

THE COMPARATIVE NEUROPSYCHOLOGY OF DEMENTIA

Thesis submitted for the degree of

Doctor of Philosophy

at the

University of Newcastle upon Tyne

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by

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January 1998

ABSTRACT

On the basis of neuropathological, neurochemical, genetic, and clinical profile studies on patients, distinct forms of dementia, such as dementia with Lewy bodies (DLB), have been distinguished which were originally thought to be Alzheimer's disease (AD). Dementia with Lewy bodies is probably the second most common form of dementia in the elderly. In this thesis, a well characterised and investigated cohort of DLB and AD patients were compared to non-demented elderly controls in order to establish profiles of cognitive decline in these groups.

Initially, comprehensively matched experimental groups were compared using the Cambridge Neuropsychological Test Automated Battery (CANTAB). The DLB group was less impaired than the AD group on a test of visual pattern recognition memory. However, the DLB group performed worse on a number of cognitive tests.

Comparison of larger, carefully matched, experimental groups using the Cognitive Drug Research Computerised Assessment Battery (CDR) also revealed differences in the profile of cognitive impairment in DLB and AD. The DLB group showed more marked deficits in attentional abilities than the AD group. In particular, the DLB group were unable to sustain attention. Conversely, the DLB group were less impaired on a test of visual secondary recognition memory than the AD group.

Further division of the DLB group into cases with and without persistent visual hallucinations revealed distinct patterns of cognitive impairment in these two groups. Generally, DLB cases with persistent visual hallucinations showed greater attentional and spatial working memory deficits than the DLB cases without persistent visual hallucinations.

A final study compared decline in cognitive function over 1 year in DLB, AD and control groups. Similar rates of cognitive decline were identified in a number of cognitive domains in AD and DLB groups. In addition, disproportionate decline in the ability to sustain attention was identified in the DLB group.

A comparative model relating known neuropsychological, neurochemical, and neuropathological features of DLB and AD was proposed.

ACKNOWLEDGEMENTS

This thesis could not have been completed in isolation and I gratefully acknowledge the help of others. I would like to take this opportunity to thank:

- My supervisors, Prof Ian G. McKeith, Dr Arjun Sahgal, and Prof Keith Wesnes for their invaluable guidance and support.
- Dr Clive Ballard, Kath Lowery, Patricia McCue, and other researchers involved in the Newcastle Prospective Study of Memory Disorders for allowing me to approach patients in their care and access to clinical data relevant to this thesis.
- Professor James Edwardson for making available the facilities of the Medical Research Council Neurochemical Pathology Unit, Newcastle upon Tyne.
- Dr Neil Spears for advice and assistance.
- Dr Andrew Scholey for his friendship, advice, support, and allowing me to win at snooker throughout the duration of this project.
- Dr Clare Pincock for her help and enthusiasm for sorting discs.
- Professor Elaine Perry and Dr Chris Morris for their help and advice.
- Arthur Oakley and Dr Mark Cookson for help with photography.
- Ros Hall and Andrew Brown for providing histopathological support.
- Maureen Middlemass and Ann Nicholson for secretarial assistance.
- All my friends and colleagues in Newcastle for providing advice and support.

Finally, I am indebted to all the people with dementia, their carers and families, for agreeing to participate in this study.

I dedicate this thesis to my family, and my partner, Lisa Knight, for their rock-solid support during the last three years.

PREFACE

The following work was undertaken at the Medical Research Council, Neurochemical Pathology Unit, Newcastle upon Tyne and the Department of Psychiatry, University of Newcastle upon Tyne between August 1994 and January 1998 under the direction of Professor I.G. McKeith, Doctor A. Sahgal, and Professor K. Wesnes.

This dissertation has not been submitted, in whole or part, for any other degree, diploma or qualification at this or any other University.

PUBLICATIONS

Some of the results reported in this thesis have been published in preliminary form in the following reports:

Ayre G.A., McKeith I.G., & Sahgal A. (1995). Neuropsychological aspects of senile dementias of the Lewy body and Alzheimer's type: Recent findings and future directions. International Workshop on dementia with Lewy bodies, Newcastle upon Tyne, October 1995.

Ayre G.A., McKeith I.G., Sahgal A., Ballard C.G., & Wesnes K.W. (1996). The profile of cognitive deterioration in Lewy body dementia. *Proceedings of the British Psychological Society*, 5(1): 48

Ayre G.A., McKeith I.G., Wesnes K., & Sahgal A.. Psychological function in dementia with Lewy bodies and senile dementia of the Alzheimer type. *Neurobiology of Ageing*. 17 Suppl. 4S: 205-206

Ayre G.A., McKeith I.G., Wesnes K., & Sahgal A. Computerised cognitive assessment: Applications in the psychology of dementia. Symposium: Advances in the assessment and understanding of cognitive dysfunction. *Proceedings of the British Psychological Society*, 4: 105

Ayre G.A., Sahgal A., Wesnes K., Ballard C.G., Lowery K.N., & McKeith I.G.. Psychological and neurochemical dysfunction in dementia with Lewy bodies. *Journal of Psychopharmacology*. 10, Suppl.: A52

McKeith I.G., & Ayre G.A. (1997). Consensus criteria for the clinical diagnosis of dementia with Lewy bodies. In: Iqbal K, Winblad B, Nishimura T, Takeda M, & Wisniewski HM. (Eds.) *Alzheimer's disease: Biology, Diagnosis and Therapeutics*. John Wiley & Sons, pp 167-178.

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ABBREVIATIONS

ACh	Acetylcholine
AD	Alzheimer's disease
ADL	Activities of daily living
ANOVA	Analysis of variance
ApoE	Apolipoprotein E
CAMCOG	Cambridge Cognitive Examination
CAMDEX	Cambridge Examination for Mental Disorders in the Elderly
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDR	Cognitive Drug Research Computerised Assessment battery
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CFE	Critical flicker fusion
ChAT	Choline acetyltransferase
cLB	Cortical Lewy body
CLPA	Conditional learning (pattern-location) paired associates
CNS	Central nervous system
CRT	Choice reaction time
CSDD	Cornell Scale for Depression in Dementia
CT	Computed tomography
CYP2D6	Cytochrome P450 2D6
DA	Dopamine
DLB	Dementia with Lewy bodies
DLB+VH	Dementia with Lewy bodies with persistent visual hallucinations
DLB-VH	Dementia with Lewy bodies without persistent visual hallucinations
DLBD	Diffuse Lewy body disease
DMTS	Delayed matching to sample
DRS	Dementia rating scale
DSM-III-R, DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (3rd edn revised, 4th edn)
EEG	Electroencephalogram
EPS	Extrapyramidal (motor) symptoms
5-HIAA	5-hydroxyindoleacetic acid
5-HT	Serotonin
H&E	Haematoxylin and Eosin
HVA	Homovanillic acid
IADL	Instrumental Activities of Daily Living Schedule
ICC	Idiopathic clouding of consciousness
ID-ED	Intra- extra-dimensional set shifting test
IMC	Blessed Information, Memory, Concentration Test
KDCT	Kendrick Digit Copying Test
KOLT	Kendrick Object Learning Test
LB	Lewy body(ies)
LBD	Lewy body dementia (disease)
LBV, LBVAD	Lewy body variant (of Alzheimer's disease)
MID	Multi infarct dementia
MMSE	Mini-Mental State Examination

MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
MTS	Matching to sample
NART	National Adult Reading Test
nbM	Nucleus basalis of Meynert
NFT	Neurofibrillary tangle
NINCDS-ADRDA	National Institutes of Neurological and Communicative Disorders - Alzheimer's Disease and Related Disorders Association
PD	Parkinson's disease
PR	Pattern recognition
PHF	Paired helical filament
SDAT	Senile dementia of the Alzheimer type
SDLT	Senile dementia of Lewy body type
SMTS	Simultaneous matching to sample
SP	Senile plaque
SRT	Simple reaction time
SWM	Spatial working memory test
THA	Tetrahydroaminoacridine (Tacrine)
TYR-OH	Tyrosine hydroxylase
UPDRS	Unified Parkinson's Disease Rating Scale
VaD	Vascular dementia
VSMTS	Visual search matching to sample
WAIS-R	Weschler Adult Intelligence Test - Revised
WCST	Wisconsin Card Sorting Test
WISC-R	Weschler Intelligence Scale for Children - Revised

Note: The terms DLB, SDLT, LBV, LBVAD, DLBD, and LBD, have previously been employed by different authors to describe dementia with Lewy bodies. The terminology used by original authors is reported in this thesis to reflect the subtle clinical, neuropathological, neurochemical and neuropsychological differences associated with these appellations.

Chapter 1:

Introduction

1.1 General Introduction

Improved social, economic, medical and nutritional circumstances, as well as falling birth rates, especially in developed countries, have led to radical changes in demographic profiles with an increasingly aged population. The number of people over retirement age has increased dramatically over the past 20 years so that already one in six of the population now falls into this category. The estimated 9.5 million retirement pensioners in the UK outnumber children of school age (Central Statistical Office, 1984). Dementia is primarily a disease of the elderly and has consequently become 'one of the most pervasive social health problems of our generation' (Royal College of Physicians Committee on Geriatrics, 1981). Dementia affects approximately 5% of the population over 65 years old and this figure rises to 22% in those over 80 years old (Kay et al, 1970).

Dementia describes a specific group of illnesses characterised by chronic irreversible and progressive deterioration of intellectual function based on primary neuronal disturbances. The three most common forms of dementia in the elderly are Alzheimer's disease, dementia with Lewy bodies and vascular dementia (Perry, R. et al, 1990).

Cerebral dysfunction is central to problems created by these progressive neurodegenerative diseases, and has a major impact on the ability of an individual to lead an independent lifestyle and places an enormous social, psychological, and economic burden on the sufferer themselves, their carers and relatives, and on state welfare services.

James Cowle Pritchard (1835) first described a syndrome of 'forgetfulness of recent impressions, while the memory retains a relatively firm hold of ideas laid up in the recesses from times long past' some 70 years prior to Alois Alzheimer's

(1907) neuropathological description of a case of essentially the same disease with an earlier onset. Forgetfulness, namely mnemonic dysfunction, is widely reported as the hallmark for the diagnosis of dementia (American Psychiatric Association, Committee on Nomenclature and Statistics, 1987), or as a prominent early symptom of Alzheimer's disease (AD) (Sjorgen, 1952; Katzman et al, 1975). 'Alzheimer's' has become a title synonymous with pathological memory loss in the elderly.

Lishman (1978) attempted to define dementia as 'an acquired global impairment of intellect, memory and personality...without impairment of consciousness...almost always of long duration, and usually progressive'. This appears indeed to be true towards the end stages of the dementing process. However, more recently many researchers have described a great degree of heterogeneity in the neuropsychological deficits seen in patients with dementia; implying differential damage to brain areas and neurotransmitter systems.

Dementia with Lewy bodies (DLB) is one form of dementia that accounts for at least some of the heterogeneity seen in 'AD'. It was almost a century after James Parkinson first described a case of Parkinson's disease (PD) that F.H.Lewy first described Lewy bodies in the substantia nigra of patients with PD 1912. The presence of Lewy bodies in the substantia nigra remains the defining neuropathological marker in PD. The techniques used for staining Lewy bodies meant that only Lewy bodies in subcortical nuclei were identified. The development of anti-ubiquitin immunocytochemistry facilitated the identification of Lewy bodies in cortical regions (e.g. Kosaka et al, 1976). Several independent groups have reported incidence rates of between 12% and 35% of Lewy bodies in the brains of dementia sufferers coming to autopsy. The relationship between the Lewy body and the pathogenesis of dementia has stimulated a great deal of research interest, yet remains unresolved.

Clinical diagnostic criteria have been published which describe the clinical syndrome associated with cortical LB pathology (McKeith et al ,1992c; Byrne et al, 1991; McKeith et al, 1996a). Moreover, McKeith et al (1994b) have

demonstrated that the majority of DLB cases were previously misdiagnosed as either possible or probable AD using NINCDS-ARDRA criteria. Such a misdiagnosis prevents patients with DLB receiving optimal treatment, notably with respect to neuroleptic medication (DLB patients show a high rate of severe sensitivity associated with reduced life expectancy). In addition, misdiagnosis of DLB is also potentially a major confounder of research results.

Dementia with Lewy bodies appears to represent a common, neurodegenerative process with neuropathological, genetic, neurochemical, psychological and non-cognitive characteristics which both overlap and are independent of those observed in Alzheimer's and Parkinson's disease. A comprehensive review of literature describing the current nosological status of DLB with respect to AD and PD is provided. The length of this introduction is testimony to the emerging acceptance and research interest in DLB as a major cause of morbidity in the elderly. An understanding of neuropathological, neurochemical, neuropsychiatric, genetic, and psychological features of DLB is essential if the neuropsychological profile of DLB is to be effectively elucidated.

1.2 Neuropathology of dementia with Lewy bodies.

1.2.1 Historical background and introduction.

Although Friederich Lewy first described cytoplasmic inclusions, now known as 'Lewy bodies' (LB), in the dorsal motor nucleus of the vagus and the nucleus basalis of Meynert in Parkinson's disease in 1912, it was in 1919 when Trétiakoff detected the presence of Lewy bodies in the substantia nigra of Parkinson's disease cases that the name 'Lewy body' became firmly established. The presence of Lewy bodies in the substantia nigra remains the definitive pathological marker for Parkinson's disease. The topographical distribution of Lewy bodies was established using conventional haematoxylin and eosin (H&E) stains, and was thought to be primarily restricted to subcortical areas. Traditional H&E staining techniques proved poor discriminators of cortical Lewy bodies (see Figure 1.1a).

The development (Kuzuhara et al, 1988) of immunohistochemical techniques using antibodies to ubiquitin, a neuronal protein found in Lewy bodies, established that Lewy bodies were more widely distributed in many cortical areas of the brains of dementia patients than previously thought (see Figure 1.1b). The discovery of these so called 'cortical Lewy bodies' has led in the last ten years to an explosion of interest and debate about the role Lewy bodies play in the pathogenesis of dementia, and the relationship with pathological markers more traditionally associated with Alzheimer's disease.

An understanding of the reported neuropathological changes is central to the comprehension of the problem facing researchers attempting to characterise dementia with Lewy bodies and its relationship to Alzheimer's disease and Parkinson's disease. As many forms of dementia are ultimately defined by neuropathological change, diagnoses made without histopathological confirmation can only be tentative. Moreover, the differences between the different sites and type of neuropathological change enlighten our understanding of brain - behaviour relationships. Finally, detailed neuropathological work may unravel the different

aetiologies of various dementia syndromes and open up possible avenues for therapeutic intervention.

1.2.2 Functional biology of Lewy bodies, senile plaques and neurofibrillary tangles.

1.2.2.1 Lewy bodies, Pale bodies, Lewy neurites and associated biochemical markers.

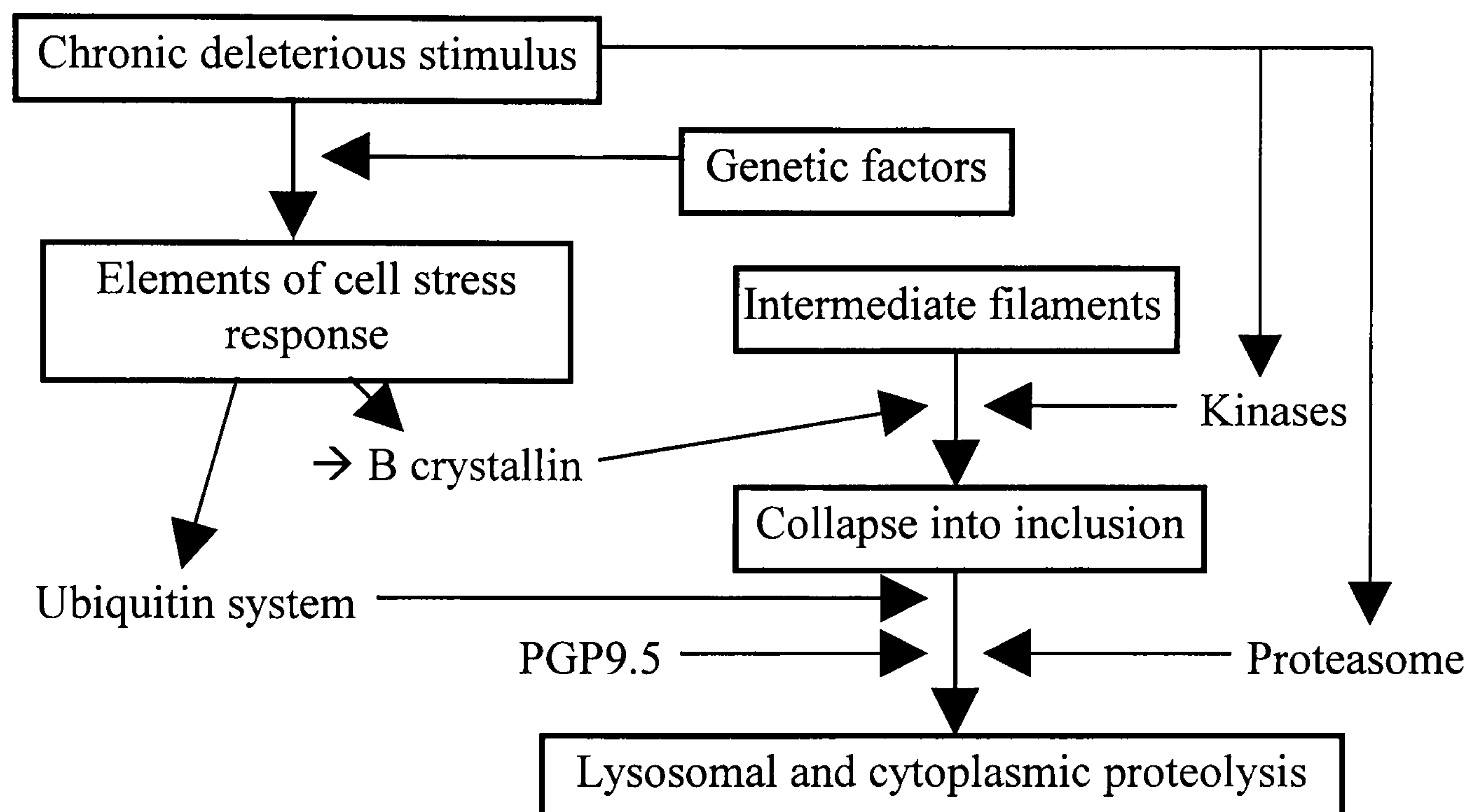
Lewy bodies (LB) are eosinophilic, intracytoplasmic, inclusion bodies which are found in a diversity of locations including cholinergic and monoaminergic neurons of the brain-stem, diencephalon, basal forebrain, autonomic ganglia and cerebral cortex (Gibb, 1989b; Fearnley et al, 1994). Lewy bodies are generally rounded and may show a multilocular or fusiform outline (see Figures 1.1a; 1.1b). Numerous authors have described two distinctive morphological types depending on their topographical location (Perry, R. et al, 1990; Kosaka, 1989; Lowe, 1994).

Classical brain-stem Lewy bodies are rounded, eosinophilic, intracytoplasmic inclusions with a hyaline core and a pale-staining peripheral halo and are typically found in the substantia nigra and locus coeruleus. Cortical Lewy bodies generally do not have a distinct peripheral halo. De la Fuente-Fernandez et al (1996) suggest that these differences reflect topographically distinct aspects of the same structure rather than different aetiologic or pathogenic factors. Other neuropathological markers in dementia with Lewy bodies are the so called 'pale bodies', which are thought to be precursors of Lewy bodies (Dale et al, 1992; Hayashida et al, 1993).

Neurofilament proteins have been found by a number of groups to be an important constituent of Lewy bodies (Goldman et al, 1983; Galloway et al, 1988; Pollanen et al, 1992). These neurofilament proteins are phosphorylated and truncated by proteolysis (Baner et al, 1989; Schmidt et al, 1991). Lewy bodies also contain several compounds (including ubiquitin, ubiquitin carboxyl-terminal hydrolase, multicatalytic protease, and α B crystallin) that represent one form of a more generalised pathological phenomenon. Other forms include: Crooke's hyaline, Mallory's hyaline and Rosenthal fibres (Lowe et al, 1988), all of which contain ubiquitin, crystallin and filament inclusions. Ubiquitin plays an important part in

the targeting of damaged or abnormal proteins for proteolysis. The fact that Lewy bodies contain several enzymes associated with the ubiquitin-mediated proteolytic pathways suggests that Lewy bodies are cytoprotective responses, and may be structural rearrangements to eliminate damaged cellular elements (See Figure 1.2). Lewy bodies do not in general contain Tau¹ protein, and this may be used to distinguish cortical Lewy bodies from small spherical tangles.

Figure 1.2: Functional biology of ubiquitin intermediate filament inclusions (adapted from Lowe et al, 1996)



