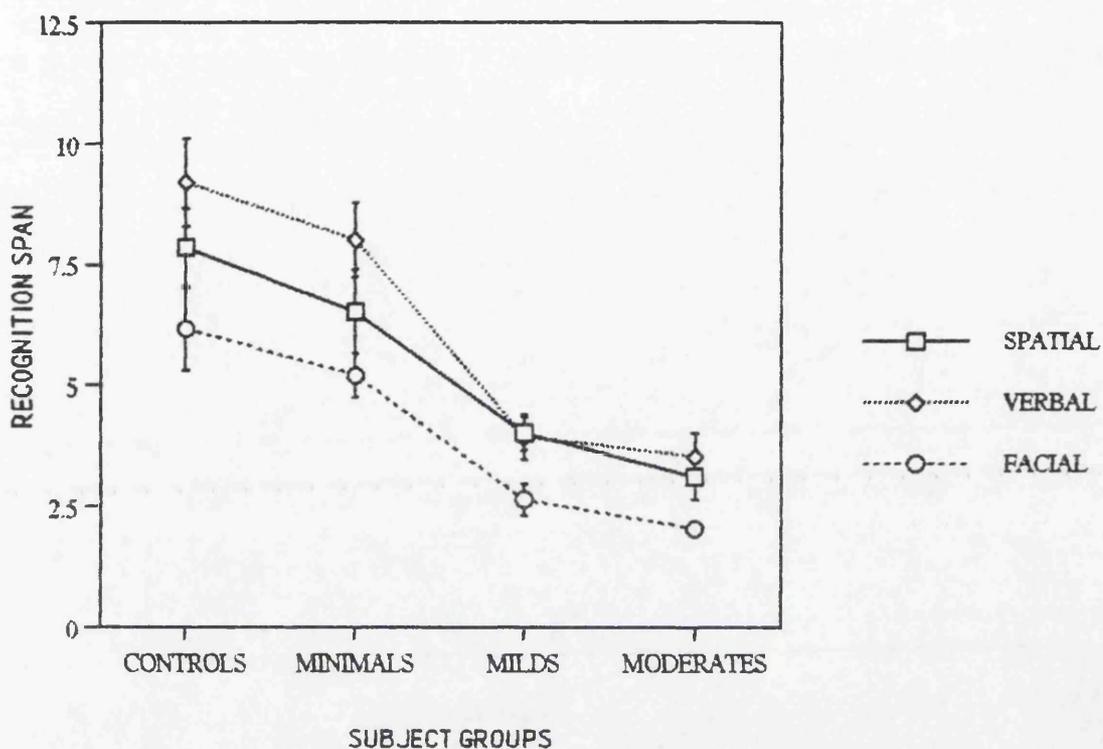


FIGURE 6(b) Recognition span of DAT patients and Controls

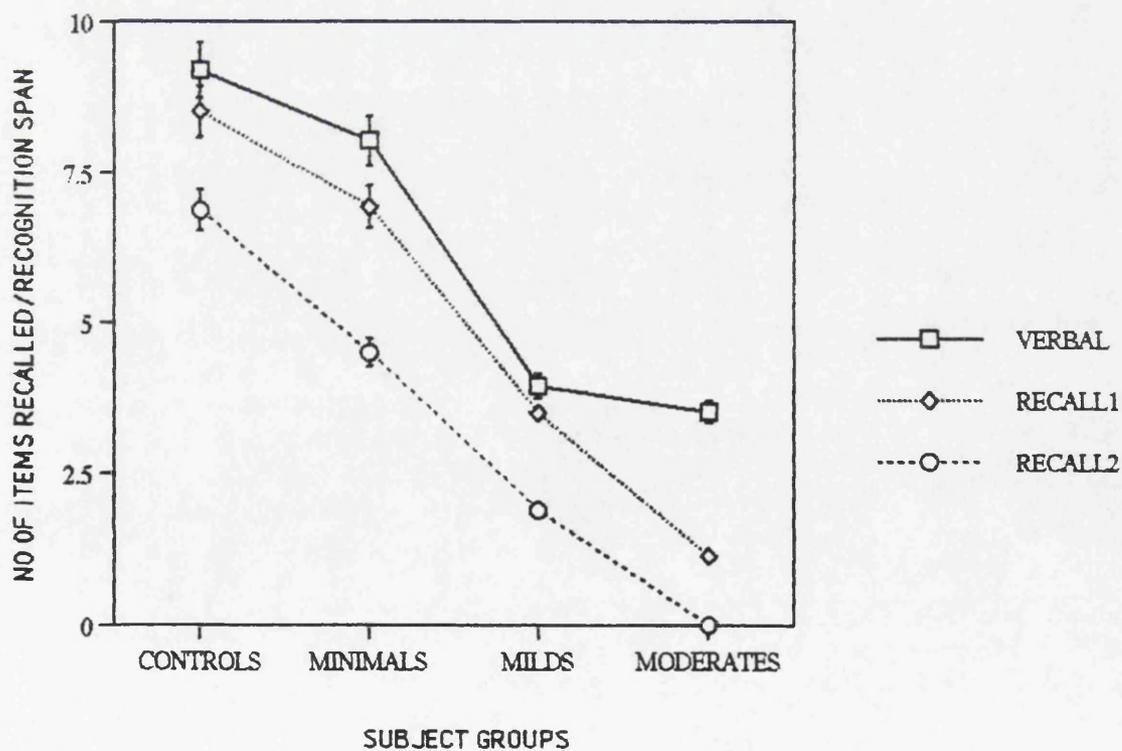


FIGURE 6(c) Verbal Recognition span, Immediate and Delayed recall in DAT patients and Controls

moderate groups perform significantly worse than the minimal and controls they clearly do not differ from each other. This strengthens the view that spatial and verbal recognition ability is lost relatively early in the disease process and might suggest that a very small sparing in recognition memory occurs late on in DAT. The analysis of the facial performance also produced a significant effect of severity. As the graph in figure 6(b) clearly illustrates, the facial recognition task is particularly demanding, not only for DAT patients but also for controls. However the results also illustrate that the impairment in facial (or configurational) recognition follows the same pattern of breakdown as the other recognition conditions; the largest impairment in performance occurs between the minimal and mild stages, while further loss following the mild stage is negligible.

Verbal Recall and Forgetting rate

Data from this section of the task is also displayed in table 6.2 and is illustrated by the graph in Figure 6(c). Again, the graph shows effects of severity on recall performance in both the immediate and delayed condition. For the purpose of investigating forgetting rate between the two recall trials, a measure of forgetting was obtained by expressing the loss of information between immediate recall (R1) and delayed recall (R2) for each subject as a percentage of immediate recall thereby producing a forgetting rate score (FR) reflecting loss of information during the two minute interval. The effects of severity on these measures of recall and forgetting rate were investigated using a one-way Anova for each of the three measures.

The effect of severity on Immediate and Delayed Recall This analysis produced a significant effect of severity for both recall conditions, (see table 6.3). In contrast to the recognition data, the data represented in the graph in figure 6(c) suggests that the relationship

Condition	F(3,39)	p
Verbal	12.56	0.0001
Spatial	8.04	0.0003
Facial	3.89	0.016
Recall 1	25.20	<0.0001
Recall 2	13.85	<0.0001
Forgetting Rate	1.99	ns

TABLE 6.3 Results of ANOVA comparing Recognition spans and Recall across all groups

Condition	t	p
Recall 1	1.65	<0.05
Recall 2	2.36	0.01

TABLE 6.4 Results of t-test comparing Controls and Minimals on Recall 1 and Recall 2

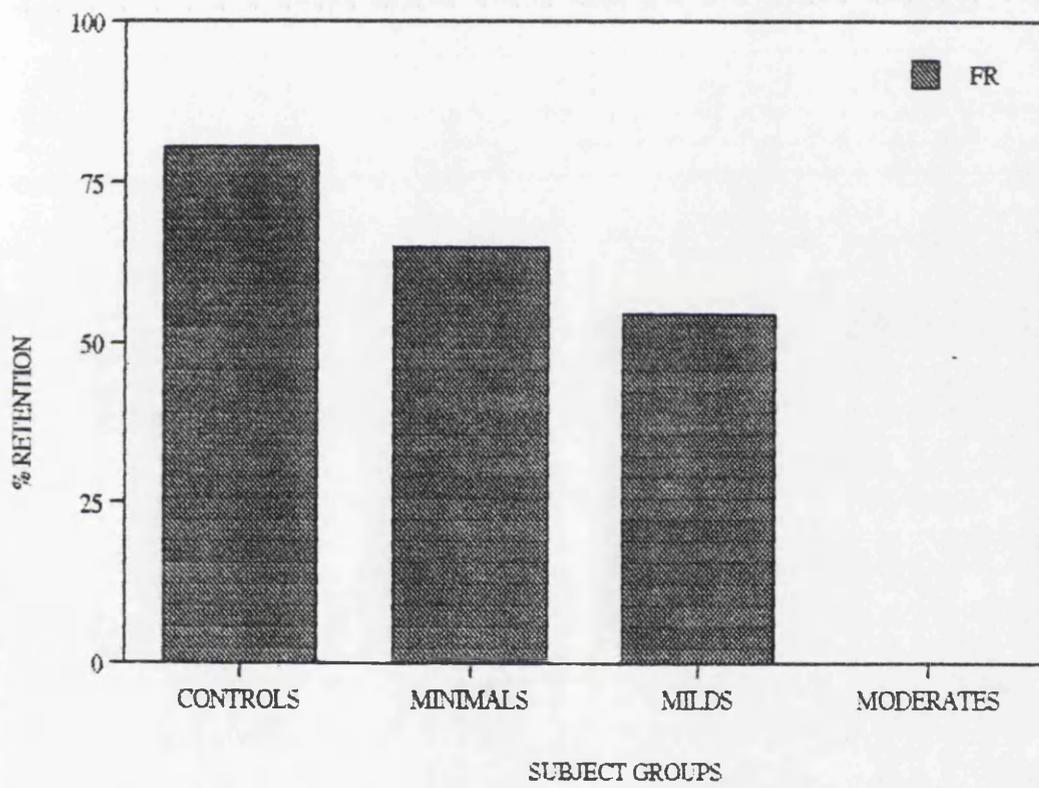


FIGURE 6(d) Differences in forgetting rate across groups

between severity and recall, (both immediate and delayed) approaches linearity. Therefore while a significant loss in recall ability occurs between the minimal and mild stages (similar to that described above for the recognition data) the graph also illustrates a comparable impairment between both the control and minimal groups and the mild and moderate groups. Since the issue of the identification of very early memory deficits is of particular importance, a post hoc t-test was carried out to compare the performance of the control and minimal groups on both the immediate and delayed recall. The results of this analysis (table 6.4) show that while the difference in immediate recall just reached significance, the difference in delayed recall was highly significant. These findings suggest that the earliest memory deficits accompanying DAT involve recall rather than recognition and that retention during a delay period is particularly vulnerable to the effects of the dementia. A further feature of the recall results is that while recognition span in the mild and moderate group does not differ, suggesting a relative sparing of a span of approximately 3 items, performance on the recall task does continue to decline during the mild and moderate stages with a floor effect in the delayed recall score of the moderate group.

The effect of severity on Forgetting Rate Measures of forgetting rate (FR) were obtained for each group as described above, the graph in figure 6(d) illustrates these results. An ANOVA performed on this data did not yield a significant effect of severity. However, the graph clearly illustrates that forgetting rate is impaired in DAT and that the forgetting rate increases with increased severity.

Regional Cerebral blood flow and performance on the DRST

Using Spearman's rank correlation coefficient, patient's performance on

ROI	SPATIAL	VERBAL	FACIAL	RECALL 1	RECALL 2
LMF				0.45*	
RMF				0.38*	
LLF					
RLF					
RHF					
LHF					
RT		0.56**	0.47*	0.71++	0.47*
LT					
RPT					
LPT			0.42*		
RP		0.52**	0.41*	0.44*	
LP		0.39*		0.44*	
RO					
LO					
RTH					
LTH		0.44*	0.47*	0.52**	
RBG					
LBG					

* Significant at individual 5% level

** Significant at individual 1% level

++ Significance at individual 0.1% level

FIGURE 6 (e) Correlations between rCBF and measures of recall and recognition memory in DAT

the 5 components of the DRST was correlated with rCBF. Figure 6(e) illustrates the results of this analysis. The table shows that the correlations tend to cluster in four cortical areas; frontal (medial and lateral), temporal, parietal and the thalamic area. The verbal and facial components of the recognition task display almost identical patterns of correlation suggesting that these correlations reflect a combination of the general underlying pathology of the DAT patients (involving temporo-parietal regions) and the overall memory demands of the task (thalamic regions) without identifying any results specific to the modality of each component (ie. verbal or facial). There were no correlations with performance on the spatial component of the recognition task which is surprising since it displayed a similar pattern of cognitive deficit to that displayed by the other recognition components. Correlations with the immediate recall component of the task reflect a similar relationship between pathology and memory performance however correlations were also found in the medial frontal region. This may be interpreted as a reflection of the difference between a recall and recognition task since the former requires a greater degree of planning and initiation than the latter. The lack of more than one correlation with delayed recall on the other hand, will reflect to some extent, the floor effect that resulted with this component of the recall task.

DISCUSSION

Investigations concerning memory loss are crucial to any study of DAT as it is generally reported to be the earliest cognitive symptom of dementia and is also one of the most debilitating. The memory loss accompanying DAT increases with the severity of the dementia and in most cases memory performance is taken to be the principal indicator of disease

severity. Moreover, as mentioned in an earlier chapter, memory loss also accompanies normal aging, non-Alzheimer-Type dementia and other neurological disorders (ch.2). For these reasons it is clear that accurate and informative memory assessment is important in this area of research. We need to find a method of assessing different aspects of memory at different stages of dementia. The Recognition Span Test described in this chapter has the potential to fulfil these requirements.

The aims of this study were firstly to investigate the differential memory deficits that accompany the various stages of DAT, to compare the present findings to the original findings of Moss et al., (1986) and the subsequent findings of Salomon et al., (1989). Secondly, to draw some useful conclusions concerning the value of the DRST as an investigative tool for DAT. Finally, this study investigates the relationship between differential memory deficits and CBF patterns in the DAT patients and assess the value of using a specific cognitive test in correlational studies.

