

**DEMENTIA WITH LEWY BODIES:
THE INVESTIGATION OF PRE- AND POST- SYNAPTIC DOPAMINERGIC
RECEPTORS WITH SPET**

MD

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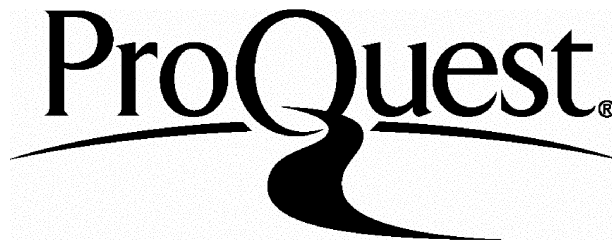
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ABSTRACT

Objective - Dementia with Lewy bodies (DLB) is one of the main differential diagnoses of Alzheimer's disease (AD). Key pathological features of patients with DLB are not only the presence of cerebral cortical neuronal loss, with Lewy bodies in surviving neurones, but also loss of nigrostriatal dopaminergic neurones, similar to that of Parkinson's disease (PD). In vivo detection of this dopaminergic degeneration and post-synaptic dopamine D₂ deregulation might help to distinguish DLB from AD during life.

Methods - Using a dopaminergic post-synaptic ligand ¹²³I-iodobenzamide (IBZM) and pre-synaptic ligand [¹²³I]-2beta-carbomethoxy-3beta- (4-iodophenyl)-N- (3-fluoropropyl) nortropane (FP-CIT) and single photon emission tomography (SPET) we assessed the integrity of the nigrostriatal metabolism.

Results IBZM study -The DLB group had a significantly lower left caudate:putamen ratio than the control and the AD group. The DLB group also had a lower right caudate:putamen ratio than the AD group and the controls, but the difference between the DLB and AD group was not significant.

Results FP-CIT study - Both DLB and PD patients had significantly lower pre-synaptic radioactivity uptake than AD patients and controls in the caudate nucleus and the anterior and posterior putamen. There was significantly greater asymmetry of uptake in the posterior putamina of PD patients than DLB patients. The mean caudate:putamen ratio for the DLB group was not significantly different to that of the controls, while the mean caudate:putamen ratio for the PD group was significantly higher than for the control group and for the DLB group.

Conclusion Our results show that FP-CIT SPET provides a means of distinguishing DLB from AD during life. There are also clear differences between PD and DLB in the pattern of striatal dopaminergic dysfunction. DLB patients do not have the characteristic selective degeneration of ventrolateral nigral neurons that has been shown in PD. Patients with DLB have also changes in striatal post-synaptic D₂ receptors, but these are unlikely to be of value in distinguishing DLB from AD during life.

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OUTLINE OF THE THESIS

The thesis is divided into eight chapters. The first chapter gives a detailed overview of DLB. The next three chapters deal with imaging in dementia. Chapter 2 summarises structural imaging in AD and DLB and Chapter 3 describes metabolic and perfusion studies in AD and DLB. The last of the imaging chapters, Chapter 4, focuses on imaging of the dopaminergic pathways with particular emphasis on Parkinson's disease as this is the condition in which most of the research has been carried out. Chapters 5-8 deal with the work carried out for the thesis and are divided into Methods, Results from the IBZM study, Results from the FP-CIT study and Discussion.

The whole research project was my idea. I carried out an extensive literature search and I reviewed all the previous relevant literature. I wrote all the protocols that formed the basis for the thesis (IBZM protocol, FP-CIT protocol and the autopsy follow-up protocol) and submitted and obtained ethical approval for all of them. In collaboration with Professor Ian McKeith, Professor Cornelius Katona, Dr Durval Costa, Dr Rodney Walker and Dr Gill Livingston I obtained charitable donations for the study from Novartis and Amersham Nycomed. I recruited and consented the majority of the demented patients and controls for the study. I personally took patients and controls for the IBZM scan and two thirds of the patients and controls for the FP-CIT scan and I was present during the scanning sessions. I was one of the three visual raters for the FP-CIT scans. I followed-up and I am still following the FP-CIT cohort at regular intervals. With one dementia

nurse specialist I have been for the last four years on an on-call rota for the brain donation program. I entered all the data and performed all the statistical analyses and made all the graphs and tables.

However the thesis involved extensive collaboration. All the SPET scans were carried out by Dr Durval Costa and Dr Svetislav Gacinovic and analysed and visually rated by Dr Durval Costa. The first seven brain autopsies were examined by Professor Paul Ince while he was at the MRC Neuropathology Unit in Newcastle and later at Sheffield University. More recently brain examinations were performed by Dr Evelyn Jaros and Professor Robert Perry. All patients with Parkinson's disease were recruited by Dr Rodney Walker, consultant neurologist, who was also one of the independent assessors for visual rating of scans. Dr Gill Livingston and Dr Tim Stevens helped with recruitment of patients with dementia. Two dementia specialist nurses – first Ms Karen Shaw and more recently Ms Lean Lee - helped to obtain brain autopsies from patients.

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Chapter 1

Dementia with Lewy bodies

1.1 INTRODUCTION

In the International Classification of Diseases ¹ dementia is defined as a syndrome due to disease of the brain, usually of a chronic and progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement in the presence of clear consciousness. Impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation.

Over the last fifteen years there has been an unprecedented interest in the different subtypes of dementia. This has been partly due to the availability of new treatments for Alzheimer's disease (donepezil, rivastigmine and galantamine), but also due to the rising number of patients suffering from dementia as a consequence of longevity. The prevalence of dementia dramatically rises with age, being relatively rare below the age of 65 but affecting 25-50% of individuals over the age of 85. Distinguishing different types of dementia is no longer just an academic pursuit but is now a clinical requirement.

1.2 HISTORICAL BACKGROUND

Eosinophilic intracellular inclusion bodies, called Lewy bodies, were first described by Friederich Lewy in 1912². The presence of many Lewy bodies in the brainstem and diencephalic nuclei, particularly the substantia nigra (SN) is considered to be the hallmark of idiopathic Parkinson's disease (PD). In 1923 Friederich Lewy published pathological and clinical description of 43 patients with parkinsonism of whom 21 cases were demented. Although there were few other reports of dementia associated with Lewy bodies, sometimes also called incidental Lewy body disease³⁻⁵, a more detailed descriptions of cases with progressive dementia with numerous Lewy bodies in the brainstem and cerebral cortex were published only in the seventies and eighties, mainly by Japanese authors⁶⁻¹². Since the late eighties, dementia with Lewy bodies (DLB) has attracted a great deal of interest and a number of research groups have shown that it is the second most common type of degenerative dementia after Alzheimer's disease (AD)¹³⁻¹⁵.

There has been a plethora of terms used to denote this condition. Presently, the favoured term is "dementia with Lewy bodies" as it acknowledges the presence of Lewy bodies without specifying their contribution to the aetiology or symptom formation. DLB has clinical and pathological features of both AD and idiopathic Parkinson's disease (PD)¹⁶.

As in AD, a definitive diagnosis can only be made by histopathological examination of the brain. A clinical diagnosis is made on the basis of probabilities by considering

the symptoms and signs, results of investigations and neuropsychological tests and, in a research setting, according to agreed diagnostic criteria. However, a large proportion of patients with the clinical diagnosis of DLB also fulfil the NINCDS-ADRDA criteria ¹⁷ for AD. Despite this, a distinctive picture has emerged of certain clinical features that strongly point towards the diagnosis of DLB.

1.3 CLINICAL FEATURES OF DLB

The core features of DLB are a progressive dementia with marked fluctuation in the cognitive state, vivid visual hallucinations and spontaneous parkinsonian features. In some cases dementia is preceded by PD. If the duration of PD has been longer than one year before the onset of cognitive symptoms, then the term "PD with dementia" is used because it is less certain that the dementia and parkinsonism have the same aetiology. Compared to patients with AD, an episodic memory deficit is frequently not the presenting complaint in patients with DLB, especially in "pure" cases (no or little concomitant AD pathology ¹⁸). Extraparamidal symptoms, behavioural disturbance, hallucinations or delusions can precede memory deficit, although eventually all patients dement.

1.3.1. Hallucinations

In addition to dementia the most striking clinical feature is complex visual hallucinations. They are typically of people, children and animals ¹⁹ and are sometimes accompanied by secondary delusions. They are more frequent in "pure" cases ^{20,21}. The persistence of visual hallucinations for more than one year has

been investigated in a prospective study by Ballard et al ²². In 77% of DLB patients, hallucinations persisted, compared to only 26% of AD patients. DLB patients also showed a trend toward being more likely to develop visual hallucinations during the follow-up year. Only very occasionally patients have hallucinations in other modalities. The presence of vivid visual hallucinations in early stages of dementia is a good discriminator between DLB and AD ²³. Visual misperceptions and misidentifications are also common. Patients have variable and sometimes fluctuating insight into these phenomena.

1.3.2. Parkinsonism

The majority of patients with DLB develop spontaneous parkinsonism at some stage of their illness. In some, this can be a presenting or early symptom. In a prospective cohort Ballard et al ²⁴ reported significant parkinsonism in 71% of DLB cases, compared to only 7% of AD and 10% of vascular dementia (VaD) cases. The frequency of parkinsonism in DLB patients did not change with the level of cognitive impairment. Patients characteristically have a stooped posture, a shuffling gait, reduced arm swinging and a tendency to trip and fall. They have hypokinesia and increased tone and, less frequently, tremor ²⁵. Interestingly no correlation has been found between the degree of (SN) degeneration at autopsy and the presence or the severity, of parkinsonian symptoms at presentation. This suggests that other factors beside SN degeneration are involved in the expression of parkinsonian features ²⁶.

1.3.4. Fluctuations in cognitive state

Marked fluctuation in patient's attention, performance of daily tasks and on cognitive testing is a further pointer to the diagnosis of DLB and represents one of the core symptoms in the operationalised clinical criteria for DLB. Fluctuating cognition is present in 45-90% of DLB cases^{21,27,28}. Attentional variability, measured on a 90-second cognitive task and EEG frequency, can be detected on a second to second basis and is more severe than in patients with VaD and AD^{29,30}. Acute confusional episodes, for which no cause is found, are observed in some cases, and can be misinterpreted as vascular episodes. Such confusional episodes may predate the clinical onset of dementia.

1.3.5. Neuroleptic sensitivity

Frequently psychotic (visual hallucinations and delusions) and behavioural symptoms present a considerable management challenge to those looking after patients with DLB. Treatment of psychotic symptoms with neuroleptics leads commonly to severe adverse reactions, in particular Parkinsonian rigidity, and the adverse effects of neuroleptics in DLB can on occasions be rapidly fatal^{28,31}. The underlying pathophysiological mechanisms seem to be twofold. Firstly, there is a 60-70% reduction of dopaminergic neurons in the substantia nigra³² with, in some cases, an associated failure to up-regulate striatal postsynaptic D₂ receptors in response to D₂ blocking drugs^{33,34}. Secondly, neurochemical studies document a profound cholinergic deficit in DLB^{35,36}. Monoaminergic / cholinergic imbalance may be responsible for the visual hallucinations and fluctuating cognitive function

characteristic of the disorder. These features could thus be exacerbated by the muscarinic receptor blocking action of standard neuroleptics³².

Clozapine, an atypical neuroleptic, with its low affinity for D₂ receptors, but high affinity for D₄, 5HT₂ and muscarinic receptors subtypes, has been found to be effective in the treatment of psychotic symptoms and behavioural disturbance in patients with Parkinson's disease³⁷. The haematological monitoring required is however cumbersome and this drug has not been sufficiently evaluated in DLB. The only published case report describes two DLB patients who were intolerant of clozapine (both cases had increased confusion and behavioural disturbance but no extrapyramidal side effects³⁸). Response of DLB patients to risperidone (another atypical neuroleptic which displays a dual D₂ and 5HT₂ receptor antagonism but is devoid of anticholinergic activity) has not been uniformly convincing. Whereas Lee et al³⁹ and Allen et al⁴⁰ reported a favourable response with 0.5-5 mg risperidone a day, McKeith et al⁴¹ reported severe extrapyramidal side effects in DLB patients on risperidone 1mg daily.

Olanzapine, which was licensed in UK in the October 1996, possesses selective receptor affinities for mesolimbic rather than nigrostriatal D₁, D₂ and D₄ receptors. As a result it is relatively free of extrapyramidal side effects as has been shown in a study of younger patients (18-65 years) with schizophrenia, in which significantly fewer olanzapine-treated than risperidone -treated patients experienced parkinsonian symptoms⁴². Olanzapine has high affinity for serotonin (5HT)_{2A},

5HT_{2C}, 5HT₃, α_1 -adrenergic, histamine H₁ and five muscarinic receptors subtypes⁴³.

Olanzapine was found in an open label study to be an effective and well tolerated treatment for psychosis in non-demented patients with Parkinson's disease⁴⁴.

However, in a case series of DLB patients treated with small doses of olanzapine⁴⁵, responses to treatment were disappointing, considering its selective affinity for mesolimbic pathways and its theoretical advantage over more conventional neuroleptics. This may be explained by the high dopamine receptor occupancy by even low doses of olanzapine in DLB patients whose dopaminergic systems are already severely depleted. The worsening of confusion and psychosis observed in this cohort may be intrinsic to DLB but on the other hand may be due to the strong muscarinic receptor affinity of olanzapine. Overall, 37.5% of patients experienced significant worsening of their symptoms (neuroleptic sensitivity) on olanzapine. This figure is similar to the 39% reported by Ballard et al³¹ in response to a range of neuroleptics in DLB patients, and to the original reports of 57% neuroleptic sensitivity rates in DLB cases coming to autopsy^{28,46}. The more recently introduced neuroleptic quetiapine has not been evaluated in DLB, but has been tried successfully in patients with PD and dementia and is theoretically superior as it has less extrapyramidal side effects than other atypical neuroleptics and weak anticholinergic effect.

1.3.6. Pattern of cognitive deficit

There is evidence that the pattern of cognitive deficits in patients with DLB is different from that in patients with AD and PD who later develop cognitive

impairment. Overall, patients with “pure” DLB (not fulfilling AD pathological criteria) are less severely demented than patients with “common” DLB (also fulfilling AD criteria; ⁴⁷) ⁴⁸. DLB patients perform worse on tests of attention, frontal lobe function and visuoperceptive tasks than AD patients, but better on tests of episodic memory ^{14,49-51}. These differences between DLB and AD patients can be detected even with standard cognitive test batteries e.g. CAMCOG ^{52,53}. Two recent studies ^{54,55} provide a more detailed comparison of the neuropsychological profile of the two disorders. In the first study Calderon et al ⁵⁵ compared 10 DLB patients with 9 AD patients and 17 controls on a number of tests designed to assess working, episodic, and semantic memory, and visuoperceptual and attentional functions. Semantic memory was equally affected in DLB and AD patients. Both groups had episodic memory deficits but the episodic memory defect was more severe in the AD group where patients could only recall 4% of stories after 30 minutes, compared to the DLB patients who could recall 28% and controls who could recall 78% of stories. The most striking differences were on tests of visuoperceptual/spatial ability and attention. DLB patients performed uniformly poorly on all tests of attention (with deficit on tests of sustained, selective and divided attention), whereas AD patients performed normally on sustained attention. The study by Lambon Ralph et al ⁵⁴, in addition to summarising the results of previous published studies, made more detail comparison of 10 DLB patients with 10 AD patients and 15 normal controls on tests of semantic memory. Both groups had impairment of semantic memory but the DLB patients had a more severe semantic memory deficit for pictures than words.

Differences have also been found in the neuropsychological impairment of DLB patients and patients with PD and dementia. Downes et al ⁵⁶ compared DLB patients with advanced PD patients who were matched for age, and verbal and performance premorbid and current cognitive state. They showed differences in performance of frontally mediated tasks, with the DLB group performing worse than the advanced PD group in tests of fluency and the Stroop test. They proposed that this was due to cortical as opposed to striatal pathology being more prevalent in DLB than in PD.

1.3.7. Other features

Both the "pure" and "common" forms of DLB occur more frequently in men, the male:female ratio being about 3:2 ⁵⁷. There is some indication that the average age of onset is earlier in DLB than in AD ^{20,57,58}. Patients with DLB tend to develop urinary incontinence at a earlier stage of cognitive impairment than patients with AD ⁵⁸. Anosmia occurs more frequently in DLB than AD ⁵⁹.

Rapid eye movement (REM) sleep behavioural disorder (RBD) is now recognised as a feature of DLB ⁶⁰⁻⁶² as well as other rigid-akinetic syndromes. Awareness of the presence of this symptom in patients with DLB is important and treatment with low dose clonazepam or a cholinesterase inhibitor may help.

There is also some preliminary evidence that patients with DLB have a high prevalence of neurocardiovascular instability⁶³, and that cholinesterase inhibitors could make this worse.

1.4 PROGNOSIS

There is continuing uncertainty about the duration of illness. The majority of information available on the prognosis of DLB is based on retrospective data from autopsy series. Although autopsy series provide the definitive diagnosis they are subject to selection bias due to the type of patients referred for post-mortem studies (e.g. younger age, atypical features, diagnostic uncertainty, patients preselected for other disease studies). The review by Lennox⁶⁴ reported that the mean duration of survival from onset of symptoms of DLB is approximately 6 years. McKeith⁶⁵ and Kalra et al¹⁵ in subsequent reviews stated that DLB survival from presentation was between 2 and 6.4 years. McKeith⁶⁵ also postulated that there may be a difference between the early onset DLB with rapid decline and parkinsonian presentation in predominantly male subjects and the more commonly occurring later onset disease with more frequent concomitant Alzheimer's type pathology. In a further review, Cercy and Bylsma⁵⁷ performed a meta-analysis of 150 cases of DLB reported in the literature and found that the mean duration of illness was 6.1 years. When looking at case series of "pure" DLB patients (no or minimal concomitant AD pathology at autopsy) Lippa et al⁶⁶ found that the mean age at onset of illness in their 5 cases was 50 years, with a mean duration of illness of 5 years. Hely et al¹⁸, in a series of nine cases, found that the mean age at onset of illness was 61.7

years and that the mean duration of illness was 8.6 years. However Gomez-Tortosa et al ⁶⁷ reported in their 13 “pure” DLB cases a mean age at onset of 68 years and duration of illness 10 years.

Looking at individual studies of neuropathologically defined cases with mixed pathology (DLB with variable degrees of concomitant AD pathology), the mean age at onset of illness in different cohorts varied between 59 and 79 years and the duration of illness ranged from 1.8 to 9.5 years. The wide range, both of age at onset and duration of illness, highlights the difficulty of drawing conclusions from pre-selected samples.

The earlier studies comparing DLB patients with patients with AD suggest that the mean duration of illness is shorter in DLB patients than in patients with AD ^{28,66,68}. However more recent studies have not found a significant difference between DLB and AD in mean age of onset, mean age at death or mean duration of illness ^{20,69-73}. One explanation for this could be the observation by McKeith et al ²⁸ that patients with DLB are particularly sensitive to antipsychotic medication and that administration of antipsychotics leads to subsequent rapid decline and death. Greater awareness of this in recent years might be contributing to increased survival. However McShane et al ⁷⁴ found an association between cognitive decline and the use of typical antipsychotic medication in all demented patients, regardless of diagnosis. Post mortem confirmed cortical Lewy body pathology in

their series did not make a significant contribution to a more rapid decline, although the numbers in this group were small (n=7).

1.5 DIAGNOSTIC CRITERIA

Originally two sets of operational criteria for DLB were proposed independently: the McKeith criteria, which put emphasis on the neuropsychiatric presentation ⁴⁶ and the Byrne criteria, which were somewhat more restrictive and relied predominantly on parkinsonian features ⁷⁵. In 1995 at a meeting in Newcastle a Consortium on dementia with Lewy bodies established "Consensus clinical and pathological criteria for DLB" ⁷⁶, Appendix 1.1.

1.5.1. Retrospective studies

There are only limited prospective data on the accuracy of these criteria. However, there are a number of studies that have retrospectively applied the Consensus criteria to histopathologically confirmed cases of DLB. Mega et al ⁷⁷ in a retrospective chart review found that the sensitivity and specificity of the consensus criteria was fairly good – 75% and 79%. They also showed that if the criteria were changed to require the presence of extrapyramidal signs (somewhat similar to the original Byrne criteria), the clinical specificity would increase to 100%. Mega et al also showed that the most difficult feature to correctly identify was fluctuations. They suggested defining "fluctuation" as a change of 5 or more points on a Mini Mental State Examination ⁷⁸ between three measurements within six months. Holmes et al ⁷⁹ showed that in their sample of 80 patients with dementia a

high specificity (100%) was associated with very low sensitivity (22%). They considered that this was due to a low prevalence of DLB (11.2%) in their sample and a high percentage (34%) of mixed pathologies. Lopez et al ⁸⁰ also found that the sensitivity of the Consensus criteria was low (34%) and that the specificity was high (94%). However the clinical data were abstracted from the records of the first visit and the sample (n=40) contained only 8 patients with DLB. Verghese et al ⁸¹ in a larger cohort of 18 DLB patients and 76 patients with other dementia showed that the Consensus criteria for probable DLB (any two core features) had a sensitivity of 61% and a specificity of 84%. If all three core features were present the specificity went up to 99% but the sensitivity dropped to 28%. Not surprisingly when only one core feature had to be present to make a diagnosis of DLB, the sensitivity became very good 89%, but the specificity was only 28%. When “common” type cases were excluded, the sensitivity of the Consensus criteria for “pure” type went up to 78% and the specificity continued to be good 85%. Similar conclusions were reached by Luis et al ⁸² who found a specificity of 90% and sensitivity of 57%, and by Gomez-Isla et al ⁷² who also found that when Consensus criteria were applied to data from the first visit they had a good specificity of 83% and moderate sensitivity of 53%, but if data were taken from all clinical assessments the sensitivity went up to 90% but the specificity went down to 68%. Contrary to the above studies Papka et al ⁸³ found the consensus criteria to have fairly good sensitivity (89%) but very low specificity (29%).