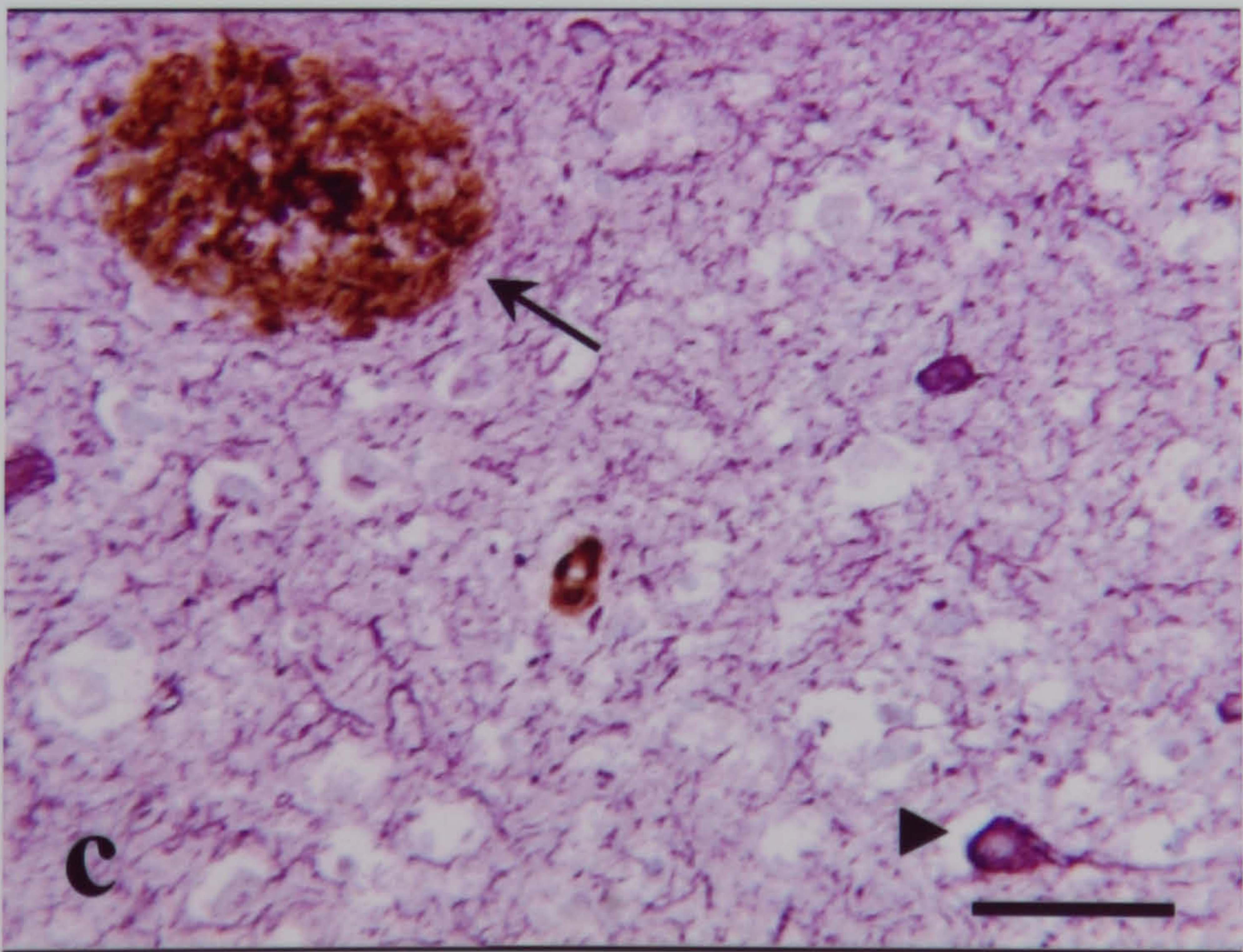
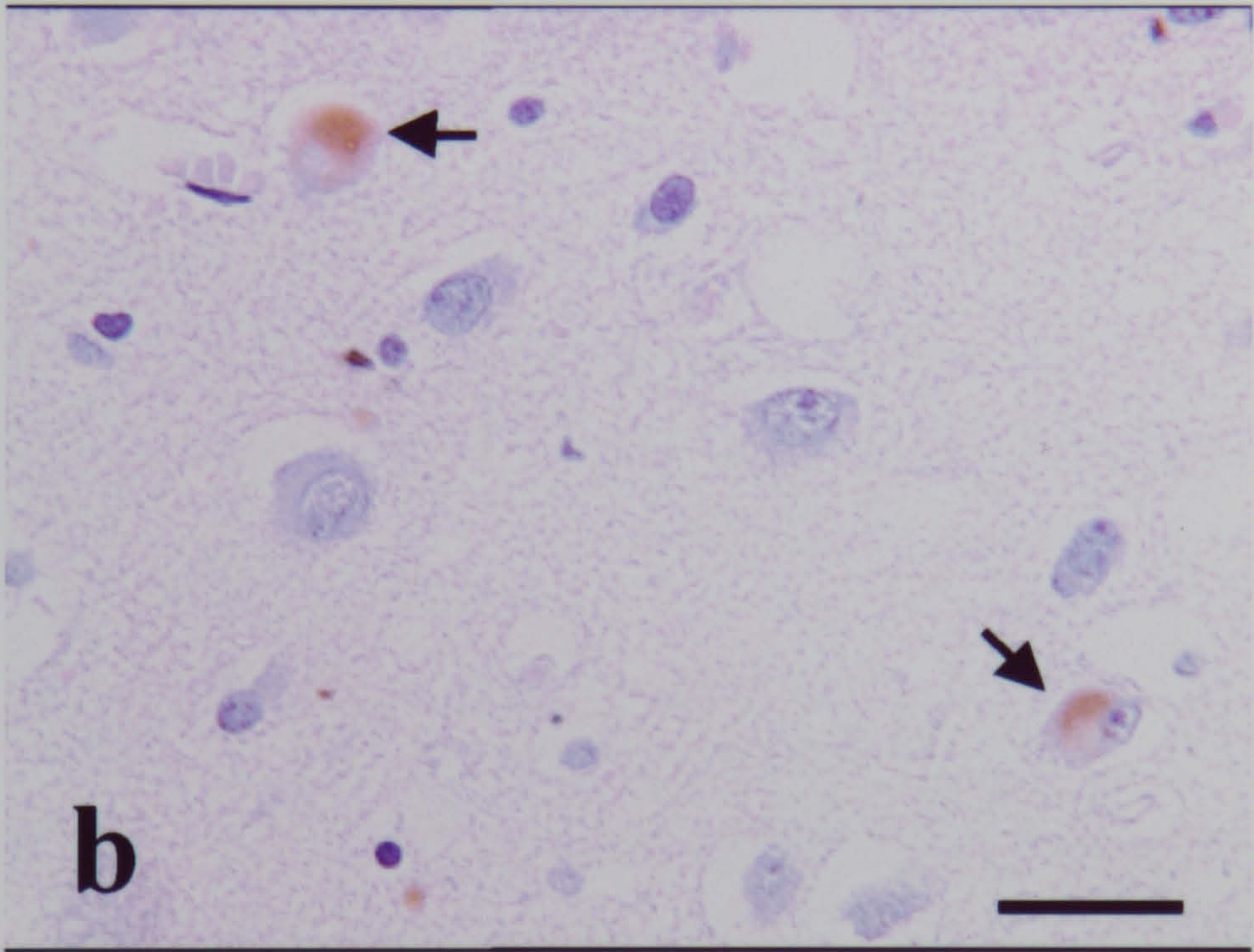
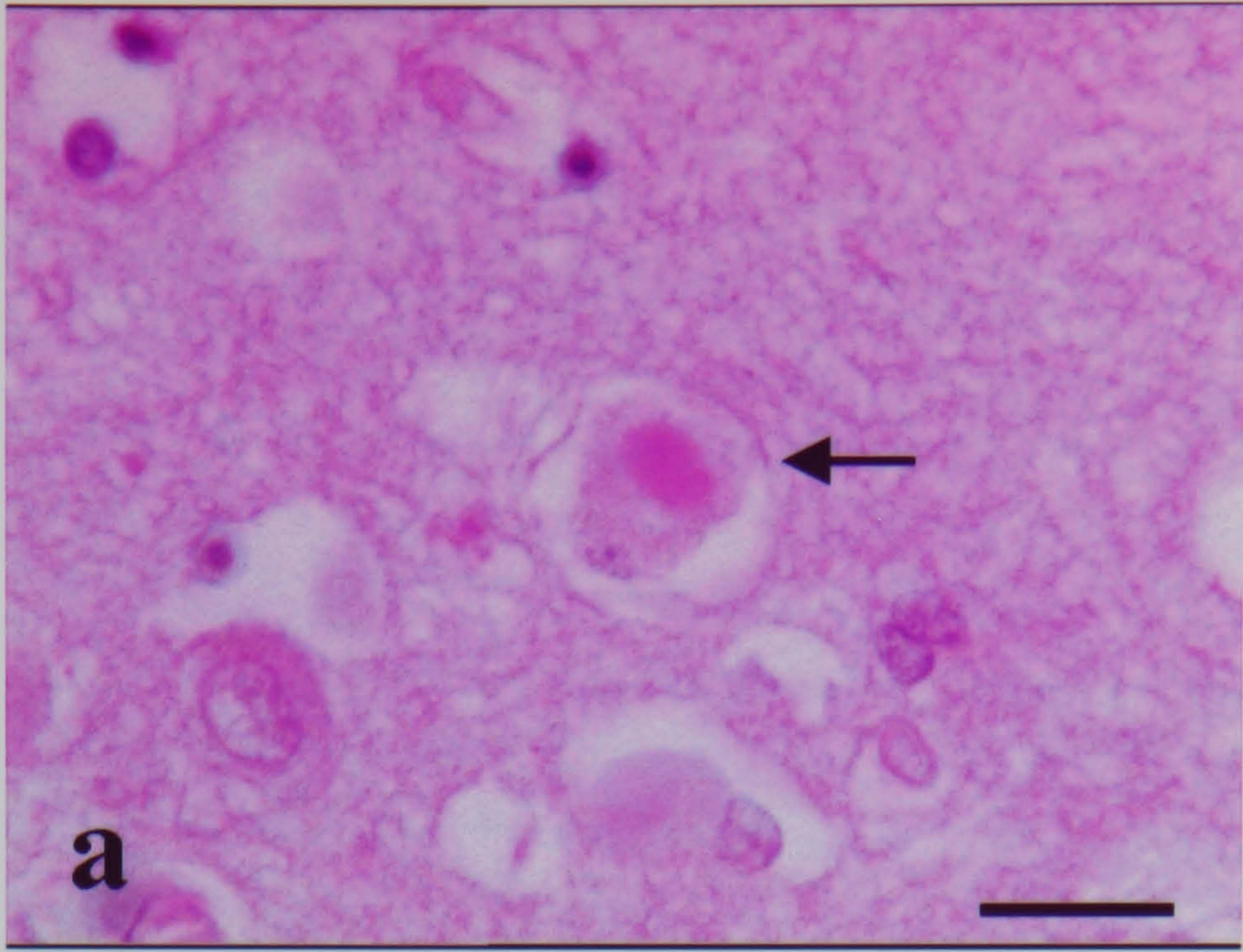
‘Lewy neurites’ depict ubiquitin-immunoreactive neuritic degeneration, a distinct process seen in Lewy body disorders. They are found in the substantia nigra, the CA2/3 regions of the hippocampus, the nucleus basalis of Meynert, and the dorsal vagus nerve. Lowe et al (1996) suggest that this particular type of neuritic degeneration should be regarded as a distinct part of the Lewy body phenomenon.

¹ Tau proteins are the basic components of paired helical filaments (PHF), the ultrastructural units of cytoskeletal neurofibrillary degeneration. Tau proteins are responsible for the polymerisation of microtubules in the neurons, and are an important factor in the maintenance of axonal transport. In AD, Tau proteins which accumulate within the neurons are abnormally phosphorylated.

Figure 1.1a: Shows a cortical Lewy body (arrow) found within a neuron located in the cingulate cortex. The section is stained with haematoxylin and eosin and the bar represents 20µm.

Figure 1.1b: Shows two cortical neurons containing Lewy bodies (arrows) from the cingulate cortex. The section was stained with ubiquitin antibodies tagged with DAB and then counterstained with haematoxylin. The bar represents 30µm.

Figure 1.1c: Shows a plaque (arrow) and a neurofibrillary tangle (arrowhead) from the frontal cortex. This section has been dual stained with a β A4 monoclonal antibody tagged with DAB to visualise the amyloid plaque (arrow) and with the Tau specific AT8 monoclonal antibody tagged with VIP to delineate the neurofibrillary tangle (arrowhead). The bar represents 50µm.



1.2.2.2 Senile Plaques.

Senile plaques are structurally complex lesions accumulating in the cerebral cortex in both pathological states and normal ageing, the development of which remains partially understood. They are round or ovoid structures, 15-200 μm in diameter (see Figure 1.1c). Most, if not all, senile plaques start as primarily non-filamentous amorphous aggregates of the β -amyloid protein. Such 'diffuse' β -amyloid depositions gradually become increasingly fibrillar and acquire the classical features of amyloid plaques: a central core of amyloid material surrounded by a peripheral rim of dystrophic neurites. These 'mature' β -amyloid plaques bind with certain histochemical dyes (thioflavin and Congo red). Associated with mature β -amyloid plaques are dystrophic axonal and dendritic processes which lie close to, or immediately next to, the fibrous amyloid deposit. The mature plaques show activated microglia associated with the central amyloid deposit and the distinguishing fibrous astrocytes rimming the plaque. Mature plaques might represent 'burnt out plaques', as they are thought to be at the latter stage of their evolution.

The ratio of differing types of amyloid plaques has received relatively little attention. However, work in Newcastle suggests there is a relative preponderance of the mature type in Alzheimer's disease (Perry, R. et al, 1986). Gentleman et al (1992) have also demonstrated the density and ratio of diffuse and mature plaques to be equivalent in AD and DLB.

1.2.2.3 Neurofibrillary tangles.

In the large majority of Alzheimer's disease cases, senile plaques are accompanied by neurofibrillary tangles (NFT). Neurofibrillary tangles are abnormal filamentous accumulations in the cytoplasm of neurons. The structure of neurofibrillary tangles have been identified by electron microscopy to reveal masses of paired, helically wound filaments intermixed with straight filaments (see Figure 1.1c).

Neuroanatomical studies have suggested that neurofibrillary tangles are often located in cells whose axons project to the sites of neuritic plaques; however this

is not an absolute prerequisite for their location. Archicortical regions appear to be more susceptible to neurofibrillary tangle formation than neocortical regions in terms of both density and proportions of neurons involved. This is true for both Alzheimer's disease and normal ageing. Specific subcortical nuclei appear to be particularly prone to neurofibrillary tangle formation, most notably the serotonergic dorsal raphe nucleus (Hirano, 1962). Neurofibrillary tangles also show a predilection for somatostatin and enkephalin neurons (Roberts et al, 1985).

Neurofibrillary tangles occur without senile plaques in a number of aetiologically diverse disorders including: sub-acute sclerosing panencephalitis, Kuf's disease, and Hallervorden-Spatz disease. Terry et al (1987) also demonstrated Alzheimer's disease cases with plentiful senile plaques but minimal or no neurofibrillary tangles. Thus the interaction between senile plaques and neurofibrillary tangles is not a simple one, indeed Selkoe (1994) is one of several who suggest that neurofibrillary tangles may well be non-specific markers of certain kinds of neuronal insult.

1.2.3 The nosological status of dementia with Lewy bodies: The necessity for a unitary title and 'gold standard' criteria for pathological diagnosis.

1.2.3.1 Introduction.

Primary Lewy body syndromes, such as Parkinson's disease, have Lewy body pathology which is believed to be the fundamental to the pathogenesis of the disease, whilst 'coincidental' Lewy body diseases are thought to show Lewy body formation in the presence of other primary pathological processes. Perhaps the most important coincidental association is that proposed by some between Alzheimer's disease pathology and Lewy body pathology.

The relationship between Lewy body and Alzheimer's disease pathology remains unclear. In attempts at clarification, American neuropathologists generally cite criteria for the diagnosis of Alzheimer's disease based principally on senile plaque

counts (Mirra et al, 1991; Khachaturian, 1985). Senile plaques are not uncommon in dementia with Lewy bodies cases, hence plaque only based neuropathological criteria incorporate many Lewy body cases and thus imply Alzheimer's disease with a 'Lewy body' flavouring (Hansen et al, 1990). However, criteria which include both plaque and neurofibrillary tangle counts exclude most cases with Lewy bodies. Indeed it is suggested by some that the Alzheimer's pathology in Lewy body disease is incidental and represents normal ageing processes (e.g. Dickson et al, 1989). These differing interpretations are reflected in the number of different titles awarded prior to the adoption of the consensus title 'dementia with Lewy bodies' in 1996.

1.2.3.2 Diffuse Lewy body disease (DLBD).

In 1980, Kosaka proposed Lewy body disease (LBD) as a disease entity and classified it into three forms reflecting the topographical distribution of Lewy bodies in cerebral tissue. He studied 55 cases of Parkinson's disease and distinguished three types of dementia associated with Parkinson's disease.

Brain-stem type LBD showed a predilection for Lewy body formation in brain-stem and diencephalic nuclei, but very few, or none, were evident in the cerebral cortex or the basal ganglia. The 'Alzheimer type' pathology was in accordance with norms for the ages of the patients. Brain-stem type DLB was identical to Parkinson's disease and the four cases reported did not develop symptoms typically associated with a cortical dementia.

In Diffuse LBD four patients suffered a progressive dementia, with or without parkinsonism, and showed numerous Lewy bodies distributed in the brain-stem and diencephalic nuclei as well as the cerebral cortex and basal ganglia. Senile plaques were present in all cases, and neurofibrillary tangles were also present in some cases.

Transitional type LBD represents an intermediary between diffuse and brain-stem type LBD and might fall under a clinical description of Parkinson's disease plus

dementia. These cases show numerous Lewy bodies in the brain-stem and diencephalon and although Lewy bodies were present in the cortex, there were less than is seen in diffuse type.

Table 1.1: Classifications and titles used to describe Lewy body disorders

- Lewy body disease (LBD) (Kosaka et al, 1984)
 - Group A: Diffuse type
 - Group B: Transitional type
 - Group C: Brain-stem type

- Diffuse Lewy body disease (DLBD) (Yoshimura, 1983)

- Diffuse Lewy body disease (DLBD) (Kosaka, 1990)
 - Common form (cDLBD)
 - Pure form (pDLBD)

- Diffuse cortical Lewy body disease (Gibb et al, 1989)
 - (Lewy body dementia)

- Senile dementia of the Lewy body type (SDLT) (Perry et al, 1990)

- Lewy body variant of Alzheimer's disease (LBVAD) (Hansen et al, 1990)

- Cerebral type Lewy body disease (Kosaka et al, 1996)

- Dementia with Lewy bodies (Consensus Term: McKeith et al, 1996)

Kosaka (1990) reviewed 37 Japanese autopsy cases with DLBD, and then repeated the analysis in 1993 with an increased cohort of 44 cases. Based on this work he divided DLBD into two forms, common and pure, based on the neuropathologic findings of whether many concomitant senile plaques and/or neurofibrillary tangles were present. In common DLBD (cDLBD) (n=33) the most manifest presenting symptom was memory disturbance (55%), whilst parkinsonian symptoms represented only 18% of presenting symptomatology. Common DLBD cases showed numerous senile plaques and neurofibrillary tangles, pathological markers traditionally associated with Alzheimer's disease and to a lesser extent in normal ageing. Cortical Lewy bodies were found mainly in the small neurons in the deeper cortical layers, mainly in the temporal, frontal and insular cortices although all lobes were involved to some extent. Moderate to severe densities of senile plaques were found in all cases. Neurofibrillary tangles were found to be widely present in 65% of the cases and all the remaining cases (bar one) showed neurofibrillary tangles restricted to the hippocampus and parahippocampal gyrus. The final case showed very little neurofibrillary tangle pathology, although there were numerous senile plaques present.

Kosaka also described 11 cases of the pure form DLBD (pDLBD) in which by far the most common presenting symptom was parkinsonism (81%) with 2 cases (19%) presenting with psychotic phenomena. The cases with pDLBD appear to have an earlier age of onset than cDLBD (Mean = 38.9 years vs. 68.5 years in cDLBD) with one case reported in a 14 year old! The clinical diagnosis was generally atypical juvenile Parkinson's disease with profound dementia towards the end stage. Lewy bodies were distributed widely in the central nervous system, however there were no cortical senile plaques or neurofibrillary tangles found. In 7 of the cases mild neurofibrillary tangle pathology was found in hippocampal and parahippocampal regions.

Very recently (Kosaka et al, 1996b) described yet another type of LBD, 'cerebral type of Lewy body disease'. He described the case of a male who started becoming forgetful at 77 years, and showed a progressive cortical dementia with delirious episodes until he died aged 79 years. Notably he showed no

parkinsonism. Neuropathological examination showed no degeneration in the substantia nigra or locus coeruleus and only rare Lewy bodies in other brain-stem nuclei. There were, however, as many cortical Lewy bodies as have been previously seen in DLBD. Kosaka et al suggest that in this 'cerebral type Lewy body disease' the development of cortical pathology precedes that of Parkinson's disease pathology, which might explain why cortical dementia precedes parkinsonism in many cases where cortical Lewy bodies are abundant.

1.2.3.3 The Lewy body variant of Alzheimer's disease (LBVAD).

Förstl et al (1993) reported 8 cases of Lewy body dementia from a cohort of 65 patients collected during a prospective study of clinically diagnosed Alzheimer's disease. These were compared with eight patients matched for age and sex from the same study with pathologically confirmed Alzheimer's disease. The Alzheimer's disease pathology in the group with Lewy bodies was less severe than in the Alzheimer's disease group without Lewy bodies. Other distinguishing features of the Alzheimer's disease cases with Lewy bodies included: the incidence of parkinsonian features, greater frontal cerebral atrophy on Computerised Tomography (CT) scans, and a greater loss of neurons in the nucleus basalis of Meynert and the substantia nigra. However, Förstl et al reported that the LBV cases in their sample were not clinically different from the cases without Lewy bodies, except for an increased risk of rigidity developing during the course of the illness.

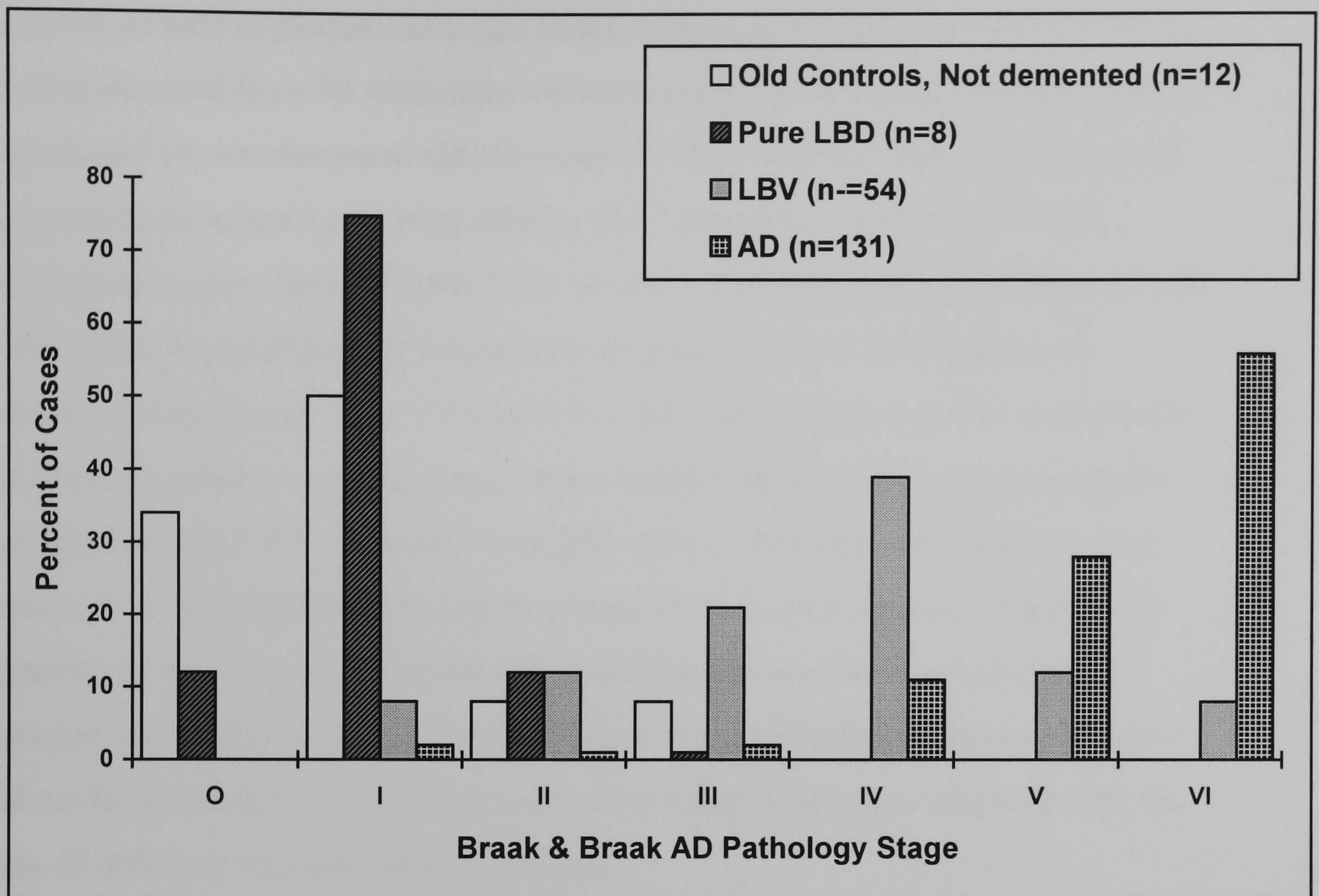
Hansen et al (1990) suggested the title of 'Lewy body variant of Alzheimer's disease' (LBVAD) reflecting their proposition that DLBD is in fact Alzheimer's disease with incidental Lewy body disease. They examined brains from 36 clinically diagnosed and pathologically confirmed cases of Alzheimer's disease. They found thirteen contained cortical and subcortical Lewy bodies. They argue that the LBVAD patients represent a neuropathologically distinct subset of Alzheimer's disease for three main reasons: i) all LBV cases fulfilled criteria for the neuropathological diagnosis of Alzheimer's disease (Khachaturian, 1985); ii) senile plaque counts in the hippocampus were equivalent in LBV and Alzheimer's

disease; iii) the gross morphological changes seen in LBV and Alzheimer's disease groups were similar. Hansen, however, argues that LBV are a distinct subset of Alzheimer's disease based on: i) the presence of Lewy bodies in LBV brains, and the universal lack of Lewy bodies in Alzheimer's disease brains; ii) the subcortical cell loss was much greater in LBV (particularly locus coeruleus, substantia nigra, and substantia inominata) than in Alzheimer's disease.

The relationship between senile plaques and Lewy bodies in the cortex was further examined by Hansen et al (1993). They examined 147 consecutive cases of neuropathologically confirmed Alzheimer's disease, and found a minority (25%) to have 'plaque-only' Alzheimer's disease, whilst a majority had both senile plaques and neurofibrillary tangles. Twenty eight percent of the total sample were shown to be LBV, and these were further delineated to show 66% were 'plaque-only' Alzheimer's disease and 33% were plaque and tangle Alzheimer's disease. Of the plaque-only cases, 75% were found to be LBV, whilst only 25% were found to be Alzheimer's disease cases. Hansen suggests that plaque-only Alzheimer's disease is usually the Lewy body variant and vice-versa.

Alzheimer's disease pathology commences and progresses insidiously, with diffuse plaques in the neocortex evolving to neuritic forms lacking paired helical filaments, and eventually to Tau-positive dense cored neuritic plaques accompanied by neurofibrillary tangles. Hansen et al (1994) used the highly consistent medial temporal lobe neurofibrillary pathology (Braak & Braak, 1991) to grade Alzheimer's disease changes in LBV (see Figure 1.3).

Figure 1.3: The extent of AD neurofibrillary pathology in four different disease categories assessed using a modified Braak and Braak Staging Scheme. (Adapted from Hansen et al, 1996)



Using the 6 stage Braak & Braak protocol, they found that LBV usually had Alzheimer's disease pathology classified in the III / IV (limbic) stage, whilst Alzheimer's disease is usually classified in stages V / VI (isocortical), and normal ageing either does not register (0) or reaches only stage I (transentorhinal) in the classification. Hansen et al suggest that stage III / IV correspond 'nicely' to the plaque-only Alzheimer's disease and achieve CERAD-probable Alzheimer's disease.

Hansen employed diagnostic criteria from the National Institute on Ageing (Khachaturian, 1985) and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Mirra et al, 1991). Both of these sets of criteria emphasise the role of senile plaques for making diagnoses, and out of the 71 Lewy body dementia brains the group received in the previous 10 years, most (nearly 90%) of

DLBD qualify as either possible or probable Alzheimer's disease.

More recently, Hansen et al (1996) have demonstrated the impact of specific pathological diagnostic criteria for Alzheimer's disease. They applied plaque based criteria, as well as plaque and tangle based criteria, to a collection of post mortem brains obtained from 58 Alzheimer's disease cases, 58 dementia with Lewy bodies cases, and 10 non-demented elderly controls. Their findings demonstrate that the proportion of mixed Lewy body disease and Alzheimer's disease (LBVAD), compared to pure forms of Lewy body disease (DLBD) is highly dependent on the utilisation of neurofibrillary tangles as a diagnostic marker for Alzheimer's disease. Using plaque based criteria 91% were LBVAD and only 9% were DLBD. In contrast, when plaque and tangle based criteria are employed, this relationship changes to 34% LBVAD and 66% DLBD. Indeed, Dickson et al (1992) suggest that beta-amyloid deposition may be a relatively non-specific manifestation of a number of disorders, and that the distinguishing feature between Alzheimer's disease and DLBD may well be the presence of neurofibrillary tangles. Arguments about the nosological status of dementia with Lewy bodies are entwined with the use of differing neuropathological criteria.