Differential memory deficits accompanying DAT

The results of this study have confirmed that verbal, spatial and configurational (facial) memory are all impaired early on in DAT. It is surprising that while recall memory which places a greater demand on cognitive resources than does recognition memory, and is therefore expected to be impaired early on in DAT, recognition processes which might have been expected to be relatively spared in mild DAT, are themselves significantly impaired. Moreover, there is little if any, further reduction in recognition span between the mild and moderate stages of DAT. This leads to the conclusion that most of the memory impairment that accompanies DAT, will have developed by this relatively early stage of the disease. This might contradict the experience of those who have cared for, or lived with a DAT sufferer and who would probably report that memory deteriorates rapidly in the later stages of the dementia. It could however, be hypothesised that while memory is severely impaired, many

sufferers of mild DAT still cope to varying degrees, with everyday demands on memory by making full use of the cognitive skills that they still have (eg. writing lists, leaving themselves notes and using their own cues). At a later stage of the dementia, when most cognitive skills have at least been impaired, if not lost altogether, the sufferer will be unable to develop and use cognitive coping mechanisms and will therefore demonstrate a disproportionate loss of memory in everyday activities. The results of this study have also highlighted a differential breakdown in recall and recognition memory in the later stages of the disease. While as described above, the recognition span does not appear to deteriorate significantly beyond that found at the mild stage, recall memory continues to decline with disease severity.

A comparison of these results with previous findings: How useful is the DRST in the investigation of DAT?

As explained earlier, the investigation of DAT requires a method of assessing different aspects of memory at different stages of dementia. The DRST has been presented as a suitable tool to fulfil these functions (Moss et al., 1986 and Salomon et al., 1989) and therefore an indepth comparison with these previous studies will now be presented. In short, this study has shown that the DRST successfully measures different aspects of memory, both in terms of material specificity and memory processes. Furthermore the recognition paradigm, while sensitive to early deterioration (as is also the recall paradigm), avoids floor effects later on in the disease process, this is a particularly attractive characteristic for a test of cognitive deficits in dementia. Having said this however, these results question the suitability of the DRST as a tool to classify the severity of individual cases or to investigate the memory breakdown accompanying the later stages of dementia. This is because while there were clear deficits associated with DAT, there was little distinction between performance on the recognition task by the mild and moderate groups.

It is often difficult to compare dementia studies since patients may be of differing severity. One major obstacle to meaningful comparisons in the study of DAT is that different strategies are adopted for the classification of severity. Moss et al., (1986) define the status of their DAT patients in terms of the Mattis Dementia Rating Scale (DRS) (Mattis et al., 1976), Salmon et al., (1989) use several rating systems including the DRS and the MMSE while the present study uses the CAMCOG and the MMSE. Table 6.5 below, describes the cognitive status of the patients in each of these three studies.

	<u>DRS</u>			<u>MMSE</u>				<u>CAMCOG</u>				
	<u>Overall mean DRS</u>											
<u>MOSS ET AL</u>	117.5 (89-135)			-----				-----				
	<u>Mod.</u>	<u>Mild</u>	<u>Min.</u>	<u>Mod.</u>	<u>Mild</u>	<u>Min.</u>	<u>Cont.</u>	<u>Mod.</u>	<u>Mild</u>	<u>Min.</u>	<u>Cont.</u>	
<u>SALMON ET AL</u>	98.8	112	121	15.7	20.9	25.6	29	-----				
<u>THIS STUDY</u>	-----			10.4	17.8	25.9	28.5	38	63	88.5	94.6	

TABLE 6.5 COMPARISON OF COGNITIVE SEVERITY

A comparison with the study by Moss et al.,(1986)

It is clear from this table that it is not always easy to match subjects across studies. Fortunately however, these three studies do overlap to some extent in their methods of severity classification. The patients used in Moss's study were not divided into severity groups but it is clear that their cognitive status ranged from the severe end of moderate through to mild. Their results can therefore only be compared to the present findings in a very general way. A similar pattern of performance was found for the three recognition tasks. Performance on the verbal recall tasks were also comparable and close examination of Moss's results shows that a similar proportion of patients display a clear floor effect on the delayed recall task. Unfortunately Moss et al., (1986) do not supply the necessary information required to establish exactly which patients show a floor effect but it is probably correct to assume that the more severe (moderate) patients are responsible for the effect. Moss et al., (1986)

conclude from their study that DAT patients display a disproportionately high forgetting rate compared to the other patient groups they studied. While this may be the case, it is clear from the present study that less severe DAT patients do not display the same rapid rate of forgetting. Therefore while Moss et al., (1986) conclude that "the memory impairments seen in AD differ qualitatively from those observed in Huntington's Disease and Korsakoff syndrome", it is entirely possible that these three patient groups differ in their general level of severity which in turn, would affect their forgetting rates. It is difficult to compare the severity of the three groups as the cognitive status of the DAT group was assessed using the DRS while the other two groups were assessed using the WAIS-R and the WMS. However, it is likely that while a few of the DAT patients may have been suffering from mild dementia, many of the group were suffering from a moderate degree of dementia. Of this group therefore, the former may be comparable in cognitive status to the KS and HD groups but the latter certainly would not. Based on the results of the present study it is probably this latter group who are responsible for the disproportionately rapid forgetting rate and the floor effect, Moss et al.'s conclusion (1986) should take into account quantitative as well as qualitative differences. Their conclusion might have been more accurate if they had divided the DAT group into mild and moderate subgroups and obtained similar results for the forgetting rate analysis in the mild subgroup as they did overall.

A comparison with the study by Salmon et al., (1989)

The patients in Salmon's study were divided similarly to those in the present study and their cognitive status can be compared directly using their MMSE scores. Their three patient groups (moderate, mild and least impaired) are comparable to the three groups described in the present study; while their mild and moderate groups may be slightly less severe in terms of mean MMSE score than those described in this study, it is remarkable that Salmon's least impaired group and this study's minimal

group produce essentially the same mean MMSE score; 25.6 and 25.9 respectively.

These similarities allow for direct comparisons between the two studies. Salmon's least impaired group performed significantly worse than controls ($p < .001$) and better than milds ($p < .05$) on the recognition paradigms, however as Salmon et al., (1989) point out, discrimination between the least impaired and the mild patients was not possible using 95% confidence limits whereas discrimination between mild DAT and normal controls was possible using this technique. On delayed recall and forgetting rate their least impaired group performed significantly worse than controls, but neither of these measurements of memory distinguished between the least impaired and the mild DAT groups in Salmon's study (1989). On the other hand, the performance of the minimal group in the present study, while clearly better than that of milds on verbal recognition and immediate and recall, was only approaching significance when compared to controls. The measures of delayed recall in the minimal group however, were significantly different from both the mild and the control groups suggesting that the delayed recall condition might be particularly useful in the identification of dementia and the early staging of the disease. Salmon et al., (1989) conclude from their study that the DRST is "both highly sensitive and discriminating of progression" and that it is "a useful neuropsychological instrument for the longitudinal assessment of Alzheimer's Disease". They also indicate that certain components of the test (ie. verbal recognition and immediate recall) are particularly sensitive to the early staging of DAT. In contrast, the results of the present study, while supporting the view that that the DRST is good at distinguishing between the early stages of DAT particularly through measures of immediate and delayed recall, these, and other components may be unsuitable for similar distinctions at later stages of the disease and floor effects become inevitable.

Therefore, while the DRST is certainly a good tool for the measurement of memory deficits in DAT both in terms of the task requirements and its ability to produce measures of various aspects of memory, Salmon's conclusion should be accompanied by recommendations concerning the severity of the patient population and the aims of the investigation using the DRST. For these reasons the DRST may be less suitable for the identification of severity and the staging of the disease than previously suggested. One further reservation must involve the use of facial stimuli which produced particularly low scores for patients and controls and is therefore less suitable for this type of test. The DRST is however, particularly suitable for the longitudinal assessment of DAT patients where intra-patient measurements are made for the purpose of monitoring of individual deterioration. Furthermore, since this test allows for measurements of different aspects of memory, it has the potential to illustrate the differential patterns of memory breakdown over time in individual DAT subjects.

CBF deficits and memory impairments in DAT

A discussion of the relationship between patterns of rCBF and performance on the various components of the DRST will attempt to answer two questions. Firstly, do the results merely reflect the underlying neuropathology of the dementia or do they reflect cognitive processes involved in memory? Secondly, in this type of correlational study, does the use of a specific cognitive tool (the DRST), produce more interesting results than those produced using the CAMCOG?

The results produced by correlating rCBF and performance on the DRST do seem to reflect, the general pathology of DAT since correlations were found predominantly in the posterior (temporo-parietal) regions and were not found in cortical areas rarely damaged in DAT (eg. occipital and basal ganglia regions). However, these results also reflect more specific relationships between CBF and cognitive function. Excluding the

modality of the information to be recognised (ie. verbal, facial), the tasks are identical in nature and therefore require similar, if not identical, cognitive processing. The results do not reflect modality specificity, which might have expected a more left-sided involvement in the verbal task and a more right-sided involvement in the facial task. They do however, show similar patterns of correlation involving cortical regions that would be expected to be implicated in the underlying cognitive processes common to both these recognition span tasks; the right temporal and parietal regions together with the thalamic region.

The involvement of the thalamic region in this correlational study is particularly interesting since the thalamus is considered to be instrumental to memory function and in particular, to short-term memory of which recognition span is a measure (see Mayes 1988, for a review). The results of the study described in the previous chapter included CBF deficits in the left and right thalamic regions of the mild DAT group and it is therefore not surprising that performance on a specific memory task should relate to thalamic damage in DAT.

Performance on the immediate recall component of the DRST also displays interesting correlations with CBF. While correlating with CBF in the parietal and temporal regions, this component of the task was also found to correlate with left thalamic blood flow. As explained above damage to the thalamus is known to effect short-term memory and since the immediate recall task is a measure of short-term memory, this correlation not only strengthens this established relationship concerning the localisation of function but also the cognitive specificity of the DRST. Another distinctive feature of these results is the presence of correlations between performance on this component of the DRST and CBF in left and right medial frontal regions. In contrast to the other correlations which were also found with performance on the recognition components of the test, these frontal correlations are specific to this particular recall

task. This finding is interesting since studies involving frontal lesions have reported damage to recall memory with a relative sparing of recognition memory (Hirst, 1985; Jetter et al., 1986)). This may be explained in terms of the differential demands of recall and recognition memory since the former requires a considerable element of planning and executive function while the latter does not. While it is very difficult, if not impossible, to remove the frontal component from a recall task it is also very difficult to produce frontal tests which are free of any memory component and this issue will be discussed further in the next chapter. The relative lack of correlations with the delayed recall task is disappointing since a similar pattern of correlations to those found with immediate recall would have strengthened the conclusions. The floor effect obtained with performance on this task may be partly or wholly responsible for this result.

Returning to the specific questions posed at the beginning of this section. Firstly, do the results reflect the cognitive processes involved in memory? While also reflecting to a degree, the neuropathology of DAT, these results clearly reflect the specific relationship between cerebral function and the cognitive processes involved in recall and recognition memory. In particular the thalamic and frontal correlations have contributed to this conclusion since their specific cognitive involvement in the memory tasks can be clearly identified. In response to the second question requiring a comparison of the suitability of the CAMCOG and the DRST as cognitive tools in this type of correlational investigation, the results suggest that use of a clearly defined cognitive task, like the DRST, produces more interesting and relevant findings than those obtained using a general cognitive assessment test.

CHAPTER SEVEN

A NEUROPSYCHOLOGICAL INVESTIGATION INTO FRONTAL LOBE INVOLVEMENT IN DAT

Dementia of the Alzheimer Type (DAT) has traditionally been thought to affect the posterior association cortex (Bonte et al.,1986; Johnson et al., 1987) particularly parietal and temporal. With an increase in the availability of sophisticated imaging techniques such as SPECT and PET, a more informed picture of areas of impaired brain function from patterns of regional cerebral blood flow and metabolism is obtained. Recently, studies have increasingly shown an anterior pathology in DAT (Duara et al.,1986; Grady et al., 1988; Montaldi et al.,1990) and it has been suggested that the use of frontal pathology as an exclusion criterion for DAT is premature and not recommended (Montaldi et al., 1990).

Recently the most important issue concerning frontal lobe involvement in DAT has been the identification of a new form of dementia, namely Frontal Lobe Dementia (FLD) (Brun, 1987). Histopathologically, it is characterised by predominantly frontal change as opposed to the more posterior change associated with DAT and is differentiated from DAT and Pick's disease by a lack of plaques and tangles and Pick cells, respectively. While FLD itself, is characterised by spongiform changes and astrocytic gliosis, these degenerative changes in FLD have so far been described as nonspecific (Gustafson, Brun & Risberg, 1990). Measurements of rCBF in suspected FLD cases indicate abnormal flow patterns and focally reduced rCBF in the frontal regions. Clinically, FLD patients have been reported to have normal EEGs and tend to present with early emotional and personality changes while memory and spatial functions have been found to be relatively spared (Gustafson, 1987). Two

recent studies have investigated the psychometric characteristics of FLD in patients whose diagnosis was confirmed at post-mortem. They found a lack of consistency in the psychometric performance of their patients and both describe emotional and personality problems interfering with test administration (Johanson & Hagberg, 1989; Knopman et al.,1990). Knopman et al., (1990) have demonstrated impairments on frontal tests such as word fluency, mazes, trail-making and recency memory. There is not, however, at present, any established differential psychometric profile of FLD and, like DAT, its diagnosis can only be confirmed at post-mortem.

Some studies have sought to diagnose FLD differentially on the basis of in vivo investigations such as clinical presentation and neuroimaging techniques (Neary et al.,1988; Jagust et al.,1989). Neary et al., (1988) reported evidence on 7 cases of a presumed frontal lobe dementia using SPECT as well as clinical and neuropsychological histories. The SPECT findings clearly indicated greater frontal blood flow deficits than normally expected in DAT. The neuropsychological assessment of these patients included the use of tasks generally regarded as sensitive to frontal lobe function (eg verbal fluency and the Wisconsin Card Sorting Task) and the results revealed deficits, although it is important to note that these deficits were related to the severity of the disease. Moreover, the study clearly demonstrated that the FLD patients, despite their orientation in space and time, performed poorly on other memory tests. In both studies mentioned above, the sample sizes were small (7 and 5 respectively) and the diagnosis remains to be confirmed histopathologically. While both Brun (1987) and Neary et al., (1988) conclude that FLD is likely to make up between 10 and 20 percent of organic dementias, Brun (1987) has stressed it may be unwise to diagnose FLD on purely clinical grounds due to strong evidence of heterogeneity within the dementias.

It has been suggested that DAT is not a single clinical syndrome but may rather consist of subgroups differentiated by their characteristic cognitive deficits. Martin et al.,(1986) using PET and neuropsychological investigations, provide evidence for the existence of subgroups in DAT based on patients presenting with specific cognitive deficits. These patients, while clearly diagnosed as suffering from DAT, displayed either a disproportionate visuoconstructive or language impairment. Further studies concentrating on clinical symptoms have shown similar heterogeneity in DAT (Mayeux, Stern & Spanton, 1985; Jagust et al., 1990). Other studies have questioned the existence of subgroups and preferred a multiple components model (Schwartz, 1987) where, in many cases, the presenting symptom may not be the usual memory loss, but could be one of a number of deficits involving other cognitive functions (eg progressive aphasia). Similarly, DAT patients could in principal, present with or develop, specific frontal deficits.