1.5.2. Prospective studies

Thus far there are only a few prospective studies. During the first three years of a study by McKeith et al ⁸⁴, 63 patients died of whom 50 had autopsies. At autopsy there were 29 cases of DLB, 5 cases of VaD, 15 cases of AD and one case of atypical progressive supranuclear palsy. The sensitivity of the Consensus criteria for DLB was 83% and the specificity was 95%. As in other studies patients with the “common” type of DLB were more difficult to diagnose than “pure” cases of DLB. Lopez et al ⁸⁵ studied a large prospective cohort of patients with dementia between 1997 and 2000. Of the 26 patients who came to autopsy, 3 had pure DLB and 10 cases had common DLB (both AD pathology and Lewy bodies). Surprisingly, only 4 out of the 13 cases with Lewy body pathology had been diagnosed clinically as having probable or possible DLB. When clinical diagnosis was compared with neuropathological diagnosis, the specificity of the Consensus criteria was excellent (100%) but the sensitivity was low (30.7%). In contrast, Hohl et al ⁸⁶ examined at post-mortem ten patients with a clinical diagnosis of probable DLB according to Consensus criteria. The clinical diagnostic accuracy was found to be 50%. Of the five misdiagnosed cases, four had AD. There were fewer hallucinations in this group and more spontaneous extrapyramidal signs. The authors concluded that the distinction between DLB and AD would be made more readily by emphasizing hallucinations rather than parkinsonian signs. The main conclusion that one can make from the above studies is that the Consensus criteria perform fairly well, particularly in specialised centres with an interest in DLB, and certainly no worse

than diagnostic criteria for AD ^{87,88} or PD ⁸⁹, but nevertheless at least 15-20 % of patients will continue to be misclassified.

1.6 CLINICAL INVESTIGATIONS

There is general agreement that the initial assessment of a dementia syndrome should comprise history, physical examination, mental state examination and basic neuropsychological testing. However, there continues to be debate about the value of additional investigations in the management of dementia syndromes. There are three questions that need to be answered:

- will further investigations help to identify reversible causes of dementia
- will they increase the diagnostic accuracy of different dementia subtypes
- and will they alter the further management of the patient.

1.6.1. Dementia blood screen

At present there is no specific marker for DLB. Most clinicians agree that laboratory blood tests are relatively inexpensive and that the cost is justified in every patient with dementia syndrome. Chui & Zhang ⁹⁰ showed that the addition of laboratory tests to the evaluation of dementia changed the diagnosis in 9% and the management in 12.6% of cases. In DLB, dementia blood screen is unremarkable and, as in AD, is performed mainly to exclude other conditions and contributing factors.

1.6.2. Structural and functional imaging of the brain

The routine use of brain imaging remains more contentious. It is discussed in detail in chapters 2 and 3.

1.6.3. EEG

Occasionally other tests are indicated as part of a DLB assessment. Briel et al ⁹¹ observed that electroencephalography (EEG) records of autopsy diagnosed patients with DLB show a greater tendency towards slowing of both dominant (alpha activity) and non-dominant rhythms. In the same study, DLB patients were found to have slow wave transient activity which correlated with a clinical history of loss of consciousness. Barber et al ⁹² compared EEG records of 18 consecutive clinically diagnosed DLB patients and 20 AD patients and found that the EEG was slow in both groups and could not separate the two groups. However, EEG may be a valuable investigation in differentiating DLB from FTD where it remains normal even in more advanced disease. EEG is also helpful in excluding non-convulsive status epilepticus as a complication of dementia. EEG helps in the diagnosis of Creutzfeldt-Jakob disease.

1.6.4. Cerebrospinal fluid analysis / brain biopsy

Lumbar puncture for cerebrospinal fluid analysis is performed very rarely. The main indication is a suspicion of primary central nervous system vasculitis or a paraneoplastic syndrome. In exceptional circumstances, where a treatable cause of

dementia is suspected (e.g. primary CNS vasculitis), a brain biopsy may be performed.

1.7 GENETICS

Familial cases of DLB are rare. Some are due to mutations of the alpha-synuclein gene (A53T, A30P) which are almost fully penetrant. However most families with several members affected by PD or DLB do not have a alpha-synuclein gene disorder. Two other loci have been reported: the first on chromosome 2p and the second on chromosome 4p, both having only about 50% penetrance ⁹³. The reason for incomplete penetrance is thought to be due to the loss of nigral neurones not reaching the critical threshold (less than 70%) to give rise to parkinsonian symptoms and signs. As in AD the frequency of apolipoprotein E4 alleles is increased in DLB ⁹⁴. However cases of DLB with no AD pathology (pure DLB) have an apolipoprotein E4 frequency similar to controls and patients with PD ^{95,96}.

1.8 MANAGEMENT

Patients with DLB are frequently difficult to manage. The combination of psychotic symptoms, extrapyramidal signs with frequent falls and hypersensitivity to all types of antipsychotics makes therapeutic options very limited ⁹⁷. Antidepressants or small doses of benzodiazepines are sometimes helpful in moderating behavioural disturbance but tend to do little for alleviation of psychotic symptoms. A small dose of clonazepam may help sleep disturbance. The main emphasis, when managing DLB patients, has to be on adjustment of environment, support and education of

carers, good nursing skills and other non-pharmacological measures such as supportive psychotherapy, and reminiscence, validation and recreational therapy. However, there is now increasing evidence from uncontrolled case reports and studies, that cholinesterase inhibitors have not only a beneficial effect on the cognitive function of patients with DLB but also on the psychotic and the behavioural symptoms^{98,99 100,101}. A two year audit of cholinesterase inhibitors in West Essex showed that there was no significant difference in response rate to cholinesterase inhibitors (donepezil, rivastigmine), as measured by MMSE, between patients with AD and DLB who were still taking treatment at one, one and half and two years (personal data, see Table 1.1).

The first, randomised, double blind, controlled study of a cholinesterase inhibitor in DLB has now been published. In this study 120 patients who exhibited the characteristics of probable DLB were randomised to rivastigmine or placebo and followed for 20 weeks at 18 centers in the UK, Italy and Spain (13 of the 120 patients were randomized in our centre). The primary efficacy variables in the study were behaviour and cognition. Behaviour was measured by the change from baseline on the Neuropsychiatric Inventory (NPI)¹⁰² and cognition was assessed by a change in reaction times using the Cognitive Drug Research (CDR) computerized test battery. The average sum of reaction times (in particular performance on tasks with a substantial attentional component) was significantly superior for patients receiving rivastigmine compared with placebo. More than 60 percent of patients treated with rivastigmine experienced clinically significant improvement in

behavioral symptoms (30 percent improvement of pre-treatment symptom severity) on the NPI. In contrast, only 30 percent of patients treated with placebo showed similar benefit ¹⁰³.

1.9 DIFFERENTIAL DIAGNOSIS OF DLB

There are two main questions that have to be answered when assessing a patient with a "dementia syndrome ":

- Is this a true dementia, defined as cognitive impairment in multiple domains with intact arousal and in the majority of cases non-treatable and progressive, or is this another, possibly treatable, condition mimicking a dementing illness (e.g. depressive pseudodementia, delirium)?
- Given that it is a dementia, which type is it?

The difficulty is that a definitive diagnoses for most cases of neurodegenerative dementia, including AD, FTD and DLB, can only be made at autopsy. Even then a fair proportion of patients are found to have mixed pathologies ⁷⁹. To complicate matters further, there remain unresolved issues about the pathological classification of all the main dementias. The two conditions that most frequently overlap with DLB are AD and vascular dementia (VaD).

There are a number of reasons why it is important to separate DLB from other conditions during life:

- Patients with DLB warrant different management of their cognitive fluctuation, psychotic symptoms and parkinsonian features ¹⁰⁴.

- They have a worse prognosis, particularly if given conventional neuroleptics.
- They may be erroneously included in AD treatment trials.

1.9.1. Depressive pseudodementia

The commonest reversible “dementia syndrome” that needs to be excluded when considering DLB is severe depressive illness with associated cognitive impairment - pseudodementia. Despite some controversy about the term pseudodementia, in clinical practice it succinctly communicates that the “dementia syndrome” is not due to a degenerative brain disorder but that it is part of a depressive illness and that vigorous treatment of depression is indicated ¹⁰⁵. The features that favour depressive cognitive impairment are: complaints by the patient themselves that their memory and concentration is poor, a relatively short history and the patient's ability to date accurately the onset of symptoms. Depressed patients may deny that they are depressed but their whole outlook tends to be negative with no hope or interest in the future, lack of enjoyment, regrets and self blame and diminished initiative to socialise. Conversation and in particular formal cognitive testing is an effort and “don't know” answers are more likely than mistakes. Other features pointing to depression are disturbed sleep, poor appetite, low energy and pessimistic thoughts. There may be a past personal or family history of depression. On cognitive testing there is poor concentration and memory but with repeated trials there is clear improvement on memory tasks, if the patient can be persuaded to cooperate. Compared to true dementia, speech is slow and scanty but nominal dysphasia is unusual. To further complicate the situation patients with DLB have a

very high prevalence of depressive symptoms, even higher than patients with AD^{23,83}. It is sometimes impossible to differentiate depressive pseudodementia from dementia with depressive symptoms on initial assessment and a therapeutic trial with an antidepressant and / or ECT with a longitudinal follow-up is usually helpful. One further caveat is that there is evidence that despite the initial reversibility of cognitive impairment a higher than expected proportion of patients with depressive pseudodementia go on to develop true dementia¹⁰⁶.

1.9.2. Delirium

Another reversible "dementia syndrome" that causes particular diagnostic difficulty in distinguishing it from DLB is delirium. Delirium is now the accepted term for what used to be called "acute confusional state". It is defined as an acute, transient, global, organic disorder of higher nervous system function involving impaired consciousness and attention. Delirium carries a significant mortality rate, particularly in the elderly¹⁰⁷. It is one of the most frequently missed diagnoses in the elderly, patients with delirium being misdiagnosed as having dementia and therefore missing out on appropriate treatment¹⁰⁸. However, pre-existing dementia, with advanced age, is one of the main risk factors for delirium, highlighting the difficulty of distinguishing the two conditions. Delirium is the result of a primary cerebral disorder or a cerebral involvement secondary to a systemic illness

The main clinical symptoms are acute onset, impaired consciousness, reduced ability to maintain attention, disorganised thinking and impairment of memory, in

particular, registration and retention of new material. Perceptual distortions, leading to misidentification, illusions and hallucinations and disturbed sleep-wake cycle are also common. Other symptoms include mood changes and a tendency to fluctuation with occasional lucid period ¹⁰⁹. A history from an informant is critical in making the diagnosis. The speed of onset of symptoms (hours, days compared to weeks, months) is one of the main clues to the diagnosis of delirium. DLB patients also experience marked fluctuations in mental state and they may manifest delirium for which no clear organic cause is found; the fluctuations in mental state and the delirium are perceived to be part of the typical symptomatology of DLB. In DLB episodes of delirium can precede cognitive impairment (personal observation). Therefore, the differential diagnosis can be at times very difficult. In all cases the cause of delirium has to be actively sought and, if found, treated. When all efforts fail, with time and hindsight, in the presence of other features of DLB, the diagnosis of delirium as part of DLB symptomatology can be made.

1.9.3. Alzheimer's disease

DLB is one of the main differential diagnoses of Alzheimer's disease. In autopsy series of patients clinically diagnosed as having AD, about 20% are found to have DLB pathology. The difficulty is that although fluctuation, hallucinations and extrapyramidal signs all point toward the diagnosis of DLB, they have all been encountered in patients with AD, albeit not as frequently and usually at a relatively later stage in the illness ¹¹⁰. This is well illustrated in a large prospective cohort of neuropathologically diagnosed patients with AD and DLB, where visual

hallucinations were present in 65% of DLB but also in 25% of AD patients at presentation and in 73% of DLB and 37.5% of AD at any stage of dementia ²³. Although extrapyramidal signs at presentation in AD are not particularly common, 5% compared to 41% in DLB ²⁰, such symptoms (with the exception of tremor) progress more rapidly, as shown in a longitudinal study of 410 patients with AD by Wilson et al ¹¹¹. On the other hand, some patients with DLB at presentation have none of the core features of DLB. The lack of visual hallucinations and extrapyramidal features, with additional vascular pathology were the main reason for misdiagnosing DLB as other dementias (AD & VaD) in the most recently published prospective study by McKeith et al ⁸⁴. The majority of patients with DLB also fulfill the NINCDS-ADRDA criteria for probable AD.

1.9.4. Vascular dementia

The distinction in life between DLB and vascular dementia (VaD) is frequently difficult. Stepwise deterioration can be misinterpreted as fluctuating cognitive state. On the other hand the striking features of marked fluctuations in cognitive performance and episodic loss of awareness in DLB can be easily misinterpreted as vascular phenomena. However, the periodicity of fluctuating cognition is different in DLB and VaD cases. In DLB, the fluctuation occurs more on a second to second basis; in VaD the fluctuation is less evident over very short periods ²⁹. An MRI scan showing periventricular and white matter hyperintensities can then erroneously support a diagnosis of VaD.

VaD is a broad term that refers to any dementia resulting from cerebral blood vessel disease. This includes multiple infarcts, strategically placed isolated infarcts, multiple subcortical lacunar infarcts, single or multiple haemorrhagic cerebral lesions, genetically determined arteriopathies and combined pathologies of AD and infarcts ¹¹². The clinical course and the symptoms of VaD vary greatly according to the sites of ischaemia (or haemorrhage) and the type of underlying cerebrovascular disease (CVD). Traditionally, patients with VaD have evidence of focal and non-localising neurological signs attributable to CVD (e.g. dysphasia, dysarthria, hemiparesis, extensor plantar responses and a wide-based small step gait), stroke risk factors, a history of abrupt onset, stepwise deterioration and a fluctuating course of illness. Vascular lesions are identified by neuroimaging either as single strategic usually cortical infarcts or multiple infarcts which may be cortical or subcortical. Hypodensities on CT scan in white matter or hyperintensities in white matter on T2 weighted MRI are not easy to interpret and are not very good predictors of VaD, since they are also associated with normal ageing, and with other dementias including AD and DLB ¹¹³. On neuropsychological testing patients with VaD have a more patchy cognitive deficit and a better preserved insight and personality.

1.9.5. Other differential diagnoses

Other differential diagnoses that have to be considered are conditions that present with a mixture of movement disorder and dementia or psychiatric symptomatology e.g.: Steele-Richardson-Olszewski disease, corticobasal degeneration, cortical

variant of motor neuron disease and fronto-temporal dementia with Parkinsonism. Variant Creutzfeldt-Jakob disease (vCJD) was first identified in UK in 1996. Until a recent report by Lorains et al ¹¹⁴ all the reported cases were young with the average age at death of 29 and the oldest patient being 54 years. Since Lorains and colleagues described vCJD in a 74 years old man with no relevant psychiatric or family history, who presented with visual hallucinations and delusions, unexplained pains, progressive cognitive impairment and later with unsteadiness and falls, and rapid decline leading to death, variant Creutzfeldt-Jakob disease has to be also considered.

1.9.6. Parkinson's disease

The last group of patient that might cause diagnostic difficulty is patients that start with a typical levodopa responsive PD and then many years later develop dementia. Although histopathologically the majority are indistinguishable from DLB, clinically there is a clear difference. The classical signs of PD are tremor, rigidity and akinesia. Characteristically the symptoms and signs at presentation are asymmetrical and patients have a good response to levodopa. Progression of symptoms is gradual but slower in patients with early onset. Louis et al ²⁵ compared the motor system features of 31 histopathologically confirmed cases of DLB and 34 cases of PD and found that rest tremor was more common in PD (85%) than DLB (55%) and myoclonus was more common in DLB (18.5%) than PD (0%), but that there was no difference in rigidity, bradykinesia or dystonia. A diagnosis of DLB was made much more likely by the presence of any one of the following clinical

features: myoclonus, absence of rest tremor, no response to levodopa or no perceived need to treat with levodopa.

As in DLB the gold standard for diagnosis of PD is histopathological examination of the brain. In an autopsy series of 100 patients with PD the accuracy of clinical diagnosis was 76% ⁸⁹. Of the 24 patients with other diagnoses, six patients had progressive supranuclear palsy, five had multiple system atrophy, three had AD, three had AD type pathology, three had VaD, two had isolated nigral atrophy with no Lewy bodies, and one had postencephalitic parkinsonism. In one case there was no pathology. The unexpected finding that six out of the 24 cases of misdiagnosis had AD pathology highlights the fact that a clinical distinction is not always successfully made between AD and PD. In the PD cases there is a positive correlation between the severity of nigral cell loss and both the disease duration and the severity of parkinsonism. This is in contrast to a study by Ala et al^{26,115} who found no correlation between substantia nigra degeneration and parkinsonian signs at presentation in patients with DLB.

Parkinson's disease is characterised by selective degeneration of pigmented neurones in the bilateral basal ganglion nuclei called the substantia nigra and of their axons which project to the striatum via the nigrostriatal pathway. The affected neurones use dopamine as their neurotransmitter ¹¹⁶. Compared with the loss of SN pigmented neurones in normal ageing, where the ventrolateral tier is relatively spared, in PD the earliest and greatest loss is in the ventrolateral tier. This regional

selectivity is most marked in early onset PD. This corresponds to a more profound dopamine deficit in posterior putamen than the caudate nucleus of the striatum and is in line with the observation that younger onset cases have mainly motor dysfunction and that age, severity and duration of PD is the main risk factor for psychiatric and cognitive symptoms ^{117,118}. Other neurotransmitters that are affected in PD are the noradrenergic (locus coeruleus), cholinergic (nucleus basalis of Meynert) and the serotonergic (dorsal raphe nuclei) systems. As already mentioned, loss of nigrostriatal neurones in PD patients leads not only to reduction of striatal dopamine, but also to a reduction of pre-synaptic uptake sites. In addition, in the striatum post-synaptic D₂ receptors are upregulated ¹¹⁹.

Patients with PD already have subtle cognitive deficits in the early stages of their illness, and possibly even sub clinically ¹²⁰. The abnormalities are mainly in executive functioning and attentional set shifting. The effect of dopaminergic and anticholinergic therapy on cognitive performance has been studied by Cooper et al ¹²¹. The authors showed that dopaminergic therapy produced improvement on tasks dependent on working memory and cognitive sequencing, but not on any other cognitive measures. Anticholinergic therapy had a detrimental effect on several aspects of memory, in particular on immediate recall of information. About 40% of patient with PD go on to develop dementia. When comparing the neuropsychological performance of PD patients with dementia and AD patients matched for age, sex and mini mental state examination score, the neuropsychological differences were limited to worse performance on tests of

visual reasoning and less severe anosognosia (lack of concern) and disinhibition in PD patients. There were no differences on tests of memory and language between the two groups ¹²².

1.10 HISTOPATHOLOGY

The characteristic markers of DLB are Lewy bodies (LB). LB are eosinophilic intranuclear inclusions surrounded by a pale halo. They are present in the brainstem and subcortical regions where they are readily identified by haematoxylin and eosin staining. LB are also present in the cortex, where they are less well defined, being slightly smaller, less round and lacking a well developed halo. Cortical LB are best detected by immunohistochemical staining techniques for ubiquitin and alpha-synuclein. The density is highest in the substantia nigra, followed by entorhinal cortex, cingulate gyrus, insula, frontal cortex, hippocampus and occipital cortex ⁶⁷. Cases are divided according to relative distribution of LB into three categories: brainstem predominant DLB, limbic (transitional) DLB and neocortical DLB ⁷⁶. Other histopathological features are Lewy related neurites, which are probably more relevant for symptom formation than the relatively sparse LB ¹⁰⁴, plaques (mainly diffuse, age related), loss of neurones in the brain stem and nucleus basalis of Meynert, spongiform changes and synapse loss ¹²³. A substantial percentage of DLB cases also have neurofibrillary tangles or neuropil threads which are characteristic of AD. There is no correlation between the density of neurofibrillary tangles or neuritic plaques and LB ⁶⁷. There are relatively few tangles in the hippocampus and parahippocampal cortex and the overall frequency

is bimodal: either frequent, or few to absent ¹²⁴. Depending on the pathological criteria used for AD, a different proportion of cases can be assigned to a "pure" type DLB (not fulfilling AD pathological criteria) or a "common" type DLB (also fulfilling AD criteria; ⁴⁷). In a third of cases of DLB there is also a significant vascular pathology ⁷⁹. Histopathologically cases of DLB are indistinguishable from PD as most PD brains have some cortical LB regardless of whether dementia was present or not.

1.11 NEUROCHEMICAL PATHOLOGY

Acetylcholine is one of the most important neurotransmitters in the brain. The enzyme necessary for the synthesis of acetylcholine is choline acetyltransferase. The acetylcholine molecule is inactivated by acetylcholinesterase which is produced in the cholinergic cell body and is transported to the synapses by slow axonal transport. In DLB the main neurochemical disturbance is a reduction in cortical pre-synaptic choline acetyltransferase with the concomitant reduction in acetylcholine. The cholinergic deficit is even more severe than that in AD, with choline acetyltransferase being 50% lower in DLB than in AD in the midfrontal cortex and similar to that for AD in the hippocampus ^{36,96}. Loss of choline acetyltransferase is thought to be most pronounced in patients with hallucinations, being down to 20% of normal, compared to 50% of normal in non-hallucinating cases ^{32,35}. In contrast to AD, where a clear relationship between choline acetyltransferase deficit and cognitive impairment has been established, the situation in DLB is more controversial. Perry et al ³⁵ reported a strong correlation

between choline acetyltransferase activity and cognitive deficit before death but no such relationship was observed between the last cognitive assessment in DLB and the level of choline acetyltransferase activity or synaptic density in a more recent report by Sabbagh et al ¹²⁵. Hansen et al ¹²⁶, showed that neocortical synaptic density, measured by synaptophysin, was significantly lower in midfrontal cortex in “common” type DLB and AD but not significantly altered in “pure” type DLB or nondemented PD. It is very likely that the mechanism of cognitive impairment is complex and that acetylcholine deficit is only one of the factors that contribute to it. Although there is a clear difference in the cholinergic metabolism between AD and DLB, the difference is not so great (there is a reduction in acetylcholine in both conditions) and it would be technically difficult to differentiate the two conditions. A more fruitful pathway of differentiating DLB from AD is to look at dopaminergic activity which is the second most striking neurochemical change in DLB.

Piggott et al ¹¹⁹ studied brains post-mortem from PD, DLB, AD and elderly controls and showed that in DLB there is 72% reduction in dopamine concentration in the putamen. This compares with 90% reduction in PD and no change in AD. DLB cases also had reduced binding to the dopamine uptake sites (pre-synaptic receptors) in the putamen (57%), but again this was not as severe as in PD (75%). There was no change in uptake sites in AD compared to controls. Interestingly post-synaptic D₂ receptor binding was reduced in DLB, but elevated in PD. The AD cases were no different from the controls. As already mentioned in section 1.3.4. the failure to upregulate post-synaptic D₂ receptors in response to loss of dopamine

and to D₂ blocking drugs is the likely mechanism of the neuroleptic sensitivity which is such a feature of DLB ³⁴.