The different interpretations by Kosaka and colleagues (1984), Hansen and colleagues (1990), and Förstl and colleagues (1993) not only show different interpretations of the neuropathology of Lewy body disease, but also strongly represent sampling extremes. The Japanese sample was taken from cases with a primary clinical diagnosis of Parkinson's disease, whilst the early samples used by Hansen et al and Förstl et al were restricted to clinically diagnosed and neuropathologically confirmed cases of Alzheimer's disease. Although both Alzheimer's disease and particularly Parkinson's disease are the two disorders most strongly associated with Lewy bodies, to obtain a more complete comprehension of the Lewy body disease spectrum it is certainly necessary to extend sampling beyond pathologically confirmed Alzheimer's disease cases (Hansen et al., 1990; 1993) or clinically diagnosed Alzheimer's disease cases (Förstl et al., 1993). There is a somewhat tautological argument suggesting that Lewy body disease is a variant of Alzheimer's disease, when selection bias

requires at least clinical if not neuropathological diagnosis of Alzheimer's disease. Employing the LBV of AD nosology is likely to omit many cases of Lewy body disease who do not present with typical Alzheimer's disease symptomatology or even more restrictively with typical Alzheimer's disease pathology.

In contrast, Kosaka and colleagues use a sample biased towards a population with Parkinson's disease, in whom the Lewy body-related cognitive impairment is unlikely to be representative of a more general population of dementia patients. Cases of Lewy body disease without extrapyramidal symptoms as a major symptom are more likely to be excluded. Kosaka and colleagues suggest a nosological spectrum of Lewy body disease which is able to explain the various clinical manifestations of dementia associated with the presence of Lewy bodies. Hansen and colleagues restrict the nosological status of Lewy body disease to within the heterogeneity of Alzheimer's disease. Hansen and colleagues omit cases where there are no Alzheimer's disease-like changes, which Kosaka suggests might represent upwards of 30% of DLBD cases. Understanding of the true nature of the Lewy body disease spectrum of diseases requires sampling which is not biased to a particular established clinicopathological entity and is representative of a clinical population of dementia patients.

1.2.3.4 Senile dementia of the Lewy body type (SDLT) - A distinct neuropathological entity.

Perry, R. et al (1990) proposed the term 'senile dementia of the Lewy body type' (SDLT) an appellation adopted by other researchers in Newcastle (McKeith et al, 1992c) which corresponds to transitional DLBD proposed by Kosaka and colleagues. They found that neither the clinical or neuropathological features of the disease were typical of Parkinson's disease or Alzheimer's disease, and suggested a distinct neurodegenerative disorder, part of the Lewy body disease spectrum, in which mental symptoms predominate over motor disabilities. Thus they suggest that SDLT is a form of dementia distinct from Alzheimer's disease and Parkinson's disease, but with some of the neuropathological markers of both; that is to say; SDLT occupies a central point on a three category spectrum with

Alzheimer's disease and Parkinson's disease occupying either end.

1.2.3.5 Consensus criteria for the neuropathological diagnosis of dementia with Lewy bodies (DLB).

In October 1995, many of the key contributors to this neuropathological debate attended the 'International Workshop on Dementia with Lewy bodies'.

Discussions were held throughout the pathology workshop as to the utility of producing neuropathological criteria. The consensus term 'dementia with Lewy bodies' was adopted by both pathologists and clinically based researchers alike.

The aim was to allow different groups to publish work based on a unitary diagnostic schedule enabling direct comparison of findings from different groups.

The criteria provide guidelines for regional brain sampling, evaluation of Lewy body distribution and density, and diagnostic rating protocol (see Table 1.2).

Table 1.2: Pathological features associated with DLB (adapted from McKeith et al, 1996a).

<p>1 Essential for diagnosis of DLB</p> <p>Lewy bodies</p> <p>2 Associated but not essential</p> <p>Lewy-related neurites.</p> <p>Plaques (all morphological types).</p> <p>Neurofibrillary tangles.</p> <p>Regional neuronal loss - especially brain-stem (substantia nigra and locus coeruleus) and Meynert Nucleus.</p>
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The criteria propose several additions to CERAD protocols for neuropathological assessment, including neocortical, limbic, and paralimbic areas. The cortical Lewy body density is assessed using a semi-quantitative scale as follows:

Table 1.3: Consensus semi-quantitative measurement of Lewy body density (adapted from McKeith et al, 1996a).

Score count	(LB/area)
0	0
1	up to 5
3	>5

The criteria also recommend that Lewy body count scores are totalled to give a final score and anatomical distribution (see Table 1.4).

Table 1.4: Total Lewy body scores providing overall index of Lewy body pathology (adapted from McKeith et al, 1996a)

Category	Transentorhinal	Cingulate	Temporal	Frontal	Parietal	Total
Brainstem Predominant	0-1	0-1	0	0	0	0-2
'Limbic' † (Transitional)	0-3	0-3	0-1	0-1	0-1	3-10
Neocortical	1-3	1-3	1-3	1-3	1-3	11-15

† Limbic category: neocortical involvement should not exceed a score of 1 in more than one lobe. Scores higher than 1 - generally indicate neocortical category.

The role of Alzheimer's disease pathology in dementia with Lewy bodies was not agreed, the focus being on establishing a common protocol for investigating neuropathological lesions in dementia with Lewy bodies.

1.2.3.6 Do Lewy bodies cause the dementia in DLB?.

The role of different pathological lesions in the genesis of cognitive deficits in DLB remains somewhat uncertain. In DLB cases with Lewy body and 'Alzheimer type' pathological changes, several authors have suggested that Lewy bodies play a significant role in the pathogenesis of cognitive impairment (Lennox et al, 1989b; Samuel et al, 1996; Hansen et al, 1990; 1993).

Hansen et al (1990; 1993) have demonstrated a similar degree of cognitive impairment in LBV and AD cases despite less severe 'Alzheimer type' pathological changes in the LBV group. Samuel et al (1996) found a significant correlation between Lewy body counts in the cingulate and superior temporal cortex and the degree of cognitive impairment assessed using the Mini Mental State Examination (MMSE), however, Lewy body counts in the mid-frontal or inferior parietal regions did not correlate with the degree of cognitive impairment.

Perry, R. et al (1990) failed to find a correlation between the degree of cognitive impairment and Lewy body counts in the limbic cortex. These studies are restricted by the use of the relatively insensitive and mnemonically biased MMSE. In addition, the design of these studies means that the correlation is between pathological burden at death and cognitive performance measured some time previously.

The most convincing evidence is provided by Kosaka et al (1984), who describe pathologically confirmed cases of pure, diffuse Lewy body disease (pDLBD) in which Lewy bodies appear to be sufficient to produce a primary dementia syndrome in the absence of significant 'Alzheimer type' pathology (Hely et al, 1996). Thus, although Lewy bodies appear to contribute to the dementia seen in DLB, methodological restrictions prevent the determination of the relative contributions of Lewy bodies, senile plaques, and neurofibrillary tangles to the dementia in DLB.

1.2.3.7 Cytoskeletal distinctions between AD and DLB.

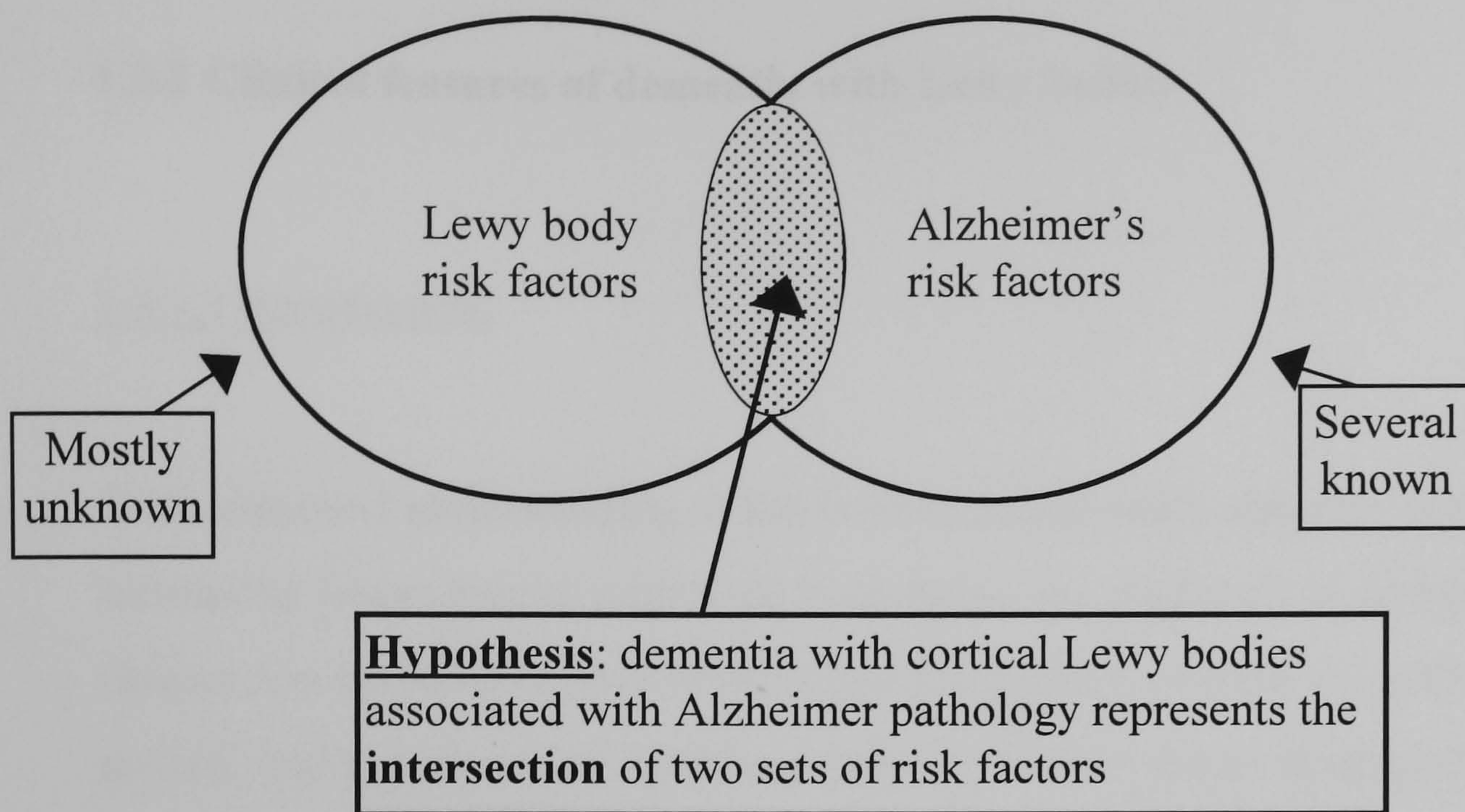
In AD the major cytoskeletal abnormalities appear to be in the altered assembly of the protein Tau which is associated with microtubules. Markers of this abnormality, namely paired helical filaments and hyper-phosphorylated Tau associated with neurofibrillary tangle formation, were found to be similar in DLB to levels found in PD and controls. Levels of PHF and neurofibrillary tangles were found to be twenty times greater in AD cases than controls, PD cases, and DLB cases (Harrington et al, 1994).

In contrast, the primary cytoskeletal abnormality in DLB appears to be associated with neurofilaments. Carter et al (1996) indicate that detailed ultrastructural analysis of both cortical and subcortical Lewy bodies shows that they consist of neurofilament-like fibrils. Bergeron et al (1996) suggest that Lewy body neurofilaments undergo normal assembly but subsequently undergo phosphorylation, proteolysis and cross-linking. Thus, the primary pathological markers in AD and DLB appear to be distinct at a molecular level.

1.2.3.8 Summary and conclusions.

Consensus terminology has now been agreed and published (McKeith et al, 1996a), but underlying debates about the nosological status of dementia with Lewy bodies remain unresolved. Criteria for the neuropathological diagnosis of Alzheimer's disease may require reformulation in the light of recent autopsy studies, which consistently suggest Lewy body disorders represent 10-30% of all cases of dementia coming to autopsy. Continued application of these now apparently outdated criteria in tautological arguments about the nosology of Lewy body disease fails to progress understanding of the neuropathological features of dementia both with and without Lewy bodies. Indeed, American neuropathological criteria for the diagnosis of AD are currently under review, and future criteria will place a greater emphasis on neurofibrillary tangle pathology. Several authors have also strongly suggested that Lewy bodies contribute to the pathogenesis of dementia in DLB, although this subject requires further consideration. In addition, AD and DLB appear to show distinct patterns of disruption to cytoskeletal structures. Lowe et al (1996) suggest that the association of Lewy bodies and Alzheimer's neuropathological changes is a reflection of the interplay of several factors common to AD and PD (see Figure 1.4).

Figure 1.4: The association between cortical Lewy bodies and Alzheimer pathology (adapted from Lowe et al, 1996)



Similarly, Hansen and colleagues in the San Diego group have employed a useful construct to summarise the status of DLB with respect to the pathological changes of PD and AD. In a recent paper they describe the LBV of AD as....

‘... a neurodegenerative hybrid separate and distinct from AD and PD but with clinical and neuropathological features of both. By analogy, just as a mule is neither a horse nor a donkey, despite being composed of nothing other than horse or donkey, so too is LBV a ‘different animal’ than AD or PD, despite sharing features with both.’

(Samuel et al, 1996).

It is to be hoped, however, that the DLB construct does not share the evolutionary limitations of the mule!

1.3 The clinical syndrome of dementia with Lewy bodies: comparison with Alzheimer's disease and Parkinson's disease.

1.3.1 Clinical features of dementia with Lewy bodies.

1.3.1.1 Introduction.

With improved understanding, it has become increasingly apparent that there is substantial heterogeneity within the boundaries of a diagnosis of Alzheimer's disease. On the basis of retrospective and prospective, clinical and pathological, genetic, and psychological studies of patients, distinct forms of dementia are now being delineated which were originally thought to be Alzheimer's disease.

Dementia with Lewy bodies is one such form of dementia and is thought to be one of the most common forms of dementia in the elderly. Dementia with Lewy bodies may represent up to 24% of clinically diagnosed, senile dementia cases (Shergill et al, 1994; Ballard et al, 1993), although post-mortem studies generally suggest prevalence rates of between 12 % and 20% (Forno et al, 1993; Byrne et al, 1989; Joachim et al, 1988; Dickson et al, 1989; Perry, R. et al, 1990; Hansen et al, 1990). Whatever the exact figure, dementia with Lewy bodies represents a major cause of morbidity in the elderly.

In-vivo distinctions between dementia with Lewy bodies, Parkinson's disease , and Alzheimer's disease are made difficult by considerable overlap between the clinical syndromes. Nonetheless, there are a number of clinical features which distinguish dementia with Lewy bodies, Parkinson's disease, and Alzheimer's disease. These are reviewed below and have become the basis of clinical diagnostic criteria for the diagnosis of dementia with Lewy bodies (Byrne et al, 1991; McKeith et al, 1992c; 1996a).

Retrospective and prospective clinicopathological studies have examined the clinical syndrome of dementia with Lewy bodies. There are a number of remarkable mental state symptoms which are strongly associated with the

presence of Lewy bodies in the cortex. These include fluctuating cognitive impairment, a high incidence of psychotic features, increased risk of depression, and extrapyramidal symptoms worsened by the administration of neuroleptics.

In a review² of 80 dementia cases reaching post mortem in Newcastle, in which 50% had classical Alzheimer's disease pathology and 20% had Lewy bodies in the cortex and brain-stem, McKeith et al (1992c) compared mental state symptoms in dementia with Lewy bodies and SDAT (see Table 1.5)

Table 1.5: Comparison of mental state symptoms in Alzheimer's disease and dementia with Lewy bodies (% of cases) (adapted from McKeith et al, 1992c).

	<i>Symptoms at presentation</i>		<i>Symptoms occurring at any stage</i>	
	SDLT	SDAT	SDLT	SDAT
Fluctuating cognitive impairment	81.0	10.8 ^{††}	86.0	18.9 ^{††}
Clouding of consciousness	38.1	8.1 ^{††}	81.0	13.5 ^{††}
Visual Hallucinations	33.3	8.1 [†]	47.6	16.2 ^{††}
Auditory Hallucinations	14.3	2.7	19.0	2.7 [†]
Paranoid delusions	47.6	8.1 ^{††}	57.1	10.8 ^{††}
Depression (Total)	38.1	16.2 [†]	38.1	21.6 [†]
Depression (Major)	14.3	0 [†]	14.3	5.4
Depression (Minor)	23.8	16.2	23.8	16.2

[†]p<0.05, ^{††}p<0.01..0.001

² Retrospective case note review is frequently used in clinicopathological studies of dementia. There are, however, a number of limitations to this type of study. No matter how comprehensively compiled, case notes are limited by the fact that they are likely to omit clinical data (possibly deemed not relevant at the time of compilation) or contain diagnostic inferences. Studies based in Newcastle reduce this effect by the use of uniform assessment procedures in psychogeriatric units.

1.3.1.2 Fluctuating levels of cognitive function.

A fluctuating level of cognitive impairment is found in the majority of dementia with Lewy bodies cases, when other causes such as delirium, medication toxicity, or concurrent illness are excluded. McKeith and colleagues (1992c) estimated around 86% of SDLT cases to display fluctuations in the level of cognitive impairment throughout the course of the illness (see Table 1.6 for review).

Ballard et al (1993) found 16 out of 58 patients who were assessed at a day hospital for probable dementia fulfilled a somewhat limited study definition for idiopathic clouding of consciousness. The identification of idiopathic clouding of consciousness required a positive response to the question ‘Are there episodes lasting days or weeks when his/her thinking seems quite clear and then becomes muddled?’. Fourteen out of sixteen (87.5%) of those patients who were identified with idiopathic clouding of consciousness also fulfilled McKeith criteria for SDLT. Ballard and colleagues found that by selecting their patients on the basis only of idiopathic clouding of consciousness they identified similar clinical symptomatology as McKeith et al (1992c).

McKeith et al (1992c) describe fluctuating cognitive impairment as essential for a diagnosis of DLB, and idiopathic clouding of consciousness as a feature supportive of a diagnosis of DLB. Fluctuating cognitive impairment is identified by changeable scores on formal psychometric testing or variable performance in daily living skills. Idiopathic clouding of consciousness is described as observable phasic drowsiness without need to resort to more sensitive methods of assessment. This distinction may be somewhat arbitrary as fluctuation also includes and, indeed may be based on, pronounced variations in attention and alertness (idiopathic clouding of consciousness).

The Consensus criteria (McKeith et al, 1996a) reflect the development of the construct of ‘fluctuation’ to acknowledge this relationship by including ‘fluctuating cognition with pronounced variations in attention and alertness’ as a core diagnostic feature. Thus, the distinction between idiopathic clouding of

Table 1.6: Comparative incidence of fluctuating cognitive impairment in dementia with Lewy bodies.

	Sample	% DLB cases with fluctuation	% Control groups with fluctuation	Comments	Type of study
Ballard et al (1997b)	DLB (n=40) AD (n=30)	N/A	N/A	100% of DLB cases showed fluctuation as this is a mandatory within the McKeith et al (1992) criteria.	Prospective
Ala et al (1997)	cLBD (n=39) AD (n=61)	8%	3%	Review of key features reported at time of <i>presentation</i> .	Retrospective
Hely et al (1996)	pDLBD (n=9)	44%	N/A	Study examining pDLBD and PD	Prospective
Klatka et al (1996)	DLBD (n=28) AD (n=56) PD (n=26)	N/A	N/A	Clinicopathologic study of psychiatric features in DLBD, using AD and PD as control groups.	Retrospective
McShane et al (1996)	cLBs present at autopsy (n=9)	N/A	N/A	“The presence of cortical Lewy bodies did not predict fluctuating cognition above the prevalence of the rest of the sample.”	Prospective
Samuel et al (1996)	LBV (n=14) AD (n=12)	N/A	N/A	Fluctuation not examined	Retrospective
Galasko et al (1995)	LBV (n=13) AD (n=13)	N/A	N/A	Describe onset in all cases as insidious. All cases had received clinical diagnosis of AD.	Prospective
Shergill et al (1994)	SDLT (n=30)	83%	N/A	Suggest fluctuating state persisting over a long period was a mental state symptom giving powerful discrimination from other forms of dementia	Prospective
Forstl et al (1993)	LBV (n=9)	0%	N/A	All cases had received clinical diagnosis of AD	Prospective
McKeith et al (1992c)	SDLT (n=20) AD (n=21) MID (n=9)	90%	5% (AD) 33% (MID)	Clinicopathological casenote review	Retrospective
Hansen et al (1990)	LBV (n=13)	N/A	N/A	All cases received a clinical diagnosis of Alzheimer's disease	Retrospective
Byrne et al (1989)	DLBD (n=15)	80%	N/A	Clinicopathological study	Retrospective
Gibb et al (1985)	Dementia + PD (n=4)	N/A	N/A	Case reviews of 4 patients with available cortical tissue	Retrospective

N/A= not available, DLBD='Diffuse Lewy body disease', cLBD='cortical Lewy body disease', pDLBD='Pure diffuse Lewy body disease', LBV='Lewy body variant of Alzheimer's disease', LBs='Lewy bodies', cLBs='cortical Lewy bodies', SDLT='Senile dementia of the Lewy body type', DLB='dementia with Lewy bodies', AD='Alzheimer's disease', MID='Multi-infarct dementia'

consciousness and fluctuating cognitive impairment may only represent differing manifestations of a similar underlying psychopathology.

Identification of episodes of clouding of consciousness may require more sensitive methods of assessment than simple observation, as initially proposed by McKeith et al (1992c). There have been subsequent suggestions that patients might show short term increases in arousal in response to environmental stimuli (McKeith et al, 1996a), which would confound formal psychometric assessment scores.

Identifying fluctuating levels of impairment is hindered by problems defining, quantifying, and distinguishing fluctuating levels of cognitive impairment and altered levels of consciousness. These difficulties become particularly apparent in the late stages of dementia when fluctuation may become indistinguishable from the severe cognitive impairment. In addition, the utility of formal psychometric assessment in end-stage dementia is restricted.

Methodological problems in the operational identification and classification of 'fluctuating cognitive impairment' are reflected in the relative paucity of studies which attempt to address this issue. Evidence from studies which do address the issue demonstrate significantly greater fluctuations in attention / alertness, formal psychometric testing and daily living skills in DLB than AD patients. In addition, altered levels of consciousness are consistent with neuropathological findings implicating disruption of the ascending reticular-activating system (ARAS) and associated nuclei (particularly in brain-stem nuclei, and cholinergic neurons in nucleus basalis of Meynert) in DLB.

1.3.1.3 Psychosis in dementia.

Psychosis is associated with patient and carer stress, as well as a reduced ability to live independently (Steele et al, 1990). Psychotic symptoms, and more specifically, visual hallucinations are a common feature in cases of dementia associated with Lewy bodies (see Table 1.8 for review). Prevalence rates have varied from between 13% (Byrne et al, 1989) and 80% (McKeith et al, 1992c). As would be expected, lower prevalence rates are found in clinical populations

associated with neurological services than those with psychiatric services.

Preliminary data from a series of 72 patients enrolled in the Newcastle prospective study of SDLT includes data from 42 SDLT cases (see Table 1.7) (Ballard et al, in press). These data suggest visual and auditory hallucinations, as well as delusions, occur more frequently in DLB and AD. Ballard et al found the content of the hallucinations in dementia with Lewy bodies and Alzheimer's disease to be similar. The most common themes were circumscribed hallucinations involving animals, objects and people.

Ala et al, (1997) also found that the presence of hallucinations at presentation helped distinguish Lewy body dementia and Alzheimer's disease; however they suggested this may not be a particularly sensitive as they were reported for less than half of the patients with LBD.

Table 1.7: Comparative prevalence of non-cognitive symptoms at baseline assessment in 42 DLB and 30 AD cases matched for severity of dementia from the Newcastle Prospective Study of Memory Disorders (adapted from Ballard et al, in Press).

	<u>DLB</u>	<u>AD</u>	Significant difference
Visual hallucinations	92.9%	26.7%	Y
Auditory hallucinations	57.1%	10.0%	Y
Delusions	59.5%	20.0%	Y
Major depression / dysthymia	19%	10.0%	NS
2 or more falls	38.1%	30.0%	NS

Table 1.8: Comparative incidence of psychotic symptoms in dementia with Lewy bodies.