The frontal lobes are thought to be involved in tasks which involve judgement, planning, the anticipation of change and dealing with novel situations (Stuss et al.,1983) and have been most popularly described as playing an executive role in human behaviour. This has been exemplified in the numerous lesion studies which have looked at frontal lobe dysfunction neuropsychologically (see Stuss & Benson, 1984 for a review). If frontal lobe dysfunction is a characteristic component of DAT, then it would be reflected neuropsychologically by poor performance on frontal tasks which, in turn, would be expected to be related to the patients' overall cognitive performance. Furthermore, the growing evidence of frontal blood flow deficits in DAT (Grady et al., 1988; Montaldi et al., 1990; Holman et al., 1992) predicts a frontal neuropsychological component could be integral to this disease.

In view of the conflicting evidence a group of DAT patients and normal controls were assessed using tests sensitive to frontal lobe function. The aims of this study were: Firstly to question whether a substantial neuropsychological component reflecting damage to frontal functions normally accompanies DAT. Secondly to determine whether frontal cognitive deficits could be used to differentiate DAT and FLD. Thirdly, based on the estimated incidence this study planned to ascertain whether any of the patient population could be identified as suffering from FLD rather than DAT by displaying disproportionate frontal neuropsychological deficits. Finally, to investigate the relationship between neuropsychologically identified frontal deficits and measures of rCBF in the DAT patient population.

METHODS

Subjects

The 37 subjects in this study comprised 25 patients suffering from DAT and 12 age-matched normal controls. Diagnosis of DAT was carried out according to the criteria in the CAMDEX (Roth et al., 1986) as described in chapter 2.

The patients were divided according to the severity of their dementia as assessed by the CAMCOG. Patients of differing severity were included in order to investigate the range of frontal involvement in DAT. As Table 7.1 illustrates, 11 patients fell into the Minimal category, 6 fell into the Mild category and 8 into the Moderate category. Table 7.1 also illustrates the means and standard deviations for the four groups on age, CAMCOG and MMSE.

GROUP	n	AGE Mean (SD)	CAMCOG Mean (SD)	MMSE Mean (SD)
Control	12	73.7 (8.27)	95.0 (6.54)	28.2 (1.64)
Minimal	11	71.5 (7.97)	88.6 (9.35)	25.5 (3.69)
Mild	6	74.0 (12.88)	65.2(7.96)	18.7 (2.73)
Moderate	8	79.7 (6.45)	39.4 (3.82)	11.8(3.95)

TABLE 7.1 Patient and Control Characteristics

Procedure

The frontal lobe tests administered to the subjects in this study have been used previously in frontal lobe lesion studies. The three tests were a Delayed Alternation Task (Oscar-Berman et al., 1982), a Subject Ordered Pointing Task (Petrides & Milner, 1982) and the Wisconsin Card Sorting Task (Milner, 1963,1964). The tasks and their administration are described separately below. Further frontal assessment was carried out adopting the widely used verbal fluency tests with the letters 'F' and 'C' and the category 'Animals' (Rosen, 1980).

Delayed Alternation Task. This reversal learning task was originally used in a non-human primate population where it was found to be sensitive to frontal-lobe damage. Briefly, the task involves the subject searching for a target stimulus in one of two boxes or wells. Once the subject has found the target, the experimenter replaces the stimulus in the alternative location out of sight of the subject who is then required to search again. There is a preset learning and failure criterion. At all times, if the subject successfully identifies the location of the stimulus its position is automatically reversed. If, however, the subject fails, the stimulus remains in the same location and the subject is required to search again. The latter is a corrective procedure which attempts to emphasise the reversal nature of the required response (Oscar-Berman, 1988). The learning criterion in this study was 12 consecutive correct responses and the subject was deemed to have failed if this was not achieved in 50 trials. The subject's total errors and success or failure were noted.

Subject Ordered Pointing Task. This task involves the use of displays of representational drawings and the subject is required to organise a

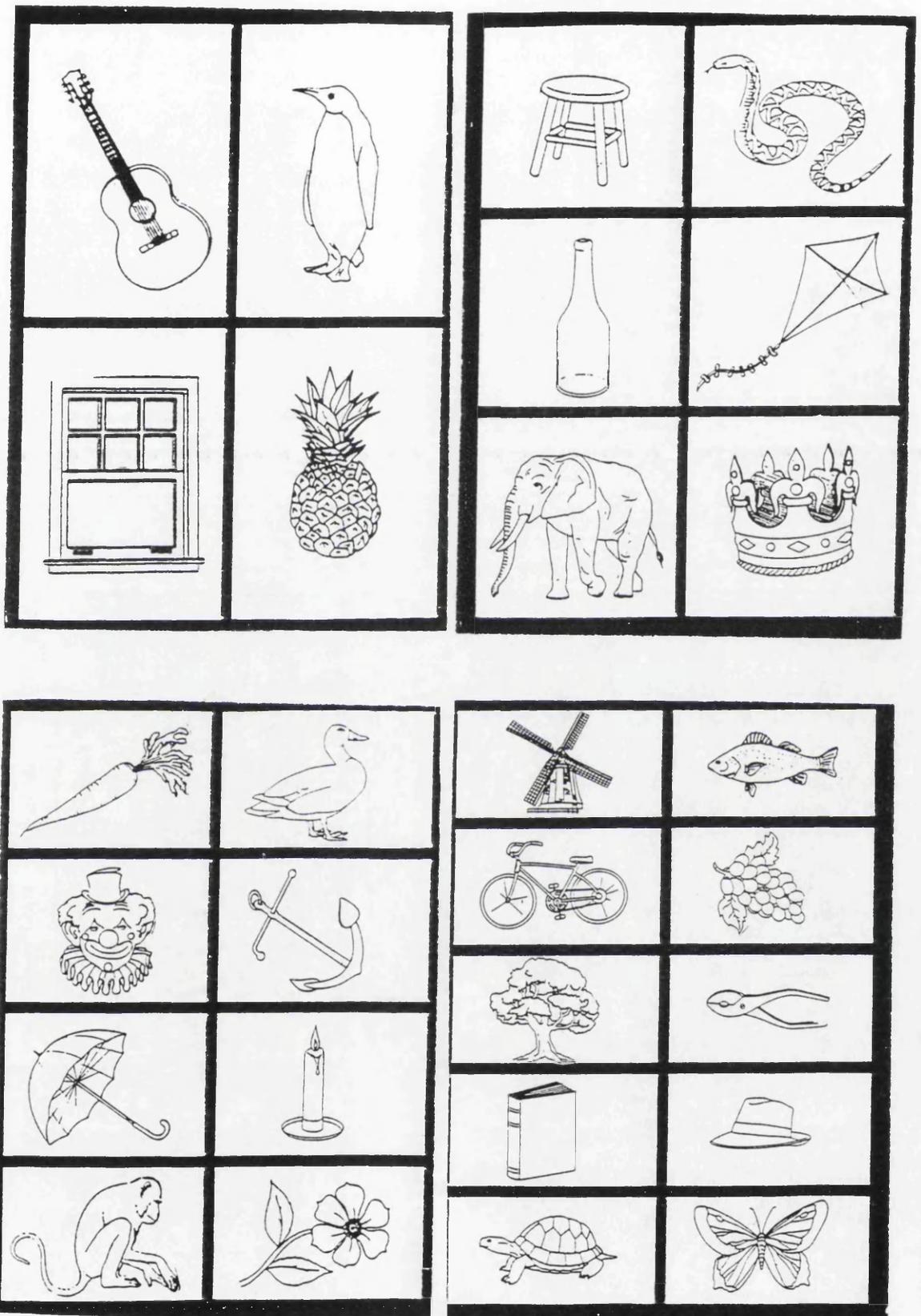


Figure 7(a) Samples of the four levels of complexity used in the subject-ordered pointing task.

sequence of pointing responses requiring self-organisation and self-monitoring. In this study task complexity is increased by introducing sets of 4, 6, 8 or 10 drawings on each display, see Figure 7(a). The displays are presented to the subject who is required to inspect them and point to each stimulus in turn. The subject must point once and only once, at each item in each condition (level of complexity). Stimulus positions in the display are varied to avoid the use of positional cues to facilitate the memory for each item. Three trials are administered for each condition in the following order: 4, 6, 8, 10. This was done in order to avoid any proactive interference. The subject's mean time and total errors were recorded.

Wisconsin Card Sorting Test This task has been used for many years in various forms as a test of shifting of set and abstraction of response and is one of the most frequently used tests in assessing frontal damage (Milner, 1963, 1964; Robinson et al., 1980; Walsh, 1987). Briefly, the subjects sort a set of cards by category (colour, form and number) to four target cards and must modify their responses according to the feedback from the experimenter. The original directions given by Milner (1963) were followed in this study with the proviso that all 128 cards were used and no discontinuation procedure was adopted.

RESULTS

Neuropsychological investigation

In order to investigate the neuropsychological evidence of frontal involvement in DAT, each task was analysed separately and the performance of the DAT patients was compared with that of the Controls. Further analysis investigated the effect of DAT severity on task

GROUP	n	'F'		'C'		'ANIMALS'	
		Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Control	12	14.9 (4.96)	9-27	13.7 (4.64)	6-21	16.5 (4.18)	9-23
Minimal	11	17.1 (6.55)	8-26	16.7 (5.67)	5-24	17.8 (7.79)	6-32
Mild	6	8.8 (4.18)	2-13	6.3 (3.66)	1-11	9.0 (3.74)	4-14
Moderate	8	3.1 (2.80)	0-9	2.4 (1.99)	0-5	3.8 (1.88)	1-7

TABLE 7.2 Verbal Fluency Scores for DAT patients and Controls

performance. These results are described below.

Verbal Fluency. The Kruskal-Wallis test was used to analyse both the number of words and perseverative errors (where perseverations were defined as any repetition of a word, eg. cry and crying or fill and filled), produced by the controls and the three severity groups. Each group's performance is summarised in table 7.2. When considering the total number of words produced, significant differences were found between the groups for each category ('F', $H=21.05$, $df=3$, $p<0.001$; 'C', $H=23.24$, $df=3$, $p<0.001$; and 'Animals', $H=22.31$, $df=3$, $p<0.001$). Analysis of simple effects via Mann-Whitney showed that the Controls and Minimals did not differ significantly on each category whereas all other group comparisons did as indicated by the Kruskal-Wallis test. An analysis of perseverative errors showed no significant differences.

Delayed Alternation Task. On this task the subjects were categorised according to their success or failure. A significant difference was found between the Controls and DAT groups (Chi-Square=7.93, $df=3$, $p<0.05$). The three DAT severity groups (Minimal, Mild, Moderate) did not differ from each other in performance (Chi-Square = 0.743, $df=2$, not significant). The results, which are displayed in Figure 7(b), are expressed as percentages of the number of subjects in each group due to the variation in group size. Finally, the total number of errors was analysed using a Kruskal-Wallis test and no significant differences were found between the groups ($H=4.34$, $df=3$, not significant). Due to the small numbers of DAT patients who succeeded in learning to criterion, the number of errors made to criterion could not be analysed.

Subject Ordered Pointing Task. In this task, the total number of errors was analysed and initial analysis using a one-way ANOVA showed that