In summary, DLB is increasingly recognised as a distinctive clinical and pathological entity despite its overlap clinically and pathologically with both AD and PD. The purpose of this thesis is to investigate the pre- and post-synaptic components of the striatal dopaminergic system of clinically diagnosed DLB patients with single photon emission tomography and compare them with patients with AD, patients with PD and healthy controls. Prior to setting the objectives of the thesis, structural and functional neuroimaging in dementia, DLB and PD will be reviewed in the next three chapters.

Appendix 1.1 Consensus criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies.

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| <p>1. The central feature required for a diagnosis of dementia with Lewy bodies (DLB) is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessary occur in the early stages but is usually evident with progression. Deficit on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.</p> |
| <p>2. Two of the following core features are essential for a diagnosis of probable DLB, one is essential for possible DLB.</p> <ul style="list-style-type: none">• Fluctuating cognition with pronounced variations in attention and alertness.• Recurrent visual hallucinations which are typical well formed and detailed• Spontaneous motor features of parkinsonism. |
| <p>3. Features supportive of the diagnosis</p> <ul style="list-style-type: none">• Repeated falls• Syncope• Transient loss of consciousness• Neuroleptic sensitivity• Systematised delusions• Hallucinations in other modalities |
| <p>4. A diagnosis of DLB is less likely in the presence of:</p> <ul style="list-style-type: none">• Stroke disease, evident as focal neurological signs or on brain imaging• Evidence on physical examination and investigation of any physical illness, or other brain disorder, sufficient to account for the clinical picture. |

TABLE 1.1. Data from a two year audit of cholinesterase inhibitors in West Essex; comparison of Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), difference on Mini Mental state Examination (MMSE) score from baseline.

	AD (number of patients)	DLB (number of patients)	Significance
Baseline score	19.3 (154)	18.5 (29)	p=ns
3 months mean difference in MMSE	1.4 (84)	1.4 (14)	p=ns
6 months mean difference in MMSE	1.0 (64)	2.2 (16)	p=ns
12 months mean difference in MMSE	-0.9 (46)	0.2 (13)	p=ns
18 months mean difference in MMSE	-1.7 (25)	-1.2 (5)	p=ns
24 months mean difference in MMSE	-1.5 (25)	-2.4 (5)	p=ns

Chapter 2

CT and MRI imaging in dementia

2.1 INTRODUCTION

The most commonly used imaging techniques in the diagnosis of dementia are magnetic resonance imaging (MRI) and computed tomography (CT) brain scans. MRI is superior to CT in number of physical and technical aspects and is the preferred investigation in dementia but not all clinicians have access to MRI and it is more expensive than CT. CT scans are less claustrophobic and therefore better tolerated by demented patients. The main aim of structural imaging is to exclude other intracranial pathology e.g. primary brain tumors, secondaries, chronic subdural haematomas, infarcts and hydrocephalus. Structural neuroimaging helps to differentiate AD and DLB from VaD where the combination of ischaemic lesions on CT / MRI scan, in conjunction with a history of abrupt onset or stepwise deterioration, favour vascular pathology. It is also helpful in supporting the diagnosis of fronto-temporal dementia where it shows preferential fronto-temporal atrophy.

2.2 CT AND MRI IMAGING IN AD

There are three types of change that can be identified on CT / MRI scans in patients with AD. These are generalised cortical atrophy, focal (hippocampal, temporal lobe) atrophy and white matter changes. Serial measurements of the hippocampal and medial temporal lobe atrophy have the most diagnostic power.

Medial temporal lobe atrophy assessed by temporal lobe oriented CT scans can improve diagnostic accuracy of AD to around 90% ¹²⁷. Although radiological evidence of hippocampal atrophy on CT or MRI scan supports the diagnosis of AD, there tends to be an overlap between atrophy associated with early stages of AD and atrophy associated with normal ageing. Acquisition of serial scans overcomes this difficulty as each individual patient's first scan becomes a reference point for further studies. Serial scanning with CT rather than MRI is cheaper, more available and better tolerated by most patients but it results in repeated irradiation of the brain and the lenses of the eyes. The cumulative dose of radiation to the eyes can produce lens cataracts.

Serial scanning with MRI offers substantial technical advantages by comparison with CT. Fox et al ¹²⁸ performed an automated image subtraction of two MRI brain scans performed one year apart in each of eleven patients with a clinical diagnosis of AD and eleven control subjects. The AD patients had a significantly greater mean rate of atrophy than controls (12.3 vs 0.3). There was no overlap between the two groups. In a further study the same group of researchers showed that the rate of global cerebral volume loss significantly correlated with the rate of cognitive decline and suggested that the serial MRI volume images could be used to monitor the effect of anti-dementia treatment, in particular as the rate of cerebral volume loss could discriminate between disease modifying and purely symptomatic therapies ^{129,130}.

Hippocampal volume measurements may be also a sensitive way of detecting pre-symptomatic individuals. Fox et al ¹³¹ described a longitudinal MRI study of seven asymptomatic individuals at risk of autosomal dominant familial AD. Over a three years period three at risk subjects developed symptoms. Volumetric measurements of the hippocampal formation showed that asymmetrical atrophy (>5% difference) developed in these subjects before the appearance of cognitive symptoms (while still gainfully employed and with Mini Mental State Examination scores above 28/30). Verbal and visual memory measures declined in parallel with hippocampal loss.

Further evidence that hippocampal atrophy on MRI is already present in the very early stages of AD and at a time of minimal cognitive impairment comes from De Leon et al ¹³² who showed that hippocampal atrophy was present in 78% of minimally impaired, 84% of mild and 96% of moderate to severe AD subjects. Controls showed hippocampal atrophy in 29% but there was a striking age dependence. In contrast the cognitively impaired groups showed atrophy independent of age.

Another study of interest ¹³³ followed a sample of 44 cognitively normal older adults for 3-4 years. One subject became demented and 13 cases developed mild cognitive impairment. Baseline MRI measurements of hippocampal formation size significantly predicted a decline in memory performance. These results indicate that

hippocampal atrophy may be a risk factor for accelerated memory dysfunction in normal ageing. Although hippocampal atrophy is a very sensitive marker for AD it cannot be used as an absolute diagnostic test because extensive hippocampal atrophy has been shown also in other dementias.

2.3. CT AND MRI IMAGING IN DLB

In DLB structural imaging with CT and MRI frequently shows generalised cerebral atrophy and white matter changes ¹¹³. There are a number of reports that suggest that patients with advanced DLB have less medial temporal lobe atrophy (MTA) than comparable patients with AD ^{134,135 136 137}. However, patients with mixed pathology (DLB with concurrent AD) can also have severe MTA ¹³⁸. This is in line with autopsy findings that medial temporal lobe size in pure DLB approaches normal but in common DLB is intermediate between AD and control cases ¹³⁹. A more recent work from O'Brien et al ¹⁴⁰ found that the rate of brain atrophy on serial MRIs, over a period of one year, was 1.4% for DLB, 2.0% for AD, 1.9% for VaD and 0.5% for controls, but there were no significant differences between the three dementia groups. The rate of atrophy increased with severity of dementia. They concluded that the change in serial whole brain volumes on MRI may be helpful in early diagnosis of dementia and in monitoring of progression of illness but not in differential diagnosis between the different types of dementia.

Finally despite increasing evidence that patients with DLB frequently have hypoperfusion and hypometabolism of the occipital lobes as measured by SPET and PET the two studies that measured occipital lobe volumes have not found

substantial atrophy in DLB ^{141 142}. This would suggest that functional imaging is more sensitive to pathological changes of projection neurons and neurotransmitters and that atrophy occurs only in later stages of DLB.



Chapter 3

PET and SPET imaging in dementia

3.1. METABOLIC AND PERFUSION STUDIES IN AD

Positron emission tomography (PET) and single photon emission computed tomography (SPET) are increasingly contributing to the assessment of various dementia syndromes. PET and SPET have the advantage of assessing functional changes that may precede structural brain changes. It is now well established that patients with AD frequently have a typical pattern of cerebral glucose hypometabolism in the posterior cingulate, parietal-temporal and prefrontal regions and that these levels decline over time with progression of dementia, although this pattern is not absolutely specific for AD and can be encountered in diseases other than AD. Reiman et al ¹⁴³ used PET to investigate the cerebral glucose metabolism in 11 cognitively normal apolipoprotein E4 homozygotes (91% of E4 homozygotes develop AD by the age of 80) and 22 individuals without the apolipoprotein E4 allele. They found significantly reduced rates of glucose metabolism in the posterior cingulate, parietal-temporal and prefrontal regions, as previously found in patients with AD, providing "preclinical" evidence that the apolipoprotein E4 allele is a risk factor for AD.

SPET perfusion studies show, in line with PET studies, that the most characteristic abnormality in patients with AD is a bilateral reduction of brain perfusion in the

temporo-parietal cortex. A number of studies addressed the issue of the diagnostic validity of visual evaluation of SPET in AD. They came to differing conclusions. The two studies that had autopsy as the gold standard found SPET to provide useful information in the differential diagnosis of dementia. The first study ¹⁴⁴ correctly predicted the pathological diagnosis in 93%, compared with clinical diagnosis, which was correct in only 74%. Although perfusion SPET was very beneficial in distinguishing AD from Jacob-Creutzfeldt disease and fronto-temporal dementia it did not differentiate AD from PD or DLB. A large clinico-pathological study of perfusion SPET showed that a positive SPET scan (bilateral or asymmetric temporal or parietal lobe hypoperfusion or both) raised the likelihood of autopsy proven AD to 92% ¹⁴⁵. Likewise Ishii et al ¹⁴⁶ found SPET of value in the diagnosis of AD among patients with dementia. The sensitivity of bilateral temporo-parietal perfusion defects for AD was 95%, but the specificity was only 56%, highlighting the fact that a temporo-parietal perfusion defect is not pathognomonic for AD. By contrast Bergman et al ¹⁴⁷ found the sensitivity of visually evaluated SPET to be only 29% and the specificity 80%, and thus inadequate as a useful diagnostic test for AD. Explanations for these discrepancies might include the difficulty of comparing results obtained from different cohorts, with a variety of instruments and different data processing protocols.

An important study employing the combination of a structural and a functional imaging technique and genetics is that of Lehtovirta et al ¹⁴⁸, who investigated fifty eight patients with early AD and 34 healthy controls. AD patients were further

subdivided depending on the number of apolipoprotein E4 alleles. All subjects had volumetric MRI images as well as an HMPAO SPET scan. In addition to confirming that patients with AD have reduced volumes of hippocampus and amygdala compared with controls, the main finding was that AD homozygotes for E4 allele had the most prominent volume loss in the medial temporal lobe structures. All AD patients had the typical temporo-parietal hypoperfusion but the subgroup with only one or no E4 alleles also had frontal hypoperfusion suggesting that AD patients differ depending on their apolipoprotein alleles.

One area where perfusion single photon emission tomography is particularly useful is in the diagnosis of FTD, in which condition a characteristic fronto-temporal perfusion defect is found ^{144,149-151}.

In relation to DLB the study by Vander Borgh et al ¹⁵² is of interest. The authors examined the differences in cerebral glucose metabolism between PD patients with dementia (n=9) and AD patients (n=9) and found that in addition to the typical hypoperfusion in temporo-parietal regions of AD, the PD patients with dementia showed greater metabolic reduction in the visual cortex and relatively preserved metabolism in the medial temporal cortex.

3.2. METABOLIC STUDIES IN DLB

The literature on cerebral glucose metabolism in DLB, using PET and [18F]-fluorodeoxyglucose, has been remarkably consistent. All the studies published

have shown that patients with DLB, in addition to the typical AD pattern of temporo-parietal hypometabolism, have a significant decrease in the metabolic rate in the occipital cortex compared to patients with AD. The first to observe this were Albin et al ¹⁵³ who reported on six cases of pathologically verified DLB (three “pure” and three “common” DLB) studied with [18F]fluorodeoxyglucose and PET. In addition to the typical AD pattern, the DLB cases also had hypometabolism in the occipital association cortex and primary visual cortex. The pattern and the magnitude of hypometabolism in primary visual and occipital association cortices were similar in both the “pure” and the “common” DLB patients. The same group reported later a larger autopsy confirmed cohort of 11 DLB cases (4 “pure” and 7 “common” DLB) and 10 AD (it was not stated if any of these cases were included in the previous cohort). DLB patients showed again significant metabolic reduction in the occipital cortex, particularly in the primary visual cortex which distinguished DLB patients from AD patients with a sensitivity of 90% and a specificity of 80% ¹⁵⁴. Ishii et al ¹⁵⁵ also observed lower metabolic rates in the occipital regions of DLB patients compared with AD patients.

Imamura et al ¹⁵⁶ compared the metabolic rate between 19 patients with a clinical diagnosis of DLB and 19 patients with AD. The DLB patients had a marked decrease in metabolic rate in the temporo-parieto-occipital association cortices and the cerebellar hemispheres. In contrast, the medial temporal and the cingulate metabolism were significantly lower in AD than in DLB patients. A further study by the same authors ¹⁵⁷ compared the metabolic rate of 16 DLB patients with visual

hallucinations, 6 DLB patients without hallucinations and 16 AD patients. The regional metabolism was significantly lower in both DLB groups than in the AD group in the primary visual area and the posterior temporal, parietal and lateral occipital association area. Interestingly, DLB patients with hallucinations had relatively preserved metabolism in right temporo-parietal association cortex compared to DLB patients without hallucinations. In a further paper ¹⁵⁸ the same authors reported that there was no difference in the occipital hypometabolism between DLB patients with or without parkinsonian features.

Higuchi et al ¹⁵⁹ showed that occipital glucose hypometabolism could distinguish DLB from AD patients with a sensitivity of 86% and a specificity of 91% when the cut off value was set as the mean minus 2 standard deviations of the metabolic rate of normal control subjects. Two other markers examined, the apolipoprotein E4 allele frequency and cerebrospinal fluid tau levels, did not differ significantly between the two groups, although apolipoprotein E4 allele frequency was significantly increased in both AD (41%) and DLB (43%) and so were the tau CSF levels in both dementia groups compared to previously published values in normal controls. In the same paper the authors further examined the histopathological correlates of the occipital hypometabolism in postmortem brains of 19 AD, 17 DLB patients and 11 controls. DLB patients had extensive spongiform change and coexisting gliosis throughout the cerebral white matter with relative sparing of gray matter. In parallel with the pattern of hypometabolism the most noticeable spongiform changes were found in the occipital region of DLB. Although all the

above studies strongly suggest that occipital hypometabolism as measured by PET very much points to the diagnosis of DLB, it does not always have to be present, as demonstrated by a case report by Cordery et al ¹⁶⁰, where an autopsy confirmed patient with DLB had normal occipital metabolism.

3.3. PERFUSION STUDIES IN DLB

Compared to PET, SPET perfusion studies have yielded rather more variable results. In keeping with PET studies, Ishii et al ¹⁶¹ showed that DLB patients had reduced relative cerebral blood flow to occipital lobes but higher cerebral blood flow to right medial temporal lobe than AD patients. Likewise Donnemiller et al ¹⁶² on visual inspection found occipital hypoperfusion in 6 out of 7 DLB patients and only in one out of 6 AD patients. Defebvre et al ¹⁶³ also found a difference in relative cerebral perfusion between DLB and AD, but the regions with most marked hypoperfusion were the frontal lobes and not the occipital lobes. However, the two studies with the largest numbers of patients have not found perfusion SPET useful in distinguishing AD from DLB ^{151,164}. The very impressive study by Talbot et al ¹⁵¹ examined 24 DLB patients, 58 patients with FTD, 132 AD patients and 22 patients with progressive aphasia (more recently called semantic dementia). They found that perfusion SPET was most useful in distinguishing AD from VaD and FTD, and least useful in differentiating between AD and DLB and between VaD and FTD. They concluded that the pattern of hypoperfusion measured with SPET is not specific to a single disease, but when used selectively can make valuable contribution to differential diagnoses.

Chapter 4

Functional imaging of dopaminergic pathways with PET and SPET

4.1. INTRODUCTION

Dopamine is one of the main neurotransmitters in the human brain. Dopamine neurotransmission involves a number of processes. Dopamine is synthesised from DOPA, transported into synaptic vesicles by the type 2 vesicular monoamine transporter and stored. Following depolarisation, dopamine is released from pre-synaptic vesicles into the synaptic cleft. Dopamine interacts with dopamine receptors on the post-synaptic neurone. Extracellular dopamine is then taken back into pre-synaptic dopamine terminals via the plasma membrane dopamine transporter. Any remaining extracellular dopamine is degraded by catechol O-methyltransferase.

Dopamine is the neurotransmitter of the nigro-striatal pathway, the mesolimbic-cortical bundle and the hypothalamic-pituitary pathway. Dopaminergic neurotransmission is important in the regulation and control of motor activity, motivation and cognition. Disturbance in the dopaminergic neurotransmission is thought to underlie a number of neurological and psychiatric disorders e.g. PD, Cortico-basal degeneration, progressive supranuclear palsy, Huntington's disease and schizophrenia. As discussed in Chapter 1, one of the main neurochemical deficits in DLB is the disruption of the nigro-striatal pathways due to a severe loss

of dopaminergic neurons in the substantia nigra. The lack of dopaminergic innervation in the striatum is likely to be the major factor responsible for the extrapyramidal signs in DLB, and may lead to some of the cognitive and neuropsychiatric symptoms as well. Although all patients with DLB have a clear loss of dopaminergic neurons at autopsy, at the time of presentation a proportion of cases have no parkinsonian symptoms or signs. The reason for this could be twofold. One possibility is that the degree of neuronal loss in DLB has not reached the critical level when clinical symptoms occur. Alternatively other neurotransmitter systems (e.g. acetylcholine, serotonin) might interact with the dopamine NS system such that the important factor in development of extrapyramidal signs is not the absolute deficit of dopamine but the loss of equilibrium between dopamine and other neurotransmitters. From a diagnostic point of view, it would be a great help to be able in vivo to visualise and quantify the state of the dopaminergic neurons in patients with DLB. Detection of the loss of pre-synaptic dopaminergic neurons and changes in post-synaptic D₂ receptors would not only facilitate the distinction of DLB from AD, where changes in dopaminergic pathways are minimal, but would also give us additional information regarding the relationship between the motor and the neuropsychiatric symptoms and dopaminergic disruption.

Positron emission tomography (PET) and single photon emission computed tomography (SPET) are at present the only neuroimaging techniques that can study neuroreceptors in vivo. PET and SPET are therefore the only imaging modalities that can demonstrate the integrity of the dopaminergic system.

SPET is less expensive and more readily available, because its tracers have a longer half-life (approximately 13 hours), and can be supplied commercially. Ligands used in PET have a very short half-life (20 minutes), which necessitates an on site cyclotron. PET is therefore mainly available in large research centres and at present is scarcely available for routine clinical practice. However SPET measures are semi quantitative and tend to provide lower reconstructed resolution than PET ¹⁶⁵.

4.2. IMAGING THE POST-SYNAPTIC NIGROSTRIATAL DOPAMINERGIC D₂ RECEPTORS WITH PET AND SPET

Dopamine receptors can be divided into two types, D₁ and D₂. D₁ type receptors are adenylyl cyclase dependent, while D₂ type receptors are not. In parkinsonian syndromes post-synaptic D₂ receptors have been shown to be of clinical interest. The most frequently used radiotracers for imaging D₂ receptors with PET are [¹¹C]raclopride and ¹¹C- or ¹⁸F-labeled N-methylspiroperidol, and for SPET ¹²³I-Iodobenzamide (IBZM). There is now extensive evidence that in untreated PD patients D₂ binding in the putamen is either normal or mildly upregulated, while caudate D₂ binding is normal ¹⁶⁶. The presence of normal striatal IBZM uptake in de-novo PD patients is a good predictor of response to dopamimetics (L-DOPA or dopamine receptor agonists) ¹⁶⁷. In a prospective study Schwarz et al showed that IBZM uptake predicted a positive or negative response to an apomorphine treatment trial in 30 out of 34 patients and response to dopamimetic therapy in 27

out of 31 PD patients. Sawle et al ¹⁶⁸ compared putamen [¹⁸F]DOPA (pre-synaptic) and [¹¹C]raclopride (post-synaptic) uptake in de-novo PD patients and showed that there was an inverse correlation between the binding of the two tracers. However in L-DOPA treated PD patients striatal D₂ binding is either normal or decreased. This would indicate that after initial upregulation of post-synaptic D₂ receptors there is a tendency for this to down regulate after exposure to treatment.

There are no in vivo studies of dopamine D₂ receptors in DLB. The only information at present comes from in vitro studies of brains from DLB patients which showed that in DLB post-synaptic D₂ receptor binding is reduced ¹¹⁹.

4.3. IMAGING THE PRE-SYNAPTIC NIGROSTRIATAL DOPAMINERGIC NEURONS WITH PET AND SPET

4.3.1. [¹⁸F]DOPA and PET

At present there are two ways of imaging the function of striatal dopamine terminals. The first method uses 6-[¹⁸F]fluoro-L 3,4,dihydroxyphenylalanine ([¹⁸F]DOPA) and PET. [¹⁸F]DOPA uptake is determined by the transfer of DOPA across the blood-brain barrier, its decarboxylation to fluorodopamine by 1-aromatic acid decarboxylase, and its retention in nerve terminals. The [¹⁸F]DOPA K_i reflects the capacity of nigrostriatal nerve terminals in the caudate and the putamen to metabolise L-DOPA into dopamine ¹⁶⁹. Until recently, most research on the dopaminergic deficit in PD has been performed with [¹⁸F]DOPA. Studies with [¹⁸F]DOPA show a more severe reduction of striatal uptake in the putamen than in

the caudate with the posterior putamen being particularly affected (45% of normal) compared to the anterior putamen (62% of normal) and the caudate (84% of normal) ¹⁷⁰. The deficit of striatal uptake of [¹⁸F]DOPA in PD is asymmetrical. Striatal uptake of [¹⁸F]DOPA correlates inversely with disease severity and it can also provide a means of monitoring progression of PD ¹⁷¹.

Using PET with [¹⁸F]DOPA Hu et al ¹⁷² observed that, patients with DLB (n=7) who have extrapyramidal signs and are responsive to L-DOPA have significantly reduced uptake of [¹⁸F]DOPA in the putamen and the caudate nuclei compared to AD patients (n=10). Tyrrell et al ¹⁷³ measured [¹⁸F]DOPA uptake in eight AD patients with signs of rigidity, six AD patients with no signs of rigidity and seven controls. Although there were no significant differences between the mean values of K_i [¹⁸F]DOPA in caudate and putamen in the three groups, the values for putamen were lower in the rigid than in the non-rigid AD group. This study did not report any autopsy findings but it is possible that some of the patients in the rigid AD group had DLB.