	Sample	% DLB reporting psychosis	% Controls reporting psychosis	Comments	Type of study
Ballard et al (1997b)	DLB (n=40) AD (n=30)	93% vis. hall. 57% aud. hall. 59.5% del.	27% vis. hall. 10% aud. hall. 20% del.	Figures given are for baseline assessment only. Visual hallucinations are also significantly more likely to persist in DLB than AD.	Prospective
Ala at al, (1997)	cLBD (n=39) AD (n=61)	23% hall.	3% hall.	Review of key features reported at time of presentation.	Retrospective
Hely et al, (1996)	pDLBD (n=9)	78% hall.	N/A	Study examining pDLBD and PD.	Prospective
Klatka et al, (1996)	DLBD (n=28) AD (n=56) PD (n=26)	DLBD 61% hall. 57% del.	AD PD 35% 54% hall. 53% 15% del.	Clinicopathologic study of psychiatric features in DLBD, using AD and PD as control groups.	Retrospective
McShane et al, (1996)	cLBs present at autopsy (n=9)	44% per hall	N/A	Suggest that hallucinations beginning within the first three years of dementia are associated with cLB pathology	Prospective
Samuel et al, (1996)	LBVAD (n=14) AD (n=12)	N/A	N/A	Occurrence of hallucinations not recorded	Retrospective
Galasko et al., (1995)	LBVAD (n=13) AD (n=13)	32% hall. 43% del.	11% hall. 29% del.	All had received clinical diagnosis of AD.	Prospective
Shergill et al, (1994)	SDLT (n=30)	67%	N/A	Suggest presence of visual or auditory hallucinations accompanied by paranoid delusions is frequently associated with LBD.	Prospective
Forstl et al, (1993)	LBVAD (n=8) AD (n=8)	25% hall.	25% hall.	All cases had received clinical diagnosis of Alzheimer's disease..	Prospective
McKeith et al., (1992c)	SDLT (n=20) SDAT (n=21)	80% vis. hall. 45% aud. hall. 80% para. del.	19% vis. hall. 0% aud. hall. 19% para. del.	Clinicopathological casenote review.	Retrospective
Hansen et al, (1990)	LBVAD (n=8) AD (n=8)	N/A	N/A	All cases received a clinical diagnosis of AD. Psychiatric symptoms described as uncommon in in both groups,	Retrospective
Byrne et al, (1989)	DLBD (n=15)	27% hall.	N/A	Clinicopathological study.	Retrospective
Gibb et al, (1985)	Dementia + PD (n=4)	75% hall.	N/A	Case reviews of 4 patients with available cortical tissue.	Retrospective

N/A = not available, 'Hall' = 'hallucinations', 'del' = delusions, 'aud' = 'auditory', 'vis' = 'visual', 'para' = 'paranoid', 'per' = 'persistent'

McShane et al (1996) examined 98 patients with dementia of whom 58 were followed up to autopsy. They demonstrated that hallucinations starting within three years of the onset of dementia were associated with Lewy body pathology as well as reduced life expectancy. In particular, recurrent hallucinations were strongly associated with cortical Lewy body pathology. McShane et al (1995) provide an operationalised definition of 'persistent' hallucinations as: 'the occurrence of hallucinations on more than 5 of the previous 28 days assessed at two consecutive visits spaced 4 months apart'. The link between persistent hallucinations was studied in a cohort of 51 cases; only 2 of 6 cases with persistent hallucinations did not have Lewy bodies at post mortem, whilst 4 out of 9 LBD cases had persistent hallucinations. Those with 'fleeting' hallucinations were no more likely to have LBD than cases without hallucinations (McShane et al, 1996).

Thus, it appears that not only is there an increased prevalence of hallucinations in DLB, but the persistency of these hallucinations means that they tend to dominate the clinical picture. Although poor vision may contribute to the intensity of visual hallucinations, it is not thought to contribute to the frequency; hence persistent hallucinations appear to be a manifestation of LBD.

McKeith et al (1992c) include 'visual and/or auditory hallucinations that are usually accompanied by paranoid delusions' as a supportive, but not essential, clinical feature for the diagnosis of DLB. Indeed, in studies which include assessment of delusion there is generally an increased prevalence in DLB compared to AD (McKeith et al, (1994b); Ballard et al, (1993), however, this finding was not supported by Galasko et al (1996a), Byrne et al (1989), or Klatka et al (1996). The most commonly described are delusions of reference (the negative interpretation of remarks which are neutral). The delusions in Lewy body disease appear to be similar to those seen in Alzheimer's disease but distinct from those seen in Parkinson's disease which tend to be less complex (Ballard et al, 1996a).

1.2.1.4 Neuroleptic sensitivity.

Dementia with Lewy bodies cases have an increased prevalence and persistency of psychotic symptomatology. Moreover, they also show severe sensitivity to the extrapyramidal side effects of neuroleptic medication (McKeith et al, 1992a). McKeith et al (1992b) described a characteristic pattern of neuroleptic sensitivity of initial sedation, followed by the sudden onset of rigidity, postural instability and falls. This is accompanied by increased confusion and decreased fluid and food intake. Death is usually due to the complications of reduced mobility and fluid intake. This occurred in 57% of 14 LBD and 54% of 16 LBD patients receiving neuroleptic medication (McKeith et al, 1992b). Neuroleptic treated LBD cases showed an increased mortality risk of 2.7 six months after presentation to services. McKeith et al (1992b) also described differences in life expectancy between neuroleptic treated and neuroleptic naive dementia with Lewy bodies cases, with the mean survival time for neuroleptic treated cases as 7.4 months as opposed to 28.5 months in cases not treated with neuroleptics.

The United Kingdom Committee on the Safety of Medicines (CSM, 1994) sent a circular indicting that when neuroleptics were to be employed with elderly patients with dementia, very low doses should be titrated against the clinical state, and extra care should also be taken in cases with symptoms suggestive of dementia with Lewy bodies. Neuroleptic sensitivity in cases of dementia associated with Lewy bodies is not a ubiquitous finding, McShane et al (1996) failed to find an increased risk of neuroleptic sensitivity in dementia associated with Lewy body disease within a year of starting neuroleptics. McShane and colleagues did however describe an increased rate of cognitive decline in male patients receiving neuroleptics, although this association was not apparent in women.

A possible explanation for this increased sensitivity is the loss of brain-stem dopaminergic neurons in the substantia nigra of DLB cases. This loss is generally reported to be approximately 60% (Perry, E. et al, 1991), and lies just below the symptomatic threshold of 70% depletion. Thus, the administration of any drugs reducing the availability of dopamine is likely to induce parkinsonian like

symptoms (see Section 1.4.3).

1.3.1.5 Affective disturbance.

Depression is the only mood disorder to have been systematically studied in DLB. Given the increasing quantity of evidence suggesting pathology in the locus coeruleus is associated with depression in both AD and PD, it would seem logical to suggest an increased incidence of depression in DLB where numerous Lewy bodies are found in the locus coeruleus. A number of studies have identified a higher prevalence of depression in DLB than AD (see Table 1.9). McKeith et al (1992c) describe higher prevalence rates of major depression at presentation in DLB than AD cases. Ballard et al (1993) found 7 out of a series of 16 patients with idiopathic clouding of consciousness fulfilled criteria for the diagnosis of depression based on the Cambridge assessment of Mental Disorders in the Elderly (CAMDEX) schedule. Fourteen of these sixteen also fulfilled McKeith criteria for the diagnosis of DLB, although neuropathological diagnoses were not available. Klatka et al (1996) retrospectively assessed the frequency of depression in 28 DLBD, 58 AD, and 26 PD cases. Depression was more common in the DLBD (50.0%) than AD (13.8%) groups, but was equivalently common in PD (57.7%) and DLBD. The authors do not comment on the relative frequencies of depression in AD and PD groups.

Most studies have reported a similar incidence and prevalence of depression in DLB and AD (e.g. Ballard et al, 1996a; Hansen et al, 1990). The prevalence rate of DSM-III-R major depression was reported as 15% in a series of 42 cases of SDLT from the Newcastle prospective study of memory disorders (Ballard et al, 1995). This is very similar to the majority of neuropathological studies, which all find prevalence rates of DSM-III-R (American Psychiatric Association, 1994) major depression of around 15%.

Table 1.9: Comparative incidence of depression in dementia with Lewy bodies.

	Sample	% DLB reporting depression	% Controls reporting depression	Comments	Type of study
Ballard et al (1997b)	DLB (n=40) AD (n=30)	19%	10%	Depression was diagnosed according to DSM-III-R criteria.	Prospective
Ala et al, (1997)	cLBD (n=39) AD (n=61)	39%	60%	Retrospectively recorded if patients were diagnosed with or had been treated for depression at time of presentation or in the preceding year.	Retrospective
Hely et al, (1996)	pDLBD (n=9)	9%	N/A	Patients studied prospectively, but specific neuropsychiatric details were not assessed, and details were obtained retrospectively.	Prospective
Klatka et al, (1996)	DLBD (n=28) AD (n=56) PD (n=26)	DLBD 50%	AD PD 14% 58%	Clinico-pathologic study of psychiatric features in DLBD, using AD and PD as control groups. Depression counted as present if documented by a primary or consulting health provider.	Retrospective
McShane et al, (1996)	cLBs present at autopsy (n=9)	N/A	N/A	Occurrence of depression not recorded	Prospective
Samuel et al, (1996)	LBV (n=14) AD (n=12)	N/A	N/A	Occurrence of depression not recorded	Retrospective
Galasko et al, (1995)	LBV (n=13) AD (n=13)	16%	16%	All cases had received clinical diagnosis of AD. Used Diagnostic Interview schedule from DSM-IV. Brief depressive episodes (< 2 weeks) and reactive depression were disregarded.	Prospective
Shergill et al, (1994)	SDLT (n=30)	N/A	N/A	Occurrence of depression not recorded	Prospective
Forstl et al, (1993)	LBV (n=8) AD (n=8)	N/A	N/A	Occurrence of depression not recorded	Prospective
McKeith et al, (1992c)	SDLT (n=20) SDAT (n=21)	14% maj dep pres 38% tot dep pres	0% maj dep pres 16% tot dep pres	Clinico-pathological casenote review. SDLT cases showed greater depression (major & minor) at presentation and during whole course. Significantly more major depression (DSM-III-R) at presentation in SDLT than AD (figures shown).	Retrospective
Hansen et al, (1990)	LBV (n=8) AD (n=8)	25%	25%	All cases received a clinical diagnosis of Alzheimer's disease. Psychiatric symptoms described as uncommon in both groups.	Retrospective
Byrne et al, (1989)	DLBD (n=15)	20%	N/A	Clinicopathological study. . Figures given are for depression and all these cases presented with parkinsonian symptoms.	Retrospective
Gibb et al, (1985)	Dementia + PD (n=4)	25%	N/A	Case reviews of 4 patients with available cortical tissue.	Retrospective

N/A = not available, maj='major', tot='total', dep='depression, pres='at presentation'.

Studies which employ less strict criteria for a diagnosis of depression (e.g. Ballard et al, 1993, Klatka et al, 1996) identify more depression in DLB than AD; whilst those using the stricter DSM-III-R criteria generally find dementia rates to be equivalent in the two syndromes (e.g. Galasko et al, 1996a). These findings raise the possibility that depressive symptoms are more prevalent in DLB than AD, but may not be severe enough to satisfy DSM-III-R criteria.

1.3.1.6 Movement disorder and DLB.

Disorders of movement, similar to those seen in PD, are common in DLB. Indeed, DLB may present with either cognitive or extrapyramidal symptomatology (EPS). Criteria for diagnosing DLB ante-mortem all include the presence of EPS as a useful discriminator between DLB and AD. There remains, however, some discrepancy over the prevalence; some authors report over 70% of DLB cases qualifying for a secondary diagnosis of PD at some stage during the illness (Gibb et al, 1989a; Byrne et al, 1989; Kosaka, 1990; & McKeith et al, 1994b) and most of the motor features of PD have been described in DLB, whilst others report only mild EPS in DLB (Perry, R. et al, 1990; Förstl et al, 1993; & Hansen et al, 1990). Moreover, there is little agreement about the type of parkinsonian syndrome in DLB. Crystal et al (1990) describe an akinetic-rigid syndrome without rest tremor, whilst Byrne et al (1989) describe resting tremor in up to 66% of cases. Once again, such discrepancy is likely to reflect different study design and sampling methodologies. Comparative study of EPS in DLB and idiopathic PD may help in ante-mortem diagnosis especially in those DLB cases presenting with motor symptoms. In a similar way, careful comparison of neuropsychological performance in DLB patients presenting with cognitive symptoms and AD patients, is likely to aid early differentiation.

Recently, Gnanalingham et al (1997) assessed EPS in 16 patients with Lewy body dementia, 15 with PD, 25 with AD, and 22 control subjects, using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) (Lang et al, 1989). Both PD and LB dementia had significantly greater overall motor impairment than AD cases; furthermore, LB dementia patients scored significantly

higher total scores (38.3) on the UPDRS scale than PD patients (29.5). Ninety-four percent of LB dementia cases qualified for a secondary diagnosis of PD. LB dementia patients showed significantly more rigidity than PD cases. EPS items assessed in the motor section of the UPDRS failed to discriminate the PD and LB dementia, with the exception of resting tremor, which was seen in a greater proportion of patients with PD (93%) than LB dementia (50%). The PD group showed significantly greater left/right asymmetry of motor signs than other groups, but similar upper/lower limb asymmetry to other groups.

A retrospective review of case notes revealed a subgroup of patients with sufficient clinical details about the onset of the clinical symptoms of parkinsonism to enable comparison in 11 PD and 12 LB dementia cases. There were no differences between PD and LB dementia in terms of tremor, rigidity, bradykinesia, or upper/lower limb asymmetry. However, PD cases showed greater (100%) left/right asymmetry than LB dementia cases (42%). Gnanalingham and colleagues conclude that the motor disability is consistent with the dopaminergic dysfunction in the brain stem in DLB, however, the subtle differences in the nature of the EPS between LB dementia and PD may be of little use for the clinical differentiation of the two disorders.

Louis et al (1996) reviewed prospective and retrospective clinical data on a large series of pathologically diagnosed cases of PD (n=34) and common form DLBD (n=31). They found the DLBD group to have an older age of onset (67.9 years) than PD cases (62.0 years). Rest tremor was present in significantly more PD cases (85%) than DLBD cases (55%); whilst myoclonus was more common in DLBD (18.5%) than PD (0%). There were no differences in rigidity, bradykinesia, dystonia, or gaze palsies. Data also suggest clinical response to levodopa might be more common ($p=0.059$) in PD (100%) than DLBD (70%). The occurrence of any one of four clinical features (myoclonus, absence of rest tremor, no response to levodopa, or no perceived need to treat with l-dopa) was 10 times more likely in DLBD than PD. The sensitivity of these features to discriminate PD and DLBD was moderate (66.7%), but showed a better specificity and positive predictive value (85.7%). These must be interpreted with caution, as the population

examined was not representative of a clinical population, as participants were recruited only from a movement disorders clinic.

Hansen et al (1990) compared 9 LBV and 9 AD cases with pathological confirmation of the clinical diagnosis. Several differences were identified between the groups in terms of the neurological findings. Essential tremor (although not considered to be a parkinsonian action tremor), masked faces, bradykinesia and nuchal rigidity were found more commonly in LBV cases than AD cases.

Parkinsonian features were generally more mild in AD than LBV, although a mild limitation in upward gaze was more common in the AD group. The LBV cases did not show parkinsonian features typical of PD such as flexed posture or parkinsonian tremor. Hansen concludes that the parkinsonian features are typical of early stage idiopathic PD which corresponds to the relatively mild degree of loss of pigmented neurons in the substantia nigra. LBV cases met clinical and pathological diagnostic criteria for AD, and as such are of limited applicability to the range of Lewy body disorders.

The studies presented above represent the most detailed assessment of movement disorders in DLB; however, they fail to show clinically useful or easily theoretically interpretable differences between the groups investigated. Subtle differences in extrapyramidal symptoms between PD and DLB are unlikely to prove useful in the clinical differentiation of the two disorders. Differentiation of DLB and PD with dementia is an under investigated area in with respect to the movement disorder, mental state symptoms, and cognitive functioning.

Nonetheless, the occurrence of extrapyramidal symptoms has been shown to be a useful discriminator of AD and DLB and is included in all sets of diagnostic criteria (see Appendices I, II, & III).

1.3.1.7 Criteria for the clinical diagnosis of dementia with Lewy bodies

DLB is identifiable during life. Different profiles of mental state symptoms and neuropsychological performance (see Section 1.5) are testimony to the possibilities for accurate clinical diagnosis. The ability to distinguish DLB from AD and PD in vivo provides benefits not only for research (especially trials of possible treatments), but also for routine clinical practice. Early recognition of DLB cases aids the differential management of the disorder, particularly with respect to administration of neuroleptic medication, and the provision of care by professionals and carers.

Diagnostic criteria are employed differently by researchers and clinicians. The primary aim of diagnosis for researchers is one of accuracy (high diagnostic specificity), even if this is achieved at the expense of the exclusion of some patients, who do in fact have the disease. Clinicians, however, require simple and robust tools which should be sufficiently broad to alert clinicians to the possibility of DLB, even in more atypical cases (high diagnostic sensitivity). Both researchers and clinicians benefit from diagnostic tools which are sensitive and specific to DLB.

Criteria proposed by groups in Nottingham (Byrne et al, 1991) (see Appendix I) and Newcastle (McKeith et al, 1992c) (see Appendix II) were developed on the basis of retrospective case note analysis. Both sets of criteria acknowledge the importance of fluctuating confusion for the identification of DLB; however, neither provides an adequate formalised method of assessing fluctuation (McKeith et al, 1996a; Mega et al, 1996). Although both criteria comprise generally similar features, there are a number of subtle differences which merit discussion. The Nottingham criteria follow the NINCDS-ARDRA³ model by suggesting diagnostic categories of probable and possible LBD, whilst the Newcastle criteria only suggest a single category of SDLT. In addition, the Newcastle criteria are

³ National Institute of Neurological and Communicative Disorders and Stroke in conjunction with the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) proposed clinical criteria for the diagnosis of AD (McKhann et al, 1984).

based on symptoms at presentation, whilst the Nottingham criteria are based on the occurrence of symptoms throughout the course of the illness. For example, the Nottingham criteria require the presence of extrapyramidal symptoms for a diagnosis of LBD to be made. However, only 9% of 21 SDLT cases from the Newcastle cohort had extrapyramidal symptoms at presentation, although this figure eventually increased to 74% of cases. The Newcastle criteria do not therefore include extrapyramidal symptoms as a feature essential for the diagnosis of SDLT.

The Nottingham and the Newcastle criteria were retrospectively applied to the case notes of a consecutive series of patients with a diagnosis of dementia, who were referred to old age psychiatry services over a one year period (Shergill et al, 1994). The study examined whether the retrospectively applied criteria produced similar prevalence rates of DLB to those rates identified in post-mortem studies. Shergill and colleagues employed logistic regression analysis to identify features from each set of criteria that were most likely to differentiate between DLB and other dementias.

McKeith et al criteria identified 26.3% of a cohort of 114 cases to have SDLT; whilst Byrne et al criteria identified 7% probable LBD and 17% possible LBD. These rates are similar to those found in post-mortem series. Shergill et al conclude, however, that the two sets of criteria identify somewhat different groups. McKeith et al criteria focus on hallucinations, neuroleptic sensitivity, and fluctuating impairment and consciousness, whilst the Byrne et al criteria focus more on the dementia of PD. This may reflect the samples employed by the two groups, as McKeith et al recruited from old age psychiatry services, and Byrne et al recruited from medical, neurological and psychiatric services. Shergill et al (1994) might overestimate the utility of the Byrne et al criteria in making an early differential diagnosis of DLB, as case notes were reviewed not just prior and subsequent to the patients' presentation to the medical services, but throughout the course of the illness.

McKeith et al (1994b) reviewed how the Newcastle criteria would classify a series of case histories of patients with autopsy confirmed SDLT and thus provide a measure of predictive validity. A range of diagnostic criteria were applied to a series of patients who suffered from dementia and who had received post mortem diagnosis. The series included 20 SDLT, 21 AD, and 9 Multi-Infarct Dementia (MID) cases. Cases with a neuropathological diagnosis of SDLT were commonly misdiagnosed as MID (35% of SDLT cases had a Hachinski score of greater than 7), or AD (50% of SDLT met current NINCDS-ARDRA criteria for possible AD, and 35% met DSM-III-R criteria for AD). If these cases of misdiagnosis are totalled, then it is evident that the majority of SDLT cases might be misdiagnosed using the most widely employed diagnostic systems, and may represent a major confound of previous research into AD.

McKeith et al (1994a) also investigated the predictive validity and inter-rater reliability of the Newcastle criteria on the same series of SDLT, AD and MID cases reviewed in the McKeith et al (1994b) study. Four clinicians retrospectively reviewed the case notes of the 50 cases and provided a diagnosis for each case. Raters one and two were experienced senior clinicians who were specialists in old age psychiatry, rater three was a clinician with higher training in old age psychiatry, and rater four was a psychiatrist not experienced with a demented elderly population. The effect of rater experience in the ability to diagnose SDLT was noted (see Table 1.10).

Table 1.10: Sensitivity and specificity of clinical diagnosis of SDLT amongst four Raters using Newcastle criteria (McKeith et al, 1992c) (adapted from McKeith et al (1994a).

Rater	Sensitivity (true positive rate) %	Specificity (true negative rate) %
One	85.0	97.0
Two	90.0	90.0
Three	65.0	97.0
Four	55.0	97.0
Mean	73.75	95.0

The sensitivity values (sensitivity is the proportion of true positives that are correctly identified by the criteria) ranged from 55 to 90% and are comparable with those found in AD using NINCDS-ADRDA criteria (46-92%) (Kukull et al, 1990), for pure MID (70 to 80%) and mixed AD / MID (17 to 50%) (Chui et al, 1992). The high specificity (specificity is the proportion of true negatives identified by the criteria) rates of between 90 and 97% suggest that the clinical syndrome of SDLT, as identified by the Newcastle criteria, is not frequently seen in MID or AD cases. More detailed appraisal of individual items on the diagnostic criteria revealed an apparent lack of clear guidance to less experienced clinicians about the identification of a fluctuating course of illness in SDLT cases. Nonetheless, McKeith et al (1994b) demonstrate that SDLT may be distinguished with a degree of diagnostic accuracy comparable to AD and MID in a clinical population. However, at this stage the criteria await prospective evaluation.

In November 1995, the first international meeting to bring together clinicians and researchers from the main centres studying DLB was held in Newcastle, England. Similar to the consensus guidelines for the neuropathological sampling and diagnosis of DLB, clinicians agreed clinical diagnostic criteria following workshops lasting two days. These criteria (see Appendix III) were published in a major journal the following year (McKeith et al, 1996a) as a refinement of the previous Newcastle and Nottingham criteria. The criteria note the need to review current diagnostic criteria for AD, PD, and SDLT and acknowledge that DLB may present as, primarily, a neuropsychiatric syndrome, or in cases which follow a primary diagnosis of PD (although this should be within a 1 year period).

The consensus criteria maintain the central feature of progressive mental impairment. However, this was broadened to include tests of memory retrieval as well as the impairments in acquisition and consolidation associated with AD. Furthermore, attentional and visuo-spatial dysfunction were included as these are thought to be particularly impaired in SDLT. Early memory impairment is not necessary for a diagnosis of DLB, although severe memory impairment is likely with disease progression.

In addition, the criteria require at least one of the following for a clinical diagnosis of DLB: fluctuation, visual hallucinations, or motor parkinsonism. Problems, previously associated with operationalising 'fluctuation', were addressed by the provision of detailed guidelines for identifying fluctuation. Fluctuation was not required as a mandatory feature of DLB as had been previously suggested (McKeith et al, 1992c), but was retained as a core diagnostic feature with considerable diagnostic weight.

Visual hallucinations were also included as a core feature for the diagnosis of DLB, as they are the only psychotic symptom to reliably distinguish it from AD. McKeith et al (1996a) suggest that it is the persistence of visual hallucinations that enable DLB to be distinguished from other forms of dementia and systemic illness (e.g. delirium) where the perceptual disturbances are usually episodic and transient.

Motor symptoms of parkinsonism were the third core feature of DLB. Rigidity and bradykinesia were identified as the parkinsonian symptoms most likely to distinguish DLB. Onset of motor and cognitive symptoms may vary. However, the onset of extrapyramidal symptoms and mental symptoms should occur within a 1 year period for a primary diagnosis of DLB to be made. To help distinguish DLB from PD, responsiveness to L-dopa was not included as necessary to the diagnosis of DLB. If the extrapyramidal motor symptoms occur late on in the dementing illness, then they are deemed as supportive, but not specific to a diagnosis of DLB, as extrapyramidal motor symptoms also occur late on in a number of dementing processes. The motor symptoms associated with dementia are distinguished from neuroleptic-induced parkinsonism by their persistence after withdrawal of neuroleptic medication.

A number of clinical features were included in the consensus criteria as supportive of, but not core to, the diagnosis of DLB. These include repeated falls, syncope, or transient losses of consciousness, neuroleptic sensitivity, or systematised delusions and hallucinations not in the visual modality. In addition, clinical features which might be employed to exclude a diagnosis of DLB in the evaluation

dementia patients include: the identification of stroke disease, physical illness, or other brain disorder. These features may be present in some cases of DLB, as concomitant illnesses are not uncommon in dementia.

The formulation, reliability, and validity of the proposed consensus criteria were evaluated by Mega et al (1996) who compared the reliability of five neurologists to identify the clinical features of DLB (see Table 1.11).