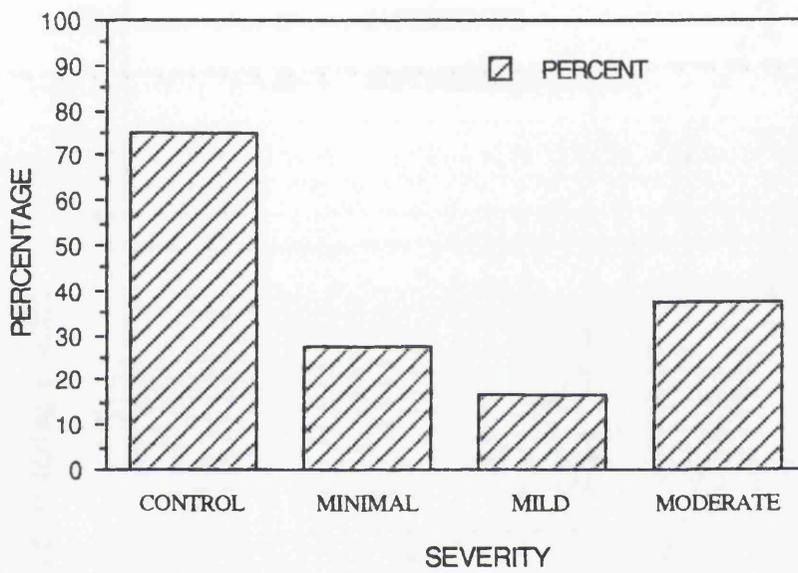


Figure 7(b) No. of successes in each group as a % of total group success

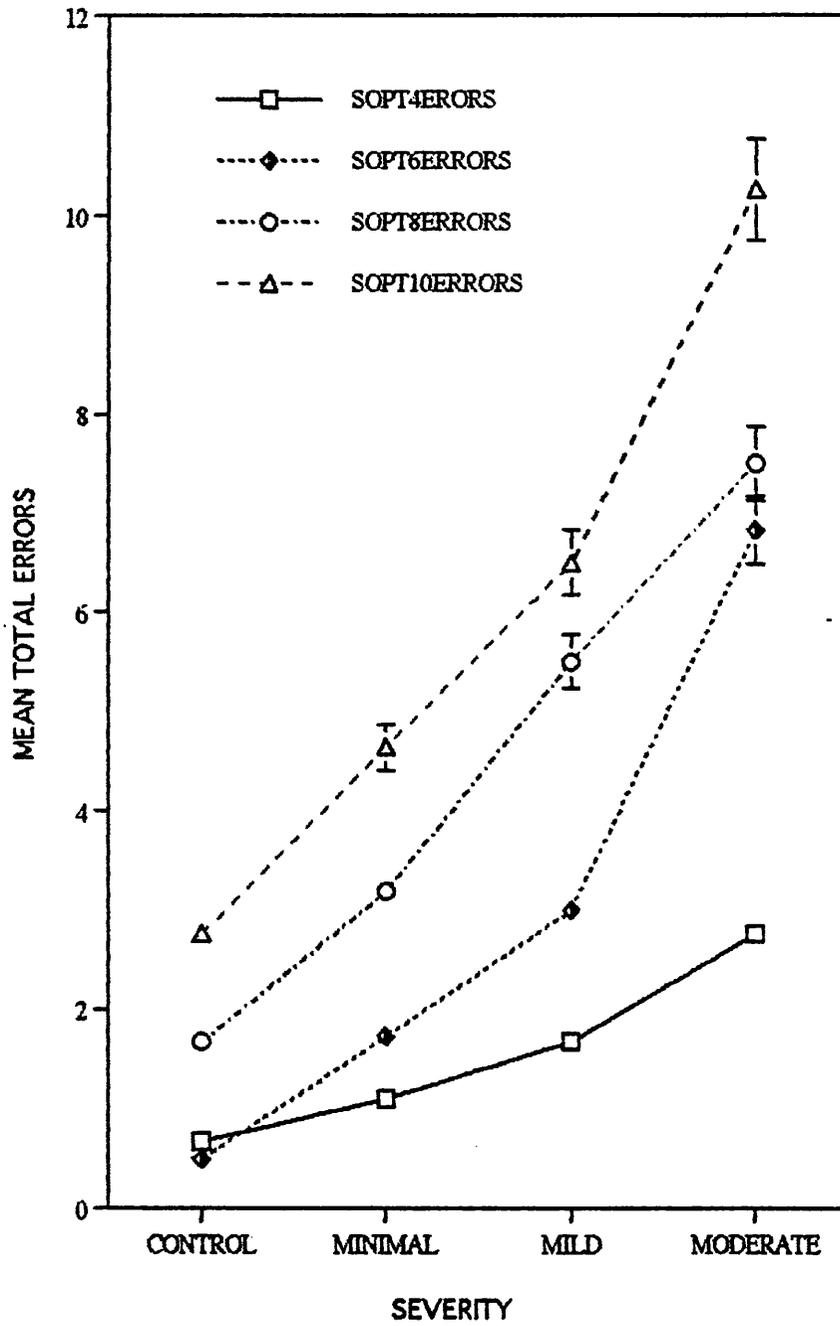


FIGURE 7(c) Performance on SOPT task for each group at each level of complexity

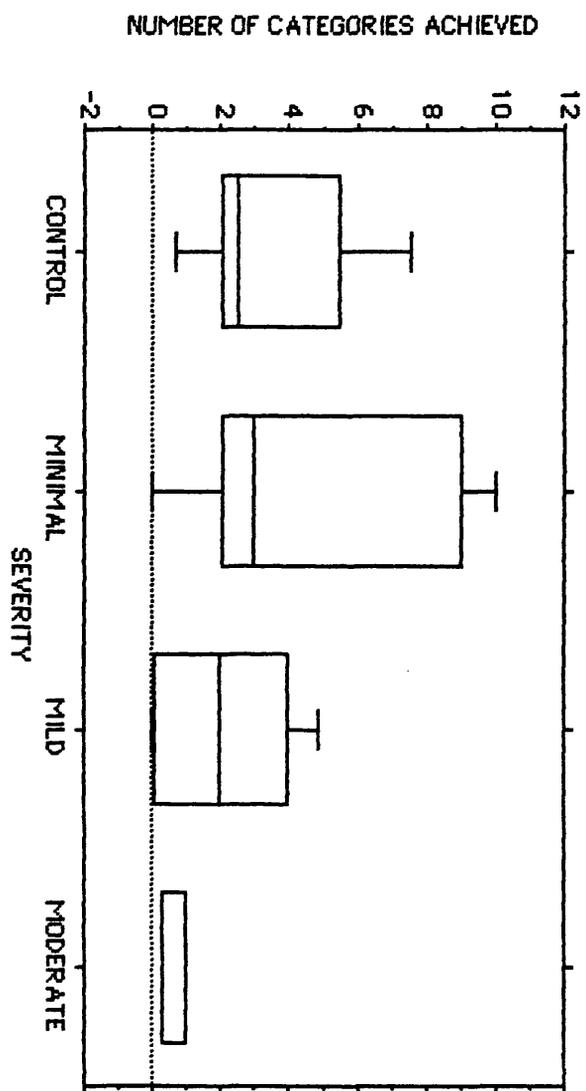


FIGURE 7(d) Number of categories achieved on the WCST for each group

the Controls and DAT patients differed significantly from each other at at least $p < 0.05$ on each level of the task. Inspection of the graph suggested an interaction between group effect and task complexity (Figure 7(c)). However, this was investigated by a repeated measures ANOVA with one within-subjects factor (complexity) and one between-subjects factor (severity) (Interaction $F = 4.48$, $df = 9, 99$, Between subjects $F = 26.32$, $df = 3, 33$ and $p < 0.001$) demonstrating that the increase in task level produced a concomitant decrease in the performance of each group of subjects (Controls and three DAT severity groups) and therefore, there was no interaction.

Wisconsin Card Sorting Test. Figure 7(d) displays boxplots of the number of categories achieved by the controls and the three DAT severity groups. There are marked floor effects, particularly in the mild and moderate cases, reflecting very poor performance on this task. However, analysis using a Kruskal-Wallis test showed that the four groups did not differ significantly ($H = 4.84$, $df = 3$), indicating that even normal elderly found this to be a difficult procedure. Further analysis was carried out on errors categorising them as Perseverative or Non-perseverative. No significant differences were found between the groups using Kruskal-Wallis tests ($H = 7.80$ and $H = 1.10$ with $df = 3$ respectively).

Outliers. The DAT data from each of these four tasks were examined for outliers who displayed particularly poor performance. Visual inspection of individual performance on the tests revealed no outliers, indicating the absence of any patient suffering a disproportionate 'frontal' deficit.

Severity and frontal performance. Finally, measures of severity in terms of overall cognitive performance (CAMCOG) were correlated with

ROI	WORD FLUENCY			SOPT LEVELS			
	F	C	Animals	4	6	8	10
LMF							
RMF					*		
LLF							
RLF							
RHF	*	* *	* *	*	* *	* *	* *
LHF	*	* *	* *	*	* *	* *	* *
RT							
LT							
RPT							
LPT							

* Significant at individual 5% level

**Significant at individual 1% level

FIGURE 7(e) Correlations between rCBF and performance on 'frontal' tasks

performance on each of the four frontal tests using a Spearman Rank Correlation Coefficient for the Delayed Alternation Task and a Pearson Product Moment Correlation for the remaining analyses. All but the error scores (WCST) correlated highly ($r=.73$, $p<0.01$) with overall cognitive performance indicating a clear relationship between these factors. The floor effects found with the WCST explain the non-significant correlations with the error scores.

2. CBF and neuropsychology

In order to investigate the relationship between CBF patterns in the frontal regions and neuropsychological performance on the frontal tests, a Spearman's rank correlation coefficient was carried out for the DAT group. The results of this analysis are displayed in table 7(e) and show that correlations were found between performance on two of the tests (verbal fluency and SOPT) and blood flow in the high frontal regions. It is surprising that correlations were not found with the medial or lateral frontal regions. However, considering the poor performance on the Delayed Alternation task and even more so on the WCST, a lack of a reasonable distribution of scores is probably the principal cause for the correlations being restricted to the verbal fluency and SOPT tests.

DISCUSSION

Is there a frontal component to the cognitive profile of DAT?

This study investigated the neuropsychological evidence for frontal lobe damage in DAT using four very different frontal tests. On the Wisconsin Card Sorting Test (WCST), probably the most commonly used frontal test, the results were characterised by clear floor effects in both DAT

patients and the controls. These floor effects, while concealing any information regarding frontal involvement in DAT, suggest that perhaps the WCST is not suitable for use with elderly and demented populations. Work by Haaland et al., (1987) corroborates this conclusion by showing that elderly people perform particularly badly on this task. Further support comes from Morice (1990) where younger control subjects also perform poorly on the WCST.

The three remaining frontal tests (Verbal Fluency, Delayed Alternation and Subject Ordered Pointing) produced performances in the DAT population which were significantly impaired in comparison to the age-matched controls. Only the word fluency task failed to show a significant difference between controls and minimal DAT (however, this deficit is clearly apparent at the mild stage). Moreover, performance on these tasks was found to be strongly related to overall cognitive performance. The frontal deficits, therefore, while clearly occurring in these cases of DAT, are not specific deficits occurring in isolation, as has been reported in other clinical populations, but appear to form part of the general dementia itself. A further inspection of all data showed no trace of outliers who may have displayed focal frontal deficits unrelated to overall cognitive decline. This study, therefore, suggests that frontal deficits form a characteristic component of DAT and consequently neuropsychological investigations of the frontal lobes would not distinguish between DAT and FLD.

Concluding then, that a frontal component does form part of the neuropsychological profile of DAT, at what stage of the disease might it develop? The performance of the minimal group was not differentiated from the Controls on a test highly dependent on verbal performance such as Verbal Fluency. This comparison, however, was found to be clearly

significant in the Delayed Alternation and Subject Ordered Pointing Task where verbal cues were less important. Therefore, the present results strongly suggest that some degree of frontal involvement does occur during the earliest stages of the disease.

Frontal deficits and the differential diagnosis of dementia.

Since DAT is frequently described as a heterogeneous disease which displays itself in terms of specific deficits, the study of these specific deficits in DAT such as frontal impairment is also essential to the understanding of the extent of the heterogeneity of the disease. Brun (1987) has described two DAT patients who presented with predominantly frontal rather than the expected posterior signs. Schwartz (1987) describes a multiple components approach in demonstrating the heterogeneity of the disease in which patients initially presenting with isolated language deficits do eventually develop into more characteristic cases of DAT. Other neuropsychological studies of cognitive breakdown in DAT (Martin et al., 1986; Freedet al., 1989) have provided further evidence of heterogeneity as have neurological studies concerning extrapyramidal signs (Mayeux et al., 1985). Consequently the exclusion of a DAT diagnosis on the basis of specific deficits should be strongly discouraged.

The memory component of frontal tasks.

A confounding feature of many neuropsychological test, especially when used with demented patients, is the memory component, and frontal tasks are no exception. Consequently, poor performance may not reflect a purely frontal impairment. Milner (1982) has proposed that a recency memory component is present in many frontal tasks, particularly in tasks where the subject has to retain considerable amounts of information. For example, the WCST relies heavily on a memory component and the floor

effects in the results reflect this. Certainly, it is difficult to devise frontal tests which do not contain memory components and tasks which minimise any memory functions need to be sought. A frontal task which does have minimal memory involvement is the Delayed Alternation (DA) task (described above). This task does not make significant demands on memory and in fact discriminates strongly between DAT and Controls. Of the four frontal tests used in this study, the results of the DA task suggest that it may be the most suitable tool for use with a demented population.

In conclusion, DAT has been described predominantly as a posterior dementia with particular reference to parietal damage. As mentioned earlier, this view has received so much support that Holman (1986) described damage to the parietal lobes as the hallmark of Alzheimer's Disease while Neary et al., (1988) in a paper concerning FLD and differential diagnosis, refer to DAT as a 'posterior dementia'. Although these conclusions may be partially justified, there is growing evidence, particularly from imaging studies, to suggest that considerable damage also occurs to the frontal cortex in Alzheimer's disease (Foster et al., 1984; Grady et al., 1988; Holman et al., 1992). This, together with reports of heterogeneity in terms of patterns of cortical damage, behaviour and cognition suggest that Alzheimer's Disease should no longer be defined as a posterior dementia. This chapter has shown that from a purely neuropsychological perspective, patients suffering from DAT display extensive frontal impairments associated with their overall cognitive performance suggesting that frontal damage may be an integral part of their dementia. The involvement of the frontal lobes in DAT requires further multidisciplinary investigations involving both neuropsychology and neurophysiology as well as, neuropathology. This area of research should pay particular attention to the recent reports in the literature of a specific frontal lobe dementia.

CHAPTER EIGHT

RELATING rCBF PATTERNS AND DAMAGE TO SPECIFIC UNDERLYING COGNITIVE SYSTEMS

INTRODUCTION

Most studies relating patterns of CBF and cognition have studied this relationship in groups of patients consisting of sufficient numbers to allow accurate statistical analysis to be carried out. While this type of study is both necessary and justified, it is possible that in some cases the most interesting features both in terms of CBF and cognition, might be obscured by the overall averaging of the data. Moreover, the majority of CBF and cognition studies focus on cognitive performance within a particular population (eg. DAT, HD,) and are therefore driven by issues concerning cognitive breakdown characteristic of the population in question. By contrast, this study aimed to investigate the relationship between CBF and cognition in a particular subgroup of DAT patients. The design of the study required that patients be selected on the basis of a very specific cognitive deficit that would indicate the dysfunction of a known underlying cognitive process or system and then question whether that particular impairment is reflected in the CBF pattern.

Language deficits are so frequently reported in studies of DAT that aphasia has been described as "an important diagnostic criterion of dementia of the Alzheimer Type" (Cummings et al., 1985). An investigation by Heir et al., (1985) described the speech pattern found in mild DAT as being similar to that of semantic or anomic aphasia while the speech pattern found in moderate to severe DAT was similar to a Wernicke or transcortical aphasia. No matter how we describe and categorise the language pattern and deficits

accompanying DAT, one of the most commonly reported language deficits is that encountered during a confrontational naming task. This type of task requires that the patient responds to the presentation of an object or picture of the object with the name of the object. This naming deficit is readily observable to varying degrees in the everyday life of the dementia patient and is often one of the first symptoms of dementia (see chapter 2). Consequently, much attention has been focussed on this particular cognitive deficit and research has produced two explanations for the impairment. Firstly, there is the view that this deficit is a result of a breakdown in the perceptual process implying that misperception of the object is responsible for the failure to name it correctly. Evidence in support of this view has been derived from studies where patients have responded to pictures of objects with names of objects which are similar in appearance to the stimulus object. Rochford (1971) carried out a study comparing cases of dementia with cases of dysphasia on a standard naming task. He found that the dementia group produced a much greater proportion of 'misrecognition' errors while the dysphasic group produced a greater proportion of 'correct recognition' errors. Rochford concluded from his study that the naming impairment in dementia is largely attributable to an impairment of visual recognition. In an earlier study, Lawson and Barker (1968) had also concluded that perception was the principal problem contributing to the naming deficit in dementia since their findings indicated that additional information on the function of the object aided correct naming. More recently, Kirshner et al., (1984) carried out a study to analyse the importance of both perceptual and linguistic (eg. word frequency) factors in the naming deficit accompanying dementia. Their study manipulated the level of perceptual difficulty of the stimuli by increasing the abstraction of the pictures and found that perceptual difficulty increased misnaming. While this is an interesting finding it does not as they suggest,

indicate that the naming deficit in DAT is caused predominantly by a perceptual deficit since the introduction of levels of abstraction would increase errors whether the primary deficit had been of a perceptual nature or not. A second possible area of cognitive breakdown contributing to the naming deficit is that of the semantic network. Those holding the view that semantic confusion is the principal cause of error conclude this from studies showing the largest proportion of erroneous responses to be other examples of the same semantic category to which the object belongs, other examples of semantic error might be linked to similarities in function or component parts of the object. Bayles and Tomoeda (1983) carried out a study where 65% of naming errors were found to be of a semantic nature and the majority were members of the same semantic category as the stimulus object. Findings by Martin and Fedio (1983) lend support to this view since their work demonstrated a failure on the part of the DAT patient to differentiate items in the same semantic category as did previous work by Pearce and Miller (1973). A breakdown in the semantic network does appear to be a common characteristic of DAT, however this breakdown could manifest itself through different types of semantic error. Smith et al., (1989) carried out a study introducing 16 error response types and found that while many DAT patients could correctly recognise objects and identify their semantic class, they could not produce the correct lexeme to name the object. While this is a form of semantic deficit it is clearly a different semantic deficit to that demonstrated in the studies of Bayles and Tomoeda (1983), Martin and Fedio (1983) and Pearce and Miller (1973) described above. This inability to produce the required lexeme constitutes an impairment in the word retrieval stage of the object naming process. Therefore while most of the literature focuses on a dichotomy between perceptual and semantic processes when addressing the naming deficit found in DAT, there are in fact three distinct stages of

the naming process which may be affected by the disease. It seems logical to conclude that damage is not restricted to a single stage of the naming process but that all three of these processes; perceptual recognition, semantic recognition and word retrieval may be affected to different extents in different people, which may in turn account for the variation in the findings of the research outlined above.