4.3.2. Imaging dopamine transporter with ¹²³Ibeta-CIT

The second approach to visualisation of dopaminergic neurones is by using radiotracers for the dopamine transporter. In PD and DLB there is a substantial loss of dopaminergic cells, with a parallel decreases in dopamine transporter and striatal dopamine.

Several ligands have been developed which have selective affinity for the dopamine transporter and can be used with PET and SPET. The most promising SPET tracers for the dopamine transporter are cocaine analogues. There are a number of SPET studies that used the tracer Iodine-123-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane [^{123}I beta-CIT] to visualise the dopamine transporter ¹⁷⁴⁻¹⁸¹. All the studies were able to show a clear loss of striatal dopamine transporter in patients with PD compared to controls, with high specific: non-specific radioactivity uptake ratios in the striatum. The values of ^{123}I beta-CIT in the striatum correlated well with disease severity as rated with Hoehn and Yahr stage (H&Y stage) ¹⁸², showing approximately 35% reduction in radioactivity uptake in H&Y stage 1 and ~ 71% reduction in stage 5 ^{183,184}. ^{123}I beta-CIT values also correlated with Unified Parkinson's Disease Rating Scale (UPDRS) ¹⁸⁵ scores, and reaction and movement time in untreated PD patients ^{174,179,180}, but not with tremor ratings ^{177,184}. Patients with PD had consistently lower binding in the putamen compared to the caudate nucleus ^{174,176,184}. Interestingly, although patients with multiple system atrophy and progressive supranuclear palsy had similar findings to PD patients the differences between the caudate nucleus and the putamen were less marked. Concerning the usefulness of ^{123}I beta-CIT in differentiating DLB from AD, the most interesting results come from studies of patients with hemiparkinsonism. Marek et al ¹⁸⁶ showed that striatal uptake was substantially reduced in the contralateral (by 53%) but also in the ipsilateral (by 38%) side to clinical symptoms. Similar result were obtained by Brucke et al ¹⁸⁴, who showed loss of striatal binding of 41% contra laterally and 30% ipsilateral to symptoms in

patients with hemiparkinsonism. This suggests that a deficit in dopamine transporter, and therefore loss of dopaminergic neurones, can be demonstrated with ^{123}I beta-CIT at a time when no clinical signs are apparent. Therefore this technique should be able to separate patients with DLB, whose dopaminergic deficit is not as severe as in PD patient, from AD patients, where dopamine transporter is unaltered.

To date there are only two studies that have investigated patients with DLB, PD and AD with ^{123}I beta-CIT. Both studies come from the same group of investigators. In the first study Donnemiller et al ¹⁶² performed a ^{123}I beta-CIT and a perfusion SPET on 7 patients with DLB, 6 patients with AD and 3 controls. The two groups of patients were matched for the Mini-Mental State Examination (MMSE) ⁷⁸ and UPDRS score. Radioactivity uptake in the striatum 18 hours post injection of ^{123}I beta-CIT was not significantly different in AD and controls. DLB patients had significantly lower values compared to both controls and AD patients. Although both the AD and DLB groups were rather unusual- the AD group surprisingly had higher UPDRS scores than the DLB group (mean 16.5 in AD compared to 12 in DLB patients), and all the DLB patients were on levodopa- nevertheless the results suggested that ^{123}I beta-CIT could distinguish AD from DLB patients. Perhaps more interesting is the second study by Ransmayr et al ¹⁸⁷. The authors, using again the ligand ^{123}I beta-CIT compared clinical parkinsonian features and striatal dopamine transporter binding in 20 patients with DLB and 24 patients with PD matched for

age and duration of illness. They found that ^{123}I beta-CIT binding measures were significantly reduced bilaterally in both DLB and PD compared to controls.

However ^{123}I beta-CIT has a serious drawback. The uptake of ^{123}I beta-CIT in the human striatum is characterised by very slow kinetics. A stable level (equilibrium in specific to non-specific radioactivity uptake) of striatal radioactivity is only achieved between 20-30 hours after injection of this radioligand ¹⁸⁸. This means that adequate image acquisition can only be performed a day after the ligand injection, which makes ^{123}I beta-CIT in our experience relatively unsuitable for out-patient use.

4.3.3. Imaging dopamine transporter with FP-CIT

Recently a new ligand, ^{123}I -labeled N-delta-(fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl)tropene [FP-CIT], has been developed with faster uptake in the human striatum than ^{123}I beta-CIT. The advantage of the fast kinetics of ^{123}I -FP-CIT is that patients can be scanned on the same day three to six hours after injection. Early studies on rats and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) lesioned monkeys showed severe loss of striatal FP-CIT uptake on the side of lesion, indicating that this ligand would be suitable for imaging loss of dopamine transporters in humans ¹⁸⁹. FP-CIT has been tested in volunteers ¹⁹⁰⁻¹⁹² and compared with ^{123}I beta-CIT in five unmedicated PD patients ¹⁹³. The mean relative specific:non-specific binding ratios of ^{123}I beta-CIT and FP-CIT in PD patients, expressed as percentages of the ratios found in healthy controls, were comparable in all regions measured (ipsilateral and contralateral striatum, caudate

nucleus and putamen) between the two ligands. However, the absolute ratios of ^{123}I beta-CIT uptake in the same regions were 2.5 times higher than those measured with FP-CIT. Both ligands showed mean uptake in the putamen to be lower than in the caudate nucleus. Similar results were obtained by Seibyl et al ¹⁹⁴ when comparing ^{123}I beta-CIT with FP-CIT in six PD patients and 5 controls. The authors concluded that FP-CIT was as good as ^{123}I beta-CIT for assessment of dopaminergic deficit in PD and that the faster kinetics were a clear advantage.

FP-CIT striatal uptake has been shown to be significantly reduced in six early (H&Y stage 1-1.5) and 12 advanced (H&Y stage 2-4) PD patients on both contralateral and ipsilateral sides. As in studies with ^{123}I beta-CIT, uptake in the putamen was lower than uptake in the caudate nucleus. Both ipsilateral and contralateral binding measures correlated with H & Y stage but not with motor UPDRS score ¹⁹⁵. However, in a further study by the same group ¹⁹⁶, no significant correlation was found between striatal FP-CIT binding and disease severity. In this study 21 drug naïve PD patients were compared with 14 controls. The mean reduction in the putamen uptake was 57% of the control mean and in the caudate nucleus 29% of the control mean. Patients with hemiparkinsonism showed bilateral loss of striatal binding and a discriminant function analysis predicted the diagnosis of all patients correctly. At present there are no in vivo studies of FP-CIT in DLB.

4.4. AIMS AND HYPOTHESES OF THESIS

The purpose of this thesis is to investigate the pre- and post-synaptic components of the striatal dopaminergic system of clinically diagnosed DLB patients and compare them with patients with AD, patients with PD and healthy controls.

In addition the thesis will explore the relationship between cognitive impairment, psychotic symptoms and extrapyramidal signs on the one hand, and the severity of pre- and post-synaptic dopaminergic dysfunction on the other in the different diagnostic groups.

1. The primary hypothesis is that patients with DLB (and those with PD) will have significantly lower uptake of FP -CIT (reflecting neuronal loss) compared with AD and controls.

2. We also hypothesised that DLB (and PD) subjects will have a statistically significant reduction in caudate/putamen dopaminergic D₂ receptor availability as measured by IBZM radioactivity uptake compared to both AD and control subjects.

3. In addition we planned to explore in all the patient groups, but particularly in the DLB group, the relationship between cognitive impairment, neuropsychiatric symptoms, extrapyramidal signs and the severity of pre- and post-synaptic dopaminergic dysfunction.

4. Other areas of interest that were explored but were not part of an a priori hypothesis were investigation of the pattern of dopaminergic disruption in DLB compared to PD patients and correlation with some of the clinical and demographic features.

5. Finally, we are prospectively following our second cohort of patients and controls, in order to validate our clinical findings by histopathological diagnosis. This work is ongoing but autopsy data available at time of submission of the thesis is presented.

Chapter 5

Methods

Two cohorts of patients and controls were studied. The first cohort was scanned with the IBZM ligand and SPET. The second cohort underwent scanning with FP-CIT and SPET.

5.1. ETHICAL CONSIDERATIONS

Research on patients with dementia raises particular ethical problems because of the question of competence to give informed consent and the possibility of undue influence by a researcher. The legal position is complex and there is currently no general consensus on how to balance the possible risks and benefits to such vulnerable individuals against the public interest in conducting research ¹⁹⁷. The diagnosis of dementia does not automatically mean that the patient does not have the mental capacity to give consent as this depends not only on the degree of cognitive impairment, but also on the complexity of the research that is proposed. With this in mind great care was taken to give the fullest possible information to the patient and carer and to stress that not taking part in the research would not in any way jeopardise their care.

Approval for the IBZM study (first cohort of patients and controls) was obtained from West Essex Health Authority Ethics Committee and the Administration of Radioactive Substances Advisory Committee of UK.

For the FP-CIT study (second cohort), approval was obtained from West Essex Health Authority Ethics Committee and the Camden and Islington Community Trust Ethics Committee and the Administration of Radioactive Substances Advisory Committee of UK. All controls, patients and, if available, their relatives gave written consent. Patients were encouraged to read the information sheet and discuss the research proposal with their family before giving consent. Although consent of a relative has no legal validity, it was obtained as part of good practice.

The amount of radioactivity involved for each scan was significantly less than a barium meal investigation (effective dose equivalent = 3.8 mSV). During the scans no adverse reactions were experienced by any of the patients or controls. All patients and controls completed the scanning session.

It was anticipated that the patients and their relatives would benefit from a comprehensive assessment, a more accurate diagnosis, detailed planning of patient management, regular follow-up and advice on prognosis. This far we have had a very positive response from patients and relatives. As an example, following the brain donation of one patient the family made a donation to the Derwent

Memory Clinic to further facilitate similar research and, in another case, a relative offered to be an advocate for brain donation.

5.2. PATIENTS

Patients for both cohorts were recruited from the Derwent Memory Clinic (set up and run by ZW), the Old Age Psychiatry and Neurology out-patient clinics, and hospital wards at Princess Alexandra Hospital, Harlow, St. Margaret's Hospital, Epping and at the Whittington Hospital, London. At the time of recruitment, there were approximately 50 new patients seen in the Memory Clinic per year. The frequency of diagnoses in the Memory Clinic was as follows: AD 55%, DLB 14%, vascular dementia 6%, mild cognitive impairment 4%, depression 4% and the rest were coded under other dementias or inconclusive. Some of the patients who took part in the present project also took part in a treatment trial. Although there was nothing to suggest that antimentia drugs would in any way interfere with the SPET scan, all scans were performed prior to starting the treatment trial. Healthy elderly controls were recruited from relatives and friends of patients (mainly spouses). Controls were not taking any drugs known to affect the dopaminergic system. DLB was diagnosed according to the Consensus DLB criteria ⁷⁶ (see appendix 1.1) and Alzheimer's disease was diagnosed according to NINCDS-ADRDA criteria ¹⁷. The diagnosis of PD was made according to the UK Parkinson's Disease Society Brain Bank criteria ⁸⁹. Patients with PD were recruited from a neurology clinic at the time of first presentation to a neurologist and had not been exposed to any antiparkinsonian medication at the time of scanning.

5.3. ASSESSMENT

5.3.1. Patients with AD and DLB

For each patient a detailed history of memory impairment was obtained from the patient and an informant. This was followed by a full psychiatric history, a mental state examination and a physical examination with an emphasis on neurological examination. To assure that all data were collected in a uniform way the memory clinic first visit schedule was used. A number of tests were performed:

- **The Mini-Mental State Examination (MMSE)**; adapted from Folstein et al ⁷⁸ is the most widely used and studied screening measure of cognitive impairment. It has the advantage of brevity, ease of administration (approximately 10 minutes), and high test/retest and inter-rater reliability. The maximum score is 30. Scores below 24 are traditionally taken as indicative of cognitive impairment. However there is a gray area of scores of 24-28 where adjustment needs to be made for age, education and socio-economic status ¹⁹⁸. The most sensitive items on the MMSE for dementia are delayed recall of three items and orientation. The MMSE is insensitive for frontal lobe deficit ¹⁹⁹.
- **The Cambridge Cognitive Function Examination (CAMCOG)** is a neuropsychological test battery which forms part of a standardised psychiatric assessment schedule the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) ²⁰⁰. The CAMCOG assesses a wider range of cognitive

functions, both distributed (attention, memory, abstraction) and localised (language, praxis, calculation, perception) than any other standardised schedule. It incorporates the MMSE within the battery of tests. The CAMCOG takes 20-40 minutes to administer. The maximum overall score is 107. A cut-off of 79/80 on CAMCOG was found in the original paper to have 92% sensitivity and 96% specificity for a clinical diagnosis of dementia but the normal range varies considerably with age and education ²⁰¹. CAMCOG has also been shown to be a useful screening instrument for dementia and cognitive impairment in patients with PD ²⁰². The main disadvantage is the lack of very easy items and poor sensitivity to frontal lobe impairment ¹⁹⁹. It is used in half of the Memory Clinics in the British Isles.

- **The Clinical Dementia Rating (CDR)** ²⁰³ has become the gold standard for global rating of primary degenerative dementia. To complete the scale the rater has to have a detailed knowledge of the patient. It is divided into six areas: memory; orientation; judgement and problem solving; community affairs; home and hobbies; and personal care. It has been extensively validated ^{204 205,206}. Its advantage is that it incorporates the clinician's assessment of patients' varying educational, cultural, socio-economic and other biases in its staging. Ratings are made on a scale of 0-3, with a score of 0.5 (questionable) in all of the domains apart from personal care. The global CDR score was derived using an algorithm where the memory score was the primary value and the rest of the domains were secondary values. The final score equalled the memory score if

at least three other domains were given the same value. If three or more secondary scores were greater or less than the memory score, the global CDR value equalled the value of the majority of the secondary categories.

- **The 15-item Geriatric Depression Scale (GDS)** ²⁰⁷ is frequently used for clinical and research purposes as a screening tool for depression in older people. It has also been used as a screening instrument for depressive symptomatology in patients with PD ²⁰⁸. It takes about 5-10 minutes to complete. A cut off 6 has been found to have sensitivity 78% and specificity 67%. However, when used in patients with moderate to severe cognitive impairment it does not retain its validity ²⁰⁹.
- **The Cornell Scale for Depression in Dementia (Cornell depression scale)** ²¹⁰ is a 19-item instrument specifically designed for the rating of symptoms of depression in demented patients. The unique aspect of the scale is its method of administration. Ratings are based on two interviews and an overall clinical judgement. The items are designed to be unambiguous and can be scored primarily on the basis of behavioural observation. A score of 8 or more suggests significant depressive symptoms. The original validation study showed inter-rater reliability kappa = 0.67, and internal consistency 0.84. Its correlation coefficient against research diagnostic criteria was 0.83. Its main drawback is high rate of false positive results.

- **The Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAV-AD)** ²¹¹ assesses the behavioural and psychiatric symptoms associated with Alzheimer's disease in the areas of delusions, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobias. Each item is rated from 0-3. There is also a global rating which records how troubling the patient's symptoms are to the carer overall. The schedule is completed by a clinician and it is based on the interview with the carer. It has been shown to be useful in prospective studies of behavioural symptoms in intervention studies.
- **The Unified Parkinson's Disease Rating Scale, motor part only (UPDRS)** ¹⁸⁵ is a standard scale for rating the severity of the extrapyramidal features of PD. It is based on a physical examination and observation by a trained examiner. It takes about 15 minutes to complete. The main difficulty with this scale is that some of the items are difficult to test in severely cognitively impaired individuals as they are unable to comprehend the instructions. Ballard et al ²¹² suggested that an abbreviated version of UPDRS with only 5 items (tremor at rest, action tremor, bradykinesia, facial expression and rigidity) should be used in demented patients. However, in the present study the original scale was used. In the few patients who were unable to follow instructions the scale was omitted.
- **The Hoehn and Yahr stage (H&Y stage)** ¹⁸² is a commonly used scale for rating the severity of PD. Although it has been extensively used in PD, its validity in

DLB has not been established. The main shortcoming of this scale is that it assumes unilateral involvement in early stages of disease. However, patients with DLB have frequently bilateral symptoms from the onset and therefore may receive an artificially high rating on the scale.

- **The Instrumental Activities of Daily Living Scale (IADL)**²¹³, is designed to assess more complex everyday functional competence in older patients. It rates eight items: the ability to use a phone, to shop, to prepare food, housekeeping, laundry, mode of transportation, ability to take responsibility for own medication and ability to handle finances. It takes only 5 minutes to administer. The higher the score the less able the patient.
- **The Clifton Assessment Procedure for the Elderly, Behavioural rating scale only (CAPE)**²¹⁴ is scored by carers. It takes about 10 minutes to complete. There are eighteen items that can be subdivided into four main areas: physical disability, apathy, communication difficulty and social disturbance. Each item is rated on a scale of 0-2. Higher score indicates worse behaviour and disability. It has good inter-rater reliability and validity in terms of correlations with other neuropsychological tests and with longitudinal studies²¹⁴.
- **Investigations**

The following investigations were arranged for all patients if not already performed by a referring doctor: FBC, ESR, U&Es, glucose, LFTs, Ca 2+, TFTs, VDRL, B12, folate and MRI brain scan.

The decision to perform an MRI and not a CT brain scan was made to keep to the minimum the overall amount of radioactivity to which each patient was exposed. MRI is also the preferred investigation in dementia, but it is more expensive than CT scan and not as well tolerated by demented patients. In the present study, in the end only 20 out of the 44 patients with dementia had an MRI scan. The two main reasons for having a CT scan were either that a CT scan had already been performed, prior to study entry, or that the patient could not tolerate a MRI scan. The main reason for performing a structural scan was to exclude other intracranial pathology e.g. primary brain tumours, secondaries, chronic subdural haematomas, infarcts and hydrocephalus.

5.3.2. Patients with PD

A detailed medical history was obtained from all patients. This was followed by a full physical examination with an emphasis on neurological examination. The following tests were performed:

- The Mini-Mental State Examination.
- The Cambridge Cognitive Examination
- The Clinical Dementia Rating
- Unified Parkinson's Disease Rating Scale (motor part)

- Hoehn and Yahr stage

5.3.3. Controls

Information was gathered from controls regarding their medical and psychiatric history and any regular medication. A mental state examination and a limited physical examination were carried out. The following tests were performed:

- The Mini-Mental State Examination
- The Cambridge Cognitive Examination
- Unified Parkinson's Disease Rating Scale (motor part)
- Hoehn and Yahr stage

5.4. IBZM and FP-CIT SPET SCANS:

SPET studies were carried out under the supervision of DDC at the Institute of Nuclear Medicine, University College London Medical School. To a minor extent both ^{123}I -Iodobenzamide (IBZM) and ^{123}I -labeled N-delta-(fluoropropyl)-2beta-carbomethoxy-3beta-(4-iodophenyl)tropene (FP-CIT) is deiodinated in vivo (<2%). Therefore to minimise the risk of uptake of radioactive iodine by the thyroid gland, the thyroid trapping metabolism was blocked by the administration of potassium iodate, 170mg, for two days prior to, on the day of, and for two days after scanning.

All subjects underwent scanning with a brain dedicated scanner, the Strichman Medical Equipment 810 linked to a Macintosh computer. The Strichman camera consists of twelve individual detectors, each equipped with a focusing collimator.

The transaxial resolution of this camera is 7.6mm full width half maximum and axial resolution is 12.5 mm. The measured concentration of radioactivity was expressed as Strichman Medical Units (SMUs; 1SMU = 100 Bq/ml). Scanning took place 1.5 to 2 hours post-injection (intravenous) of IBZM (185 MBq) and between 3 and 4 hours after injection of FP-CIT (185 MBq). Usually 8-10 slices were acquired starting at the cerebellum level upwards to include basal ganglia. A few patients were difficult to scan, and in these a smaller number of slices (3-5) were acquired at the level of the basal ganglia to include the entire basal ganglion region. The overall scanning time for each patient was 30-45 minutes.

All scans were analysed by DCC who was unaware of the diagnostic status of the subjects. No clinical examination was carried out on the day of SPECT data acquisition. After acquisition and data processing all studies were randomised and identified only by a "coding system". They were then analysed as described below. Only after data collection the identification of studies and patients was performed. No changes in the analysis were introduced after identification of studies and patients.

The images were automatically reconstructed. For the analysis of striatal binding, the ratio of specific to non-specific binding was calculated by summing up two to three adjacent transverse slices that showed the most intense striatal uptake. Regular circular regions of interest were employed to calculate the average striatal (caudate nucleus, anterior and posterior putamen) to non-specific (areas with little

or no dopamine receptors, e.g. frontal, occipital lobes) radioactivity ratios for both hemispheres (Figure 5.1 and 5.2). This method has been shown to have an excellent inter- and intra-operator agreement ²¹⁵. The formula used was:

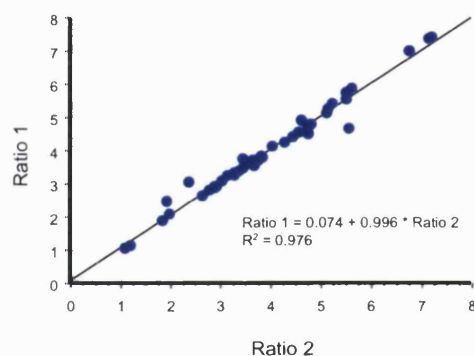
$$\text{IBZM binding} = \text{STR} / \text{FRO}$$

$$\text{FP-CIT binding} = \text{STR} / \text{OCC}$$

where STR is the mean radioactivity (in SMU) in the striatum (caudate, anterior and posterior putamen) and OCC is the mean radioactivity in the occipital cortex and FRO is the mean radioactivity in the frontal cortex. There were several reasons why in the second FP-CIT cohort the occipital and not the frontal cortex was used as the reference (the non-specific) area. There are dopaminergic terminals in the frontal cortex grey matter and these terminals release dopamine that stimulates post-synaptic dopamine receptors not of the D₂ or D₂ like type (these are mainly in the temporal cortex, caudate-putamen, nucleus accumbens, and olfactory tubercles), but the D₄ type, similar to the diencephalon and brain stem. In addition to that our elderly population was also likely to have cortical atrophy (even in controls). By using the occipital cortex as reference we would expect to minimise the difference in radioactivity ratios of DLB and AD patients because of more hypometabolism in the accessory visual cortex and calcarine cortex in DLB than in AD even though there is no significant cortical atrophy in the posterior regions of the cortex in the CNS of DLB patients.