Table 1.11: Inter-rater reliability for components of the three clinical criteria amongst five raters (adapted from Mega et al, 1996)

Signs and Symptoms	% Agreement Mean (range)	Kappa score Mean
Delusions	92 (88-100)	0.82
Cogwheeling	84 (76-92)	0.68
Hallucinations	80 (68-92)	0.59
Rigidity	78 (68-88)	0.52
Bradykinesia	74 (64-80)	0.46
Unexplained falls	74 (64-80)	0.46
Changing consciousness	71 (64-84)	0.27
Neuroleptic sensitivity	66 (36-88)	0.45
Episodic confusion	66 (48-80)	0.36
Fluctuating ADL (activities of daily living)	60 (40-80)	0.25
Fluctuating test performance	58 (32-80)	0.25

According to Mega et al (1996), the attempts to operationalise fluctuations in a clinical setting would appear to have had limited success, as this remains the feature with the lowest agreement amongst raters. Mega et al attempt to quantify fluctuations as variability in MMSE scores of greater than 5 points over three administrations in a six-month period, which is based on half of the patients in their study with consensus DLB meeting this criterion. The other half of consensus DLB cases do not meet this criterion, but do show fluctuations in either attention or word list memory. Mega et al conclude that the criteria require further refinement of the fluctuation criterion to facilitate their application in the clinical setting. Mega et al (1996) suggest an improvement in diagnostic sensitivity

afforded by the increased emphasis placed on extrapyramidal symptoms in the consensus criteria.

Despite being an early indicator of possible refinements to the consensus criteria, the Mega et al (1996) study is limited by a number of factors. Firstly, the study has a very small and poorly defined sample of only 24 dementia cases. These cases were apparently biased towards a neuropsychiatric population, as most received a clinical diagnosis of AD. This bias is likely to improve the differentiation of DLB from AD by the presence of extrapyramidal motor symptoms. However, this would not be appropriate for a more representative population, including patients presenting with primarily motor symptoms. Secondly, the study design was a retrospective case note analysis and is thus limited by factors previously described.

Ballard et al (1997b) assessed a cohort of 72 dementia patients using standardised assessments, as well as operationalised definitions, to diagnose non-cognitive symptoms in a series of 42 SDLT and 30 AD cases. Although Ballard and colleagues do not directly address the question of validity of the consensus clinical criteria, their findings support the changes in diagnostic criteria made in the consensus criteria. Moreover, Ballard et al suggest that the core features, included in the recent consensus criteria, remain useful in distinguishing the two disorders after one year follow-up.

In summary, early diagnostic criteria were published by groups in Nottingham (Byrne et al, 1991) and Newcastle (McKeith et al, 1992c). Continuing research and discussion has led to refinements to these criteria and the publication of consensus criteria for the antemortem diagnosis of DLB (McKeith et al, 1996a). The consensus criteria await substantive validation with a representative cohort of psychiatric and neurological patients who are prospectively evaluated and receive post mortem evaluation. Such a study is currently underway in Newcastle upon Tyne. Nonetheless, experienced clinicians are able to make a differential diagnosis of DLB with a similar specificity and sensitivity to that seen in AD (McKeith et al, 1994a; 1994b). Improvements in the clinical diagnosis of DLB also require revisions of clinical diagnostic criteria for AD, PD and MID.

1.3.1.8 Summary and conclusions.

Dementia with Lewy bodies represent a major form of dementia in the elderly. Early differential diagnosis is essential if therapeutic intervention is to be maximised. Operationalised criteria for the clinical diagnosis of DLB have been developed following a series of retrospective and prospective studies. One feature which is essential for a diagnosis of DLB is a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Unlike AD, early cognitive decline is not always associated with short term memory loss, indeed, attentional and visuo-spatial dysfunction may be early indicators of DLB.

Clinical symptoms which have been identified in the literature as strongly associated with a diagnosis of DLB are included in the consensus criteria as core features; whilst clinical symptoms which are associated with DLB, but less persuasively, are included as supportive features. Core clinical symptoms associated with DLB include: fluctuating cognition, visual hallucinations, and spontaneous extrapyramidal motor symptoms. Clinical symptoms supportive of DLB include: repeated falls, syncope, transient losses of consciousness, neuroleptic sensitivity, systematised delusions, and hallucinations in non-visual modalities. Early diagnostic criteria have been shown to be useful in the differential diagnosis of DLB, however, the more recent consensus criteria await substantial prospective validation in a representative population.

1.3.2 Genetics of dementia with DLB.

1.3.2.1 Introduction (Apolipoprotein E).

Apolipoprotein E (ApoE) is a polymorphic secretory glycoprotein expressed by a wide variety of tissues in mammals, particularly the liver and the brain (Mahley, 1988). ApoE is involved in the mobilisation and distribution of cholesterol and other lipids which would be insoluble in aqueous solutions such as the blood, and is expressed during neuronal growth and after injury. The brain produces about 20% of the body's ApoE and this glycoprotein is a major (4-5%) component of the cerebro-spinal fluid. The main neural cells responsible for the production of ApoE are astrocytes and macrophages.

There are three major isoforms of ApoE (E2, E3, and E4) that are the product of three alleles (e2, e3, and e4), which are co-dominantly expressed in humans and determine 6 different ApoE phenotypes. These alleles are encoded for by a single gene (ApoE) which is located on the long arm of chromosome 19. The distribution of ApoE phenotypes varies between populations. However, in the general Caucasian population, e3 is the most common allele with an approximate frequency of 0.78, whereas the e4 allele has a relative frequency of 0.14 (Davignon et al, 1988).

There are several indicators that ApoE is associated with the pathogenesis of AD. Firstly, Diedrich et al (1991) demonstrated increased levels of ApoE e4 messenger ribo-nucleic acid (mRNA) in AD compared to controls. Secondly, apolipoprotein has immunohistochemical associations with both senile plaques and neurofibrillary tangles (Wisniewski et al, 1992). Thirdly, it has been suggested that ApoE is able to bind and transport β -amyloid in cerebrospinal fluid in a manner that prevents paired helical filament formation (Wisniewski et al, 1993). Lastly, The presence of the e4 allele is associated with both late-onset familial and sporadic AD, suggesting that e4 may be a risk factor for AD, although the observation that AD can occur in persons without the allele is consistent with the heterogeneity of AD (Saunders et al, 1993).

1.3.2.2 The role of apolipoprotein in the pathogenesis of DLB.

The role of apolipoprotein genotype in DLB has received considerable research interest (Betard et al, 1994; Harrington et al, 1994; Galasko et al, 1994; Benjamin et al, 1995; Hardy et al, 1994, Arai et al, 1994; Katzman et al, 1995; Lippa et al, 1995; Martinoli et al, 1995; Olichney et al, 1996).

Betard et al (1994) describe increased e4 allele frequency in presenile and senile AD cases, in AD cases with LB pathology, and in AD with evidence of cerebrovascular disease, when compared with cases of vascular dementia from the same cohort. The increased relative frequency of e4 allele in LBD cases suggests that the aetiology of LBD may be somehow linked to AD. Betard and colleagues suggest that LBD may share a common underlying genetic susceptibility factor with AD, or have a different genetic causal origin that is enhanced by ApoE susceptibility.

Harrington et al, (1994) studied ApoE allele distribution in autopsy confirmed AD, SDLT, PD, Huntingdon's disease (HD), and controls with and without coronary complications. There was increased frequency of the ApoE e4 allele in SDLT (0.365), and AD (0.328) as compared to controls (0.147), PD cases (0.098), or HD cases (0.171). They found a 1.8 fold increase of β -amyloid protein in AD as compared with controls. Notably, the levels in SDLT were intermediate between those in AD and controls. AD was associated with a 20 fold increase in Tau pathology compared to controls. However, despite possessing increased e4 allele frequencies there was no significant Tau pathology in SDLT. Harrington and colleagues suggest that defective Tau processing is most strongly associated with AD, and that overrepresentation of the ApoE e4 allele is important in the formation of β -amyloid plaques, but plays little role in the formation of Tau pathology. This somewhat contradicts immunohistochemical findings from Wisniewski et al (1993), who suggest apolipoprotein is associated with both plaques and tangles.

Galasko et al, (1994) determined ApoE genotypes in 122 dementia cases who had come to autopsy. Their study investigated 74 cases of AD, 40 cases with LBV, and 8 with DLBD. They demonstrated increased ApoE e4 allele prevalence in both AD (39.6%) and LBV (29.0%) but not in DLBD (6%) when compared to 1000 controls taken from a study by Menzel et al. (1983). They suggest these findings indicate that ApoE e4 is associated with AD lesions, but not with Lewy bodies. The increased level of ApoE e4 in LBV cases suggests a link between some forms of DLB and AD. Although cases where both Lewy bodies and AD type changes are present show higher frequencies of ApoE e4, the relationship between LB formation and ApoE e4 frequency does not appear to be causal, as 8 DLBD cases without AD changes show a similar ApoE e4 allele frequency to that seen in controls.

Hardy et al (1994) also found elevated ApoE e4 allele frequencies in AD and SDLT compared to both PD and controls. ApoE e4 allele frequencies in SDLT were intermediate between AD and controls. SDLT cases include cases with LB pathology alone, as well as with concomitant AD type pathology, which might provide some explanation for the intermediate frequency. They suggest that SDLT represents the co-occurrence of AD and PD.

Lippa et al (1995) investigated whether ApoE genotype affected neuropathology in LBD by investigating ApoE genotypes, β -amyloid and LB density in different brain regions, the intensity of ubiquitin-positive neurites, vacuolar change, nigral pathology, amyloid angiopathy, and subpial amyloid deposition. They found a relationship between ApoE genotype and β -amyloid deposition such that the e3/e3 LBD cases showed a lower density of β -amyloid density than other genotypes. Interestingly, the mean number of β -amyloid plaques was greater in e2 than e4 groups, which appears contradictory to the finding that possession of ApoE e2 alleles is protective against AD. The CA2-3 neuritic degeneration was greater in cases with the e4/e4 allele than those with the e3/e3 allele. Lippa and colleagues suggest that although ApoE genotype does have an impact on the pathological burden in LBD, it is neither necessary or sufficient to account for

either β -amyloid formation or the motor and cognitive changes seen in LBD patients.

Martinoli et al (1995) determined the frequency of ApoE alleles in cases with pathologically confirmed AD, PD, DLBD, AD with concomitant PD pathology, demented PD cases with or without concomitant AD pathology and in cases of schizophrenia with a progressive dementia. Only the AD group showed increased ApoE e4 allele frequency compared to control, although this might have been more to do with small group sizes than with real distinctions.

Olichney et al (1996) performed a retrospective genetic-neuropathologic study to determine the relationship between ApoE genotype and neuropathologic lesions in AD and LBV. Their study of 127 neuropathologically diagnosed cases (AD n=84; LBV n=43) found the ApoE e4 allele to be strongly associated with increased β -amyloid deposition, but not with NFTs, in both AD and LBV.

The finding that ApoE e4 allele frequency is associated with senile plaque burden is not ubiquitous. Arai et al (1994) described ApoE e4 allele frequency in a small series of cases, clinically and pathologically diagnosed as DLBD, 5 of which were diagnosed as having concomitant AD. ApoE e4 allele frequency was elevated in DLBD cases with (50%) and without (40%) concomitant AD pathology. Arai and colleagues imply that ApoE is a risk factor for LB dementias, and that both DLBD and AD may share a common pathogenic mechanism driven by the ApoE gene. Caution should be exercised in the interpretation of these results due to the very small sample size.

Benjamin et al. (1995) investigated 45 AD, 28 SDLT, and 46 control who had pathological confirmation of their clinical diagnosis. ApoE e4 allele frequency was significantly elevated in both SDLT and AD groups with a parallel reduction in ApoE e3 frequencies. Benjamin found no significant association between SP density and NFT density in the neocortex and ApoE allele dose in SDLT or AD, which lends no support to the hypothesis that ApoE promotes β -amyloid deposition, particularly via the e4 allele. They suggest that ApoE may play a role

in initiating the β -amyloid deposition cascade, but the subsequent degree of deposition is dependent on a self-sustaining mechanism with β -amyloid self-assembling on the initial framework.

The role of ApoE alleles in the pathogenesis of dementia syndromes remains somewhat enigmatic, especially with respect to DLB. The only certainties are that increased ApoE e4 frequency is the most potent genetic risk factor known for AD, and that increased frequency is also associated with earlier onset (Saunders et al, 1993). Although ApoE e4 allele frequency appears to be increased in DLB, the exact role of ApoE allele expression in the pathogenesis of DLB remains somewhat unclear. Whilst the majority of evidence suggests that the increased ApoE e4 frequency in DLB are associated with the senile plaque burden (Betard et al, 1994; Harrington et al, 1994; Galasko et al, 1994; Benjamin et al, 1995; Lipka et al, 1995; Martinoli et al, 1995; Olichney et al, 1996), some studies have failed to identify a link between senile plaque burden and ApoE allele frequency (Benjamin et al, 1995; Arai et al, 1994). Moreover, the frequency of the ApoE e4 allele has not been reported to be increased in other amyloid-forming diseases such as Creutzfeldt-Jacob disease and familial amyloidotic neuropathy (Saunders et al, 1993). Although some cases of DLB may share the genetic risk factor associated with elevated ApoE e4 frequency, this appears to be only for cases associated with senile plaque formation. ApoE e4 allele frequencies appear not to be elevated in pure DLBD cases and in PD, thus, the e4 allele does not appear to be associated with LB burden in cases without concomitant AD changes.

Whether, e4 alleles might play a role in the pathogenesis of Lewy bodies in DLB with concomitant AD changes remains unclear, and is central to the nosological status of DLB. It may be the changes in the abnormal processing of Tau, rather than β -amyloid deposition in senile plaques, which is associated with the clinical, pathological, and immunohistochemical factors that distinguish AD from both DLB and normal ageing.

The presence of the ApoE e4 allele is neither sufficient or necessary to cause AD, indeed the only firm conclusion to be drawn is that it affects the age of onset of

AD (Roses, 1995). There is no evidence that ApoE e4 allele frequency affects the age of onset of PD, however, it remains to be determined whether it affects the age of onset of DLB.

1.3.2.3 Cytochrome P450 2D6 Genetic Polymorphism.

It has been proposed that alleles of CYP2D6, one of the P450 monooxygenases, are associated with the metabolic degradation of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and tetrahydroisoquinoline which are toxins known to be capable of inducing lesions to produce parkinsonism. The CYP2D6 allele has several common alleles. The most common (wild type) allele is present in most individuals and ethnic groups. The 'A' and 'B' variant alleles are associated with reduced debrisoquine hydroxylase activity. Armstrong et al, (1992) reported an association between the CYP2D6 'B' allele and PD. In a larger series, Smith et al (1992) failed to report the increased frequency of 'B' alleles. In fact Smith and colleagues reported an increased (1.8 times) 'A' allele frequency in PD. Kondo et al (1991) found that having two mutant alleles (they investigated only 'A' and 'B') was 2.4 times more frequent in PD. Saitoh et al (1995) described an increased frequency of the 'B' allele in DLB.

Bordet et al (1994) investigated genetic polymorphism of the cytochrome P450 2D6 gene in idiopathic Parkinson's disease (IPD) and DLBD. They failed to establish a relationship between CYP2D6 impairment and neuropathological lesion diffusion in IPD and DLBD cases. However, their study was unable to exclude involvement of neuronal expression of CYP2D6 due to complex neuroanatomical regional differences in the expression of CYP2D6 in IPD and DLBD.

1.3.2.4 Summary.

Increased ApoE e4 allele frequencies are observed in DLB cases, this appears to be associated with senile plaque burden. ApoE e4 allele frequencies do not appear to be increased in pure DLBD cases or in PD. Thus, ApoE e4 allele frequencies do not appear to be associated with Lewy body formation without concomitant senile

plaque formation. Mutations of the CYP2D6 gene appear to act as susceptibility factors for PD as well as DLB. There are evidently further genes to be delineated which describe the relationship between PD and DLB, especially those which determine the topographical distribution of Lewy body pathology. Whether the complex nature of the genetic interactions between DLB, AD, and PD will eventually prove to be useful in the clinical diagnosis of DLB remains to be ascertained.

1.3.3 Macroscopic and neuroimaging features of Alzheimer's disease, Parkinson's disease, and dementia with Lewy bodies.

On a gross macroscopic level, Alzheimer's disease is accompanied by widespread cortical atrophy and associated increase in ventricular size (Perry, R. et al, 1982). However, considerable atrophy can be found in the brains of patients with non-dementing conditions (Tomlinson, 1980) and, furthermore, there may be as much as a 20% overlap between pathological and non-pathological atrophy. A similar pattern for brain weight is observed (Terry & Katzman., 1983).

Neuroimaging data for Alzheimer's disease suggest the medial temporal lobe to demonstrate the most consistent changes, and indeed Jobst and colleagues (1995) suggest a simple measure of atrophy in the medial temporal lobe by computed tomography as a useful diagnostic tool for identifying Alzheimer's disease in life. Neuroimaging has not yet been able to show any specific discriminatory indices between Alzheimer's disease and dementia with Lewy bodies. Macroscopic features do not at present provide a peripheral marker or diagnostic test to identify and discriminate between the two disorders.

Parkinson's disease patients also show cortical atrophy, particularly in the frontal lobes (Cummings et al, 1983). However, as the course of Parkinson's disease is relatively easily distinguishable from Alzheimer's disease and dementia with Lewy bodies, the implications for use as a clinical diagnostic tool are rather limited. There are, however, interesting implications for the subclassification of Parkinson's disease as a 'subcortical' dementia.

Patients with vascular dementia can usually be identified without recourse to specialised imaging. A background of cerebrovascular risk factors, and in particular hypertension, a history of stroke like events and stepwise deterioration, focal motor and sensory signs, early urinary disturbance and patchy cognitive deficits are all indicative of vascular pathology (Hachinski et al, 1975). However, infarcts lead to cell death and a characteristic alteration of density of representation on both CT scan and MRI, making identification of vascular

involvement in dementia relatively simple to distinguish. Evidence of significant infarcts are included as a feature to exclude a diagnosis of DLB in the consensus criteria (McKeith et al, 1996a). Furthermore, a sizeable proportion of cases who show multiple infarcts in-vivo, display coexistent Alzheimer's disease pathology post mortem. This condition, called mixed dementia, adds a pitfall to the use of neuroimaging techniques as a clinical diagnostic tool, although it is commonly used as an aid to clinical diagnosis

Crystal et al, (1990) suggest that electroencephalogram measures might be useful in distinguishing dementia with Lewy bodies and Alzheimer's disease. They found that four out of six patients with Lewy body disease had abnormal EEGs showing background slowing and bursts of frontal 2-4 Hz activity when only mildly demented, and comment that EEG changes in Alzheimer's disease patients tend to be relatively less severe. Although similar non-specific changes have been reported by Gibb et al (1989a) these findings await validation and clarification in a larger cohort.

Neuroimaging in DLB is an under researched area which awaits systematic investigation with large cohorts of patients. Whether this reveals distinctions between AD and DLB which are of sufficient magnitude to aid in the differential diagnosis of the two disorders remains to be elucidated.

1.4 Neurochemical dysfunction in dementia with Lewy bodies, comparisons with Alzheimer's disease and Parkinson's disease.

1.4.1 Introduction.

That neurochemical alterations underlie many of the cognitive and clinical problems seen in AD is well documented especially with respect to cholinergic dysfunction in AD (e.g. Perry, E. 1978). The interaction between the topography and extent of neurochemical and neuropathological deficits in DLB is less well documented. There is, however, a significant emergent literature to suggest neurochemical distinctions from both PD and AD, but with common features of both. The prevalence of clinical symptoms in DLB reflects neurochemical dysfunction unique to DLB.

1.4.2 Cholinergic systems in DLB.

1.4.2.1 The cholinergic hypotheses revisited.

The disproportionate disturbance in cholinergic function seen in AD was implied at the same time by a number of teams in the 1970's (Davies et al, 1976; Perry, E. et al, 1977). A reduction in the enzyme choline acetyltransferase (ChAT), was described in AD. ChAT levels are typically reduced by 50% (30-90%) in cortical areas, but remained relatively preserved in the brainstem, thalamus, pre and post-central gyrus, occipital cortex, and cerebellum (Davies et al, 1978). Whitehouse et al (1981) showed marked loss of the nucleus basalis of Meynert neurons, the nucleus projecting to most cholinergic neurons in the cortex, in AD. The subsequent cortical cholinergic dysfunction and reductions in ChAT are attributed to pathology of the nucleus basalis of Meynert.

The discovery of cholinergic dysfunction in AD led to much of the cognitive impairment of the disease being attributed to loss of this transmitter, giving rise to the so called 'cholinergic hypotheses'. This is supported by other human and animal, experimental and clinical, psychopharmacological investigations. Human

psychopharmacological investigations have demonstrated that a profile of cognitive changes similar to AD can be induced in healthy volunteers by administration of anticholinergic agents such as scopolamine. These effects are reversed by the administration of physostigmine which enhances cholinergic functioning by inhibiting cholinesterase breakdown of acetylcholine (Wesnes et al, 1983a, 1994, 1988a; 1988b; Drachman, 1977). Alzheimer's disease cases are also more sensitive to the administration of anticholinergic treatments than non-demented elderly (Sunderland et al, 1985). In addition, cortical ChAT is reduced in autopsy and biopsy samples, and the ChAT levels correlate with the degree of cognitive impairment (Perry, E. et al, 1978; Sims et al, 1983).

The status of cholinergic receptors in diseases of the human brain associated with cholinergic dysfunction in the cortex is of interest, particularly with respect to putative cholinergic therapy. There remains a great deal of interest in drugs which aim to alleviate AD symptoms by enhancing cholinergic function. Although a number of cholinesterase inhibitors are now licensed, results to date have been somewhat disappointing. In the trial of Eagger et al, (1991) only about 1 in 3 'AD' patients showed a clinically significant response in terms of improvements in MMSE scores to the administration of tetrahydroaminoacridine (THA; Tacrine). Interestingly, most responders in this trial who have reached autopsy have shown Lewy bodies, as well as very dramatically reduced cholinergic activities. Not all studies have, however, demonstrated such an improved rate of response in DLB cases to THA (Wilcock et al, 1994). These findings suggest that DLB may represent a subset of clinically identifiable dementia patients who respond to cholinergic therapy.

1.4.2.2 Choline acetyltransferase (ChAT) activity.

Perry, E. et al (1990a: 1990b; 1994) described cholinergic and dopaminergic activities in SDLT, AD and PD in post mortem tissue. SDLT cases showed even greater reductions in the cortical cholinergic enzyme choline acetyltransferase (ChAT) than AD cases which is consistent with previous findings in DLBD (Dickson et al, 1987). Neocortical ChAT was more profoundly reduced in SDLT

cases with hallucinations (80% reduction) compared to those without hallucinations (50% reduction). There was a strong correlation between choline acetyltransferase levels and mental test scores (Blessed et al, 1968), as measured shortly before death. Indeed, this correlation is considerably greater than the correlation (0.52) between cholinergic loss and mental test score previously described in a series of 16 AD cases (Perry, E. et al, 1978). Langlais et al, (1993) have also demonstrated significantly depleted neocortical ChAT activity in the LBV cases compared to the pure AD cases, and also suggest that this is related to degeneration of the nucleus basalis of Meynert.

Topographical distinctions between ChAT depletion in SDLT and AD have been demonstrated (Perry, E. et al, 1994). Archicortical cholinergic dysfunction has been shown to be more severe in AD than DLB (Perry, E. et al, 1994) which contrasts the more severe cholinergic dysfunction in many neocortical areas in DLB (Perry, E. et al, 1990a; 1990b; Langlais et al, 1993). The mechanism by which Lewy body pathology preferentially affects the nucleus basalis of Meynert which provides cholinergic innervation to the neocortex, and senile plaque and neurofibrillary tangle formation primarily affect pathways projecting from the septal area to archicortical structures remains unclear. Perry and colleagues did not find an association between the topographical variations in the degree of cholinergic enzyme loss and prevalence of Lewy bodies in the cortex. Nonetheless, Perry, E. et al (1994) suggest the 'pathological processes which contribute to degeneration of cholinergic neurons in the nucleus basalis of Meynert and the development of widespread cerebral Lewy body formation are likely to be linked'.

1.4.2.3 Muscarinic receptor alterations in DLB.

In AD muscarinic receptors are generally not reported to undergo major changes in their overall population, the ratio of subtypes (M_1 or M_2) of receptor, or the agonist affinity states, although M_2 receptor binding is generally moderately reduced. In PD, however, cortical muscarinic receptors (particularly M_1) actually increase in number (Nordberg et al, 1985). Similarly, Perry, E. et al, (1990b) have

demonstrated increases in cortical muscarinic receptors in SDLT. In all cortical areas investigated, (temporal, parietal and occipital) there were increases in the M₁ receptors in PD and SDLT, but not AD. There is relative sparing, and increased binding, of the M₁ muscarinic receptors in SDLT. The M₁ muscarinic receptors are thought to be primarily post-synaptic. This finding has important implications for therapeutic treatments, as it may be indicative of a capacity of intrinsic cholinceptive neurons in the cortex to compensate for cholinergic denervation. This is less apparent in AD, where in particular M₂ but also M₁, muscarinic sites are reduced in end-stage AD. Perry and colleagues postulate that neurofibrillary tangles, which are sparse in SDLT, may affect the ability of M₁ receptors to up-regulate (Perry, E. et al, 1990b).