The aims of this study were firstly, to investigate the naming deficits in this particular DAT population by analysing the types of error responses produced on a confrontational naming task. The second aim was to examine the possibility of relating specific naming deficits to patterns of CBF, and in particular, examining whether CBF patterns can reflect impairment to underlying cognitive processes.

METHODS

Patient Population

Forty patients diagnosed as suffering from DAT (see chapter 2) were used in the preliminary selection process of this study. Twenty-nine patients had a severity classification of minimal dementia and 11 had a severity classification of mild dementia (table 8.1).

Procedure

In order to assess naming errors in this DAT population, a confrontational naming task was administered to all patients. The particular test used here was the Graded Naming Test developed by Warrington and McKenna (1983). This task requires that patients name objects presented in the form of line drawings. The test consists of 30 line drawings which are graded in terms of difficulty;

	N	AGE		MMSE		CAMCOG	
		mean	range	mean	SD	mean	SD
Minimal DAT	29	68.7	45-84	26.5	2.6	89.3	7.8
Mild DAT	11	73	51-85	18.7	2.6	61.9	6.8

Figure 8.1 Characteristics of minimal and mild DAT patients

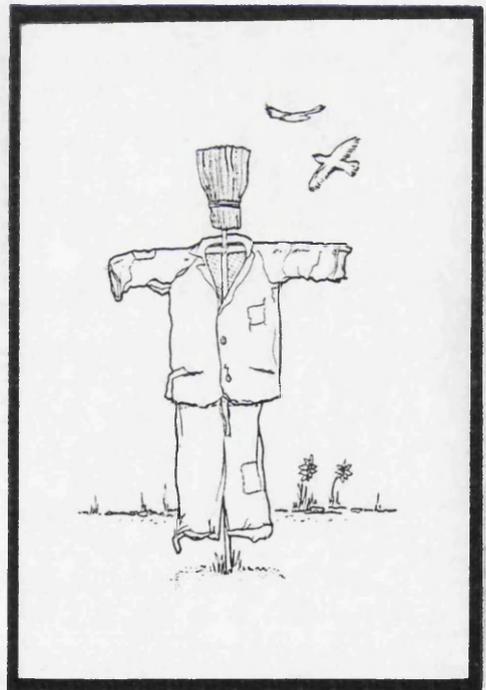
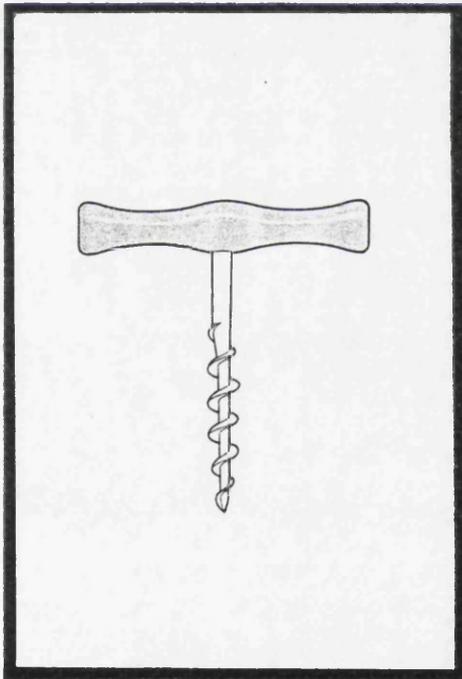
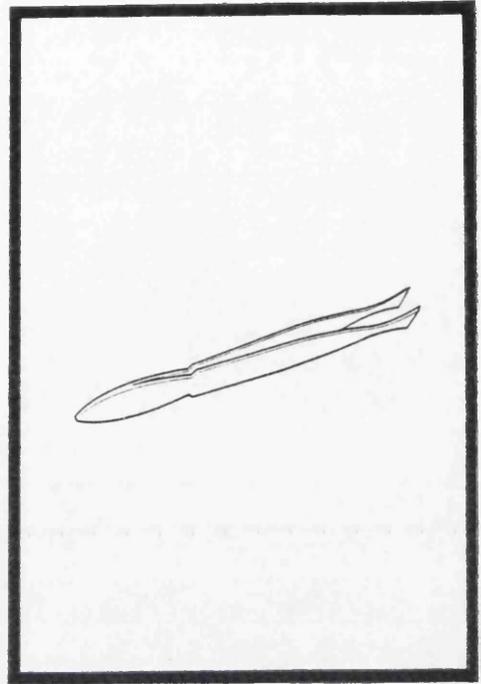
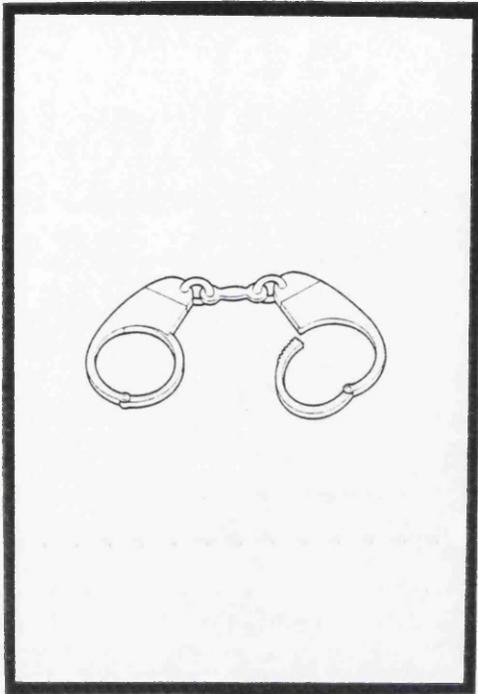


FIGURE 8(a) Examples from the Graded Naming Test

the patient starts with the easiest item and then proceeds to the next. Figure 8 (a) illustrates a few of these items. On presentation of each item the patient is requested to name the object, a correct response or any incorrect response is noted. In order to categorise the errors according to the underlying cognitive process that appears to have failed for each error response, a set of error categories were devised.

ERROR CATEGORY DESCRIPTIONS

LEXICAL- Response must involve some lexical/phonemic confusion.

eg. Handcuffs.....cufflinks

Corkscrew.....screwdriver

Tweezers.....twigs

VISUAL- Response must involve visual misperception.

eg. Handcuffs.....spectacles

Scarecrow.....man

SEMANTIC- Response must involve semantic confusion by giving name of another member of the same semantic category.

eg. Kangaroo.....dog

Pagoda.....temple

GENERIC- Response must be a generalisation of the correct response.

eg. Pagoda.....building

Tutu.....skirt

FUNCTIONAL- Response must relate to the function of the correct response.

eg. Buoy.....used for boats

Tweezers.....used for taking out

little things

CONCEPTUAL- Response must describe the concept behind the object.

eg. Sundial.....time

Buoy.....floats

DESCRIPTIVE- Response must literally describe the object.

eg. Scarecrow....brush with clothes on it

Each error was then assigned to one of the above categories unless the response implied complete lack of knowledge of the object ("I've never seen one of those before") or a response that could not be assigned to any category. For the purpose of this investigation, responses categorised as Generic, Functional, Conceptual or Descriptive were grouped together as one error category and given the label Anomic since these types of error all reflect an impairment in word retrieval.

Neuroimaging

Measurements of rCBF were made for each patient as described in Chapter 3. The methodology adopted in this investigation varied from the others described in this thesis in one important way. Normalisation of the CBF data was carried out using the slice as the reference area rather than the occipital or calcarine regions. The reason for this was that at the time of this study calcarine measurements were not being made and therefore the calcarine region could not be used. The occipital region on the other hand, could have been used as a reference area for normalisation purposes but as explained in chapter 3, if a region is used for normalising, a CBF value cannot be obtained for that region. Since the occipital region contains the primary visual cortex and considering both the visual component of the naming task and the

possible visual deficits involved in misnaming it was considered that occipital CBF values would be of particular interest and should not be used for normalisation purposes. Normalised CBF measurements were obtained for the following ROI's: Left and Right Frontal (medial and lateral combined), High Frontal, Temporal, Posterior Temporal, Parietal and Occipital.

RESULTS

The results of the naming task are displayed in table 8.1. Patients are grouped according to dominant error category (ie. the category that the majority of their errors fell in).

<u>ERROR TYPE</u>	<u>Number of Subjects</u>	<u>% RESPONSES IN DOMINANT CATEGORY</u>	
		<u>MEAN</u>	<u>RANGE</u>
VISUAL	9	53%	33%-80%
SEMANTIC	20	52%	28%-100%
ANOMIC	9	52%	40%-67%
LEXICAL	2	34%	33%-35%

Table 8.2 General distribution of dominant error types.

It is evident from Table 8.1 that the most common type of error produced by this DAT group is Semantic (50%). While both Visual (25%) and Anomic (25%) errors are also frequently found in DAT patients they are not as common as Semantic errors. The results displayed above indicate that the Lexical error category is rarely a dominant error category in confrontational naming when compared to the Visual, Semantic and Anomic categories. While 2 patients (both minimal cases) did produce more lexical than any other error

type, for both these cases the proportion of errors in the dominant category was low (33% and 35%) indicating a relatively even spread of errors. By comparison, the Visual, Semantic and Anomic categories show a range of scores including some cases in each group with a very high proportion of errors in their dominant error category.

Relating rCBF deficits and impairment of
specific cognitive processes

The results of this semi-quantitative (qualitative) investigation into the dominant error types produced by DAT patients on a standard confrontational naming task are used directly in the next stage of this study.

As suggested by the literature reviewed earlier, each of the three dominant error categories identified in the first part of this study are thought to reflect impairment to a specific underlying cognitive process:

VISUAL ERROR	----->	PERCEPTUAL RECOGNITION DEFICIT
SEMANTIC ERROR	----->	SEMANTIC DEFICIT
ANOMIC ERROR	----->	WORD RETRIEVAL DEFICIT

The next part of this study aims to examine whether an impairment in these specific cognitive processes is reflected in deficits in CBF in specific cortical regions.

Identification of subgroups.

Individual DAT cases who produced 75% or more of errors in any one error category were interpreted as having a disproportionate deficit in one of the three specific cognitive processes and were therefore selected for this part of the study. Table 8.3 illustrates the cases identified.

	<u>VISUAL</u>	<u>SEMANTIC</u>	<u>ANOMIC</u>
N	2	5	2
AGE (mean)	74	76	60
MMSE (mean)	18	23	21

Table 8.3 CHARACTERISTICS OF SELECTED SUBGROUPS

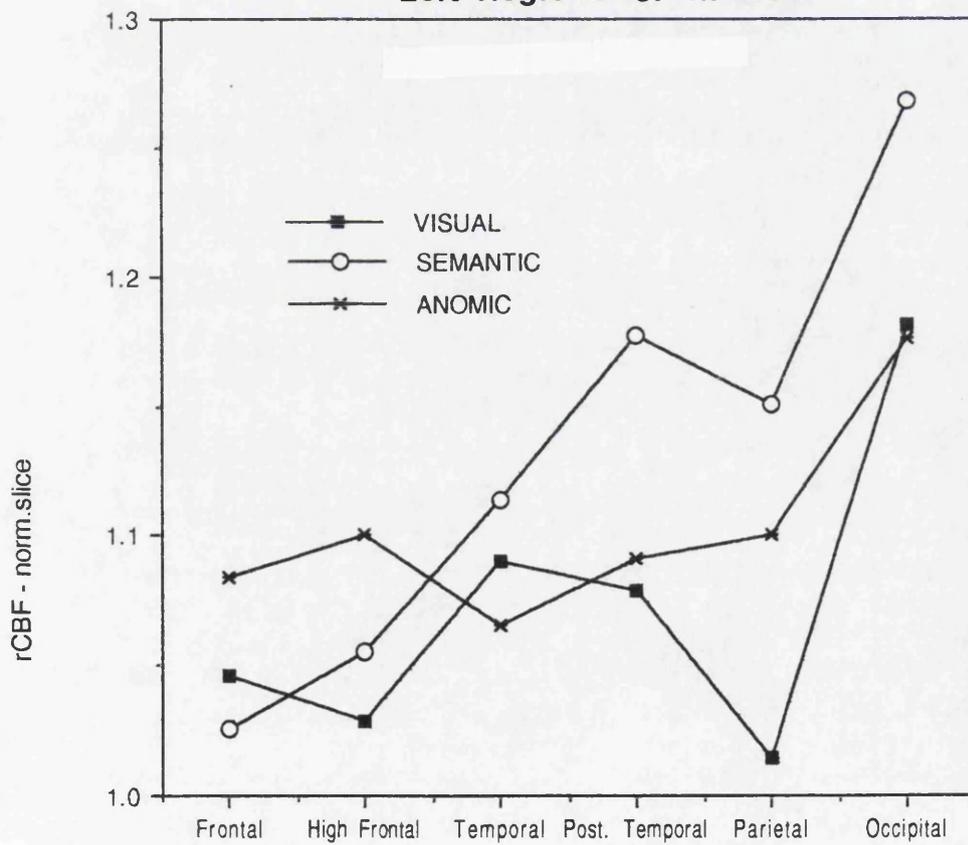
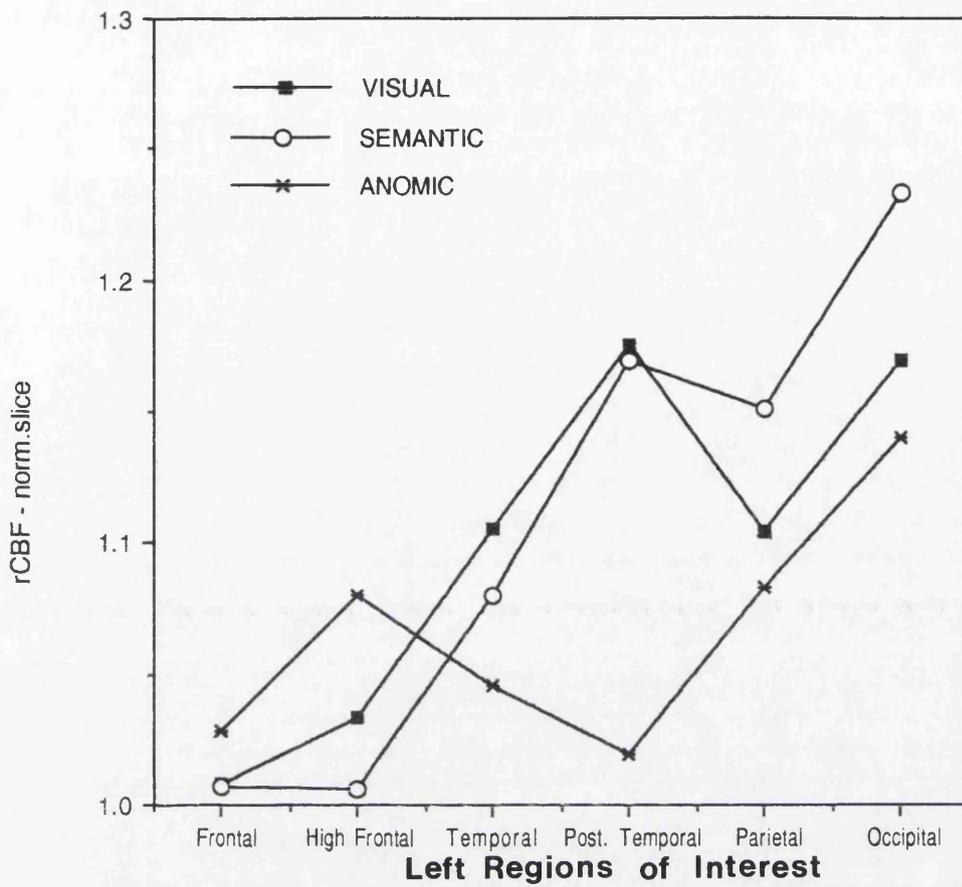
As explained above, the majority of DAT patients displayed a relatively even spread of error types, however, 9 cases were shown to have highly specific cognitive deficits. As table 8.3 illustrates, of these 9 cases, 5 were found to have a disproportionate semantic deficit, 2 were found to have a disproportionate perceptual deficit and a further 2 to have a disproportionate anomic deficit. While these groups are small, they are highly specific and their selection does not allow for the controlling of age or dementia severity. The difference between groups in terms of age reflects the differences in the ratio of minimal to milds since with a degenerative disorder minimal tend to be younger than milds. This difference in the minimal to mild ratio also explains the difference in MMSE scores between the groups. Although, as will be explained later, the control of these two factors is not crucial in this particular study, they will be considered when interpreting the results.