For a subgroup of patients and controls (N=11) a comparison between measurements on two different occasions was performed. There were 44 ratios (left and right caudate and putamen for each subject). Regression analysis showed a high correlation coefficient ($R^2 = 0.976$) see graph below.

Intra-operator reproducibility for striatal to occipital cortex radioactivity ratios



From the FP-CIT binding measurements the asymmetry of binding between the two sides was expressed as an asymmetry index:

$$\text{Asymmetry index (\%)} = \left[\frac{\text{better side} - \text{worse side}}{(\text{better side} + \text{worse side}) / 2} \right] \times 100$$

The asymmetry clearly has to be related to the absolute counts on each side. It cannot be expressed as an absolute difference between the two sides. We therefore expressed it as a ratio of the absolute difference divided by the average counts on each side.

The relationship between IBZM binding in the caudate nucleus and the putamen for each individual was expressed as:

$$\text{Caudate:putamen ratio} = \frac{\text{caudate binding}}{\text{putamen binding}}$$

The relationship between FP-CIT binding in the caudate nucleus and the putamen for each individual was expressed as:

$$\text{Caudate:putamen ratio} = \frac{\text{caudate binding}}{\text{posterior putamen binding}}$$

Ratios were calculated for the sum of the binding values of the caudate of each side divided by the sum of the binding values of the posterior putamen of each side for each individual (bilateral ratios). In addition ratios were calculated for each side, identifying the side with the higher posterior putamen binding and the side with the lower posterior putamen binding (less and more affected unilateral ratios).

5.5. VISUAL RATING OF SCANS

As a separate exercise, all the scans were presented randomly and assessed visually, purely qualitatively, by three independent raters (DCC, ZW and RHHW) who were blind to the clinical and autopsy diagnoses. Scans were scored as follows: normal uptake in all regions (right and left caudate and whole putamen) = 0; slight reduction in uptake in any of the four regions = 1; significant reduction in uptake in any of the four regions = 2. Subsequently for all correlations and statistical analyses, scans with scores 0 or 1 were combined into a 'normal' group and scans with a score 2 were declared 'abnormal'.

5.6. STATISTICS

5.6.1. Power calculation

For the first cohort no power calculation was performed as this research had never been done before. For the second cohort a power calculation to determine the sample size was based on preliminary results from the first cohort. The requirement was set as 90% power to detect a real difference in the radioactivity ratios between DLB and AD group at the 0.05 significance level. In the pilot study, the mean caudate/putamen ratio in the DLB group was 0.929 and in the AD group 1.075. This reflects a true difference of 0.146. With the SD for all three groups being 0.143 this gives a standardised difference $d = 0.146/0.143=1.02$. We anticipated that the difference between groups in the second cohort would be similar to the pilot study.

Using the tables in Campbell et al ²¹⁶ the minimum sample size for each group was 22.

5.6.2. Data analysis of IBZM cohort

Data were analysed using SPSS / PC+ version 10.0 (Statistical Package for Social Sciences). In the first cohort IBZM binding was calculated for the right and the left caudate and putamen. Analysis of variance (ANOVA) and the Student's t-test were used to assess differences between the four groups (DLB, AD, PD and controls) and their IBZM binding in the caudate and putamen and in the caudate: putamen ratio.

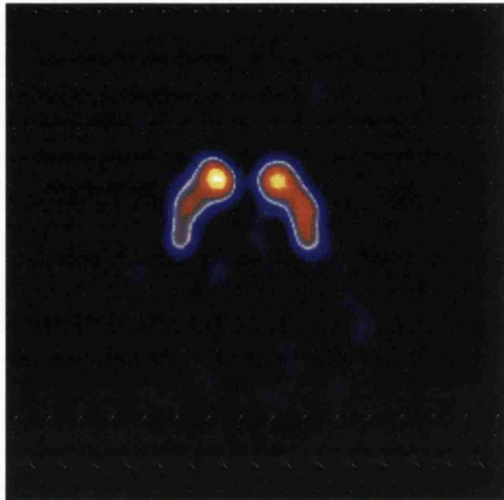
5.6.3. Data analysis of FP-CIT cohort

In the second cohort FP-CIT binding was calculated for caudate, anterior and posterior putamen separately for each hemisphere. For PD patients "contralateral side" was defined as the side opposite to the clinically worse affected side. For DLB and AD patients it was difficult clinically to decide which side should be taken as the more affected, as some patients did not have any extrapyramidal signs, and therefore contralateral was arbitrarily assigned to the left side and ipsilateral to the right side. Analysis of variance (ANOVA) and the t-test were used to assess differences between the four groups (DLB, AD, PD and controls) in the ipsilateral and the contralateral FP-CIT binding in the caudate and anterior and posterior putamen, and differences in basic characteristics (age, MMSE, CAMCOG, CDR, BEHAVE-AD, UPDRS scale, Cornell depression scale and CAPE).

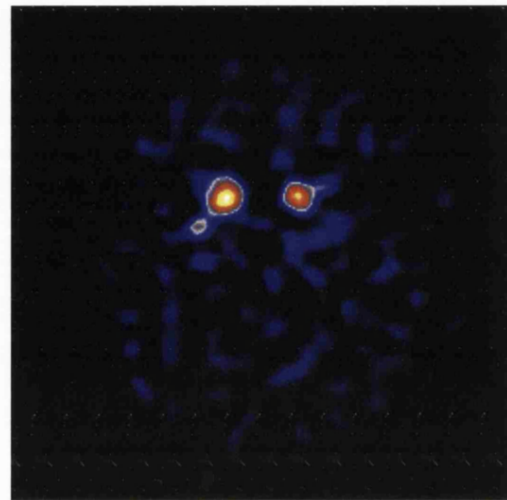
Caudate:putamen ratios and asymmetry indices between the four groups (DLB, AD, PD and controls) were analysed using the non-parametric Kruskal-Wallis and Mann-Whitney tests.

Cohen's kappa test was used for inter-rater reliability. Relationships between variables were explored using Spearman's rank correlation for nominal or ordinal data.

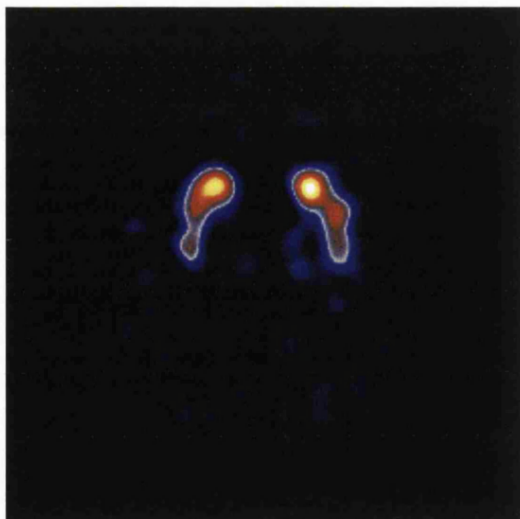
FIGURE 5.1: FP-CIT scans of a) control, b) PD patient, c) AD patient, and d) DLB patient



a



b

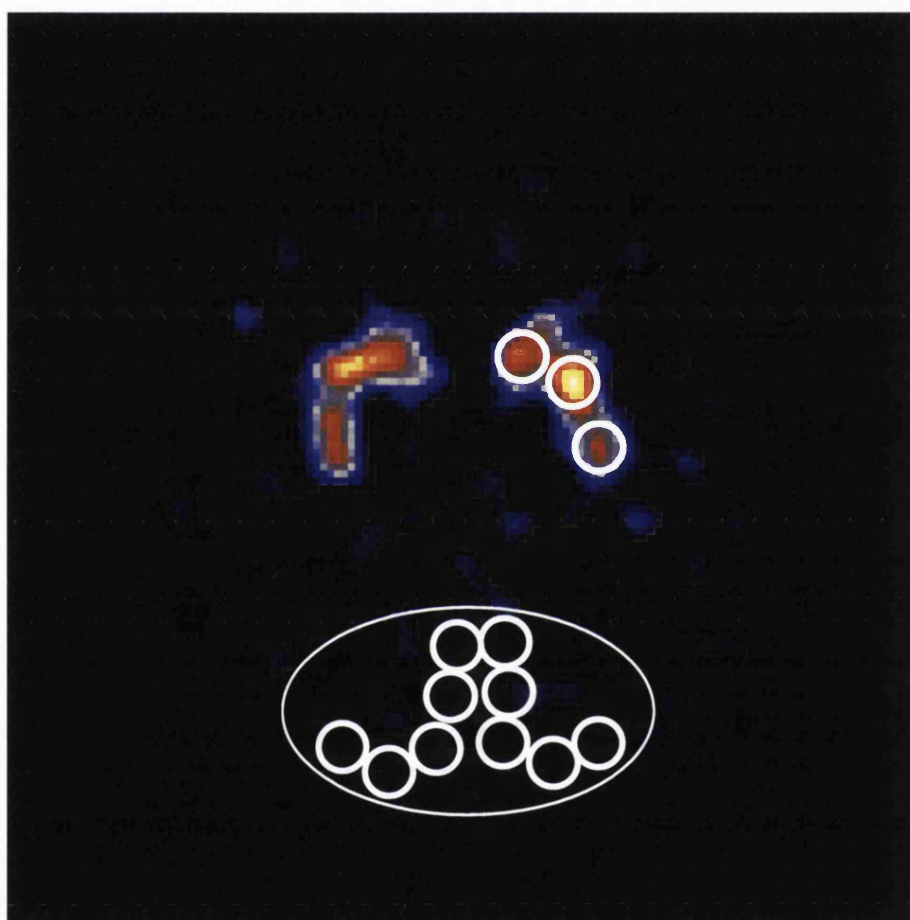


c



d

FIGURE 5.2: FP-CIT scan showing regions of interest (ROI) in caudate nucleus, anterior and posterior putamen and occipital cortex.



Chapter 6

Results of IBZM study

6.1. DEMOGRAPHIC FEATURES OF THE COHORT

The first cohort comprised 16 DLB patients, 13 AD patients, 3 PD patients and 15 healthy controls. The means for age at time of the IBZM-SPET scan, age at onset of dementia, MMSE, CAMCOG, CDR, CAPE and GDS and gender ratio for the DLB, PD and AD groups are shown in Table 6.1. There was no significant difference in mean ages of the controls (68.2 years), the AD patients (74.2 years) and the patients with DLB (75.6 years). There was no significant difference between the AD and DLB groups with regard to MMSE, CAMCOG, CDR, or GDS scores, but DLB patients scored significantly worse (higher score) on CAPE than AD patients (t-test: $p < 0.03$; see Table 6.1).

6.2. RADIOACTIVITY BINDING IN CAUDATE AND PUTAMEN

The radioactivity binding (all groups) in the caudate nucleus and in the putamen, in both hemispheres, is shown in Table 6.2. The DLB and PD group had higher binding in the putamen and lower binding in the caudate than the AD and the control group; however this did not reach statistical significance (ANOVA: Right caudate $F=2.756$, $p=0.054$; Left caudate $F=1.525$, $p=0.22$; Right putamen $F=0.264$, $p=0.85$; Left putamen $F=2.02$, $p=0.125$).

6.3. LEFT CAUDATE:PUTAMEN RATIO

The DLB group had a significantly lower left caudate:putamen ratio than the control and the AD groups (ANOVA: $F = 6.36$, $p < 0.01$; 95 % confidence intervals: DLB 0.896 to 0.972, AD 0.973 to 1.168, controls 1.031 to 1.168). There was a significant difference between the DLB and the AD groups (t-test: $p < 0.01$) and between the DLB group and the controls (t-test: $p < 0.001$), but no difference between the AD group and the controls or between the DLB and the PD groups (see Table 6.3, Figure 6.1).

6.4. RIGHT CAUDATE:PUTAMEN RATIO

The DLB group also had a lower right caudate:putamen ratio than the AD group and the controls (ANOVA: $F = 3.21$, $p < 0.05$), but there was a considerable overlap in the 95% confidence intervals (DLB 0.943 to 1.025, AD 0.954 to 1.104, controls 1.022 to 1.142). When comparing individual groups, although there was a significant difference between the DLB group and controls (t-test: $p < 0.01$), the difference between the DLB and AD group was not significant. There was no difference between the DLB group and the PD patients (see Table 6.3)

6.5. RELATIONSHIP BETWEEN RADIOACTIVITY BINDING AND PATIENTS CHARACTERISTICS

Psychiatric symptoms were present in 14 out of 16 DLB patients and in 2 out of 13 AD patients. Extrapyramidal signs were present in 13 out of 16 DLB patients and in 3 out of 13 AD patients. Patients (DLB + AD + PD) with psychotic symptoms had

consistently higher binding in the putamen and the caudate in both hemispheres, but this did not reach statistical significance (see Table 6.4). DLB patients with psychotic symptoms had a significantly higher binding in the left putamen (t-test: $F = 1.191$, $p < 0.01$) than DLB patients without psychotic symptoms but the numbers were very small in the non-psychotic group ($n=2$).

6.6. AUTOPSY RESULTS

Five autopsy results are available from the first cohort. In all five cases the clinical diagnosis was confirmed at autopsy (four DLB patients and one AD patient).

FIGURE 6.1: Right and Left Caudate:putamen ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and healthy controls (means and 95% confidence intervals)

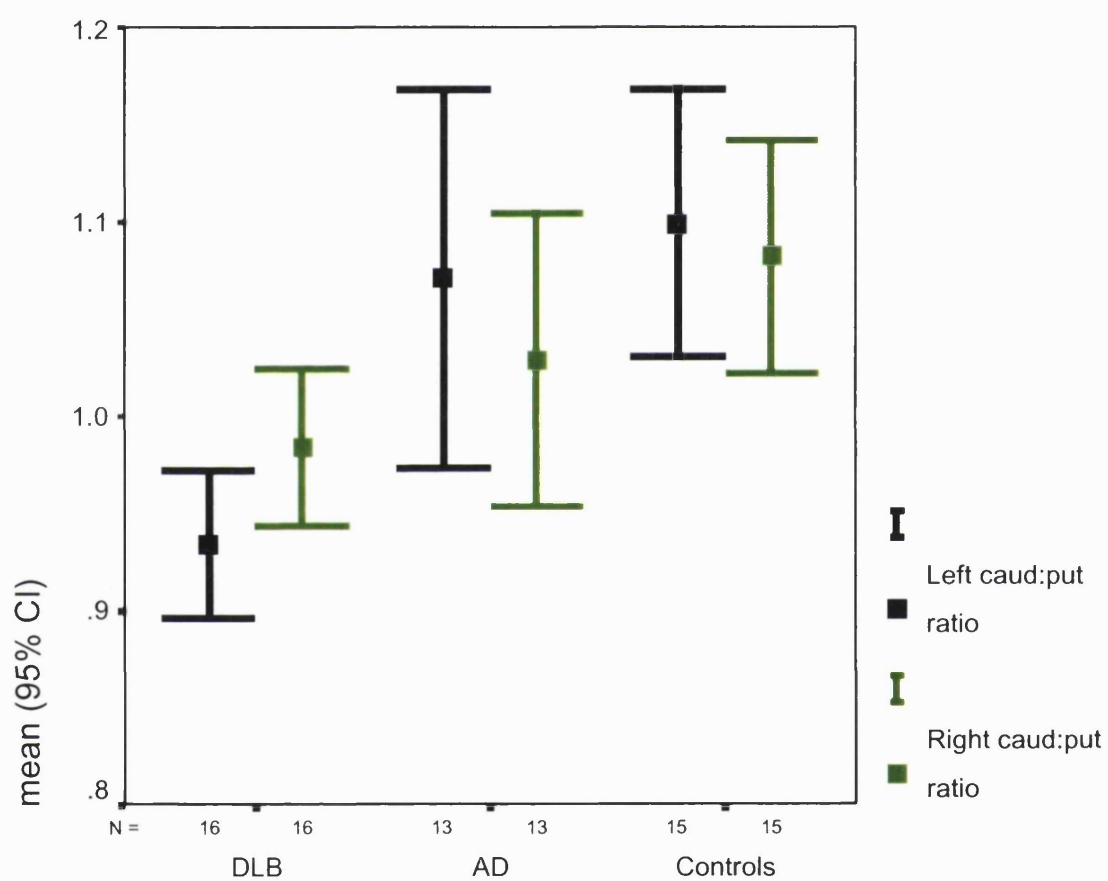


TABLE 6.1 Cohort characteristics of patients with DLB, AD, PD and controls

(* CAPE: AD vs DLB, $p < 0.03$; rest AD vs DLB not significant).

	DLB n=16	AD n=13	PD n=3	Controls n=15
Age at time of IBZM				
Mean (SD)	75.6 (8.5)	74.2 (8.1)	73.7 (9.1)	68.1 (8.6)
Median	75	73	67	70
Age at onset of dementia				
Mean (SD)	72.3 (8.8)	70.5 (7.0)		
Median	72	71		
MMSE				
Mean (SD)	19.6 (4.0)	17.8 (7.4)	28 (1.7)	
Median	18	22	29	
CAMCOG				
Mean (SD)	69.5 (15.1)	59 (24.2)	93.7 (2.5)	
Median	71	60	94	
CDR				
Mean (SD)	1.03 (0.53)	1.1 (0.62)	0.17 (0.29)	
Median	1.0	1.0	0.0	
CAPE *				
Mean (SD)	12.6 (5.1)	8.23 (4.8)	0.0 (0.0)	
Median	14	9	0	
GDS				
Mean (SD)	4.31 (1.8)	3.62 (2.9)	6.33 (5.9)	
Median	4	2	4	
Gender ratio M:F	11:5	5:8	1:2	7:8

TABLE 6.2 Semi-quantitative IBZM binding measures: mean, standard deviation (SD) and median. There were no significant differences in radioactivity binding between different groups.

	DLB n=16	AD n=13	PD n=3	Controls n=15
Right caudate binding				
Mean (SD)	1.60 (0.22)	1.60 (0.16)	1.48 (0.09)	1.74 (0.17)
Median	1.63	1.59	1.53	1.74
Left caudate binding				
Mean (SD)	1.64 (0.25)	1.72 (0.21)	1.53 (0.23)	1.76 (0.18)
Median	1.67	1.73	1.40	1.80
Right putamen binding				
Mean (SD)	1.63 (0.21)	1.57 (0.18)	1.61 (0.15)	1.62 (0.19)
Median	1.66	1.53	1.63	1.55
Left putamen binding				
Mean (SD)	1.74 (0.19)	1.61 (0.15)	1.66 (0.04)	1.61 (0.17)
Median	1.76	1.58	1.65	1.58

TABLE 6.3 Right and Left Caudate:putamen ratios: mean, standard deviation and median.

	DLB N=16	AD N=13	PD N=3	Controls N=15
Right Caudate:putamen index				
Mean (SD)	0.98 (0.08)	1.03 (0.12)	0.93 (0.12)	1.08 (0.11)
Median	0.97	1.04	0.87	1.03
Left Caudate:putamen index				
Mean (SD)	0.93 (0.08)	1.07 (0.16)	0.92 (0.15)	1.1 (0.12)
Median	0.95	1.09	0.85	1.10

TABLE 6.4 Semi-quantitative IBZM binding measures in patients with and without psychotic symptoms: mean and standard deviation

	DLB + AD + PD with psychotic symptoms n=16	DLB + AD + PD without psychotic symptoms n=16	DLB with psychotic symptoms n=14	DLB without psychotic symptoms n=2
Right caudate binding Mean (SD)	1.64 (0.22)	1.54 (0.13)	1.62 (0.23)	1.50 (0.04)
Left caudate binding Mean (SD)	1.69 (0.25)	1.63 (0.21)	1.66 (0.25)	1.44 (0.08)
Right putamen binding Mean (SD)	1.63 (0.21)	1.58 (0.17)	1.65 (0.22)	1.50 (0.15)
Left putamen binding Mean (SD)	1.74 (0.19)	1.63 (0.13)	1.77 (0.19)	1.58 (0.03)

Chapter 7

Results - FP-CIT study

As classified using clinical criteria, there were 27 patients with DLB, 17 patients with AD, 19 patients with PD and 16 controls.

7.1. DEMOGRAPHIC FEATURES OF THE COHORT

The frequency of: a family history of PD or AD; past psychiatric history; alcohol consumption; history of smoking; fluctuating course of illness, acute confusional states, visual hallucinations; tremor; rigidity and akinesia/bradykinesia for DLB, AD, PD patients and controls are shown in Table 7.1 and 7.2. There were no significant differences between the DLB and AD groups or between DLB and PD groups in the frequency of: a family history of PD or AD; past psychiatric history; alcohol consumption and history of smoking.

There was no significant difference between DLB and AD patients in gender ratio, the age at time of scan, age at onset of dementia, duration of symptoms, systolic blood pressure and years of education (Table 7.3).

There were differences between DLB and AD patients on the Clinical Dementia Rating, the MMSE and the CAMCOG scores, DLB patients being more severely demented. The Cornell Scale for Depression in Dementia scores were higher for

DLB than AD, but in neither group were they in the range indicating significant depression. DLB patients scored significantly worse (higher score) on Behave-AD and CAPE than AD patients (Table 7.4).

PD patients had a shorter duration of symptoms ($p < 0.05$) than DLB patients. PD patients and controls were also significantly younger than DLB patients ($p < 0.01$; Table 7.3) and scored higher on the MMSE ($p < 0.001$) and the CAMCOG ($p < 0.001$; Table 7.4).

As was to be expected both PD and DLB patients scored higher on the UPDRS scale and on the Hoehn & Yahr staging than did AD patients and controls (Table 7.3; $p < 0.001$). There were no significant differences between the DLB and PD groups in H&Y stage, UPDRS score, and frequency of tremor, rigidity and akinesia/bradykinesia. There were no significant differences between the DLB and the PD patients in systolic blood pressure and years of education, but the PD patients had significantly higher Hachinski scores than DLB patients ($p < 0.001$).