1.4.2.4 Nicotinic receptor alterations in DLB.

Central nicotinic receptors have been consistently found to be reduced in numbers by approximately 50% in AD, and PD (Perry, E. et al, 1987; Nordberg et al, 1988). Perry, E. et al (1995a) studied high-affinity nicotine binding in brain regions most severely affected by AD and PD type pathology in AD, PD and SDLT cases. In the midbrain, significant reductions in the density of nicotinic binding in the pars compacta of the substantia nigra were described in PD and Lewy body dementia. Reduction in nicotinic receptor binding is thought to parallel the degeneration of dopaminergic neurons in this region, as there is neurophysiological evidence that cholinergic neurons control striatal dopamine metabolism via the cholinergic input to the pars compacta (Hernandez-Lopez et al, 1992).

A selective vulnerability of dopaminergic neurons in PD such that the lateral portion of the pars compacta is more severely affected than the medial portion has been demonstrated, and is paralleled in Lewy body dementia (Agid et al, 1993). In SDLT the loss of nicotinic receptor binding in the substantia nigra pars compacta exceeds the reduction in dopaminergic neuron number. The selective vulnerability of dopaminergic neurons and alterations in nicotinic binding in PD and SDLT are anatomically consistent with a degree of overlapping neurochemical pathology.

The extensive receptor compared to neuron loss in Lewy body dementia raises the possibility that nicotinic receptor attenuation precedes cell death in PD. This, combined with the finding that smoking appears to be protective against PD, and that administration of nicotine increases the density of nicotinic binding (in smoking and experimental animals), may have important implications for the mechanism of cell death in PD. On this basis, DLB may be part of a spectrum of Lewy body diseases including PD, and may represent a less advanced form of PD.

The more extensive cortical pathology in AD compared to Lewy body dementia, especially in terms of tangle formation, is reflected in greater receptor loss in AD. Indeed, temporal lobe acetylcholine disruption appears to differentiate AD and DLB. In AD, temporal cortex nicotinic binding is diminished due to a greater nicotinic receptor loss in the temporal cortex than is observed in Lewy body dementia. In neocortical areas, a relationship has been described between the decreasing nicotinic receptor binding and increasing density of senile plaques in neocortical areas. However, the reductions in the hippocampus and adjacent cortex in AD do not appear to precisely parallel the areas of highest plaque density. Moreover, DLB cases show a greater reduction in choline acetyltransferase in the temporal neocortex, despite the nicotinic binding sites being less disrupted (Perry, E. et al, 1990a; 1990b; 1994).

Relatively selective reductions of nicotinic binding in the subicular complex and parahippocampal gyrus in have been demonstrated in AD, but not Lewy body dementia (Perry, E. et al, 1994). Thus, although the parahippocampal gyrus is one of the most affected areas in LBD in terms of Lewy body density, this is not reflected in terms of nicotinic receptor abnormalities. The disruption of the perforant path (with projections from the entorhinal cortex to the dentate) seen in AD, but not Lewy body dementia, may account for the relatively greater memory loss often reported in AD.

1.4.3 Monoaminergic Function in AD, SDLT, and PD.

1.4.3.1 Dopamine in dementia with Lewy bodies.

SDLT shares with PD a significant (although less extensive) loss of dopamine from the caudate nucleus, which correlates with a less severe reduction in substantia nigra pigmented neurons and the severity of the extrapyramidal movement disorder (Perry, E. et al, 1990b). In the neostriatum (caudate nucleus), loss of dopamine and increased homovanillic acid (HVA) : dopamine ratio correlates with the loss of substantia nigra neurons in Lewy body dementia but not PD, despite the greater loss of neurons and dopamine and the higher dopamine turnover ratio in PD. Marshall et al (1994) indicate that unlike AD, in which the dopaminergic system is relatively spared, or PD, in which the turnover of dopamine in the caudate is higher than normal, despite considerable loss of nigral dopamine-containing neurons, DLB cases exhibit changes in the dopamine metabolism in the caudate nucleus that suggest abnormalities of dopamine synthesis or storage. Unpublished results (Marshall et al, 1994) suggest that whilst the putamen is more affected than the caudate in PD, the reverse is true in Lewy body dementia. Nigrostriatal pathology may, then differ both quantitatively and qualitatively in Lewy body dementia and PD (Marshall et al, 1994).

Langlais et al (1993) showed the LBV cases to have severe reductions in several biochemical markers of dopamine activity in the caudate that closely resemble PD. However, neocortical monoamines, indolamines and their metabolites showed no significant difference between LBV, AD, and controls. In the LBV brains, dopamine levels were reduced to 5% of the control value in the putamen, and to 19% of the control group in caudate. Previous studies have also shown the loss of dopamine in typical PD to be also greater in the putamen than caudate. This contrasts with findings of Perry and co-workers and unpublished findings of Marshall et al, who found loss of dopamine in the caudate to be greater than the putamen (Perry, E. et al, 1993; Marshall et al, 1994). A significant reduction of tyrosine hydroxylase (TYR-OH) was observed in the putamen of the LBV cases (Langlais et al, 1993), which is consistent with functional disruption of the nigral

cells and terminals. Reductions in 5-HT and metabolites in both the caudate and putamen of the LBV cases were similar to those seen in typical PD brains. Despite the severe loss of dopaminergic innervation to the basal ganglia, extrapyramidal symptoms were relatively mild compared to PD cases. Langlais and colleagues suggest this might be explained by the significant reduction in cholinergic activity in the caudate of the LBV cases, as some theories of the pathophysiological basis of PD implicate a dopamine : ACh imbalance (Hornykiewicz et al, 1993).

Possibly related to the moderate reduction in dopamine levels in SDLT, is the observation that 64% of cases treated with dopaminergic blocking, neuroleptic drugs show severe extrapyramidal symptoms associated with high morbidity (McKeith et al, 1992b). Piggot et al (1994) measured dopamine and its metabolites and receptors in post-mortem brain specimens of 19 Lewy body disease cases. They compared Lewy body disease without neuroleptic exposure (n=6) to Lewy body disease groups exposed to neuroleptics who had either shown adverse reactions (n=9) or no adverse reaction (n=4). The findings suggest that severe neuroleptic reactions are associated with a failure to up-regulate D₂ receptors. In untreated PD, where substantia nigra neuron density and dopaminergic input to the striatum are reduced, striatal D₂ receptor binding is up-regulated, at least in the early stages of the disease. In the Lewy body dementia group with severe neuroleptic reactions, substantia nigra neuron density was significantly reduced, but there was no compensatory rise in striatal D₂ receptors. They suggest caution in the administration of neuroleptics.

1.4.4 Serotonin in dementia with Lewy bodies.

Measurements of serotonergic activity such as 5-hydroxyindoacetic acid (5HIAA) : 5-HT turnover ratios have suggested relative hyperactivity of the serotonergic neurotransmission in DLB (Perry, E. et al, 1993b). Despite the relative serotonergic hyperactivity, individual measures of this transmitter and metabolite are generally lower in Lewy body dementia compared to other groups. This is suggestive of dorsal raphe system dysfunction and that compensatory

hyperactivity has occurred in cortical projections of surviving neurons (Perry, E. et al, 1993b).

1.4.5 The psychopharmacological basis of psychosis in DLB.

An increased prevalence of psychotic symptoms in DLB compared to other common forms of dementia has been described by a number of groups (Alai et al, 1997; Hely et al, 1996; McShane et al, 1996; Galasko et al, 1995; Shergill et al, 1994; McKeith et al, 1992c; Gibb et al, 1987). Initial retrospective studies identified an increased incidence of hallucinations in DLB (57%). However, with the increased attention of clinicians, this incidence has risen to 80% in DLB compared to 20% in AD, in a larger, prospectively assessed and autopsy confirmed series (Perry, E. et al, 1996). The raised incidence of hallucinations observed has encouraged neurochemists to investigate the relationship between neurotransmitter systems and the occurrence of psychosis in dementia.

In a series of studies, Perry and co-workers have suggested a role for cortical cholinergic systems in the pathogenesis of psychosis in DLB. This is primarily based on three research findings:

1. Neocortical cholinergic deficits are more extensive in hallucinating compared to non-hallucinating cases of DLB (Perry, E. et al, 1990a);
2. There is reduced neocortical cholinergic activity, and increased incidence of psychosis in DLB compared to AD cases (Perry, E. et al, 1996);
3. Drugs with anticholinergic properties such as scopolamine induced hallucinations in normal individuals which are qualitatively similar to those seen in DLB cases (Perry, E. et al, 1995b).

Furthermore, Perry, E. et al (1993) have distinguished the Lewy body dementia group with hallucinations from other categories by an increase in the 5HIAA : 5-HT turnover ratio measured in the frontal cortex, and by the serotenergic (5-HIAA or 5-HIAA : 5-HT) : cholinergic (ChAT) ratio in frontal and temporal cortex. The evidence of relative serotonergic hyperactivity and hypo-cholinergic activities on hallucinating Lewy body dementia cases is compatible with the

psychopharmacological effects of drugs active on these systems. Further evidence of relative serotonergic hyperactivity is provided by Cheng et al (1991) who demonstrated that although SDLT subgroups do not differ from each other in terms of senile plaque, neurofibrillary tangle, or Lewy body density, 5-HT₂ binding in the deep cortical layers in SDLT cases with hallucinations is preserved; whilst in SDLT cases without hallucinations a marked deficit was recorded.

The temporal cortex may be involved in the pathogenesis of hallucinations, since it has connections with the hippocampus, amygdala and other cortical areas associated with sensory information processing. It has also been reported that patients with lesions in specific areas of the temporal cortex experience visual and or auditory hallucinations (Crosby et al, 1962). The possibility of a neurotransmitter imbalance in critical temporal lobe areas in SDLT may indicate a putative substrate for the high prevalence of perceptual disturbances seen in this group.

1.4.6 Summary.

Although there are a number of groups who have described distinctions in neurochemical alterations in AD, DLB, and PD, the neurochemistry of DLB remains relatively under-investigated. Studies reviewed above suggest that DLB cases share some of the neurochemical features characteristic of AD and idiopathic PD, i.e., loss of neocortical ChAT and basal ganglia dopamine. However, DLB appears to be different from pure AD cases in the degree of ChAT loss in the neocortex and the extent of AD pathological markers. Equally, DLB appears distinct from PD in the loss of cholinergic biochemical markers in basal ganglia, and the relatively mild extrapyramidal symptoms. The severe loss of dopamine in the basal ganglia of PD cases distinguishes them from SDLT in which basal ganglia dopamine loss is relatively mild. In addition, an imbalance between depleted cholinergic activity and relative monoaminergic hyperactivity may underlie the increased prevalence of psychotic symptoms in DLB.

1.5 Neuropsychology of dementia with Lewy bodies.

1.5.1 Introduction.

Neuropsychology is the branch of science which attempts to elucidate the relationship between behaviour and the structure and function of the nervous system. Organic changes in brain structure lead to observable alterations in cognitive function. Until relatively recently, the dementias have received little attention from neuropsychologists. The global nature of the cognitive impairment renders interpretation of performance difficult and places severe restrictions on the sophistication of tasks which can be undertaken. In addition, approaches with essentially anatomical models of brain-behaviour relationships have difficulty in interpreting behavioural changes due to diffuse damage.

Despite these pragmatic difficulties, the past decade has seen a very rapid increase of research interest in dementia. Neuropsychologists have been a core part of these efforts, and are not only advancing knowledge about the nature of the psychological deficits of patients with dementia but are interpreting the behavioural implications of advances made in other areas.

It has been demonstrated that aetiologically distinct forms of dementia show characteristic patterns of neuropathological changes. The aspects of cognition predominantly disrupted vary between aetiologically distinct forms of dementia. Neuropsychological characterisation of the nature of the cognitive decline seen in DLB has been somewhat hampered by generally small sample sizes, the use of different clinical diagnostic criteria, and variations in study design.

The main question for neuropsychologists investigating DLB is whether the cognitive decline seen in DLB has a distinct nature and course which will enable the condition to be distinguished from other forms of dementia, both quantitatively and qualitatively. Although quantitative differences between the different forms of dementia under investigation are of great interest, they may prove to be an artefact of procedures used to match dementia groups. Qualitative

distinctions in the neuropsychological performance of dementia groups are important, as they are unlikely to simply reflect imperfect matching procedures. However, the most powerful evidence of distinct profiles of cognitive impairment comes from double-dissociation of performance between groups, as such a finding cannot be attributed to a failure to adequately match groups. Furthermore, distinct profiles of neuropsychological performance may highlight subtle, but important, differences in sites of neurodegeneration in DLB and AD, which add further support to the nosological status of DLB as a distinct entity.

This section presents a review of neuropsychological investigations of DLB, and is divided into four subsections based upon the type of study employed by the investigators. A single case report with biopsy-confirmed Lewy body disease is presented as an example of the cognitive decline seen in DLB. The second section covers retrospective studies based on cases coming to autopsy whose WAIS-R are subsequently reviewed. This technique is useful in the respect that cases have autopsy confirmation of the disease state, but is limited by inconsistencies in the collection of information during life.

To overcome the problems of inconsistent data collection associated with retrospective studies, prospective studies use standardised assessment procedures. The third section reviews prospective studies where cases have received autopsy confirmation of the disease state. Autopsy-confirmed, prospective studies are the most powerful design for examining aetiologically distinct forms of dementia, but require considerable resources.

The fourth section reviews prospective studies which employ clinical criteria for the diagnosis of DLB (Byrne et al, 1991; McKeith et al, 1992c; 1996a) and AD (McKhann et al, 1984). The good predictive validity of these criteria (McKeith et al, 1994a; Mega et al, 1997) enables researchers to accurately predict underlying neuropathological status without the need for autopsy confirmation of the diagnosis (although autopsy confirmation remains desirable).

A number of neuropsychological tests are referenced in the review. A brief description of the procedure, and cognitive functions assessed can be found in

Appendix IV. These descriptions are not intended to be comprehensive and are included to inform the reader of the primary cognitive areas assessed by each test and the procedures for test administration.

The terminology describing DLB (see Section 1.2.3) employed by the original investigators is retained in this review, as the distinctions in clinical and neuropathological status associated with each term have important implications for the neuropsychological characterisation of DLB.

1.5.2 Single Case Review Studies.

Wagner et al (1996) provide a detailed review of a 60 year old man with biopsy-proven Lewy body disease, who was followed over a 24 month period. During the patient's illness he underwent four neuropsychological examinations (6, 10, 12, and 14 months) which revealed an atypical, rapidly progressive dementia.

Psychomotor speed, as measured by the digit symbol substitution (WAIS - R, Wechsler, 1981) and Trails A (Retain et al, 1985) tests, was affected early in the course, a finding not common in AD cases. Immediate and delayed verbal and figural memory (Russell, 1988) were weak throughout the course, although Wagner & Bachman suggest that the focal progressive disturbance seen in AD was absent. This was "ecologically" substantiated by findings from the Memory and Behaviour Checklist (Teri et al, 1992), which suggested that deficits in day to day memory were not the prominent symptom. The prominent symptoms were identified as behavioural dyscontrol and hallucinatory episodes. Wagner et al found orientation and information questions (Wechsler, 1987) to be relatively preserved throughout the course of the disease. The patient presented with motor symptoms (which were rapidly followed by cognitive symptoms) and showed perseverative motor behaviour on both the Behavioural Dyscontrol Scale (Gigsby et al, 1992) and a test of perseverative graphic motor responding (Goodglass et al, 1983). Language initially included occasional paraphrasic errors in speech, and evolved to frequent semantic paraphrasic errors.

Wagner et al (1996) suggest this approach 'uniquely contributes to the understanding of the syndrome expression of DLBD by providing a detailed, prospective clinical and serial neuropsychological, description of a biopsy-proven case'. This case review provides a good example of the type of cognitive deficits associated with DLB. However, single case studies are relatively insensitive in characterising neuropsychological dysfunction in aetiologically different disorders. More substantial comparative studies are presented in the following sections.

1.5.3 Retrospective neuropsychological studies of dementia with Lewy bodies - a review.

The studies described are subject to the same limitations that apply to all retrospective studies described previously (Footnote 2; Section 1.3.1.1).

In one of the first studies to describe clinical and cognitive symptoms, Gibb et al (1987) described four LBD cases from a retrospective study of idiopathic Parkinson's disease with severe dementia and a parkinsonian syndrome. At autopsy two of the cases showed significant, concomitant Alzheimer's disease pathology and two did not. Three of the four cases showed mild dysphasia or confrontation naming deficits, and one was impaired on the digit span, block design and object assembly sub-tests from the Wechsler Adult Intelligence Scale - Revised (WAIS - R). The participants in the Gibb et al study did not receive standardised assessment, and thus, comparisons between cases is difficult. Furthermore, no control group was included, which precluded comparison with other forms of dementia. Implications from the neuropsychological aspects represent a series of four single case studies and should be interpreted as principally descriptive.

A more substantial retrospective study by Byrne et al (1989) investigated 15 DLBD cases, using retrospective case-note analysis to examine clinical features. All cases were pathologically confirmed DLBD with varying degrees of AD pathology. Most cases underwent prospective clinical evaluation as part of a continuing study of dementia in old age which included: the mental status questionnaire; the Mini Mental State Examination (MMSE; Folstein et al, 1975); a more detailed psychometric evaluation using the Clifton Assessment Procedure for the Elderly (CAPE); and the WAIS - R.

All cases showed impairment of mnemonic function. However, case 2 showed a mild impairment, which was attributed as secondary to severe depressive symptoms. Of the cases able to complete more detailed neuropsychological investigations, 8 out of 9 showed marked dysphasia, 9 out of 9 cases demonstrated

dyscalculia, and 8 out of 8 cases showed visuo-constructional and ideomotor dyspraxia. Conclusions drawn from this study about whether these deficits are different from those seen in AD are speculative due to the lack of an appropriate group for comparison.

A larger retrospective study, which included an AD group, was described by McKeith et al (1992c). Twenty-one patients with autopsy-verified SDLT and 37 autopsy verified AD cases were reviewed. Although the AD and SDLT groups were matched for age and gender, the SDLT group was less impaired on the Blessed Information Memory Concentration (IMC) test (Blessed, 1968) than the AD group. Comparison of the recall component of the IMC test revealed the SDLT cases to be less impaired than the AD cases.

Although a large cohort of AD cases was included in this study for comparison, interpretation of the findings is hampered by another methodological problem - SDLT and AD cases were not matched for 'overall' severity of cognitive impairment. The reported differences in recall ability may reflect a later stage of dementia in AD than SDLT, rather than the proposed preservation of recall ability. This assertion is supported by data from the study, which indicated SDLT cases had a significantly shorter duration of illness at presentation.

The three retrospective studies presented describe cases of LBD, DLBD, and SDLT. As has been previously discussed (Section 1.2.3), these different nosological titles reflect samples of DLB cases recruited from subtly different, clinical populations, and this is hence reflected in the neuropathological degeneration seen at autopsy. This limits the compatibility of the results for comparative interpretation. Nonetheless, there is some suggestion that in DLB visuo-spatial ability is impaired; that there is disruption of normal speech; and there are prominent problems with arithmetic (Gibb et al, 1987; Byrne et al, 1989). Whether these deficits are relatively more severe than those seen in AD and PD was not addressed by these studies. The nature and the relative severity of the mnemonic impairment associated with DLB are also equivocal. Byrne and colleagues identified mnemonic impairment in DLB. However, they did not have a

comparison group. McKeith and colleagues suggest recall to be less impaired in DLB than AD cases, however, this may just be an artefact of inadequately matched groups.

1.5.4 Prospective neuropsychological studies of dementia with Lewy bodies.

1.5.4.1 Autopsy Confirmed Studies of dementia with Lewy bodies.

Förstl et al (1993) compared 8 LBV cases with 8 patients with AD who had histopathological confirmation of diagnosis. The LBV and AD cases were matched for age, gender, and duration of illness. They used the Mini Mental State Examination (MMSE) (Folstein et al, 1975) and the CAMCOG schedule (Roth et al, 1986) to compare cognitive functioning in the two groups. A summary of these findings is presented in Table 1.12.

Table 1.12: A comparison of means (\pm SD) of neuropsychological findings in eight patients with Alzheimer and concomitant Lewy body type pathology, and eight age and gender matched patients without concomitant Lewy body pathology (Adapted from Förstl et al, (1993))

	LBV	AD
Mini Mental State Examination (MMSE) (max. 30)	9.8 (6.7)	7.5 (9.1)
CAMCOG Total Score (max. 107)	26.6 (19.1)	23.0 (18.9)
<i>CAMCOG Subsections:</i>		
Language (max. 21)	9.1 (9.4)	10.6 (8.6)
Praxis (max. 12)	3.5 (4.3)	3.9 (3.4)
Memory (Max. 27)	2.5 (2.1)	2.8 (2.4)

Analysis revealed no differences either in the total scores assessed using either the MMSE or CAMCOG, or in scores from subsections of the CAMCOG schedule. Unfortunately, the cohort investigated by Förstl and colleagues had MMSE scores of less than 10. The low average MMSE scores indicate that both patient groups fall into the 'severe' dementia category. The usefulness of psychometric testing on groups with such severe cognitive impairment is dubious, as tools may become insensitive in the latter stages of cognitive decline (Lezak et al, 1983).

At the Alzheimer's Disease Research Centre, San Diego, Hansen et al (1990) carried out a detailed, comparative, neuropsychological investigation of dementia associated with Lewy bodies. Thirty-six clinically diagnosed and pathologically confirmed cases of Alzheimer's disease were examined which included a group of 13 cases with cortical and sub-cortical Lewy bodies. The Alzheimer's disease and LBV groups were matched for age, gender and level of education. Matching for overall degree of cognitive impairment used the Blessed Information Memory Concentration test.

All patients completed a neuropsychological test battery which included: the Digit Span, Vocabulary and Arithmetic sub-tests from the Wechsler Adult intelligence Scale – Revised (WAIS-R) (Wechsler, 1981); the Block Design sub-tests of the Wechsler Intelligence Scale for Children - Revised (WISC - R; Wechsler, 1974); an adapted version of the Visual Reproduction Test (Russell, 1975) a 30 item version of the Boston Naming test (Kaplan et al, 1978); a selective reminding test (Buschke-Fuld, 1974); and the letter and category fluency tests (Benton, 1968). The median scores achieved by LBV and Alzheimer's disease groups on each neuropsychological test are presented in Table 1.13.

Although matched for overall severity of cognitive decline using the Blessed IMC Test, the groups showed different patterns of cognitive decline on tests assessing specific aspects of cognitive function. Both groups performed equivalently on tests of episodic memory (both verbal - Buschke Selective Reminding Test, and non-verbal - Visual Reproduction Test); on some tests of language and memory (Boston Naming Test, Category Fluency Test, writing from dictation, and

Vocabulary Sub-tests of the WAIS-R); on a test of motor sequencing (Luria-3-Step); and problem solving (Arithmetic sub-test of the WAIS-R).

Table 1.13: Matched groups of 9 LBV and 9 AD subjects: Neuropsychological examination (median scores). Taken from Hansen et al, Neurology 1990; 40:1-8.

	(n1/n2)*	LBV	AD	p†
Attention				
Digit Span Sub-tests (WAIS-R)	(7/6)	10.00	14.00	0.02
Language and semantic memory				
Boston Naming Test (30 items)	(9/9)	17.00	15.00	N.S.
Letter Fluency Test (F,A,S)	(9/9)	6.00	17.00	0.02
Category Fluency Test (animals, fruits, vegetables)	(9/9)	9.00	14.00	N.S.
Vocabulary Sub-test (WAIS-R)	(7/6)	34.00	44.50	N.S.
Error on writing from dictation	(9/9)	5/9	0/8	0.02
Visuo-spatial Processing				
Block Design Sub-test (WISC-R)	(8/8)	0.00	15.00	0.02
Copy-a-Cross Test	(7/6)	4.00	1.50	0.03
Visuospatial Reproduction Test (Copy)	(7/7)	2.00	12.50	N.S.
Episodic Memory				
Buschke-Fuld Selective Reminding Test	(7/6)	13.00	14.00	N.S.
Visual Reproduction Test	(7/6)	19.1%	32.3%	
N.S. (0-sec delay; % of copy)				
Conceptualisation/problem solving				
Similarities Sub-test (WAIS-R)	(7/6)	2.00	9.00	0.04
Arithmetic Sub-test (WAIS-R)	(7/6)	4.00	6.50	N.S.
Motor Sequencing††				
Error on Luria-3-Step	(9/9)	8/9	8/9	N.S.

* n1 = LBV; n2 = AD

† p value based on Mann-Whitney U test.

†† Item from neurologic examination (proportion of subjects producing errors)

In addition to the deficits seen, which are typical of AD, the LBV group also showed especially poor performance in tests thought to be severely disrupted in

sub-cortical dementia. LBV cases performed significantly worse on the digit span Test, which assesses aspects of working memory and auditory attention. The two groups also showed differences in performance on the Verbal Fluency Test. Although LBV and AD groups performed equivalently on the category fluency task, the LBV group performed significantly worse on the Letter fluency task. The general and severe decrease in verbal fluency in LBV cases is similar to that described in sub-cortical dementia, and contrasts with the pattern typically observed in AD, where there are greater problems generating words from semantic categories than words beginning with a particular letter. The LBV group also showed severe visuo-spatial deficits as measured by the block-design sub-test, and were also significantly more impaired on a test of conceptualisation - the similarities sub-test of the WAIS-R.