RESULTS

Having selected the three groups, the CBF patterns for each group were then examined and are illustrated in Figure 8(b). It would be inappropriate to use much statistical analyses to interpret these rCBF

patterns since the subgroups are so small, therefore a more qualitative approach will be adopted in this study. Careful observation of the graphs in figure 8(b) reveals distinctive CBF patterns for each group. There are four important features of these graphs which require attention:

- 1 In all six graphs frontal blood flow is reduced compared to occipital blood flow. In several of the graphs the frontal flow is also lower than that in number of other regions. In none of the graphs is the occipital flow lower than any other region.
- 2 When comparing the CBF patterns in the right and left cortices of the Visual group, there is disproportionate deficit in the right parietal region.
- 3 When comparing the CBF patterns in the right and left cortices of the Anomic group, a disproportionate deficit is found in the left posterior temporal region.
- 4 The Semantic group displays relatively symmetrical CBF patterns in the left and right cortices.



Right Regions of Interest

FIGURE 8(b) CBF PATTERNS IN SUBGROUPS

DISCUSSION

Naming errors in DAT

The results of this study clearly illustrate that the naming deficit commonly reported in DAT is not caused by a single cognitive deficit but rather by a combination of possible deficits (impaired recognition, semantic differentiation and word retrieval). It is also clear from these results that the naming deficit in most sufferers of DAT is caused by a combination of error types resulting from deficits in more than one cognitive process. In a small proportion (22.5%) of cases however, the naming deficit in DAT is restricted predominantly to one cognitive process. Of those who display a relatively even spread of error types, the semantic category is found to be the most common dominant error category. Bayles and Tomoeda (1983) might interpret this as supporting their view that naming deficits in DAT result from a breakdown in the semantic network, however as explained, Anomic and Visual errors are not uncommon in DAT and future debates concerning this subject should avoid attempting to show that there is a unitary cognitive deficit behind naming disorders in DAT. It may be that the conflicting results described above (Lawson and Barker 1968; Rochford 1971; Bayles and Tomoeda 1983; Kirshner et al., 1984) are a result of one of two confounding factors. Firstly all these investigations adopted different methods of assessing confrontational naming. Many of the naming tests used had been developed for the purpose of that specific investigation and varied both in number of items and most importantly, in the degree to which the investigators had controlled for word frequency. Variations in word frequency could easily produce variations in naming performance since the more frequent a word occurs in the English language the easier it is to retrieve from the lexicon. No attempt has been made to control across studies for word frequency differences which has been reported to effect the naming impairment in DAT (Hodges, Salmon & Butters 1992). Moreover since

visual misperception is a key issue in this debate, some degree of control for the representational level of the stimuli should be introduced such that all drawings are similar in both the strength of the lines and the definition of the features. The other factor which may contribute to the conflicting results is the difference between studies in the patient populations used. While the more recent investigations refer to a specific form of dementia, namely DAT, the older studies refer to dementia generally. Although there is no evidence to suggest that different types of dementia produce different naming deficits, DAT has very clear diagnostic requirements (see chapter 2) while the diagnosis of dementia does not. Therefore, a dementia population may be relatively impure, and if the sample is small this may significantly affect the results. Related to this issue is that of severity which itself is crucial when comparing results of studies concerning DAT. As the results of this study illustrated, while semantic errors appear to occur independently of severity the anomic errors reflect the minimal stage and the visual errors occur more commonly during the mild stage of DAT. Therefore variations in severity may also have contributed to the conflicting results of previous studies.

Patterns of rCBF and impairments in underlying cognitive processes

The discussion will refer separately to each of the four features of the CBF results outlined above. Firstly, frontal blood flow is low relative to both the occipital region and in a number of cases, other cortical regions. The involvement of the frontal regions in DAT is an issue which has been referred to elsewhere in this thesis (see chapters 2, 4 and 5 and 7) and while it is becoming clear that the frontal regions are affected by DAT, it is not clear to what extent. It is most likely that the frontal CBF deficits seen here are attributable to the general DAT picture rather than to the naming impairment. In contrast all three groups display a relative sparing of the occipital regions, this finding is interesting for two reasons; firstly it adds further support to the use of the occipital (calcarine) region as a reference region for normalising the CBF data in the earlier studies. Secondly it

provides evidence that the naming deficit in the three groups is unlikely to be a result of a primary visual deficit since the visual cortex is contained within the occipital regions.

The CBF pattern found with the visual group includes one particular asymmetric feature; a disproportionate deficit in the right parietal region. This group produced errors reflecting visual perceptual confusion which is a cognitive deficit that has previously been associated with posterior cortical damage and in particular with right parietal damage. Warrington and Rabin (1970) carried out an extensive study from which they concluded that damage to the right parietal region is fundamental to visuo-perceptual disorders. Earlier on, Warrington had illustrated that an intact right parietal region is crucial for the accurate processing of visual sensory data (Warrington and James, 1967) and visual recognition deficits had also been related to right parietal damage by the earlier work of De Renzi and Spinnler (1966). Taylor and Warrington (1973) found a similar relationship between the right parietal region and performance on visual discrimination tasks. Benton and his colleagues (Benton et al., 1983) investigated the effect of side of lesion on a complex form discrimination task. This work also concluded that the right hemisphere is particularly involved in visuo-perceptual tasks and that the posterior (parietal) regions are more implicated in these tasks than are the anterior regions. While the task we are investigating in this study is not itself a visuo-perceptual task, it has a visual component and the visual subgroup of patients show an impairment in this single component. Therefore the finding that this subgroup also display CBF deficits in the right parietal region lends further support to this well-established link between cognitive deficit and site of damage. Most importantly, within the context of this thesis, this finding strengthens the case for relating patterns of rCBF and cognition in DAT as well as in other organic disorders.

The CBF pattern produced by the anomic group, whose naming errors

resulted from a word retrieval deficit, also displayed one assymmetric feature; a disproportionate blood flow deficit in the left posterior temporal region. Word retrieval deficits are frequently reported in organic disorders especially within the aphasias and have often been investigated with respect to localisation of function. Deficits in confrontational naming is a symptom common to both Broca's and Wernicke's aphasias and when existing as an isolated symptom is often referred to as nominal aphasia. As Walsh (1987, p.176) describes " the patient perceives the objects and their significance and can, usually in a round-about fashion known as circumlocution, describe their use or function." All three of these forms of aphasia are thought to be related to damage in the left (dominant) temporal lobes. While Broca's aphasia is associated with damage to the inferior portion of the posterior temporal lobe, Wernicke's aphasia has been associated with damage to the superior portion of the posterior temporal lobe. Nominal aphasia has not been linked to a specific region of the cortex but as Walsh (1987) reports, damage to the left posterior temporal lobe can produce nominal aphasia. Benson (1979) has linked lesions in the posterior temporal regions to deficits in word retrieval and numerous studies have identified the temporal and in particular, the posterior temporal region as being involved in phonological and lexical processing (Demonet, et al., 1992; Howard et al., 1992; Selnes et al., 1985). The reduction in left posterior temporal blood flow found in the anomic group is therefore consistent with previous reports of the localisation of the cognitive processes involved in word retrieval.

The relative absence of assymetrical features in the CBF patterns of the semantic group is not surprising and may be interpreted as directly reflecting the type of cognitive breakdown associated with semantic confusion. Semantic memory contains an individual's conceptual knowledge and naming errors resulting from semantic confusion involve an impairment in differentiating between items within the same semantic category while broader categorical information remains relatively

preserved. There is no established cortical site of semantic function and it may be unlikely that such a concept is appropriate since the very complex nature of semantic processing involves a cognitive network interlinking numerous cognitive systems for its own successful functioning. Geschwind, Quadfasel & Segarra (1968) reported that widely distributed regions of cortex were involved in semantic processing and more recent work by Cappa, Cavallotti & Vignolo (1981) supports a similar conclusion. Other studies investigating the localisation of semantic function have identified specific cortical regions including the angular gyrus (Bouchard, Lecours & Lhermitte 1979), the posterior temporal lobe (Hart & Gordon 1990; Rubens & Kertesz 1983) and the dorsolateral prefrontal area (Alexander, Benson & Stuss 1989). Recently, a study by Demonet et al., (1992), compared the the metabolic activation patterns produced by phonological processing with the activation pattern produce with lexico-semantic processing in normal subjects. They found that semantic processing activated much of the cortex and "is likely to implicate a more widely distributed network than the earlier stages of word comprehension". Therefore, it may be fair to conclude that the lack of assymetrical features in the CBF patterns of the semantic group reflects relatively small decreases in CBF spread over a wide area of cortex.

In conclusion, this study indicates that on a confrontational naming task, the naming deficit displayed by DAT patients is not a result of a breakdown in a unitary underlying cognitive process but rather of a breakdown in a number of such cognitive processes (visual recognition, semantic recognition and word retrieval) all of which play a part in confrontational naming. The majority of DAT patients produced errors in two or more error categories (which particular ones may be related to severity), while only about 25% will display a naming deficit resulting from one specific cognitive deficit. In those cases where errors are largely restricted to a one category, CBF patterns have been found to have a

high degree of concordance with established theories of cortical organisation. Walsh (1983) claims that "a careful qualitative analysis of the precise form of difficulty which the patient has.....will point more precisely to the location of the lesion", this view is borne out in the present study since it has been the "careful qualitative analysis" of each patient's naming deficit which has produced CBF patterns relating to theories of localisation of function.

CHAPTER NINE

CONCLUDING DISCUSSION

A clear and constructive effort has been made over the past decade to increase our knowledge and understanding of dementia and in particular Dementia of the Alzheimer Type. The investigation of DAT, like many other medical disorders, demands the involvement of numerous areas of medical research including psychiatry, neuropsychology, gerontology, neurology, neurophysiology, and molecular biology. DAT also makes a dramatic impact on numerous areas of social living and therefore research in the area of social medicine including community nursing, family breakdown and coping with dementia, is also indispensable. It is therefore clear that many approaches to the study of DAT can and should be multidisciplinary. The context of this thesis has been multidisciplinary involving three main areas of investigation; the recruitment and diagnosis of early DAT, the neuropsychological impairments that accompany DAT and its underlying neurophysiology as reflected in patterns of CBF. The aims of this chapter are three-fold; firstly to summarise the findings of these studies and identify the principal methodological issues associated with this research; secondly to discuss the findings with relation to a number of issues pertinent to this thesis; and finally to suggest promising directions for future research.

SUMMARY OF FINDINGS

The recruitment value of a memory clinic

While the diagnostic problems encountered in studies of DAT will not be overcome until some form of antemortem test is established, studies of DAT should ensure both the use of large numbers of patients and of patients in the early stages of DAT. The present use of a memory clinic to

provide a suitable patient population has been found to be valuable. The rate of recruitment of dementia was approximately 1 in 3 and 73% of recruitments from the memory clinic were displaying only minimal signs of dementia; reflecting the earliest stage of the degenerative process. While memory clinics have been used previously for recruitment purposes (Philpot & Levy, 1987) there does not appear to have been any whose focus was on the identification of minimal DAT. The results of this study have also suggested that at the earliest stages of DAT, when objective cognitive deficits may not be found, the semi-structured use of presenting symptoms to distinguish the possible DAT cases from the normal elderly may prove to be significant. This study showed that while problems with memory and naming were common to both the normal elderly and the minimal DAT groups, changes in concentration, thought processes, organisational ability, personality and transient feelings of disorientation are reported only in the minimal DAT group.

Regional Cerebral blood flow patterns in DAT

Rather than focusing on one stage of DAT, this thesis has investigated the rCBF patterns that accompany the different stages of degeneration. As would be expected, the results of these studies show that the number of regions displaying CBF deficits increases as the severity of the dementia increases. At the earliest, or minimal stage the CBF deficits are found to be restricted to the left temporal and parietal regions while the mild stage produces deficits involving much of the cortex, including frontal, temporal and posterior temporal, as well as a significant deficit in the thalamus. The moderate and severe stages were found to display deficits in all regions with a relative sparing of the occipital (calcarine) cortex.

The results of this investigation have identified clear frontal CBF deficits accompanying DAT. However, the pattern of these frontal deficits appears to vary with disease severity. While at the minimal stage of DAT

there are no signs of frontal CBF deficits, the mild stage involves deficits in both the medial and lateral regions. The results also suggest that at the mild stage the high frontal (premotor) area may remain relatively spared. As the disease progresses to the moderate and severe stages however, the CBF deficits spread to this area as well resulting in significant blood flow deficits in the frontal regions generally.