7.2. FP-CIT RADIOACTIVITY BINDING (SEMI-QUANTITATIVE METHOD)

The mean values for contralateral and the ipsilateral radioactivity binding in the caudate nucleus and in the anterior and the posterior putamen in the four groups are shown in Table 7.5 and Figures 7.1, 7.2 and 7.3. Both the DLB and PD groups had significantly lower radioactivity uptake in all striatal areas than the AD group and controls (ANOVA: $p < 0.001$, in the contralateral and the ipsilateral caudate

nucleus and anterior and posterior putamen). There were highly significant differences between DLB and AD, and DLB and controls for all ipsilateral and contralateral binding measures (t tests; $p < 0.001$). There was a clear separation of the AD and the DLB group with no overlap of the 95% confidence intervals for the means of radioactivity binding. There were no significant differences in binding measures between AD patients and controls in the ipsilateral and the contralateral caudate, the ipsilateral and the contralateral anterior putamen and the ipsilateral posterior putamen, but AD patients had lower binding than controls in the contralateral posterior putamen ($p < 0.05$).

There were highly significant differences in all binding measures between PD and controls ($p < 0.001$) and between PD and AD ($p < 0.005$). When comparing the PD and the DLB groups, the DLB patients had significantly lower binding in the ipsilateral caudate ($p < 0.01$) than the PD patients. However PD patients had significantly lower binding in the posterior putamen (ipsilateral $p < 0.05$; contralateral $p < 0.001$) than DLB patients.

7.3. ASYMMETRY INDEX

Asymmetry indices for the posterior putamen for DLB, AD, PD and control groups are shown in Figure 7.4. There was a significant difference in the asymmetry indices for the posterior putamen between the four groups ($p < 0.04$, Kruskal-Wallis test). The difference in the asymmetry indices in the posterior putamen was due to more marked asymmetry of binding in patients with PD. There was no statistical

difference in the posterior putamen asymmetry indices of the DLB and AD or DLB and control groups. There was a significant difference in the posterior putamen asymmetry indices of the PD and DLB patients ($p < 0.03$, Mann-Whitney test), the PD and AD patients ($p < 0.03$) and PD and control groups ($p < 0.01$, Mann-Whitney test).

7.4. CAUDATE:PUTAMEN RATIOS

The bilateral caudate:putamen ratios for all four groups are shown in Figure 7.5. There was a significant difference in the caudate:putamen ratios between the four groups ($p < 0.04$, Kruskal-Wallis test). The mean ratio for the DLB and AD groups was not significantly different to that of the controls, while the mean ratio for the PD group was significantly different from the control group ($p < 0.001$, Mann-Whitney test), from the DLB group ($p < 0.001$) and AD group ($p < 0.001$). The unilateral ratios gave the same results. For the side with the lower posterior putamen counts the mean values were: PD 2.26, DLB 1.47, AD 1.44, controls 1.40 ($p < 0.001$ Kruskal-Wallis test); for the other side the mean values were: PD 1.78, DLB 1.27, AD 1.32, controls 1.29 ($p < 0.001$).

7.5. SUBGROUP OF DLB AND PD PATIENTS MATCHED FOR AGE AND DURATION OF ILLNESS

To ensure that the significant differences between DLB and PD patients were not due to inappropriate age matching and different disease duration the same analyses were repeated for a subgroup of DLB and PD patients matched for age

and disease duration (12 cases in each group, the oldest DLB and the youngest PD patients were excluded). There was no significant difference between the subgroup of DLB and PD patients in years of education, UPDRS score or H& Y staging. DLB patients continued to have significantly lower binding in the ipsilateral caudate ($p < 0.001$, t-test) and the contralateral caudate ($p < 0.002$) than the PD patients. There continued to be significant difference in the asymmetry indices for the posterior putamen ($p < 0.04$, Mann-Whitney test) and the bilateral caudate:putamen ratios ($p < 0.002$, Mann-Whitney test) for the two groups. However there was no longer a significant difference in the binding measures in the posterior putamen between the two groups.

7.6. CORRELATION OF FP-CIT BINDING AND CLINICAL AND DEMOGRAPHIC FEATURES

There was a significant negative correlation between all striatal binding measures and both the UPDRS scale and the H&Y stage (higher scores on UPDRS and H&Y staging correlated with lower binding measures) for the whole cohort ($p < 0.001$). When analysing individual diagnostic groups, for the PD group there continued to be a significant negative correlation between the UPDRS scores and both the ipsilateral and the contralateral posterior putamen binding. There was also negative correlation between the H&Y stage and the ipsilateral anterior putamen binding in the PD group, see Table 7.6. There were no correlations between either the UPDRS score or the H&Y stage and any striatal binding measures in either the DLB group or the controls (Table 7.7).

We found no correlation between age at the time of scan or gender and any of the striatal binding measures. As expected there was a good correlation between UPDRS scores and H&Y stage (Spearman's ρ 0.86, $p < 0.001$). There was a strong correlation between MMSE and CAMCOG (Spearman's ρ 0.87, $p < 0.001$).

A negative correlation was found between visual hallucinations at time of scan and the binding measures in the caudate and the anterior putamen (the more frequent the hallucinations the lower the striatal binding; $p < 0.01$) and a weak negative correlation between visual hallucinations and the posterior putamen ($p < 0.02$).

There was a negative correlation between the Behave AD scores and the binding measures (higher scores reflecting more psychopathology, have lower binding) in the caudate and the anterior putamen ($p < 0.05$). There was a negative correlation between the CAPE and all the binding measures. The CDR and MMSE significantly correlated only with binding in the caudate ($P < 0.02$) and ipsilateral anterior putamen ($p < 0.03$) but not in the contralateral anterior and posterior putamen. Likewise, CAMCOG correlated ($p < 0.03$) with binding measures in the caudate but not in the putamen (Table 7.7).

7.7. COMPARISON OF FP-CIT BINDING AND MOTOR SYMPTOMS

In 16 out of 19 PD patients the posterior putamen binding was lower on the side contralateral to the clinically worse affected side. However in 3 patients the

clinically worse affected side recorded in the clinic by the neurologist did not match up with lower counts in the contralateral posterior putamen.

7.8. SIMPLE QUALITATIVE VISUAL ASSESSMENT OF SCANS

There was excellent agreement between the independent assessments of the specialist in nuclear medicine, the old age psychiatrist and the neurologist (kappa values 0.85, 0.89, 0.9). We compared the visual rating with the semi-quantitative results by defining as abnormal any scan with contralateral posterior putamen binding which was more than two standard deviations below the mean of the controls (<3.02). The consensus visual rating (two or all three assessments in agreement) and the semi-quantitative rating gave the same result (normal or abnormal scan) in 72/79 scans (91%), with kappa 0.82, again an excellent agreement.

7.9. AUTOPSIES

To date we have results of autopsies on 11 of the patients with dementia (Table 7.8). These highlight shortcomings in the accuracy of the diagnoses made using the clinical diagnostic criteria, with an apparent tendency to overdiagnose DLB. The autopsy data have a number of effects on the results reported above. Reanalysing the data in the light of autopsy diagnoses where available, there are no longer significant differences between the DLB and AD groups with respect to: MMSE, CAMCOG, CDR, Cornell Scale for Depression in Dementia, Behave-AD, and CAPE. The confidence intervals for the semi-quantitative binding measures for the

DLB group are all somewhat tighter, and importantly the separation of the DLB group from the AD group becomes greater (Table 7.9, Figure 7.6, 7.7, 7.8, 7.9, 7.10, 7.11). Most importantly, with one exception (Case 5), an abnormal scan always associates with an autopsy diagnosis of DLB, giving a sensitivity of 100% and a specificity of 86%, by comparison with high sensitivity but very low specificity for the clinical consensus criteria for DLB in our clinics. In Case 5 the explanation for the scan being misleading is that the autopsy showed an infarct in the putamen on the side with low binding of ligand, and in fact the binding values in the five other regions of that scan were well maintained, arguing in retrospect against a nigrostriatal degenerative process.

FIGURE 7.1 Caudate nucleus radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), Parkinson disease (PD) and healthy controls (means and 95% confidence intervals)

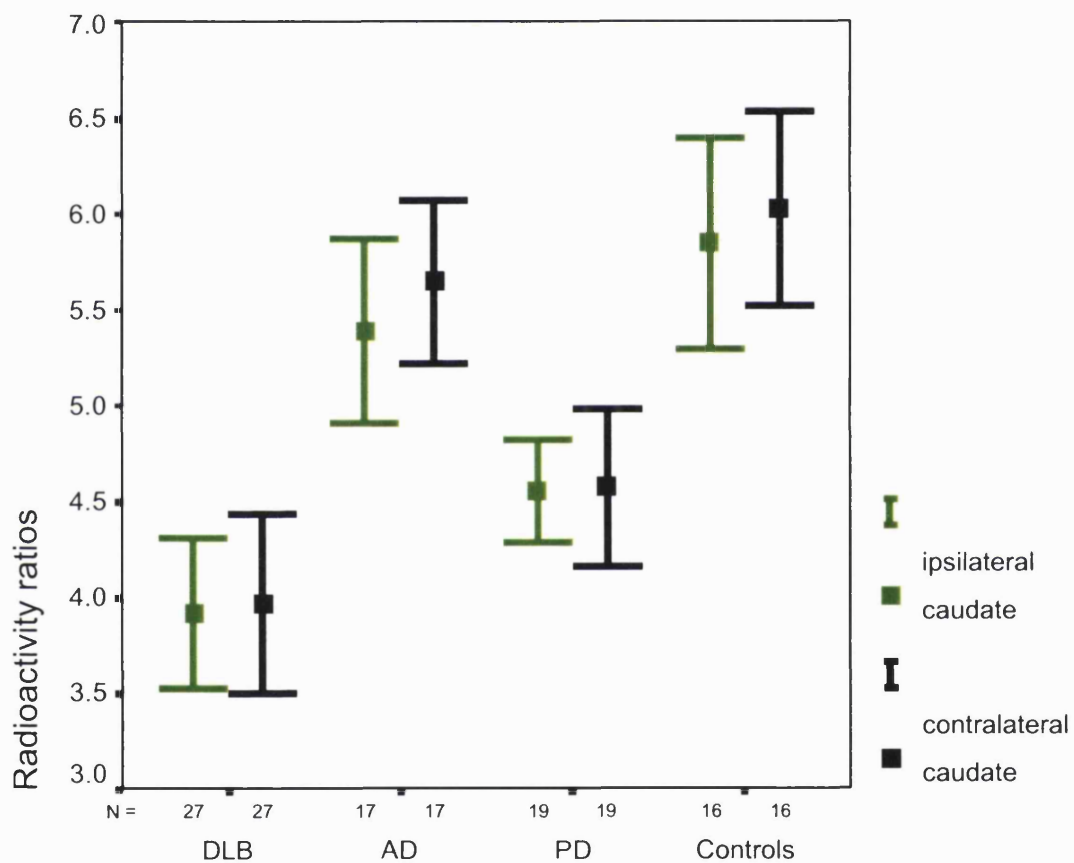


FIGURE 7.2 Anterior putamen radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), Parkinson disease (PD) and healthy controls (means and 95% confidence intervals)

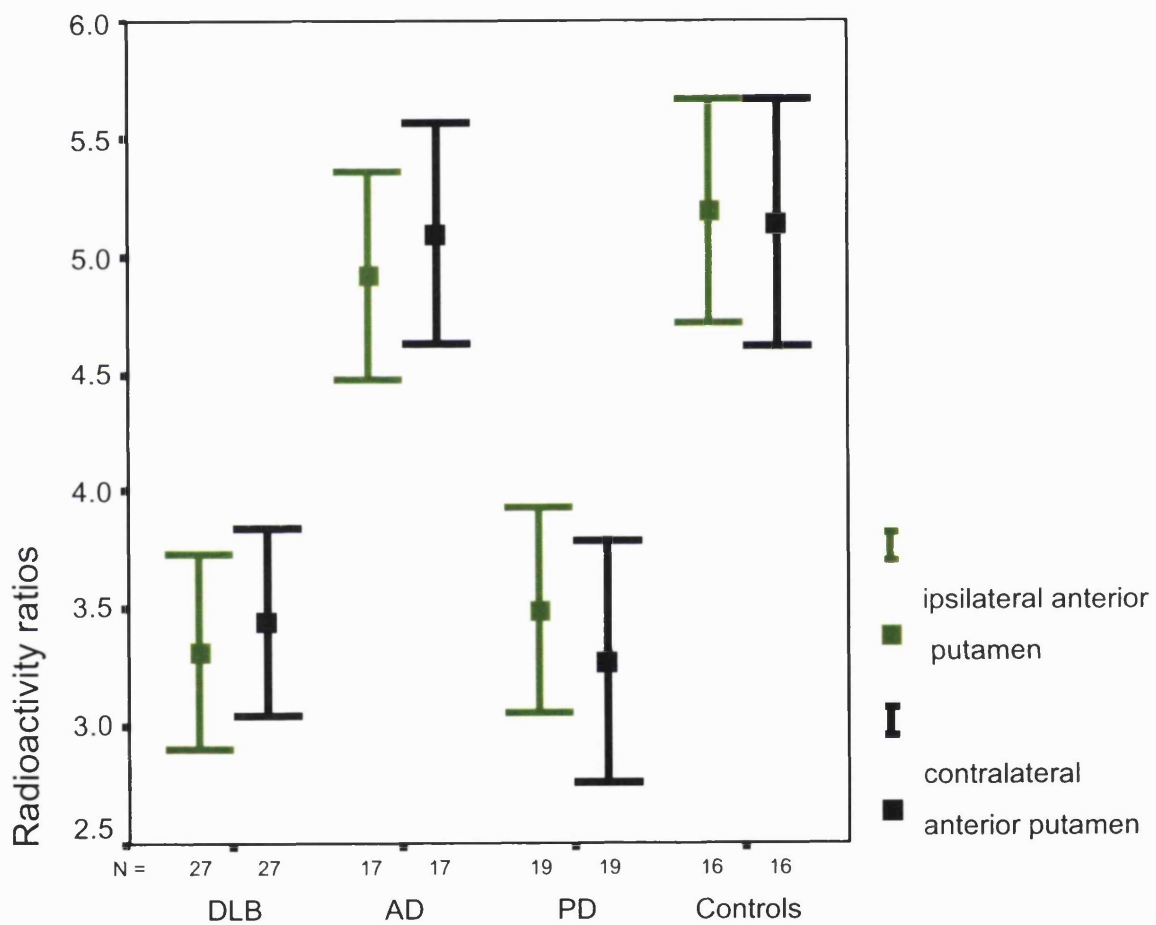


FIGURE 7.3 Posterior putamen radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD), Parkinson disease (PD) and healthy controls (means and 95% confidence intervals)

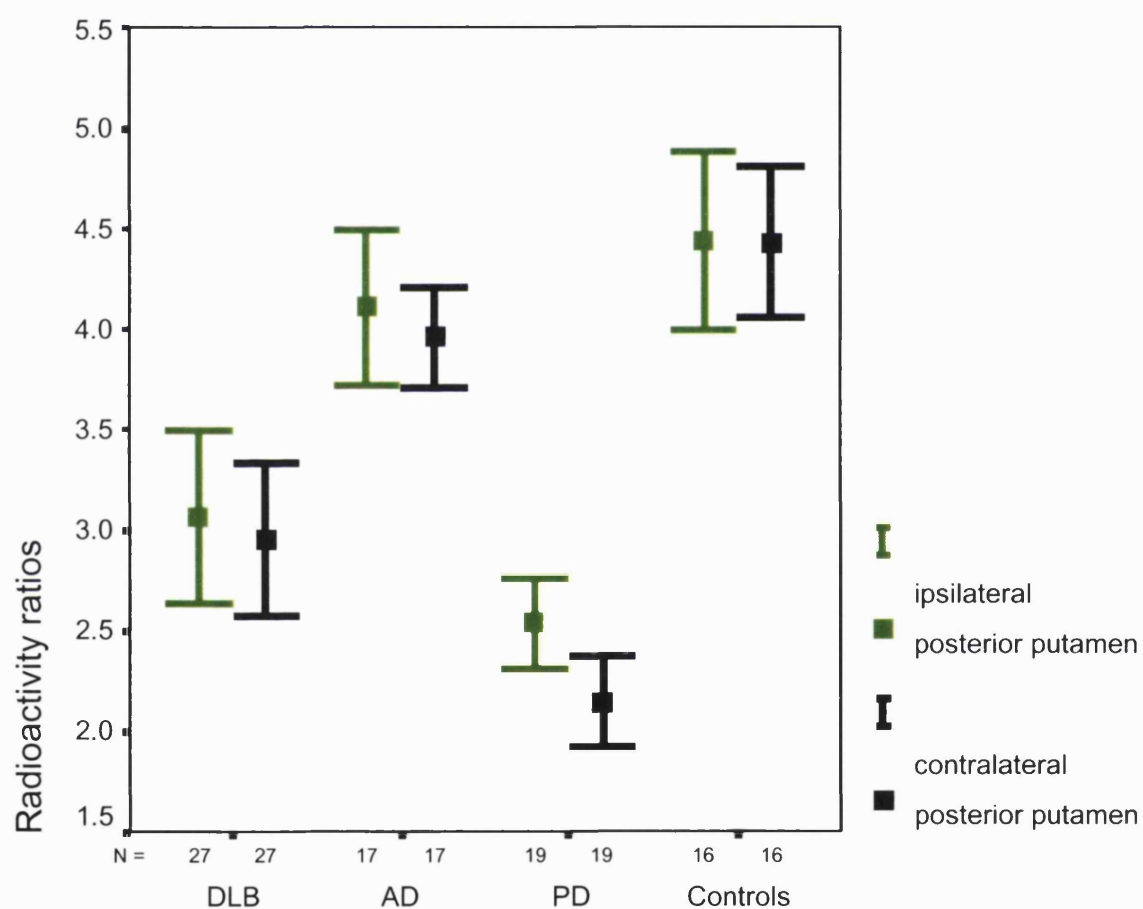


FIGURE 7.4 Posterior putamen asymmetry index for Parkinson's disease (PD), Dementia with Lewy bodies (DLB) and healthy controls (means and 95% confidence intervals)

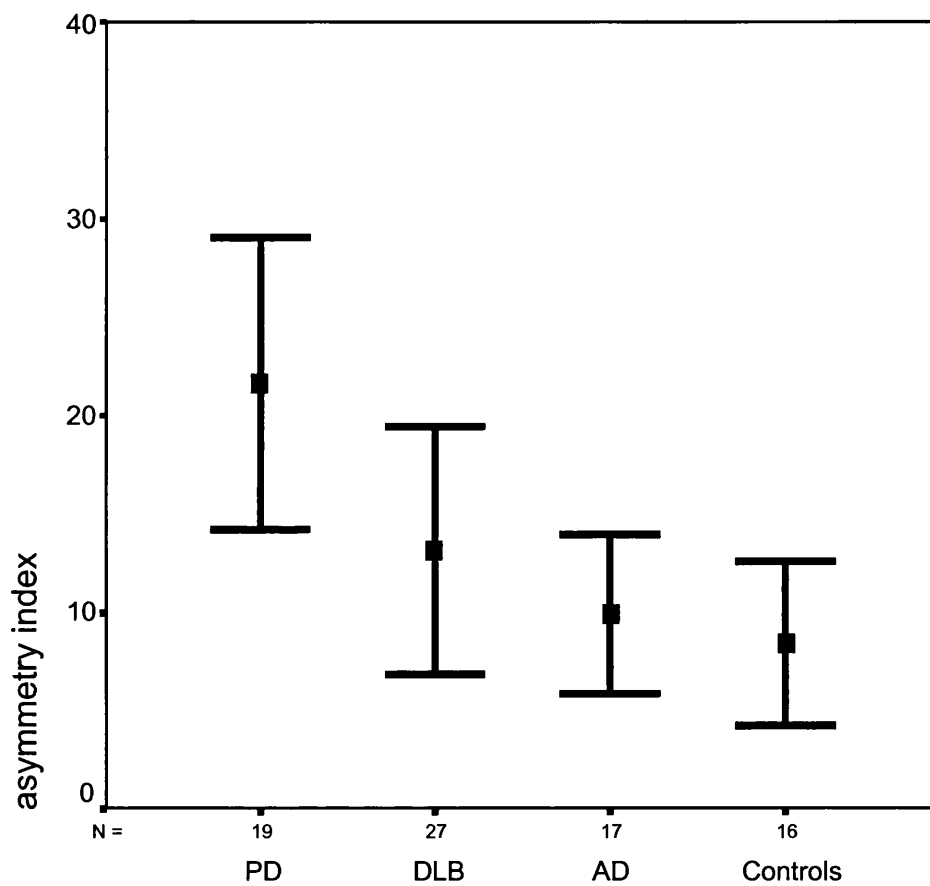


FIGURE 7.5 Caudate:putamen ratio for Parkinson's disease (PD), Dementia with Lewy bodies (DLB) and healthy controls (means and 95% confidence intervals of the means)

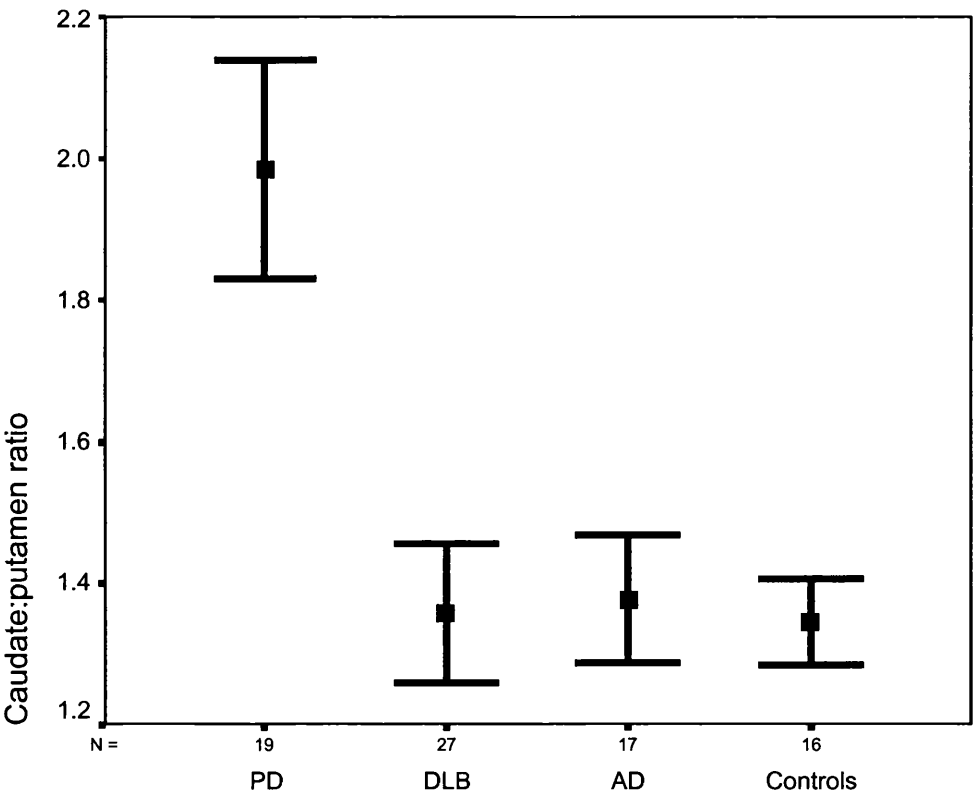


FIGURE 7.6 Left caudate nucleus radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and healthy controls; contralateral caudate nucleus radioactivity ratios for Parkinson disease (PD); after 11 autopsy results (scatterplot, means and 95% confidence intervals)