Hansen et al (1990) demonstrated differences in the neuropsychological profile of LBV and AD groups. Although the LBV group has many of the cognitive deficits associated with AD, many cognitive deficits previously observed in disease states with sub-cortical pathological changes were also recorded in the LBV group. As the distinctions in neuropsychological performance were observed between relatively small AD and LBV groups, the magnitude of the neuropsychological differences between groups must have been relatively large. These data suggest that LBV and AD might be readily discriminated by neuropsychological examination. However, the small number of cases examined and their method of selection (all LBV cases met criteria for the clinical and neuropathological diagnosis of AD and therefore represent only a subgroup of DLB cases) limits the applicability of the findings to a more clinically representative dementia population.

In addition, although cases were matched for severity of global cognitive impairment, the LBV cases showed at least equivalent impairment in all tests administered, and significantly greater impairment on tests of working memory; visuo-spatial ability; conceptualisation and language. Although the dementia in LBV cases might possibly affect a broader range of cognitive functions than in AD, a more consistent explanation would be that groups were inadequately

matched for the overall degree of cognitive impairment. The Blessed IMC Test (used to match dementia groups for overall severity of cognitive impairment) is strongly mnemonically biased and will thus, primarily, match dementia groups for the degree of mnemonic dysfunction. Thus, an a priori assumption has been made that the relative mnemonic dysfunction in each dementia group is equivalent.

Hansen and colleagues also matched LBV and AD cases for the interval between time of testing and death. However, this further assumes the duration of LBV and AD to be equivalent. There is some evidence that LBV cases have a shorter duration of illness (Byrne et al, 1989; Hansen et al, 1989), especially when administered neuroleptic medication (McKeith et al, 1992b).

Assuming that DLB is a more rapidly progressive dementia, then at equal times prior to death the LBV cases might be less cognitively impaired than the AD cases. Hansen et al, however, suggest a more severe global cognitive impairment in the LBV cases at equal time prior to death. These findings highlight the difficulties associated with matching patients for duration of illness prior to death, especially when the duration of the illness may not be equivalent.

Distinct profiles of cognitive impairment in different types of dementia may only be established by systematic investigations using patient groups matched for global cognitive impairment. Such matching of groups continues to pose massive methodological problems.

Although the quantitative differences between LBV and AD cases reported by Hansen and colleagues should be interpreted with a degree of caution, due to matching problems, there are a number of qualitative differences which imply distinct patterns of cognitive impairment in DLB and AD. These differences are interesting when viewed within the framework of 'sub-cortical' and 'cortical' dementia described by Cummings (1986). The classic example of a 'cortical dementia' is AD, which is classically characterised by: prominent amnesia; deficits in language, semantic knowledge (aphasia), abstract reasoning and other 'executive' functioning; as well as visuo-spatial, and constructional abilities.

Parkinson's disease and Huntington's disease are classically ascribed as 'sub-cortical' dementia. The 'sub-cortical' dementias typically show a less pronounced memory deficit attributed to retrieval problems, which contrasts the ineffective consolidation and rapid forgetting associated with 'cortical' dementia. In addition, bradykinesia; bradyphrenia; attentional dysfunction; problem solving deficits; as well as visuo-perceptual, constructional and arithmetic deficits are thought typical of 'sub-cortical' dementia.

Hansen and colleagues (1996) revisited their 1990 study from the perspective of the 'cortical' – 'sub-cortical' framework. They suggested that LBV represents the 'superimposition of cortical and sub-cortical neuropsychological impairments' and suggested 'the neuropsychological features of cortical and sub-cortical dementia in the LBV patients is consistent with the distribution of neuropathological changes in the brains of these patients'. LBV and AD groups show similar impairments on tests assessing 'cortical' functions, namely memory and confrontation naming, whilst LBV cases were more severely impaired in cases assessing 'sub-cortical' functioning such as attentional, verbal fluency and visuo-spatial tasks.

To further explore the influence of sub-cortical pathology in the genesis of the cognitive deficits associated with LBV, (Connor et al, in Press) compared the performance of 23 patients with autopsy confirmed LBV and 23 patients with autopsy confirmed AD. The AD and LBV patients were pair-matched for their overall level of cognitive function using MMSE and total Mattis Dementia Rating Scale scores (DRS; Mattis, 1976). Patient groups were also matched for age, and years of education.

The Mattis DRS is a standardised 144-point mental status examination with a cut off of 13 1/2 for separating normal from impaired subjects. The DRS consists of five subscales which assess attention (37 points), initiation/perseveration (37 points), construction (6 points), conceptualisation (39 points) and memory (25 points). Connor and colleagues also compared AD and LBV cases on the subsections of the MMSE.

The performance of the AD and LBV groups on subsections of the DRS were shown to be distinct. AD cases showed more marked impairment on the memory subscale. There were no group differences in terms of the attention, construction, and conceptualisation sub-tests. A more detailed examination of the subscores in the memory subscale reveal the AD group scored significantly lower on the orientation items, a test of free recall. On a second test of free recall the AD group were marginally ($p < 0.06$) more impaired than the LBV group. The two tests of free recall of sentences are different in that the first is standard to the DRS, whilst the second is self-generated. There was no difference in performance between the two groups on tests of word and design recognition memory. These findings represent quantitative, but not qualitative, differences between the AD and LBV groups. Both groups performed better on the recognition tasks than they did on the recall tasks. However, the LBV group did not show the dramatic improvement usually seen with recognition testing over free recall testing associated with the access difficulties of 'sub-cortical' dementia.

In contrast, LBV cases showed more severe impairment on the initiation / perseveration sub-scale. More detailed analysis revealed that, although the mean scores of LBV patients were lower than those of the AD group for each item (fluency for supermarket items, fluency for clothing items, verbal repetition, double alternating movements, and grapho-motor), this only achieved significance for the fluency for clothing items. There was no significant difference, however, for the other test of semantic proficiency - the fluency for supermarket items. Performance on the graphomotor component failed to discriminate the two groups. However, a significantly greater proportion of the LBV cases failed to complete the most difficult component of the task, which involved switching between drawing "sawtooth" and "rampart" designs. Performance on the initiation/perseveration subscale of the DRS failed to reveal consistent or readily theoretically interpretable differences between the AD and LBV groups.

Connors et al subdivided the cases into those that were mildly to moderately demented (DRS total scores between 125 and 106) and those that were moderately to severely demented (DRS total score between 106 and 80). For the mild to

moderately impaired group, the findings were similar to the findings for the overall group comparisons. However, the LBV group was also significantly more impaired on the construction subscale which requires patients to copy geometric designs. The comparison between the moderately to severely demented LBV and AD groups revealed exactly the same distinctions found for the overall group comparisons, namely that the LBV were more impaired on the initiation/perseveration subscale, but less impaired than the AD group on the memory subscale. There was no difference between the AD and LBV groups on the construction subscale. The absence of the difference in performance in the moderate-severe group appears to be primarily due to worse performance in the moderate-severe AD group. Tests of visuo-constructional abilities may be discriminatory only at early stages of the disease process. Interestingly, the graphomotor section of the initiation/perseveration subscale was significantly more impaired in LBV than AD groups. This is considered to be a test of constructional and executive abilities and was more impaired in the LBV than the AD group, whatever the overall DRS scores.

A discriminant function analysis derived from a linear discriminant function analysis comparing the DRS subscale scores of AD and HD patients was performed to investigate whether the performances of the LBV and AD groups were indicative of cortical or sub-cortical dementia. Cases classified as “cortical” included 23 AD cases (74%) and 9 LBV cases (40%). LBV cases classified as “cortical” were not significantly different in terms of the demographic factors or level of dementia. The LBV cases identified as “cortical” by the discriminant function analysis showed an increased burden of neurofibrillary tangles, largely in the medial temporal lobe. This was shown at autopsy by higher Braak & Braak staging than those who were classified as “sub-cortical”. When Connor and colleagues applied a discriminant function analysis adjusted to incorporate the findings of their current study, only the memory and initiation/perseveration subscales were maintained as discriminant between the two diseases. These two variables alone were able to correctly classify 78% of the LBV patients and 74% of the AD patients. This is consistent with the notion that LBV patients are more

likely to manifest a sub-cortical-like pattern on the DRS compared with LBV patients.

Comparisons of performance of the LBV and AD groups on the subscales of the MMSE revealed a pattern similar to that seen previously when comparing AD and HD groups. LBV performed worse than the AD patients on the memory registration and writing items, whereas the AD group performed worse on the free recall and orientation items. Again the pattern of deficits is consistent with the hypothesis that that sub-cortical pathology significantly influences the cognitive performance of the LBV group, and Lewy body burden affects the profile of cognitive impairment seen in LBV.

The validity of a 'sub-cortical - cortical' framework is, however, somewhat uncertain, and a number of objections have been raised about the distinction (Hart et al, 1996). The distinction is undermined by neuropathological evidence of 'sub-cortical' damage in 'cortical' dementia and vice-versa. Furthermore, not all AD patients show pronounced disturbance of language on clinical evaluation. This is especially true of older patients with AD, in whom pathological change tends to be restricted to the cortex. Whilst linguistic deficits are more characteristic of younger patients in whom pathological damage is more likely to affect sub-cortical structures.

Samuel et al (1996) investigated how neuropathological burden influenced cognitive deficits in LBV and AD. They remark that it is difficult to account for the equivalent dementia severity in LBV and AD in terms of the neuropathological changes typical of AD. In LBV cases neurofibrillary tangle counts are not significantly higher, and may even be lower in the temporal lobe (Hansen et al, 1990; Masliah et al, 1993). Neurofibrillary tangle pathology correlates fairly strongly with declining mental status in AD. However, senile plaque density does not correlate well with dementia severity (Terry et al, 1987; Arriagada et al, 1992; Bierer et al, 1995). Thus neocortical neuron loss does not seem to correlate well with dementia severity in LBV. Sub-cortical neuron loss in LBV is equivalent to, or greater than that seen in AD. Several authors have found equivalent or greater

loss of the magnocellular neurons in the nucleus basalis of Meynert (e.g. Hansen et al, 1990). Samuel and colleagues tested the hypothesis that neuronal function is compromised by the presence of Lewy bodies in the neocortex and elsewhere, with a consequent impairment of similar magnitude to that seen in AD despite a lighter burden of AD pathology in LBV.

Fourteen LBV and 12 AD cases who had equivalent age at death, gender proportions, disease duration, education, and time lapsed between last assessment and death, were assessed using the MMSE, the Blessed IMC test, and the Mattis Dementia Rating Scale. The authors found the mean neuropsychological test scores to be similar in each of the three mental status measures. They did not, however, present any subsection breakdown of the neuropsychological assessment. In LBV cases, the neuropsychological test scores did not approach correlation with neocortical neurofibrillary tangles counts. Whilst in AD neurofibrillary tangle counts in several areas correlated significantly with mental status. Senile plaque counts did not correlate significantly with neuropsychological test scores in either LBV or AD. In the LBV cases, the relationship between mental status and Lewy body counts were in the anticipated direction, and most achieved significance. Thus, it appears that neocortical Lewy body counts, or neurodegenerative processes associated with their formation, are related to dementia severity.

Data from the previous three studies suggest that Lewy bodies contribute significantly to the cognitive impairment in DLB. Hansen et al (1990) and Connor et al (In Press) both suggest that a profile of neuropsychological deficits which has aspects of both 'cortical' and 'sub-cortical' dementia. The Lewy body pathological burden is most concentrated in sub-cortical brain regions (e.g. Substantia Nigra), and Samuel et al (1996) have demonstrated that Lewy body pathology correlates with cognitive impairment in LBV cases, and yet appears relatively independent of the pathological markers typically associated with AD.

The study by Connor and colleagues may be more readily interpreted than the Hansen et al (1990) study, as the authors effectively matched LBV and AD groups

for the global severity of dementia. The findings suggest that mnemonic performance is less impaired in LBV than AD cases, and subsequently the use of brief, mnemonically biased matching tools such as the MMSE and IMC test, are of little use for matching LBV and AD patients for overall severity of dementia. Both studies, however, suggest a distinct profile of cognitive impairment in LBV cases. All the autopsy confirmed studies of psychological functioning have included LBV cases which must fulfil clinical and neuropathological criteria for inclusion in the study. As previously discussed in the neuropathology section, this nomenclature is somewhat exclusive of patients with Lewy body disease without significant concomitant AD type pathology. This nomenclature appears weak especially in the light of the findings of Samuel et al (1996) which imply typical AD pathology does not correlate significantly with the cognitive decline in LBV. A more logical nomenclature might be the Alzheimer's disease variant of Lewy body disease, which acknowledges the primary cause of the dementia as the Lewy body.

1.5.4.2 Neuropsychological studies of clinically identified dementia with Lewy bodies.

As previously described (see Section 1.3.1.7), clinical criteria for the diagnosis of dementia with Lewy bodies have been established (Byrne et al, 1991; McKeith et al, 1992c; 1996a). These are generally based on the comparative, retrospective evaluation of neurological and neuropsychiatric findings in autopsy verified cases. Operational criteria for diagnosing dementia with Lewy bodies are currently undergoing evaluation in Newcastle upon Tyne, England. However, preliminary reports suggest them to be relatively specific (true negative rate of 95%) and sensitive (true positive rate 74%) (McKeith et al, 1994b; Mega et al, 1996). These criteria allow investigators to identify individuals with DLB pre-mortem, and provide the opportunity to study neuropsychological features of the disorder prospectively. The results of these studies should, however, be accepted tentatively in the absence of autopsy confirmation of the disease, or indication that diagnosis is accurate within an experimental group.

In a series of studies reported by Sahgal and colleagues, (Sahgal et al, 1992a; 1992b; 1992c; 1995; Galloway et al, 1992) computerised assessment procedures were used to investigate neuropsychological function in clinically identified cases of SDLT and AD. The Cambridge Neuropsychological Test Automated Battery (CANTAB) uses experimental neuropsychological models to investigate the neuroanatomical basis of cognitive deficits in different disorders, and has been employed in a number of patient populations including both PD and AD (see Sahakian et al, 1988, Owen et al, 1992; 1993). The battery focuses on non-verbal memory (spatial and non-spatial), attention and planning ability. A brief description of the constituent tests of CANTAB is included here; a more detailed review is provided elsewhere (see Chapter 3). Many of the tests were developed from animal lesion studies where circumscribed lesions can be made and thus poor performance in tests can be attributed to precise anatomical locations. This approach links neuropathological deficits to cognitive deficits, which can be measured in-vivo. Care must be taken when interpreting results from such an approach. The diffuse neuropathological changes evident in the later stages of

dementia are difficult to relate to discrete lesion studies in animals, and findings may be the result of damage to a number of areas and not simply attributable to specific nuclei or groups of neurons. Nonetheless, CANTAB has proved to be useful in the investigation of mild to moderately demented patients (e.g. Sahakian et al, 1988; Sahgal et al, 1991).

Sahgal and colleagues compared 10 AD cases diagnosed according to McKhann criteria, 10 SDLT cases diagnosed according to McKeith criteria and 16 elderly healthy controls. The number of patients completing different sections of CANTAB varied. The two spatial tests groups included 9 AD and 10 SDLT, and in the four non-spatial tasks the groups included 10 AD and 7 SDLT cases. Patient groups were matched for age and stage of dementia using the MMSE and the Clinical Dementia Rating scale (Hughes et al, 1982). Patient groups were also matched for pre-morbid abilities using the National Adult Reading Test (NART) (Nelson, 1982), in which they performed significantly worse than the control group. Patient groups were also matched for performance on the Kendrick Object Learning Test (KOLT) and the Kendrick Digit Copying Test (KDCT) (Kendrick, 1985). However, both dementia groups performed worse on both the KOLT and KDCT tests than the control group. Motor screening revealed the SDLT group to be significantly slower than the SDAT and control groups; the SDAT and control groups were not significantly different from each other.

In a test of pattern recognition memory (which assesses temporal lobe function) (see Owen et al, 1993 for review), a list of 12 abstract line patterns is presented, each pattern appearing for 3 seconds. Each stimulus pattern is subsequently represented alongside a novel stimulus pattern, and the participant is required to point to the pattern previously displayed. Both AD and SDLT groups performed worse (in both accuracy and speed) than controls, but there were no differences between the patient groups. Both patient groups performed at, or near, chance on the pattern recognition task, which may reflect floor effects. Thus, the pattern recognition test was unable to discriminate the two types of dementia, although it is demonstrably sensitive to changes in dementia.

In the simultaneous and delayed matching to sample task (MTS) (a test of temporal lobe function), participants are to memorise a sample abstract dot pattern required on a given trial. Then, the sample stimulus must be selected from four choice patterns presented to the participant. The choice patterns are presented either with the sample pattern or following varying delays (0, 4 and 12 seconds). Both AD and SDLT groups were impaired at simultaneous presentation relative to controls, implying a non-specific problem such as visuo-perceptual or attentional deficits, or a failure to comprehend the test. Despite the fact that SDLT cases showed lower accuracy than the AD group at simultaneous MTS, this difference did not reach significance, implying the groups to have equivalent non-specific impairment on the MTS task.

In delayed MTS, both patient groups were less accurate than controls and, in addition, the SDLT group were less accurate than the AD group. Response latencies for the patient groups were impaired with respect to control, but not with respect to each other. Differences in general responsiveness cannot account for the group difference in performance accuracy.

Spatial memory was assessed using a computerised version of the Corsi block-tapping test. This task assesses spatial span and is sensitive to right hippocampal damage (Milner, 1971). Participants are required to point to boxes in the order in which they change colour. The control group was able to successfully complete significantly longer pointing sequences than the patients groups, although there was no difference between the patient groups.

In a task described as Pattern-Location Paired Associates (CLPA), which is a test of conditional learning and is sensitive to damage to frontal and temporal lobe structures and circuitry, participants are required to remember the spatial location in which a particular pattern is located. Patient groups performed significantly worse on this task than the control group. Moreover, SDLT patients performed significantly worse than AD cases.

Spatial working memory was assessed using a task requiring efficient search strategies to find tokens hidden behind a number of boxes. This test is especially sensitive to damage to frontal lobe structures. Performance is measured in terms of the time taken to respond, as well as the pattern of responses made. By also examining the type of errors made, a numerical index for the efficiency of the strategy employed was calculated. In general the SDLT group made more errors than the AD group who in turn were worse than control. An analysis of the strategy employed by the different groups suggested no differences between the patient and control groups. Poor performance on the spatial working memory task was not due to poor strategy, nor due to a worse spatial memory.

Visual search matching to sample (VSMTS) is a test of focal attentional ability, which is sensitive to damage to fronto-striatal circuitry (see Sahgal, 1996). Participants are required to depress a hand-switch to reveal the sample stimulus in the centre of the screen, which is followed 2 seconds later by the presentation of the choice stimuli around the periphery of the screen. The number of choice stimuli varies (1, 2, 4, or 8). The participant must point to the choice stimulus which is the same as the sample stimulus. The task is similar to the simultaneous presentation MTS task, except that the spatial arrangement of the choice stimuli is different, and in addition, the number of choice stimuli vary. Control and SDAT groups performed at similar levels, however, the SDLT group performed significantly worse than both other groups.

The intra- and extra-dimensional (ID-ED) set-shifting is a computerised analogue of the Wisconsin card sorting test, and is sensitive to frontal lobe dysfunction task (see Downes et al, 1989). The ID-ED task measures aspects of attentional processing, including selective perception, and the ability to shift attentional set from one focus to another. The task involves 9 successive stages, and the participant only progresses to the next stage upon completing 8 successive correct responses. If this criterion is not achieved within 50 trials, the task is terminated. Both dementing groups were significantly impaired compared to control. Although the dementia groups performance did not differ, a trend ($p=0.057$) towards worse performance in the DLB group was observed.

As both pattern recognition and matching to sample tasks are disrupted by temporal cortical lesions, Sahgal and colleague suggest that there is degeneration of temporal lobe structure in both SDLT and AD. They also suggest that the impairment in the DLB group, even at relatively short delays in the matching to sample task, reflects severe degeneration of hippocampal and other temporal lobe structures early in the course of DLB. Sahgal and colleagues support the suggestion of early damage to hippocampal structures early in both AD and SDLT, with data from the spatial span task which show both patient groups to be impaired with respect to controls.

Group differences in the CLPA task showed the SDLT group to be more severely impaired than the AD group, who in turn performed worse than controls. This might reflect relatively severe degeneration of medial temporal and perhaps frontal lobe structures. Sahgal et al suggest that the evidence from the spatial working memory (SWM) task lead to a similar conclusion. Although both patient groups were capable of forming a search strategy, inspection of errors showed that SDLT patients made more errors. Other non-specific factors might be considered to explain the poor performance of SDLT cases in the SWM task, such as the inability of SDLT cases to sustain attentional resources over the period of time required to complete the task (approximately 25 minutes).

The two tasks sensitive to attentional dysfunction, namely the visual search matching to sample (VSMTS) and attentional set-shifting (ED/ID) paradigm, provide evidence of qualitative differences between the patient groups. On the VSMTS task the AD group performed at, or around, the same level as controls, whilst SDLT cases performed significantly worse. Sahgal and colleagues suggest that 'focal' attentional ability is more severely affected in SDLT than AD, and attribute this to substantia nigra degeneration (Sahgal et al, 1992a; Downes et al, 1989). Data from the attentional set shifting task (ED/ID) task are more difficult to interpret. Although both patient groups were impaired with respect to controls, there were no significant overall differences. Nonetheless, Sahgal et al (1992a) demonstrated a trend ($p=0.057$) towards worse performance by the SDLT

compared to the AD group when required to make intra-dimensional shifts of attention. Attentional performance appears to be significantly more affected in SDLT than in AD. A review of the results of Sahgal and colleagues series of studies is presented in Table 1.14.

Table 1.14: Summary of main outcome measures from CANTAB neuropsychological investigation of SDLT and AD cases (adapted from Sahgal et al, 1992a; 1992b; 1992c; 1995; Galloway et al, 1992)

CANTAB sub-test (outcome measure in brackets)	AD	SDLT
Spatial recognition (percent correct)	↓	↓
Pattern recognition (percent correct)	↓	↓
Delayed matching to sample (percent correct)	↓	↓↓
Conditional learning paired associates (total trials)	↓	↓↓↓
Spatial working memory (number of errors)	↓	↓↓
Visual search matching to sample (percent correct)	=	↓
Intra / Extra-dimensional set shifting:	↓	↓
Simple rule learning (percent correct)	↓	↓
Reversal learning (stage of task completed)	↓	↓

(↓ = worse performance; ↓↓ = markedly worse performance; ↓↓↓ = severely disrupted performance); (Performance is described relative to control group).

Sahgal and colleagues have described both quantitative and qualitative differences between SDLT and AD groups using sophisticated neuropsychological paradigms. Mnemonic function (both working and long term) and visuo-spatial skills are

equally, or more greatly, impaired in SDLT than in AD, and there are qualitative differences in attentional function in AD and SDLT. How mnemonic, visuo-spatial and attentional dysfunction contribute to performance of tests of cognitive function remains difficult to delineate. The use of computerised neuropsychological assessment tools represents a considerable advance, especially for the assessment of attentional and mnemonic function, which require the accurate temporal and spatial control of stimuli. Furthermore, the standardised presentation of tests encourages high inter-rater reliability.

There are, however, a number of methodological problems common to most studies comparing distinct forms of dementia. Firstly, diagnoses are prospective and await post-mortem confirmation. However, the Newcastle research group has been shown to have high sensitivity (74%) and specificity (95%) in the clinical diagnosis of SDLT and AD (McKeith et al, 1994b). Secondly, the MMSE which was used to match for global levels of cognitive impairment, has been criticised for a bias towards mnemonic dysfunction. Indeed, attentional, visuo-spatial, and, particularly, visuo-perceptual deficits are not comprehensively assessed by the MMSE. It has become apparent that all of these aspects of cognitive function are relevant for matching DLB and AD groups. The lack of a comprehensive matching tool for SDLT and AD groups cases suggests that the equivalently poor or worse performance of the SDLT group on all tests might reflect a more advanced dementia in the SDLT group.

Matching patient groups for pre-morbid IQ on the basis of NART scores also requires consideration. The NART verbal IQ score correlates strongly with degree of cognitive impairment in dementia (O'Carroll, 1995), although this may be particularly apparent only at the later stages of dementia (Fromm et al, 1991).

A number of authors have prospectively investigated cognitive decline in SDLT using the CAMCOG schedule (Roth et al, 1986). Ballard et al (1996b) investigated cognitive decline in a series of 124 patients with DSM-III-R diagnosed dementia. Which included 55 cases of probable AD, 33 possible AD, 20 vascular dementia (VaD), and 12 SDLT. Patients were assessed using a

standardised battery of schedules including the Geriatric Mental State Schedule (Copeland et al, 1976), the History and Aetiology Schedule (Dewey et al, 1992), the CAMCOG schedule (Roth et al, 1986; Hooper et al, 1993), the Cornell Depression Scale (Alexopoulos et al, 1988), and for the assessment of psychotic symptoms, the Burns Symptom Checklist (Ballard et al, 1995). Of the 89 cases followed up after one year, 76 completed repeat CAMCOG profiles, these included 53 AD, 14 VaD, and 7 SDLT.