Cognition and DAT

The CAMCOG which is a general cognitive test, has been used for two purposes in this thesis. Firstly as a measurement of overall cognitive performance used to rate a patient's dementia severity and secondly as a specific tool for characterising cognitive breakdown and relating it to CBF. As a severity rating tool it has proven very useful as it assesses cognition in greater detail than some other screening tests. However, it requires at least half an hour to administer and, depending on the aims of the assessment, the MMSE which takes five minutes might be sufficient. Moreover, the work described above involving the distinction between cases of minimal DAT and the normal elderly, suggests that the CAMCOG may be less sensitive than the MMSE in the detection of very early cognitive deficits. This would have important implications for clinicians, memory clinics and research projects including therapeutic trials, and therefore warrants further investigation.

The suitability of the CAMCOG as a more specific cognitive tool focussing on particular subtests to obtain a cognitive profile may also be questionable. While the CAMCOG does assess performance in a number of cognitive domains its design does not consider the interaction between test difficulty and dementia severity across these domains. Therefore, while the praxis subtest is reasonably difficult for the moderate to severe group, it is extremely easy for the mild group and results in a substantial ceiling effect. Likewise, the memory subtest while being reasonably difficult for the mild group, is close to impossible for moderate

to severe group and results in a floor effect. This highlights the problem of using general cognitive tests to measure specific cognitive deficits in dementia since it is very difficult to design a test which measures performance in a number of cognitive domains over a wide range of dementia severities without producing floor and ceiling effects.

The Delayed Recognition Span Test (Moss et al.,1986) was used as a more specific measurement of memory. The DRST measured recognition memory for verbal, spatial and facial material and showed that memory span for all three forms of information is impaired in DAT. While recognition might have been expected to be relatively spared in the early stages, the results show that impairment in recognition memory starts very early on in the dementia process and deteriorates gradually with severity, leaving the moderately demented patient with a recognition span of approximately 4. Recall memory is also shown to be impaired early on in DAT but unlike recognition, it is found to have fallen to floor level by the moderate stage. Furthermore, performance on this recall task is found to distinguish between the minimal DAT group and the control group; a finding which has important implications for the task of identifying early DAT.

Frontal neuropsychological deficits in DAT were investigated using four different tests. The findings indicate that frontal deficits develop early on in DAT and are related to the overall severity of the dementia. No evidence of outliers were found, showing that of the 25 patients included in this investigation, none were displaying disproportionate frontal signs suggestive of a frontal lobe dementia. Taken together, these findings suggest that frontal deficits form an integral part of the dementia profile that accompanies DAT.

The third area of neuropsychological investigation covered in this thesis was that of the naming deficit produced by DAT sufferers on a

confrontational naming task. This study was purposefully designed as an experiment to investigate the possibility of relating a highly specific cognitive deficit to CBF patterns. Analysis of the naming errors produced by the DAT patients showed that most DAT sufferers produce a mixture of error types reflecting impairment to perceptual, semantic and word retrieval processes. However 25% of the patients were found to have a highly specific impairment restricted to only one of these processes.

Regional cerebral blood flow and cognition in DAT

These studies have shown that relating rCBF and cognitive performance on the CAMCOG produces multiple correlations. As discussed in both chapters 4 and 5, multiple correlations of this type are difficult to interpret and can lead to oversimplistic conclusions. The results from both the study involving the moderate and severe DAT populations (chapter 4) and the study involving the minimal and mild DAT populations (chapter 5) produced similar results in terms of multiple correlations. However, it is important to note, at this point, that in the second study the actual potential for correlations was greater since the number of ROI's was 18 in comparison to the 10 used originally in chapter 4. Therefore, while a similar number of correlations were found, the second study involving the less severe patients, produced relatively fewer correlations. The principal difference between the two sets of data lies more in the strength of the correlations rather than the pattern of correlations. While correlations involving the later stages of the disease varied from 0.5 to 0.74, the correlations obtained for the earlier stages of DAT were much weaker ($r=0.24$ to $r=0.5$). The patterns of correlation displays one particular similarity between the two studies; approximately 50% of each of the sets of correlations involve measures of overall cognitive performance. A problem specific to the first study was that correlations (weak or strong,) were found with all ROI's and therefore meaningful conclusions concerning the relationship between cognition and CBF were difficult to reach. The second study, involving the earlier stages of DAT, while

producing a relatively restricted number of correlations, produced few correlations that reflected measures of cognition other than overall severity. The results of both studies strongly reflect the dependence of these measures of cognition on language ability since correlations involving the language component of the CAMCOG display a very similar pattern to those involving overall cognitive performance.

Correlations involving measures of cognition obtained from specific cognitive tasks have proved to be more meaningful. Correlations of memory performance (on the DRST) and blood flow have involved both the regions most commonly affected by DAT (temporo-parietal) and the regions normally associated with memory (temporal and thalamic). The results of this study have also reflected specific differences in the demands of different memory process. This has been shown by the presence of correlations between immediate recall and medial frontal blood flow and the absence of such correlations with performance on recognition tasks.

While the presence of frontal deficits either in cognition or blood flow are of particular interest in this study of DAT, the relationship between these measures did not reflect previous knowledge relating to the structure and function of the frontal lobes. Correlations were found involving the high frontal (premotor) regions and performance on the Subject Ordered Pointing Task (SOPT) and tests of verbal fluency. Possible methodological reasons for the lack of significant relationships were mentioned in chapter 7.

A different experimental design was adopted for the third study relating CBF to specific cognitive impairments. A less quantitative, and more qualitative analysis was used to relate CBF and the naming errors in this investigation. The perceptual group displayed CBF deficits in the right parietal region, while the anomic group showed CBF deficits in the left

posterior-temporal region and the semantic group had symmetrical CBF patterns. The results of this study indicated a degree of concordance between the patterns of CBF in each error group and established knowledge of the localisation of function.

METHODOLOGICAL ISSUES

Research within the area of DAT raises a number of methodological issues, the next section of this chapter will outline these issues and suggest ways of avoiding them.

Diagnosis of DAT

Methods of diagnosis of DAT have been described in chapter 2 where the problems of differential diagnosis were pointed out. The main methodological issue associated with the diagnosis of DAT is the lack of neuropathological confirmation of Alzheimer's Disease in most research projects and therefore a degree of uncertainty as to the strength of any conclusions made. While some multi-disciplinary studies may have a neuropathological component as does the present study, and therefore ultimate diagnostic confirmation is possible, this confirmation may not be available for a long time. As this thesis has pointed out, research into the early stages of DAT is very important, however the problems associated with the lack of confirmed diagnosis become greater at the earlier stages since there is less information available to aid an accurate clinical diagnosis and there is also, on average, a longer time before post mortem confirmation becomes available. It is impossible to solve this problem until an antemortem marker for DAT becomes available. However, in order to reduce the confounding effect of cases of Dementia of the non-Alzheimer Type, researchers should beware of small samples.

Dementia Severity

The classification of the severity of a case of dementia is almost as

important as the classification of the type of dementia. Due to the progressive nature of dementia, the clinical, cognitive or neurophysiological picture will differ with severity, however, information concerning severity is often omitted in published work. This may result in a difficulty in deriving firm conclusions from a study, or in comparing one study with another. Since dementia severity should always be described in reports and publications for the reasons outlined above, it is worth considering in some detail the various severity rating scales at the time of designing a study. Depending on the aims of the study, severity might be best rated using a general clinical tool (eg. Berg et al., 1982), or using a well-established and extensive cognitive tool (eg. CAMCOG, DRS) or using an equally well established but less extensive cognitive tool (eg MMSE). The choice of what form of severity assessment to use should take into consideration the general severity of the patients required for the study. For example, if a study is to focus mainly on neuropathological investigations, the required population would be quite severe, therefore using the CAMCOG might be wasteful since very severe patients cannot perform it. It would be more sensible instead, to use a short test like the MMSE. Likewise, the aims of the study should dictate whether a clinical or cognitive severity scale should be used. One point to bear in mind when designing a study is that it can be very awkward to compare the results of studies if different severity scales are used, this issue was discussed in chapter 6. While it is not always appropriate to use the same severity scale as another research group, it is very important that a well established and standardised scale be used, if necessary, in conjunction with a more experimental tool.

Investigating relationships with cognition in DAT

It has become clear through this thesis that there is an interaction between the severity of dementia and the success of the cognitive investigation carried out. In other words, the design of any investigation

into cognitive performance in DAT must depend almost totally on the severity of the population. As we have seen, a lack of distribution of scores either through floor or ceiling effects, greatly reduces the chances of producing significant correlations with CBF. While this thesis also emphasises the particular value of investigating the early stages of DAT, it is equally valid to focus an investigation on the later stages of the disease. Whichever stage of DAT is under investigation however, it is important that any cognitive tests selected as investigative tools should be suitable to the severity of the population in question. Finally, it is also clear from these studies that if specific areas of cognition (eg. learning, recall, aspects of aphasia) are to be investigated, then considerable attention should be paid to the method of assessment. This should not be carried out in a post hoc manner using a cognitive severity test as has been done frequently before. Instead, the most relevant and meaningful results will be obtained by a very careful qualitative and quantitative assessment and analysis of cognitive performance.

GENERAL DISCUSSION AND CONCLUSIONS

Having outlined the principal findings of this thesis and discussed the methodological issues, the next section of this chapter will aim to discuss a number of these findings with reference to three important issues; 1) Early CBF changes, 2) Differential diagnosis and Frontal Lobe Dementia, 3) Relating CBF and cognition in DAT.

1) Early cerebral blood flow changes

While the relationship between disease severity and CBF deficits is well established, there has been little work focusing on the early stage where patients do not yet display objective cognitive deficits. The study described in chapter 5 demonstrates evidence of CBF deficits accompanying the very earliest stage of DAT. The SPECT scan displayed in figure 9(a) and (b) provides a clear example of such deficits in a case of minimal DAT whose total CAMCOG score was 78. This supports the proposal of Haxby et al., (1986) that metabolic abnormalities appear to precede non-memory cognitive impairments. The accurate diagnosis of DAT is of major importance especially in the study of its cause and potential treatment, and attempts have been made to integrate CBF measurements into the diagnostic decision making process (Neary et al., 1987; Jagust et al., 1989). In fact, one may infer from the results of this study, that CBF measurements using SPECT might contribute to the diagnosis of DAT. However, while these results do indicate that CBF changes occur very early on in the disease process, this conclusion is based on group data and cannot be generalised to the use of SPECT and CBF deficits in the diagnosis of individual cases. In contrast, the work by Holman et al., (1992) addresses this particular issue in attempting to evaluate the diagnostic probability of a number of CBF patterns found to accompany dementia. As mentioned in chapter 5, while this work by Holman and his team does contribute to the evaluation of SPECT as a diagnostic tool, the lack of both information concerning patient severity and postmortem confirmation of DAT, greatly reduces the strength of their conclusions. Therefore while CBF changes do seem to occur in the "preclinical" stage of DAT, at present we are unable to use this information to increase the diagnostic accuracy of early DAT.

Figure 9 (c) and (d) illustrate predominantly left-sided posterior CBF deficits in a case of early DAT. The reasons for the early involvement of

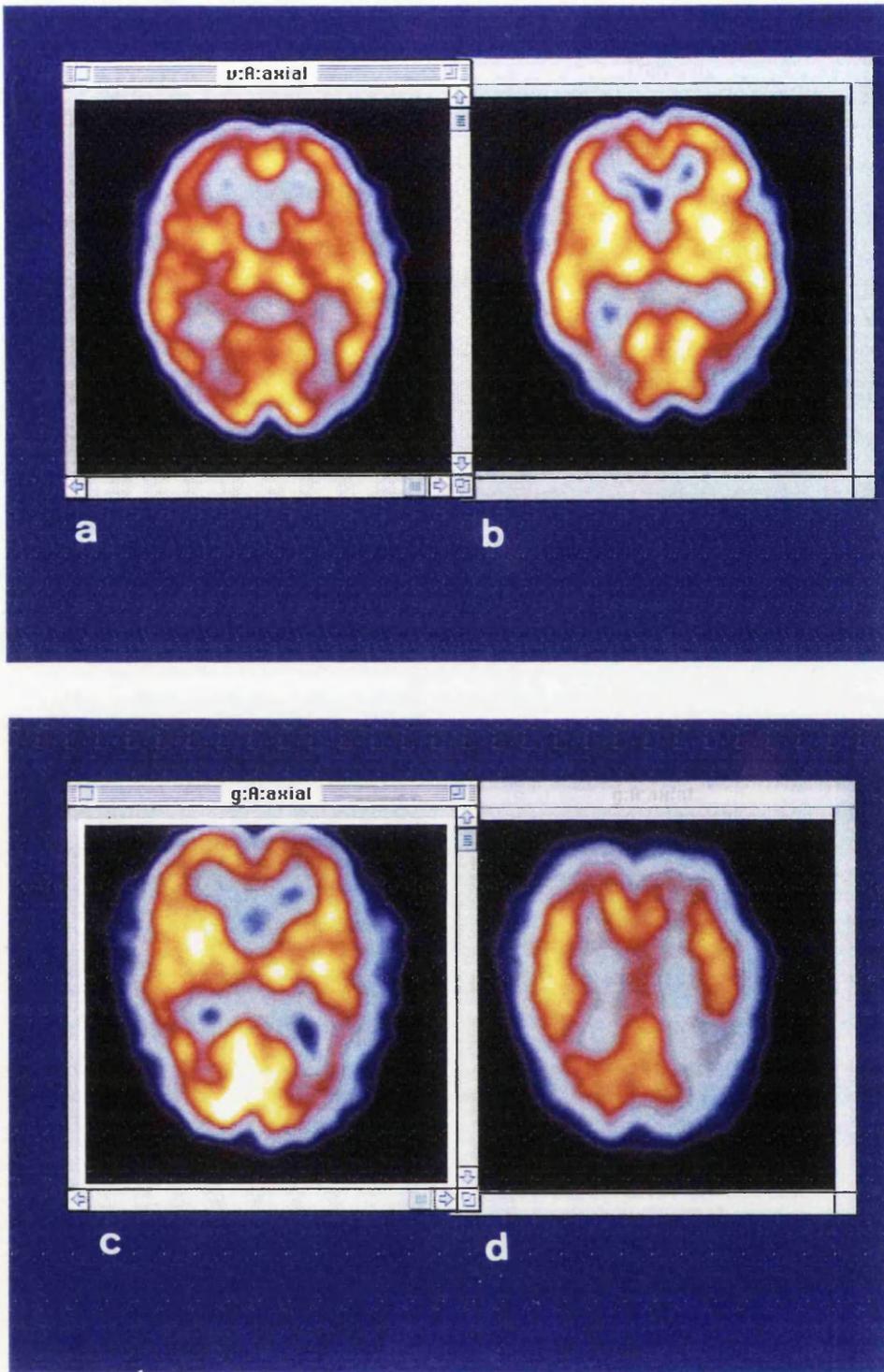


Figure 9(a-d) Illustrating slight posterior CBF deficits in a case of minimal DAT (b) compared to a control (a) and left-sided posterior temporal (c) and parietal (d) deficits in a case of DAT.

the left hemisphere in the minimal DAT group are not clear. It has been suggested that the left hemisphere is particularly vulnerable to early damage as has been concluded from neuropsychological studies by Seltzer & Sherwin (1983) and Filley, Kelly & Heaton (1986). Alternatively, some form of selection bias might be occurring. It is most likely that these findings are a result of a selection bias which may be explained by the relationship between the left hemisphere and verbally related tasks. Slight impairments in the verbal components of cognitive tasks may well be more noticeable in daily life than similarly slight impairments in the visuo-spatial components of tasks. It is therefore quite likely that someone with mild verbal impairments will more readily refer themselves or be referred to a GP, a specialist or a memory clinic than will someone with mild visuo-spatial impairments. This may therefore result in an over representation of cases with early left hemisphere involvement. It was once thought that examples of stroke occurred more frequently in the left than the right hemisphere because there were more reports of left-sided strokes. This has since been explained in terms of the type of selection bias described above (Walsh 1987). Because of this probable bias, it is inadvisable to draw firm conclusions at this point, concerning the differential involvement of the hemispheres in early DAT.