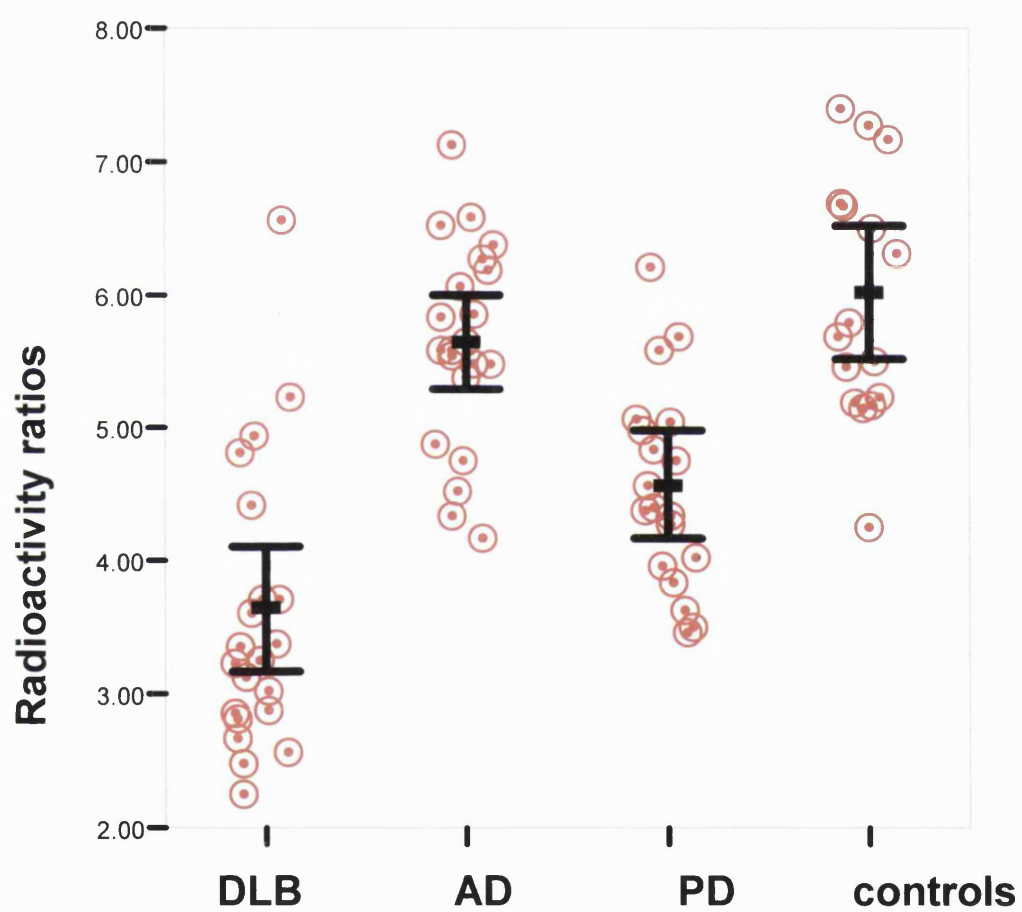


FIGURE 7.7 Right caudate nucleus radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and healthy controls; ipsilateral caudate nucleus radioactivity ratios for Parkinson disease (PD); after 11 autopsies results (scatterplot, means and 95% confidence intervals)

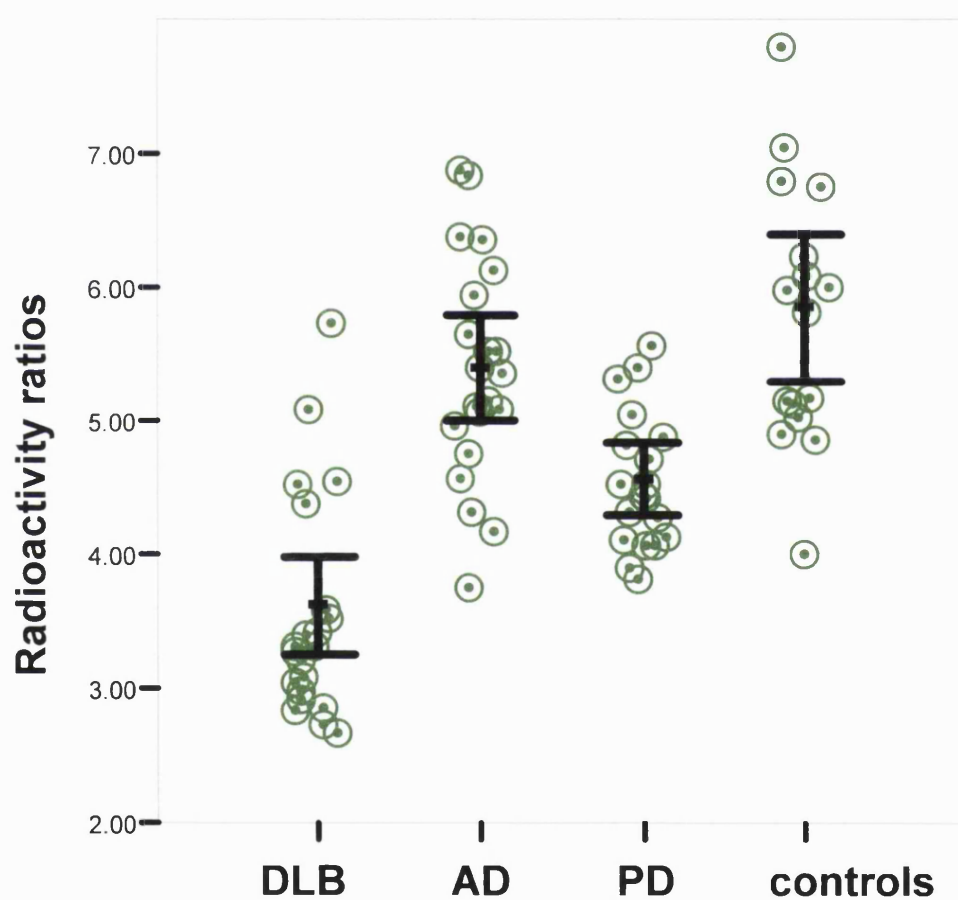


FIGURE 7.8 Left anterior putamen radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and healthy controls; contralateral anterior putamen radioactivity ratios for Parkinson disease (PD); after 11 autopsy results (scatterplot, means and 95% confidence intervals)

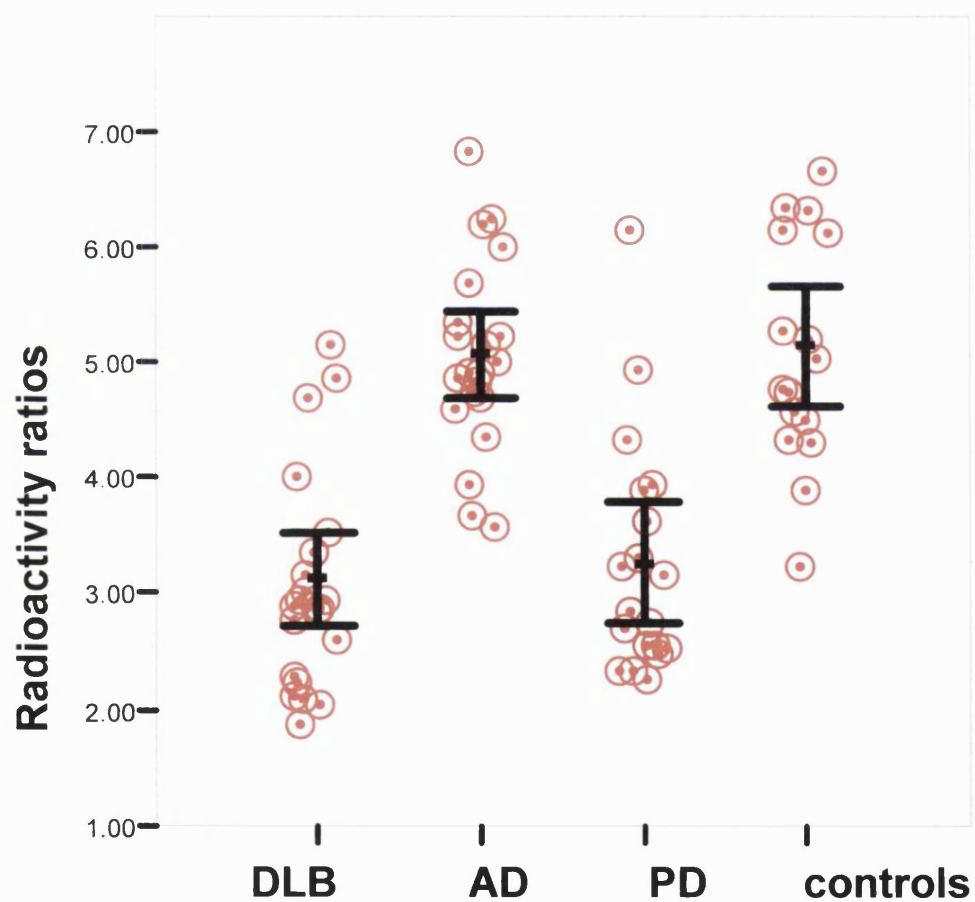


FIGURE 7.9 Right anterior putamen radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and healthy controls; ipsilateral anterior putamen radioactivity ratios for Parkinson disease (PD); after 11 autopsy results (scatterplot, means and 95% confidence intervals)

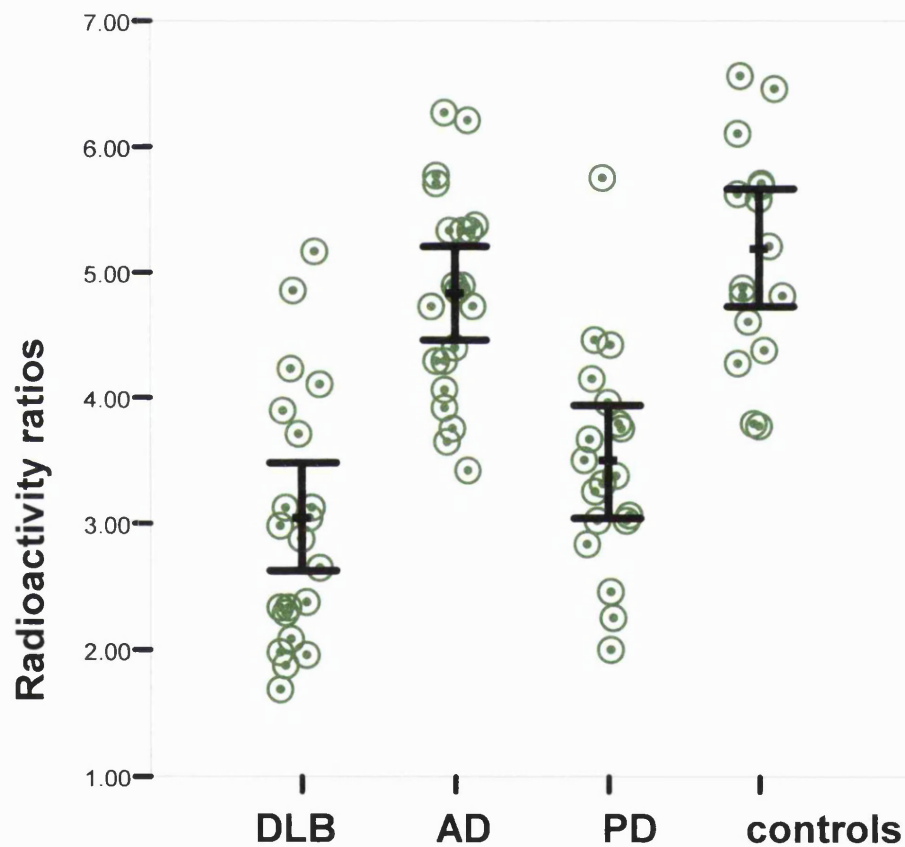


FIGURE 7.10 Left posterior putamen radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and healthy controls; contralateral posterior putamen radioactivity ratios for Parkinson disease (PD); after 11 autopsy results (scatterplot, means and 95% confidence intervals)

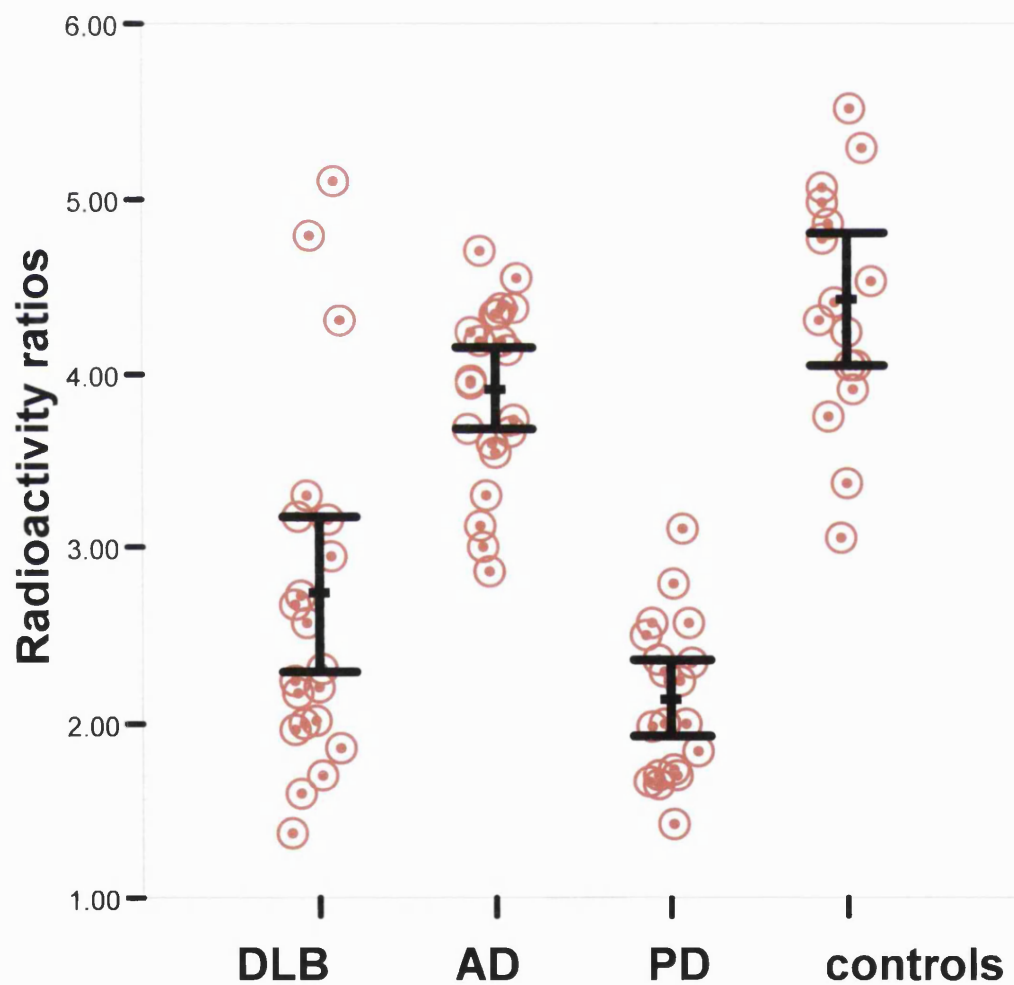


FIGURE 7.11 Right posterior putamen radioactivity ratios for Dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and healthy controls; ipsilateral posterior putamen radioactivity ratios for Parkinson disease (PD); after 11 autopsy results (scatterplot, means and 95% confidence intervals).

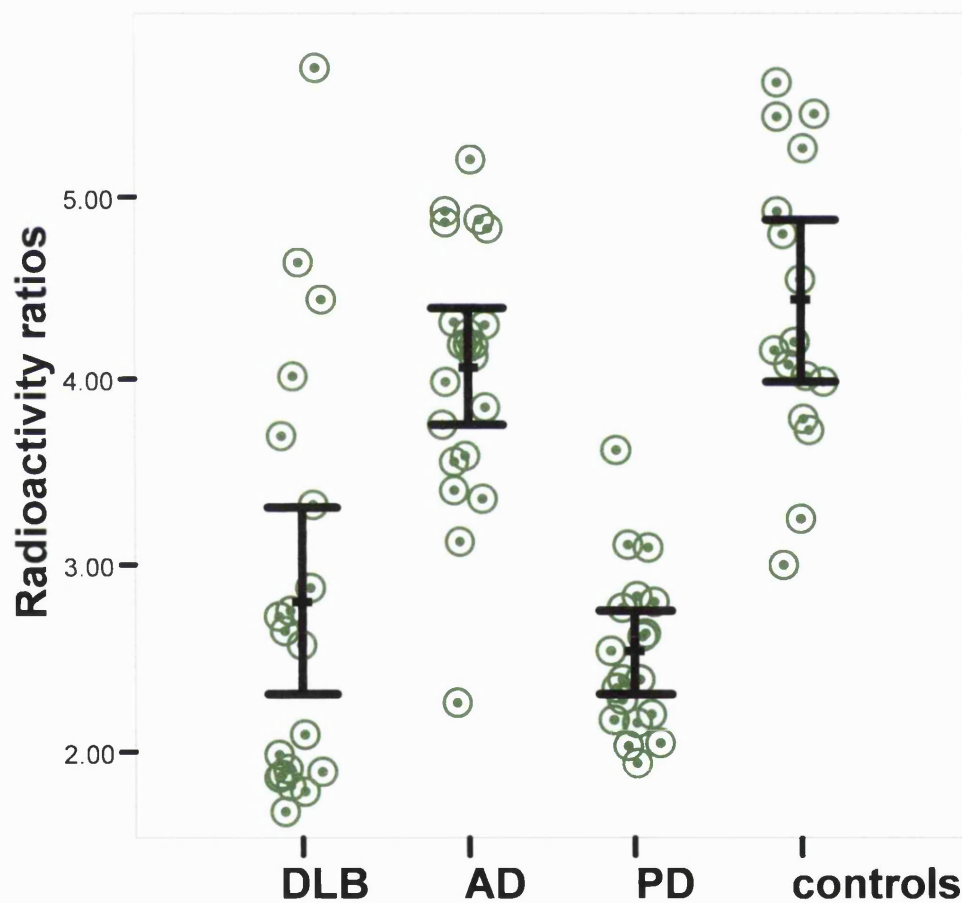


TABLE 7.1 Cohort characteristics of patients with DLB, AD, PD and controls

Characteristic	DLB (n=27)	AD (n=17)	PD (n=19)	Controls (n=16)	Significance	
					DLB vs AD	DLB vs PD
Positive family history of PD Yes	22%	6%	21%	0%	ns	ns
Positive family history of dementia Yes	33%	35%	10%	25%	ns	ns
Past psychiatric history Yes	19%	24%	10%	6%	ns	ns
Alcohol consumption: Moderate Excessive	56% 4%	70% 6%	84% 0%	87% 6%	ns	ns
History of smoking: Smoker Ex-smoker	4% 11%	12% 18%	10% 0%	0% 25%	ns	ns

TABLE 7.2 Cohort characteristics of patients with DLB, AD, PD and controls

Characteristic	DLB (n=27)	AD (n=17)	PD (n=19)	Controls (n=16)	Significance	
					DLB vs AD	DLB vs PD
Fluctuating course of illness						
Yes	85%	12%	0%	0%	p<0.001	p<0.001
Acute confusional states						
Yes	22%	12%	0%	0%	ns	p<0.05
Visual hallucinations						
Once only	26%	6%	0%	0%	p<0.001	p<0.001
Persistent	67%	0%	0%	0%		
Tremor						
Yes	59%	24%	79%	6%	p<0.03	ns
Rigidity						
Yes	63%	6%	79%	0%	p<0.001	ns
Akinesia/ bradykinesia						
Yes	67%	18%	89%	19%	p<0.01	ns

TABLE 7.3 Cohort characteristics of patients with DLB, AD, PD and controls

Characteristic	DLB (n=27)	AD (n=17)	PD (n=19)	Controls (n=16)
Gender ratio M:F	10:17	9:8	15:4	10:6
Age at time of FP-CIT Mean (SD) Median	77.3 (7.9) 77	78.0 (7.2) 77	64.9 (9.1) 62	66.6 (10.8) 70
Age at onset of dementia Mean (SD) Median	73.1 (8.0) 73	73.1 (6.8) 73		
Duration of symptoms in years Mean (SD) Median	4.2 (3.8) 3	3.9 (2.7) 3.5	1.9 (1.5) 1	
Systolic pressure Mean (SD) Median	138.4 (28.6) 135	140.1 (24.4) 140	149.6 (23.9) 143	
Years of education Mean (SD) Median	9.7 (1.9) 9	9.3 (1.5) 9	10.6 (2.7) 10	11.9 (3.4) 11
H&Y staging Mean (SD) Median	2.2 (1.2) 2	0.3 (0.8) 0	1.7 (0.6) 1.5	0.1 (0.2) 0
UPDRS score Mean (SD) Median	18.0 (11.2) 18	3.1 (5.0) 1	14.8 (4.9) 16	2.2 (3.5) 1

TABLE 7.4 Ratings of patients with DLB, AD, PD and controls

Scale	DLB (n=27)	AD (n=17)	PD (n=19)	Controls (n=16)	Significance AD vs DLB
CDR Mean (SD) Median	1.6 (0.82) 2.0	0.94 (0.48) 1.0	0.1 (0.2) 0.0	0.0 (0.0) 0.0	p<0.01
MMSE Mean (SD) Median	16.2 (6.2) 17	21.5 (5.3) 23	27.7 (2.5) 29	28.9 (1.2) 19	p<0.01
CAMCOG Mean (SD) Median	49.3 (26.0) 58	69.8 (15.2) 73	98.9 (5.8) 99	102 (3.7) 102	p<0.01
Cornell Scale for depression in dementia Mean (SD) Median	6.7 (5.4) 6	3.5 (3.5) 3			p<0.05
Behave-AD Mean (SD) Median	10.0 (5.9) 9	3.1 (4.5) 1			p<0.001
CAPE Mean (SD) Median	12.4 (7.6) 12	4.9 (5.0) 2			p<0.001

TABLE 7.5 Semi-quantitative FP-CIT binding measures (means and 95% confidence intervals and % controls means)

	DLB (n=27)	PD (n=19)	AD (n=17)	Controls (n=16)
Ipsilateral caudate binding				
Mean	3.91	4.55	5.39	5.85
95 % CI of the mean	3.52-4.30	4.28-4.82	4.90-5.87	5.30-6.40
% controls means	67%	78%	92%	100%
Contralateral caudate binding				
Mean	3.97	4.57	5.65	6.02
95 % CI of the mean	3.50-4.43	4.16-4.98	5.22-6.07	5.52-6.53
% controls means	66%	76%	94%	100%
Ipsilateral anterior putamen binding				
Mean	3.31	3.49	4.91	5.19
95 % CI of the mean	2.90-3.73	3.05-3.93	4.47-5.35	4.72-5.67
% controls means	64%	67%	95%	100%
Contralateral anterior putamen binding				
Mean	3.44	3.27	5.10	5.14
95 % CI of the mean	3.04-3.84	2.75-3.78	4.62-5.57	4.62-5.66
% controls means	67%	64%	99%	100%
Ipsilateral posterior putamen binding				
Mean	3.06	2.53	4.11	4.44
95 % CI of the mean	2.63-3.50	2.31-2.76	3.72-4.49	3.99-4.87
% controls means	69%	57%	93%	100%
Contralateral posterior putamen binding				
Mean	2.95	2.14	3.96	4.43
95 % CI of the mean	2.56-3.33	1.9-2.36	3.71-4.21	4.05-4.81
% controls means	67%	48%	89%	100%

TABLE 7.6 Correlation coefficients and significance levels (p) between striatal binding and UPDRS and H&Y for the PD group (n=19)

	UPDRS	H&Y
Ipsilateral caudate binding Correlation Coefficient Significance	-0.13 p=ns	-0.2 p=ns
Contralateral caudate binding Correlation Coefficient Significance	-0.14 p=ns	-0.23 p=ns
Ipsilateral anterior putamen binding Correlation Coefficient Significance	-0.4 p=ns	-0.66 p<0.001
Contralateral anterior putamen binding Correlation Coefficient Significance	-0.32 p=ns	-0.23 p=ns
Ipsilateral posterior putamen binding Correlation Coefficient Significance	-0.71 p<0.02	-0.22 p=ns
Contralateral posterior putamen binding Correlation Coefficient Significance	-0.64 p<0.04	-0.2 p=ns

TABLE 7.7 Correlation coefficients and significance levels (p) between striatal binding and UPDRS and H&Y for the DLB group (N=27)

	UPDRS	H&Y
Ipsilateral caudate binding Correlation Coefficient Significance	-0.18 p=ns	-0.1 p=ns
Contralateral caudate binding Correlation Coefficient Significance	-0.14 p=ns	-0.1 p=ns
Ipsilateral anterior putamen binding Correlation Coefficient Significance	-0.15 p=ns	-0.1 p=ns
Contralateral anterior putamen binding Correlation Coefficient Significance	-0.13 p=ns	-0.1 p=ns
Ipsilateral posterior putamen binding Correlation Coefficient Significance	-0.16 p=ns	-0.12 p=ns
Contralateral posterior putamen binding Correlation Coefficient Significance	-0.14 p=ns	-0.1 p=ns

TABLE 7.8 Comparison of clinical diagnosis, FP-CIT scan result and autopsy in the 11 patients for whom autopsies have become available

Case	Clinical diagnosis	Scan result	Autopsy diagnosis
1	DLB	Abnormal	DLB
2	DLB	Abnormal	DLB
3	DLB	Abnormal	DLB
4	DLB	Abnormal	DLB
5	DLB	Abnormal	AD/VaD
6	DLB	Normal	CBD
7	DLB	Normal	FTD
8	DLB	Normal	AD
9	DLB	Normal	AD
10	DLB	Normal	AD
11	AD	Normal	AD

TABLE 7.9 Semi-quantitative FP-CIT binding measures following 11 autopsy results (means and 95% confidence intervals)

	DLB (n=21)	PD (n=19)	AD (n=21)	Controls (n=16)
Ipsilateral caudate binding				
Mean	3.62	4.55	5.39	5.85
95 % CI of the mean	3.25-3.99	4.28-4.82	5.00-5.79	5.30-6.40
Contralateral caudate binding				
Mean	3.64	4.57	5.65	6.02
95 % CI of the mean	3.17-4.11	4.16-4.98	5.30-6.00	5.52-6.53
Ipsilateral anterior putamen binding				
Mean	3.05	3.49	4.84	5.19
95 % CI of the mean	2.61-3.48	3.05-3.93	4.46-5.21	4.72-5.67
Contralateral anterior putamen binding				
Mean	3.13	3.27	5.07	5.14
95 % CI of the mean	2.73-3.53	2.75-3.78	4.69-5.44	4.62-5.66
Ipsilateral posterior putamen binding				
Mean	2.81	2.53	4.07	4.44
95 % CI of the mean	2.30-3.31	2.31-2.76	3.76-4.38	3.99-4.87
Contralateral posterior putamen binding				
Mean	2.74	2.14	3.92	4.43
95 % CI of the mean	2.29-3.18	1.9-2.36	3.69-4.15	4.05-4.81

Chapter 8

Discussion

8.1. IBZM STUDY

In the first part of the work described here the changes in post-synaptic D₂ receptors in patients with a clinical diagnosis of DLB and AD were investigated. We found that DLB patients had overall higher binding in the putamen and lower binding in the caudate than AD patients and controls but this did not reach statistical significance. There are no in vivo studies of D₂ post-synaptic receptors in DLB and one has to be careful when comparing in vivo results with autopsy findings. However studies of post-mortem brains of DLB patients suggest that overall there is a reduction of D₂ receptor binding in both the caudate and the putamen¹¹⁹. Our result is therefore not in line with autopsy studies. Piggott³⁴ showed that binding of dopamine D₂ receptors varied among DLB patient depending on the exposure to neuroleptics and the presence of neuroleptic sensitivity. DLB patients tolerant of neuroleptics had D₂ receptors up-regulated compared to DLB cases that were intolerant of neuroleptic or not exposed during life to neuroleptics. In our sample only two patients were exposed to neuroleptics and therefore the majority of our DLB patients were neuroleptic naïve.

There are no other IBZM-SPET studies of patients with DLB, but there are SPET and PET studies examining the post-synaptic dopaminergic system in patients with

Parkinson's disease²¹⁷⁻²²⁰. Brooks²¹⁷ summarised the findings of seven studies of untreated PD patients and concluded that the post-synaptic putamen D₂ binding potential ranges from normal to upregulated but that the caudate D₂ binding potential is usually normal. Where side to side striatal uptake has been compared with PET or SPET in patients with PD there was a 10-28% greater post-synaptic uptake in the putamen contralateral to the more affected limbs²²⁰⁻²²². It is likely that the raised putamen D₂ binding potential, when present, represents an adaptive response in PD patients to loss of nigro-putaminal dopaminergic afferents²¹⁷.

The DLB and PD patients had significantly lower left caudate:putamen ratios than either controls or AD patients. Although overall there was a significant difference in the right caudate:putamen ratio between the three groups and between DLB and controls, the difference between DLB and AD was not significant. The decreased caudate:putamen ratio in the DLB and PD patients was due to the combination of upregulation of post-synaptic D₂ receptors in the putamen and a marked decrease of binding sites in the caudate. In our study the post-synaptic dopaminergic dysfunction in DLB was more pronounced on the left (contralateral) but clearly also affected the right side. Possible explanations for this laterality are that the sample was too small to reach statistical significance on the right or that, as in PD, tracer uptake is greater in the putamen contralateral to the more affected limbs. In patients with DLB the extrapyramidal symptoms are often fairly mild or even absent

and in most DLB patients it is not possible to decide which side is the more severely affected.

In the IBZM cohort the three groups were poorly matched for gender, the male:female ratio being 11:5 for DLB group, 5:8 for AD group and 7:8 for controls. This discrepancy mirrors the unequal prevalence of AD in both genders, women being more commonly affected than men, and the greater male:female ratio in DLB patients compared to AD patients reported by McKeith ⁴⁶. In the IBZM cohort DLB patients also tended to be less cognitively impaired as measured on MMSE and CAMCOG but more behaviourally disturbed and dependent as scored on the behavioural part of CAPE. Despite these differences they were well matched for the overall severity of their dementia as indicated by their clinical dementia score.

In conclusion, our data from the first IBZM cohort show that in vivo, patients with DLB have clear changes of post-synaptic striatal D₂ receptors compared to patients with AD and controls. However there is an overlap in the dopamine D₂ binding measures between different diagnostic groups and therefore IBZM SPET is unlikely to be useful in the differential diagnosis of AD and DLB. However our findings add to knowledge regarding the fairly complex post-synaptic dopaminergic metabolism in DLB and future studies involving larger cohorts of different clinical groups of DLB patients (neuroleptic tolerant, neuroleptic sensitive, patients with and without hallucinations and delusions) are likely to elucidate further the underlying mechanism of neuroleptic sensitivity and perhaps of psychotic phenomena.

8.2. FP-CIT STUDY

The second part of the thesis concentrated on the pre-synaptic dopaminergic metabolism using FP-CIT SPET. The main finding was that FP-CIT and SPET distinguishes clearly a group of clinically classified AD patients from a group of clinically classified DLB patients and that it is a much more promising technique than IBZM SPET. Furthermore, in this thesis, on the basis of final diagnoses made at autopsy, we showed that FP-CIT SPET scans performed better than consensus clinical criteria as a means of supporting the diagnosis of DLB in patients with dementia. The implication therefore is that FP-CIT SPET would be effective in improving the accuracy of diagnosis of DLB during life. Importantly, FP-CIT SPET could only be expected to add support to a clinical diagnosis, since any dementia which also involves nigrostriatal pathology, such as corticobasal degeneration or frontotemporal dementia with parkinsonism, or mixed pathology, might give rise to an abnormal FP-CIT SPET result, as indeed the case of putamen infarction in our cohort showed. Our patients with corticobasal degeneration and FTD had scans which were 'slightly abnormal or abnormal' by visual inspection, but the posterior putamen semi-quantitative binding was not in the abnormal range as we defined it.

This is the first study to show that it is possible to detect a clear reduction of striatal dopamine transporter in patients with DLB using FP-CIT SPET. It extends the observation by Donnemiller et al ¹⁶² and Ransmayr ¹⁸⁷ that patients with DLB have reduced striatal beta-CIT uptake and the observation by Hu et al ¹⁷² using PET that

patients with DLB who have extrapyramidal signs and are responsive to L-DOPA have significantly reduced uptake of ^{18}F -fludopa in the putamen and the caudate nuclei. Our findings are in keeping with autopsy studies of DLB that show loss of neurones in substantia nigra with concomitant reduction in dopamine re-uptake sites and dopamine levels in the striatum ^{36,119}.

The data show that simple visual rating of scans is effective, though we consider that the semi-quantitative analysis of scans considerably enhances the information which can be obtained from the scans as shown by the cases of FTD and corticobasal degeneration. Nevertheless in clinical practice where time is limited, the visual method can contribute substantially to the accuracy of the diagnosis. We have shown that there is a good agreement between the visual rating and the semi-quantitative rating method.

There were no significant differences in binding measures between AD patients and controls apart from measures in the contralateral posterior putamen where AD patients had 10% lower counts than controls. Lavalaye et al ²²³ have shown that the dopamine transporter density declines with age with a decrease of FP-CIT binding in the striatum of about 4% per decade. The healthy controls were approximately 10 years younger than AD and DLB patients and the age difference might explain the slightly lower counts in AD patients. It is also possible that some of the patients assigned clinically to the AD group actually have DLB.

Although other groups have reported good sensitivity and specificity figures for the Consensus criteria for DLB^{72,77,82,84} the diagnostic accuracy of the Consensus criteria of DLB has so far, particularly for our second cohort, been disappointing. The reason for the lower specificity of the Consensus criteria in the second cohort is not clear. It may simply be a chance phenomenon, as the number of cases are still small. Nevertheless the study reported here suggests that the incorporation of the results of functional imaging of the striatum into diagnostic criteria would greatly improve the precision of diagnosis of DLB during life.

The second important finding from the FP-CIT study is that there is a clear difference between PD and DLB in the pattern of striatal dopaminergic dysfunction. DLB patients had a very uniform decrease in the mean dopamine uptake sites compared to controls in both the caudate and the anterior and posterior putamen (in all sites ~33%). In contrast, patients with PD had less severe mean loss of binding sites in the caudate (~23%) but much more pronounced loss of binding sites in the putamen, in particular, in the contralateral posterior putamen (~52%). The different pattern of loss of dopamine transporter was further highlighted by the caudate:putamen ratio which was significantly different between PD and DLB for both the ipsilateral and the contralateral side but not different between DLB, AD and controls. These observations suggest that DLB patients do not have the characteristic selective degeneration of ventrolateral nigral neurons that has been repeatedly shown in PD in both autopsy and imaging studies^{116,177,195}.

The substantia nigra zona compacta can be divided into a ventrolateral tier, a dorsomedial tier and a paranigral tier, each projecting respectively to the putamen, caudate nucleus and the nucleus accumbens. The pathway from the ventrolateral tier is crucial for motor function and the other two pathways may be important for cognitive and emotional functions ¹¹⁶. The more severe loss of caudate binding in DLB, compared to early PD, might be one of the reasons for some of the cognitive and psychiatric symptoms in DLB. This view gains support from the relatively strong negative correlation ($r = -0.4$) between visual hallucinations and binding measures in the caudate and anterior putamen (the more frequent the hallucinations the lower the striatal binding) and the low correlation with posterior putamen binding ($r = -0.2$). There was also a tendency for other cognitive (MMSE, CAMCOG) and behavioural measures (CAPE, CDR, Behave-AD) to correlate with caudate but not with posterior putamen (a positive correlation with MMSE and CAMCOG scores and negative correlation with behavioural measures).

The second difference between the PD and DLB groups was in the asymmetry index in the posterior putamen. Patients with PD had a more asymmetrical loss of binding sites in the posterior putamen than DLB patients and controls. This accords with the clinical observation of Gnanalingham et al ²²⁴ and Ransmayrl et al ¹⁸⁷ that patients with DLB present with more symmetrical motor signs than patients with PD and with the observation of Aarsland et al ²²⁵ that symmetrical extrapyramidal features are associated with dementia. However curiously Ransmayrl et al ¹⁸⁷ did not find a significant difference in the asymmetry index between DLB and PD

patients using ¹²³Ibeta-CIT and SPET despite a significant difference on clinical measures of asymmetry between the two groups. The reason for this might be that Ransmayrl et al did not make a distinction between binding measures of caudate and putamen. They calculated the asymmetry index for the total ipsilateral and contralateral striatal binding and so could have failed to detect asymmetry which is most marked in the posterior putamen. Their DLB group also had a significantly higher mean UPDRS score than the PD group and consequently had lower overall striatal binding. Our cohort of PD patients was in the early stages of the disease, drug naïve to antiparkinsonian medication and at the point of first visit to a neurology clinic, with a mean UPDRS score of 14.8 compared to 26.6 in the Ransmayrl et al cohort.

In our study there was no significant difference between the DLB and PD groups in the UPDRS and the H&Y stage, but PD patients and controls were significantly younger than DLB patients. Lavalaye et al ²²³ and Tissingh et al ¹⁹⁶ showed that in healthy volunteers there is a clear decline of FP-CIT uptake with aging. However in the PD group, age did not account for a significant part of the variance in striatal measures ^{196,226}. In our study we did not find a relationship between age at time of scanning and any of the individual binding measures. When we repeated all the statistical analyses with a subgroup of DLB and PD patients matched for age and duration of illness there continued to be significant differences between the two groups in binding measures, asymmetry indices and caudate:putamen ratios

indicating that in the original cohort age did not have a significant influence on the results.

As expected we found that FP-CIT uptake is significantly decreased in PD patients in both the contralateral and ipsilateral striatum at the time when they present for the first time to a neurologist and have not been exposed to any antiparkinsonian medication. The other study that investigated drug-naïve PD patients with FP-CIT and SPET was that of Tissingh et al ¹⁹⁶. In that study 21 drug naïve PD patients were compared with 14 controls. The PD patients had early disease (mean H&Y stage 1.8) and the mean reduction in uptake in the putamen was 57% and in the caudate 29% of the control mean. Our results for PD patients were very similar with the mean H&Y stage 1.7 and the mean reduction in the putamen 52% on the contralateral side, 43% on the ipsilateral side and in the caudate 22% on the ipsilateral side and 24% on the contralateral side.

We found that in the PD group there was a significant correlation between the motor UPDRS scores and the ipsilateral and contralateral posterior putamen binding. However there was no significant correlation between the UPDRS scores and the striatal binding in the DLB group. This is in line with the report by Ransmayrl et al ¹⁸⁷ in whose DLB group there was no correlation of ¹²³Ibeta-CIT binding with UPDRS scores, but in whose PD group there was a clear negative correlation. Three studies have examined the correlation of parkinsonian signs and FP-CIT binding measures. In a study of 6 early and 12 advanced PD patients by

Booij et al ¹⁹⁵, both ipsilateral and contralateral binding measures correlated with H&Y stage but not with motor UPDRS score. Surprisingly however, in a further study by the same group ¹⁹⁶, no significant correlation was found between striatal FP-CIT binding and PD severity. More recently, Benamer et al ²²⁷ studied 41 PD patients of varying severity. The FP-CIT binding measures in the striatum correlated with disease severity as assessed by UPDRS and with duration of illness. One can conclude from the above that there is increasing evidence that in PD there is a good correlation between the severity of motor symptoms and FP-CIT binding, but that in DLB the relationship is not so clear. The explanation for this could be that in DLB degeneration in other neural pathways involved in motor control, using other neurotransmitters, confound the clinical picture or that the UPDRS is less reliable in this group of patients. The UPDRS has not been validated for DLB patients and its accuracy could be influenced by factors such as cognitive deficit, fluctuating attention and apraxia.

An important potential shortcoming of the present study is that some of the PD patients may turn out to have an alternative diagnosis at autopsy. The clinical misdiagnosis rate in PD is about 10%-15%. The non-PD conditions which are most frequently clinically misdiagnosed as PD are progressive supranuclear palsy and multiple system atrophy ⁸⁹, and they generally cause a more symmetric rigid akinetic syndrome than PD. Thus the observations concerning the asymmetry index presented here might be even more striking if autopsy data were available for all PD patients. Similarly the lower caudate binding in DLB by comparison with PD

might become more pronounced if autopsy data were available for all the DLB patients, since some of the clinically diagnosed DLB patients may have Alzheimer's disease or another diagnosis.

In summary the results above show that there is a clear difference in the striatal dopamine uptake as measured by FP-CIT and SPET between DLB and PD and we suggest that this could explain some of the clinical differences between the two groups. It would appear that the same underlying pathology (i.e. Lewy body disease) can give rise to different phenotypic expression, depending at least partly on the topography of involvement. The question as to what determines the topography remains open, though it is likely that age is one of the factors.

Finally, SPET scanning with both IBZM and FP-CIT appears to be feasible and clinically helpful. The scanning procedure was well tolerated by patients and controls. It was possible to obtain a good quality scan for all participants of both cohorts and no serious adverse effects were observed.

8.3. CONCLUSIONS

- Our results show that FP-CIT SPET provides a means of distinguishing DLB from AD during life. Furthermore, on the basis of final diagnoses made at autopsy, we showed that FP-CIT SPET scans performed better than consensus clinical criteria as a means of supporting the diagnosis of DLB in patients with dementia. We therefore suggest that the incorporation of the results of

functional imaging of the striatum into diagnostic criteria would greatly improve the precision of diagnosis of DLB during life.

- The second most important finding is that there are clear differences between PD and DLB in the pattern of striatal dopaminergic dysfunction. DLB patients do not have the characteristic selective degeneration of ventrolateral nigral neurons that has been shown in PD. We suggest that this could explain some of the clinical differences between DLB and PD.
- Our data also show that patients with DLB have changes in striatal post-synaptic D₂ receptors. However, this is unlikely to be of value in distinguishing DLB from AD during life.

8.4. LIMITATIONS

- The main limitation of the work presented is that the prospective follow-up of the FP-CIT cohort is still ongoing. At present only a relatively small number of patients have died and come to autopsy. More than half of the DLB, most of the AD and all of the PD patients and controls are still alive.
- All the imaging data presented is cross sectional and therefore no comments can be made about the changes in dopaminergic pathways (pre- and post-synaptic) with disease progression in the different diagnostic groups.

- The PD patients were significantly younger than the DLB patients. It also became apparent that an additional group of patients fulfilling the diagnostic criteria for “PD with dementia” would have greatly enhanced our results.
- Finally, there is no prospective follow-up planned for the IBZM cohort. It is therefore unlikely that we will get many more autopsy results from this cohort.

8.5. FUTURE DIRECTIONS

In this thesis we have shown that it is feasible to investigate dopaminergic pathways in vivo in patients with DLB, AD and PD. To date only limited research has been carried out in this field and there are a number of areas that we would like to investigate further:

- Foremost, we plan to continue prospectively to follow-up our FP-CIT cohort and obtain as many autopsy results as possible to assess further the accuracy of FP-CIT SPET and the clinical criteria. We have already obtained agreement of intention to donate brain after death for research purposes from a number of patients and their relatives.
- We plan to scan a cohort of patients with “PD and dementia” and compare them with our early, drug naïve PD and DLB patients.

- We would like to re-scan with FP-CIT SPET our PD cohort, in particular PD patients that have developed psychotic phenomena and/or dementia.
- At present we do not plan to carry out any further work with IBZM SPET.
- Finally we wait for other centres to reproduce our findings.

List of publications and presentations

Publications

WALKER Z., COSTA D.C., D'ATH P.J., JANSSEN A.G.M. & KATONA C.L.E. (1997)

Can SPET distinguish Lewy body dementia from Alzheimer's disease during life? In

SPECT in Neurology & Psychiatry DeDeyn P.P., Dierckx R.A., Alavi A., Pickut

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