2) Differential diagnosis and Frontal Lobe Dementia

In chapter 2 where the differential diagnosis of dementia was discussed, it was pointed out that there are two areas of differential diagnosis. One of these areas involves the distinction between DAT and other forms of dementia which have in vivo markers (eg. Multi-Infarct Dementia, Normal Pressure Hydrocephalus, Alcoholic Dementia), the other involves the distinction between DAT and other forms of dementia which do not, as yet, have antemortem markers. Of the latter group, which includes Pick's Disease, Frontal Lobe Dementia is of particular interest here. The reason for this is that Frontal Lobe Dementia is a relatively new and

unestablished form of dementia around which there remains some controversy.

Brun (1987) identified this new form of dementia as Frontal Lobe Dementia on the basis of the involvement of the frontal lobes and contrasted it neuropathologically with Pick's disease. Gustafson (1987) provided strong evidence of distinctions between the clinical pictures of FLD and DAT, however, possible differences in severity between the two populations may account for this finding. Hagberg (1987) described the behavioural correlates of frontal dysfunction and concluded that while neuropsychological distinctions do not yet exist between FLD, DAT and Pick's disease, the differences between these dementias might be best expressed in terms of behaviour and personality changes rather than cognitive deficits. It is clear from the results of the present study that frontal cognitive deficits are common in DAT and occur at all stages of the dementia. Moreover, if cases of FLD are reported to have frontal deficits which are unrelated to dementia severity (Neary et al., 1988), then they would have been identified within this DAT population as outliers, however, no outliers were found. These findings therefore support the conclusion of Hagberg (1987) that patterns of cognition may not differentiate DAT and FLD.

The problem of the differentiation of DAT and FLD has been tackled by numerous studies involving CBF measurements. Neary et al., (1988) concluded that frontal CBF deficits were a characteristic of FLD while DAT patients displayed posterior deficits. Jagust et al., (1989) also found frontal CBF deficits in presumed cases of FLD. However these are dangerous conclusions since the argument can be circular unless neuropathological confirmation of non-Alzheimer Type dementia is obtained. In the absence of a neuropathological confirmation, the selection of cases of FLD is based purely on the presence of frontal symptoms. These symptoms, by definition, are related to frontal

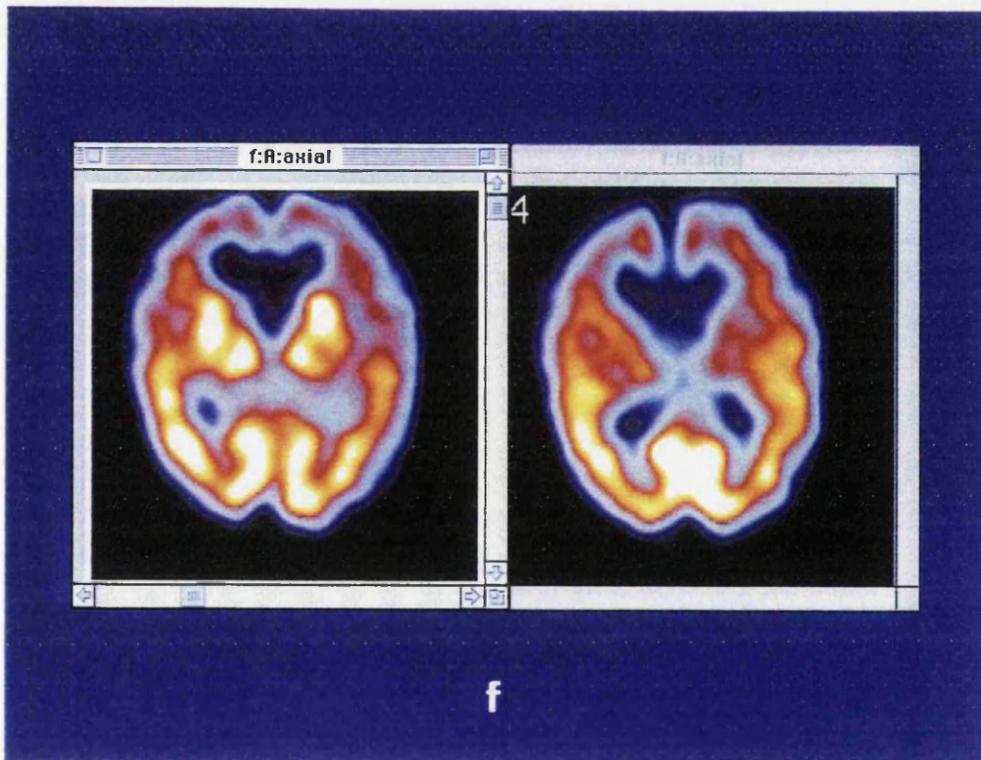
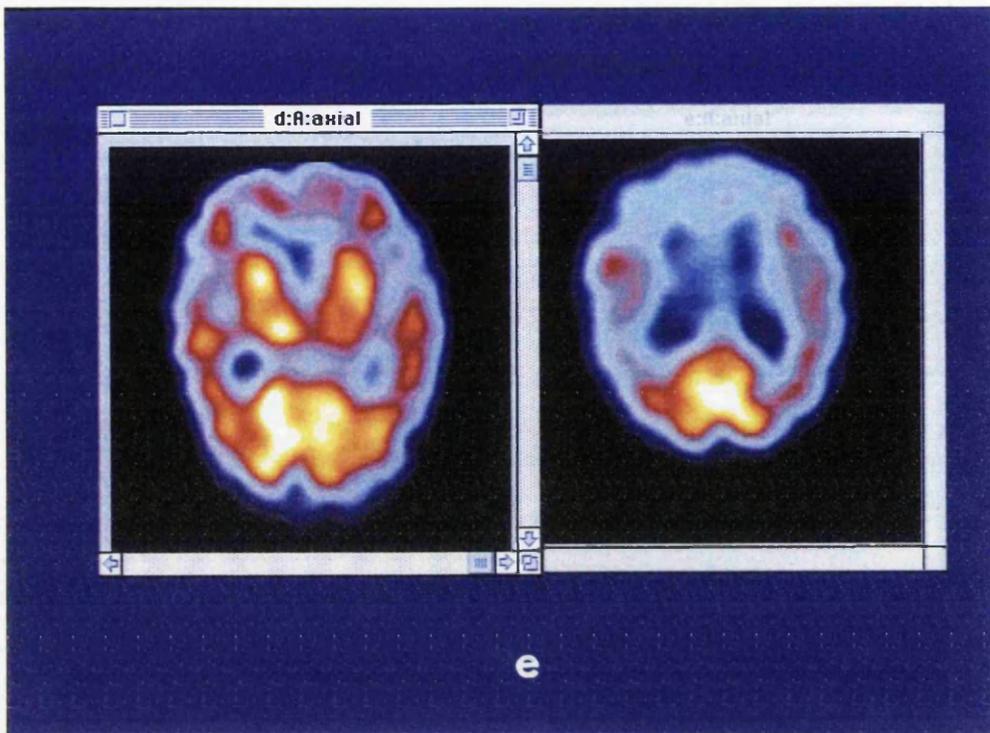


Figure 9 (e) and (f). Illustrating frontal CBF deficits in a case of confirmed DAT (e) compared to a case of confirmed FLD (f).

pathology and therefore patients with such symptoms would be expected to produce frontal blood flow deficits, whether they be DAT, FLD, MID or Jacob-Kreutzfeldt cases. Figure 9(e) displays the clear frontal CBF deficits in a case of neuropathologically confirmed DAT, while figure 9(f) displays the CBF pattern of a confirmed case of FLD. While these two CBF patterns may differ in the extent of posterior deficits present, the frontal patterns are similar. The CBF studies described in this thesis have illustrated evidence of medial and lateral frontal deficits accompanying not only the moderate to severe stages of DAT but also the mild stage. Therefore, while it has been suggested that the frontal pathology may develop later on in DAT (Foster et al., 1984; Montaldi et al. 1990), the present findings show that a frontal component develops relatively early. The work by Holman et al., (1992) adds further support to the theory that a frontal pathology is not uncommon in DAT. They report that 43% of patients with frontal CBF deficits only, were diagnosed independently as cases of DAT. It is therefore not merely the presence of a frontal pathology that might distinguish DAT from FLD but rather the histopathological characteristics of that pathology. It should be concluded that evidence of a frontal pathology, whether alone or together with other areas of damage, must not be used to give differential diagnoses of dementia. More extensive research will be required involving a greater degree of postmortem information, to establish antemortem markers for FLD, Pick's disease and DAT.

3) Relating cerebral blood flow and cognition in DAT

The recent developments in SPECT scanning, including its relative availability in clinical centres, has led to the enthusiastic application of this neuroimaging technique to numerous clinical disorders. As SPECT is a form of functional neuroimaging it is considered to be particularly suitable for use in studies attempting to bridge the 'brain-behaviour gap'. For this reason numerous studies, concerning a variety of clinical disorders have attempted to relate rCBF information obtained using

SPECT, to cognitive information. However, not all forms of cognitive assessment are equally suitable for this type of investigation. Because of the nature of DAT (and other forms of dementia), all antemortem investigations generally include an assessment of overall cognitive performance. With the development of the CAMCOG (Roth et al., 1986) and the DRS (Mattis et al., 1984) these forms of cognitive assessment have become much more extensive; measuring performance in a number of cognitive domains. There has therefore been the temptation to use these general cognitive tests to produce measures of cognition for studies of the relationship between rCBF and cognition (Burns et al., 1989; Hunter et al., 1989; Montaldi et al., 1990). While this may be sufficient for the investigation of the relationship between dementia severity and rCBF and although these studies have produced some interesting findings, they have also shown that multiple correlations resulting from the analysis have obscured specific findings. As described in chapter 4, there are two possible causes of these multiple correlations; firstly the failure to use specific cognitive tasks and secondly, the severity of the dementia populations used in these studies. The results of the studies in chapters 4 and 5 lead to the conclusion that both these causes play a part in the production of multiple correlations. In chapter 4 where moderate and severe DAT patients were studied, a greater proportion of correlations were obtained, however in chapter 5 where the DAT patient population was minimal and mild, multiple correlations were still found. While there were relatively fewer correlations in the second study, these correlations were noticeably non-specific; reflecting little more than the general relationship between dementia severity and rCBF. Furthermore, as explained earlier, the application of general tests of dementia can lead to ceiling and floor effects which can noticeably effect the pattern of correlations obtained. Since the results of such studies can produce vague and misleading conclusions, investigations aiming to relate particular patterns of cognitive breakdown, to patterns of CBF should avoid using general cognitive assessment tests to identify the cognitive

deficits, focussing instead on the use of cognitive tasks designed for the identification of that specific deficit. Evidence in support of this recommendation has been obtained from the studies described in chapters 6,7 and 8. All of these studies have focused on specific cognitive deficits; memory, frontal and confrontational naming respectively. All three studies have indicated fewer but on the whole, more interesting and more specific relationships between CBF and cognition, than did either of the previous studies.

DIRECTIONS FOR FUTURE RESEARCH

The results of this thesis lead to a number of suggestions for future research both in terms of the directions research should take and methodological recommendations.

The investigation of the earliest stages of DAT requires the careful recruitment of minimal DAT cases. This would be best carried out using a memory clinic model. Further investigation into the value of using presenting symptoms as a distinction between cases of very early dementia and normal healthy elderly should be given serious consideration. While research into the early stages of DAT will contribute to the accurate differential diagnosis of DAT, this process ultimately requires the neuropathological confirmation of Alzheimer's Disease in order for it to have any valuable medical or therapeutic implication. Therefore while the recruitment and diagnosis of DAT may be a costly pursuit, considerable attention to this matter will be worthwhile if neuropathological information can be obtained at postmortem. The logistics for such a requirement are not straightforward since many years may lapse between initial diagnosis and confirmation. However, future research into DAT should always be linked to a neuropathological research centre so that where possible, data on this very challenging question can be obtained.

The recruitment of early DAT cases should focus on two further issues which have been referred to in this thesis. Firstly the reported prevalence of a left hemisphere sensitivity to DAT. This thesis has suggested that this may simply be a result of a selection bias, and in order to establish whether this is the case, recruitment procedures should allow for a specific search of early cases of DAT displaying symptoms normally associated with right hemisphere damage. In light of the debate concerning frontal damage in DAT and the existence of a separate 'Frontal' dementia, the second issue on which recruitment should focus is on cases where personality change is reported early on in the dementia. At present personality is not considered to be an early symptom of DAT but of FLD, however in view of the findings of both cognitive and CBF frontal deficits in DAT, the involvement of personality factors early on, requires clarification.

The identification of early cases of DAT will also allow for areas of neuroimaging such as SPECT and MRI activation to be developed within the context of dementia. Since these forms of neuroimaging can be demanding and require a high degree of cooperation on the part of the patient, they are unsuitable for the more demented population. However, use of a mild and minimal population will allow for the investigation of the breakdown in specific mental processes in DAT. A particularly interesting focus would be on the imaging of CBF patterns produced during the administration of tasks which are successfully carried out despite evidence of damage to cortical areas normally associated with the task. This might contribute to the understanding of how the brain adapts to damage in adulthood.

The focus of future research relating CBF and cognition in DAT should stress two points. Firstly, the need to investigate specific cognitive domains. This might be done by identifying the component parts of a

cognitive task and carefully assessing both quantitatively and qualitatively the particular deficit displayed by the patient or group of patients. The other issue with which future studies of this type should concern themselves is the interaction between the CBF-cognition relationship and dementia severity. There is some evidence from these studies that the CBF-cognition relationship changes as severity increases; this is a particularly interesting hypothesis and deserves considerable attention. Any findings concerning this issue may have substantial implications for all studies relating brain and behaviour in both degenerative and non-degenerative organic syndromes.

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