There was no difference between groups in terms of severity of dementia at presentation, as measured by total CAMCOG scores, although stepwise logistic regression analysis revealed differences between groups on subsections of the CAMCOG schedule. The VaD group had significantly better recent memory and visual memory than AD. The SDLT group also had significantly better recent memory than the AD group, as well as significantly better visual memory than patients with VaD. Linear regression analysis was undertaken on a number of variables including: female sex; age at onset; age at assessment; Cornell depression score; deafness; years of education; and the presence of one or more psychotic symptoms. The only variable associated with CAMCOG scores at onset was that male patients had better total scores on the CAMCOG schedule than female patients.

At 1 Year follow-up, decline in CAMCOG scores for the AD and VaD groups were similar (13.2 & 13.5 points respectively). The SDLT group trended towards a more rapid rate of decline (27.0 points) compared to AD and VaD groups ($p=0.05$ & $p=0.07$ respectively). Unfortunately only 7 (out of the original 12) SDLT cases completed follow-up CAMCOG assessment. None of the variables assessed in the linear regression were associated with a greater rate of cognitive decline. In the CAMCOG schedule, there were no differences between AD and VaD cases in deterioration in subsections of the CAMCOG. SDLT cases showed greater decline in verbal fluency than both AD and VaD groups, which is consistent with the findings of Sahgal and colleagues who suggest greater frontal lobe types of dysfunction in SDLT than AD. The SDLT group also showed a greater deterioration in remote memory than the VaD group.

These data are taken from a relatively large cohort of dementia sufferers, although the number of SDLT cases at 1 year follow up is relatively small. This is the first longitudinal study directly demonstrating a more rapid rate of cognitive decline in SDLT than AD or VaD. The study does not, however, address the link between neuroleptic medication and an increased rate of decline which has previously been suggested in SDLT (McKeith et al 1992b; McShane et al 1996), and there is no neuropathological confirmation of diagnostic accuracy for any of the cohort.

More recently, Walker et al (1997) compared performance of AD and Lewy body disease (LBD) patients on sub-tests of the CAMCOG schedule. They examined 17 LBD patients diagnosed according to McKeith criteria (McKeith et al, 1992c) and 17 AD patients diagnosed according to NINCDS-ADRDA criteria (McKhann et al, 1984), who were attending a memory clinic. Patients also completed the MMSE, the behavioural part of the Clifton Assessment Procedure for the Elderly (CAPE; Pattie et al, 1979), a 15 item version of the Geriatric Depression Scale (GDS; Yesavage, 1988) and the Clinical Dementia Rating schedule. The CAMCOG scores were grouped according to Richards et al (1995). Patient groups were matched in terms of age; gender; years of education; length of illness; and Clinical Dementia Rating. Formal assessment revealed no differences between LBD and AD groups on the CAPE, GDS, MMSE or total CAMCOG scores.

Statistical analysis revealed differences between the patient groups in scores for subsections of the CAMCOG. The LBD group were less severely impaired than the AD group on the recall subsection. This section requires the participant to recall a name and address, and the names of three objects presented to them earlier on in the schedule. In contrast, the AD group were more impaired than the DLB group on the visuo-spatial praxis subsection. This section requires the participant to copy a number of items (pentagon, spiral design, 3-D house), as well as spontaneously drawing a clock with the hands showing ten past eleven. Walker and colleagues suggested that poor performance on the visuo-spatial task is unlikely to be related to motor dysfunction, as most of the LBD patients had only very mild motor symptoms and, cognitive dysfunction is thought to be largely

independent of motor disability in the early stages of Parkinson's disease (Cooper et al, 1991).

Unlike Hansen et al (1990), Walker and colleagues did not find any group differences in verbal fluency. However, the CAMCOG schedule only assesses category fluency, which was found to be only marginally impaired in the Hansen et al study. Letter fluency, found to be more impaired in LBD than AD (Hansen et al, 1990), is not assessed in the standard CAMCOG schedule. Similar to the study by Ballard et al (1996b), Walker and colleagues demonstrated less severe memory impairment in LBD patients. In addition, Walker et al described more severe deficits in visuo-spatial-praxis in LBD, which were not evident in the Ballard et al study.

In probably the most comprehensive neuropsychological study of LBD to date, Gnanalingham et al (1997) compared motor and cognitive function in 16 patients with LBD, 15 patients with Parkinson's disease, 25 patients with AD, and 22 control subjects. There was no difference in age, sex, years of education, and social class between groups. The only significant difference was found in Parkinson's disease cases who had a longer duration of illness than the AD group (means 9.2 and 3.7 years respectively).

Psychiatric assessment included the MMSE, the Clinical Dementia Rating Scale, and the Cornell Scale for Depression in Dementia (CSDD). As expected, controls were less demented than patient groups measured using MMSE scores.

Comparisons of MMSE scores between patient groups showed AD (mean 13.4) and LBD (mean 12.5) groups to be equivalently impaired, but both groups were more severely impaired than the Parkinson's disease group (mean 24.1). Scores from the CSDD indicated LBD cases to have the highest prevalence of depression, scoring significantly higher than both the control and other patient groups.

Parkinson's disease and AD groups were scored equivalently for the depression rating, although they showed a higher prevalence of depression than the control group.

Neurological assessment included the Unified Parkinson's Disease Rating Scale (UPDRS; Lang et al, 1989). Isolated extrapyramidal symptoms (EPS) were identified as a score of greater than one on any subsection of the UPDRS, and were recorded for 18% of controls, 72% of AD patients, 100% of LBD patients, and 100% of Parkinson's disease patients. Patients meeting Hughes et al (1992) criteria for parkinsonism included 12% of the AD cases, 94% of the LBD cases, and 100% of the Parkinson's disease cases. None of the controls were found to have extrapyramidal symptoms sufficient to warrant a diagnosis of Parkinson's disease. Both PD and LB dementia had significantly greater overall motor impairment, measured using total UPDRS scores, than AD and control cases. Furthermore, LBD patients scored significantly higher total scores (38.3) on the UPDRS scale than PD patients (29.5). Ninety-four percent of LB dementia cases qualified for a secondary diagnosis of PD. LB dementia patients showed significantly more rigidity than PD cases. EPS items assessed in the motor section of the UPDRS failed to discriminate the PD and LB dementia, with the exception of resting tremor, which was seen in a greater proportion of patients with PD (93%) than LB dementia (50%). The PD group showed significantly greater left/right asymmetry of motor signs than other groups, but similar upper/lower limb asymmetry to other groups.

Bradykinesia was also assessed by requiring participants to tap two keys situated 20 cm apart, as many times as possible in 30 seconds (Merello et al, 1994). The LBD, PD, and AD groups performed significantly worse than the controls on the tapping test. The LBD group were selectively more bradykinetic than the other patient groups. Walking was also quantitatively assessed, by requiring the patient to rise from an armless chair, walk 6 metres, return and then sit down. Time taken and number of steps were multiplied to produce an index of walking ability in 'step-seconds'. Both LBD and PD groups performed worse on this walking test than AD or controls, taking more steps, longer to complete the test, and more overall 'step-seconds'.

Neuropsychological tests were administered to characterise the cognitive profile of LBD cases and to identify characteristics which might distinguish LBD from PD

and, in particular, AD. Findings from the neuropsychological assessment are presented in Table 1.15, and a simplified comparison of group performance is included in Table 1.16.

The MMSE failed to distinguish LBD and AD, either in terms of the overall scores, or the subsections which make up the task. On the digit span sub-test of the WAIS-R (Wechsler, 1981), AD and LBD groups were similarly impaired with respect to each other, but performed worse than both control and PD groups. On the verbal and category fluency tests (Benton et al, 1968), there was a similar pattern of performance with all patient groups impaired with respect to controls, but AD and LBD groups were also impaired with respect to the PD group. The Nelson Card Sort Test (Nelson, 1976) assess the patients' ability to develop new concepts and shift sets, and has been shown to be sensitive to frontal lobe dysfunction. Performance on this test was somewhat varied, but overall analysis of the components suggest the LBD and especially the AD groups performed less well than controls. Thus, LBD and AD cases were not distinguished by tests of digit span, verbal or category fluency, motor sequencing, or the Nelson card sort test.

Table 1.15: Comparison of neuropsychological findings between controls (n=22), AD (n=25), PD (n=13) and LBD (n=16) (adapted from Gnanalingham et al, 1997).

	<u>Controls</u>	<u>AD</u>	<u>PD</u>	<u>LBD</u>
Digit span				
Forward	6.2 (0.3)	4.2 (0.4) **	6.1 (0.4) ††	3.7 (0.5) ††**
Reverse	4.0 (0.3)	2.2 (0.4) **	4.2 (0.5) ††	2.1 (0.4) ††**
Verbal fluency (total words for letters S, A, F)	32.1 (3)	9.2 (2) **	21.0 (5) ††*	8.3 (2) ††**
Category fluency (animals in 1 min)	14.1 (1)	5.1 (1) **	10.9 (2) ††**	4.9 (1) ††**
Motor sequencing tasks (median)	0 (0-1)	2.5 (0-4)	0 (0-3.5)	4 (0-4)
Nelson card sort				
Categories	5.0 (0.5)	1.9 (0.4)	4.1 (0.8) †	2.7 (1.1) *
Total errors	12.2 (2)	25.2 (2) *	17.7 (5)	22.0 (5) **
Perseverative errors	5.2 (1)	17.7 (3) **	12.9 (4)	11.2 (6)
% Perseverative errors	29.4 (4)	58.9 (6) *	36.0 (11)	46.4 (15)
Clock draw test				
Draw part	8.2 (0.2)	3.7 (0.5) **	6.2 (0.7) †*	2.4 (0.4) ††**
Copy part	9.6 (0.1) ^{ΔΔ}	5.5 (0.7) ^{ΔΔ} **	7.1 (0.8) ^{Δ†} *	2.4 (0.6) †††**

- Values are means (± SEM) {unless otherwise stated}
- Post-hoc comparisons *p<0.05; **p<0.01 v controls. †P<0.05; ††p<0.01 v AD. ‡P<0.05; ††p<0.01 v PD. ^ΔP<0.05; ^{ΔΔ}p<0.01 v corresponding score for draw part of Clock Face Test.

Table 1.16: Simplified comparison of performance on neuropsychological tests reported in Gnanalingham et al (1997).

	BestWorst Performance
Digit span Forward & Reverse	{Con = PD} >> {AD = DLB}
Verbal fluency (total words for letters S, A, F)	Con > PD >> {AD = LBD}
Category fluency (animals in 1 min)	Con > PD >> {AD = LBD}
Motor sequencing tasks (median)	Con > PD >> {AD = LBD}
Nelson card sort	
Categories	Con > LBD; Con >> AD; Con = PD; PD > AD; LBD = AD; PD = LBD.
Total errors	Con = PD; Con > AD; Con >> LBD; AD = LBD = PD
Perseverative errors	Con >> AD, Con = PD = LBD; AD = PD = LBD
% Perseverative errors	Con > AD; Con = PD = LBD; AD = PD = LBD.
Clock draw test	
Draw part	Con > PD > {AD = LBD}
Copy part	Con > PD > AD >> LBD

'>' represents significantly better performance on a test and not the absolute scores for the test.

'>' p<0.05; '>>' p < 0.01

'Con' = Controls

The Clock Face Test (Libon et al, 1993) examines executive and visuo-spatial functioning, and is split into two halves - draw and copy. In the draw part of the Clock Face Test, participants are required to spontaneously draw a clock face with the hands pointing to ten past eleven (as in the CAMCOG schedule); whilst in the copy part, participants are required to copy a correctly drawn clock face. Patients were tested after an overnight drug free period to minimise the effect medication might have on the test scores. Analysis of results included the UPDRS scores as covariates to partial out effects due to poor motor performance on this task, and CSDD scores as covariates to eliminate the potentially confounding influence of depression on performance. On the draw part of the task, AD and LBD groups were equivalently impaired, and significantly more impaired than both PD and control groups. The PD group was also impaired with respect to the control group. For the copy part of the test, the pattern of impairment was different with particularly severe impairment to the LBD group who were more impaired than all of the other groups. AD and PD groups were equivalently impaired and performed less well than controls. The LBD patients were the only group not to show significant improvement in performance in the copy versus draw sections. As medication, depression and motor difficulties have been investigated and eliminated as potential causes of the differential impairment in cognitive function, the described differences in performance appear to reflect distinct patterns of cognitive impairment between the patient groups.

Gnanalinghan and colleagues considered the clock-draw task in more detail. They employed the construct that a 'draw' score greater than the 'copy' score equated to a diagnosis of LBD. This showed high specificity (98%), positive predictive value (the probability of a clinically diagnosed patient having pathological confirmation of the disease state) (80%) and negative predictive value (82%), but low sensitivity (25%) and misidentification rates (18%). Despite the relatively low sensitivity of the test, patients who perform worse on the "draw" than the "copy" subsections of the clock drawing test are very likely to have LBD. Indeed, only one PD case tested positive for LBD according to the clock drawing test. The poor performance on tests of visuo-spatial functioning has previously been noted by

Hansen and colleagues (1990), Walker et al (1997), Sahgal et al (1992a; 1992b; 1992c).

There are, however, inconsistencies between the Gnanalingham et al study of LBD cases and the series of autopsy confirmed cases of LBV studied by Hansen et al (1990). Hansen and colleagues found LBV cases to be more severely impaired on the digit span and verbal fluency tests than AD cases, which was not replicated by Gnanalingham and colleagues. Furthermore, the observation that AD cases are, if anything, more impaired than LBD cases on the Card Sort task is contrary to the findings of Sahgal et al (1992a; 1992b; 1992c), who employed a computerised version of the test paradigm (ED / ID shift) and found a tendency for SDLT cases to be more impaired than AD cases.

The study by Gnanalingham and colleagues provides further evidence that, although AD and LBD patients have similar impairments in a number of neuropsychological tests, there are both quantitative and qualitative differences between the groups. Neuronal degeneration and subsequent depletion of acetylcholine in the nucleus basalis of Meynert has been strongly linked to impairment of visuo-spatial attentional function (Everitt & Robbins, 1997), which may underpin the severe visuo-spatial problems demonstrated by Gnanalingham and colleagues in LBD.

1.5.5 Summary.

The studies reviewed above are testimony to the increased research interest in DLB. Studies have identified both qualitative and quantitative differences between DLB and AD. Early studies, which were constrained by methodological problems, have provided a basis for the continuing study of the psychology of DLB by larger prospective studies with groups of carefully matched dementia patients.

Mnemonic function has been extensively described in DLB. Most, but not all, studies indicate equivalent or worse performance of AD cases compared to DLB cases on tests assessing memory. Attention has received relatively little interest

from researchers investigating DLB. Some studies have cited the ability to repeat a string of numbers as evidence of more impaired attentional performance in DLB patients (e.g. Hansen et al, 1990). However, more systematic investigation of attentional function has been aided by the use of computerised assessment techniques. In the only study to date to employ such paradigms, Sahgal and colleagues have demonstrated both quantitative and qualitative differences in the ability of SDLT cases to focus visuo-spatial attention.

A number of studies have also suggested that visuo-spatial and constructional ability is particularly severely affected in DLB cases. Indeed, Gnanalingham et al (1997) suggest that qualitative differences in performance on the Clock Draw Test might discriminate LBD and AD cases in the clinical environment.

Groups working in San Diego have additionally attempted to classify LBV into a 'cortical' versus 'sub-cortical' framework. They suggest that LBV cases show a degree of 'sub-cortical' contribution to the cognitive deficits which is consistent with the more 'sub-cortical' distribution of neuropathology in LBV cases.

The profile of neuropsychological deficits between AD, DLB, and PD suggests that DLB shares features of both AD (particularly mnemonic impairment) and PD (particularly visuo-spatial and attentional dysfunction), but is equally, qualitatively distinct from both. These observations echo findings by neuropathologists, neurochemists, and clinicians, which suggest that DLB both overlaps, and is distinct from, AD and Parkinson's disease.

1.6 Experimental aims and hypotheses.

The primary aim of this body of work is to characterise neuropsychological profiles in DLB and AD groups. The methodological limitations (described in detail in the preceding section), which have somewhat restricted comparison between many of the previous studies comparing cognitive impairment in DLB and AD, will be addressed by using larger cohorts of patients diagnosed using consensus criteria (McKeith et al, 1996). In addition, the experimental groups will be carefully matched for: pre-morbid IQ; overall severity of cognitive impairment; activities of daily living skills; and age. Computerised assessment procedures will be employed to enable accurate spatial and temporal control of stimuli and provide detailed measures of performance.

- Based on previous neuropsychological, neurochemical, neuropathological and clinical studies, it is predicted that both AD and DLB groups will both show global impairment compared to non-demented elderly controls. However, the profiles of cognitive impairment will differ between AD and DLB groups. The profile of cognitive impairment described in the AD and DLB groups will reflect the corresponding neurochemical and neuropathological changes in these two disorders.
- This study also aims to investigate the relationship between known clinical and neurochemical characteristics of DLB. This will include a comparison of hallucinating and non-hallucinating DLB cases, where distinct neurochemical differences have been observed (Perry et al, 1992). In addition an investigation of the relationship between fluctuating cognitive impairment and neuropsychological performance is planned. It is predicted that DLB patients with marked fluctuations will show a profile of cognitive impairment with particularly severe attentional deficits compared to DLB cases without marked fluctuations.
- The rate of cognitive decline in DLB compared to AD is somewhat disputed. Although several studies have reported more rapid decline in DLB cases, other

- The rate of cognitive decline in DLB compared to AD is somewhat disputed. Although several studies have reported more rapid decline in DLB cases, other authors have attributed this to adverse responses to neuroleptic medication and suggested equivalent rates of decline in AD and DLB. The final study will examine change in profile of cognitive impairment over a one year period in DLB, AD, and control groups.

Chapter 2:

General Methods.

2.1 General introduction.

This chapter describes general details concerning study design, participant recruitment, clinical and preliminary psychometric assessment. Any deviations from these general methods, as well as the more detailed methods particular to each study, are described in the appropriate experimental chapters.

2.2 Methods.

2.2.1 Design.

The experimental work described in this thesis is drawn from three studies investigating psychological function in DLB. Methodology for these studies is described in detail in chapters 3, 6, and 9.

1. The first study compares cognitive functioning in AD (n=8), DLB (n=6) and elderly controls (n=10) using the Cambridge Neuropsychological Test Automated Battery (CANTAB).
2. The second study compares cognitive function in a larger cohort of DLB (n=24), AD (n=46) and matched elderly controls (n=26) using the Cognitive Drug Research Computerised Assessment Battery (CDR).
3. The third study compares the rate and profile of cognitive decline at 1 year follow-up of DLB (n=9), AD (n=16), and elderly controls (n=8) using the Cognitive Drug Research Computerised Assessment Battery (CDR).

2.2.2 Participants.

2.2.2.1 Patient groups.

Participants were recruited from the Newcastle Prospective Study of Memory Disorders. This case register consisted of consecutive referrals to Old Age Psychiatry services in hospitals in Newcastle and Gateshead, supplemented by consecutive referrals to a specialist clinic receiving regional referrals of patients diagnosed as DLB. All patients with an MMSE (Folstein et al, 1975) score of at least 8 were invited to participate in the Prospective Study, involving clinical assessment at annual intervals and, wherever possible, brain tissue donation for autopsy confirmation of the diagnosis and neurochemical analysis.

Clinical diagnosis was established by the application of NINCDS-ADRDA criteria for the diagnosis of probable and possible AD (McKhann, 1984) and consensus criteria for the clinical diagnosis of probable and possible DLB (McKeith et al, 1996a). These criteria were independently applied to the case-notes for each patient by three senior Psychogeriatricians (Prof IG McKeith, Dr CG Ballard and Dr J O'Brien) and following discussion a consensus diagnosis was agreed.

2.2.2.2 Control group.

Cognitively 'normal' elderly controls were recruited from two main sources. The majority of the control group were relatives (spouse or siblings) and / or carers of dementia patients included in the study. In addition a number of controls were recruited from the Newcastle Project for Health in Later Life, a large MRC funded epidemiological study of cognitive function in the aged, based in Newcastle upon Tyne. Controls were screened for a recent history of major psychiatric disorder, neurological illness, alcoholism or drug abuse. Although recent minor reactive depression was reported in two controls, these cases were not excluded from the study.

2.2.3 General Procedures.

2.2.3.1 Clinical assessment protocol.

Patients who were included in the Newcastle Prospective Study of Memory Disorders underwent a standardised psychiatric history schedule using the History and Aetiology Schedule (HAS) of the Geriatric Mental State Examination (Dewey et al, 1992). The HAS contains detailed information regarding history, medication use, and mental state, with detailed questions regarding fluctuation and disturbances of consciousness. A number of patients included in the studies were taking medication, however detailed appraisal of medication and performance is considered beyond the scope of this thesis.

The Cornell Depression scale (Alexopoulos et al, 1988) was used to assess depression and was augmented by several extra items, such as the duration of the mood disturbance and its effect on social functioning, to allow the application of DSM-III-R criteria for depression. A diagnosis of depression was made using the DSM-III-R criteria (American Psychiatric Association, 1987), ignoring the caveat regarding exclusion if there is evidence of organic causation. Persistent depression was defined as mood disturbance lasting at least 6 months. Psychotic symptoms were evaluated using the Columbia University Scale for the Assessment of Psychosis in Dementia (CUSPAD) (Devanand et al, 1992). Definitions regarding the presence and classification of psychotic features were taken from the criteria of Burns et al (1990).

A full physical examination was performed on all cases and included the Secondary Dementia Schedule (Dewey et al, 1992) and the assessment of parkinsonism with the modified Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al, 1987). Seven parkinsonian features were rated (Ballard et al, 1997a) which included: reduced facial expression; resting tremor; action tremor; rising from chair; stooped posture; parkinsonian gait; and bradykinesia. Parkinsonism was also rated using the Hoehn and Yahr scale (Hoehn, 1967), with a rating of 1 or more taken as evidence of significant parkinsonism.

Consenting participants also underwent additional assessments. These included: apolipoprotein E genotyping; visual acuity tests; balance assessment; and magnetic resonance imaging. However, only clinical details deemed directly relevant to the measurement of psychological dysfunction were reported.

2.2.3.2 Standardised psychometric assessment procedures.

Standard demographic variables such as age, years of education, and sex were recorded for all participants. In addition, estimates of pre-morbid IQ (National Adult Reading Test; NART) (Nelson, 1982), and overall level of cognitive decline (CAMCOG; Cambridge Examination for Mental Disorders in the Elderly) (Roth et al, 1986), were obtained for all participants. Activities of daily living schedules were also used to match groups for impairment in day to day living skills (see Ballard et al, 1997b).

The National Adult Reading Test (NART; Nelson, 1982) was employed to estimate pre-morbid intellectual functioning. The NART is based on the observation that reading ability and general intelligence level are significantly correlated. Furthermore, the residual vocabulary ability of patients with dementia may be the most accurate measurable estimate of general pre-morbid intellectual ability, as this is relatively resistant to the dementing process (Nelson et al, 1978). The NART requires the participant to read phonetically irregular words which can only be read correctly if the participant has prior familiarity with them.

All participants were asked to pronounce the following words:

chord, ache, bouquet, psalm, capon, deny, nausea, debt, courteous, rarefy, equivocal, naive, catacomb, gaoled, thyme, heir, radix, assignate, hiatus, subtle, procreate, gist, gouge, superfluous, simile, banal, quadruped, cellist, facade, zealot, drachm, aeon, placebo, abstemious, détente, idyll, puerperal, aver, gauche, topiary, leviathan, beatify, prelate, sidereal, demesne, syncope, labile, campanile.

Pre-morbid intellectual ability was estimated from the number of words correctly pronounced according to Nelson et al (1982).

The Cambridge Cognitive Examination (CAMCOG) is a subsection of the Cambridge Mental Disorders in the Elderly (CAMDEX) schedule (Roth et al, 1986). The CAMCOG is a scale for the objective assessment of cognitive function in the elderly and in dementia. Subscales of the CAMCOG were described following Hooper et al (1993). The Hooper et al procedure omits several items previously included in the original schedule, and scores cognitive performance out of a total of 103. Questions omitted from the original CAMCOG were added as a final section to facilitate comparison with total CAMCOG scores derived according to Roth et al (1986). The CAMCOG subscales described include;

1. **Orientation** (10 points)

Day of the week; date; month; year; season; country; town; two streets nearby; floor of building; name of place at time of assessment.

2. **Language comprehension** (9 points)

Motor response: Please nod head; Touch right ear with left hand; Before looking at ceiling look at floor; Tap each shoulder twice with two fingers keeping eyes shut.

Verbal response: Is this a hotel?; Are villages larger than towns?; Was there wireless before TV was invented?.

Reading: Close your eyes; If you are older than 50 please close your eyes.

3. **Language expression** (12 points)

Naming pictures: Shoe; typewriter; scales; suitcase; barometer; lamp.

Definitions: What do you do with a hammer?; Where do people usually buy medicine?; What is a bridge?; What is an opinion?.

4. **Visuo-spatial praxis** (15 points)

Copying and drawing: Copy of pentagon; spiral design; 3-D house; drawing from memory of a clock face with hands showing 10 past 11.

Ideational: Take paper in right hand, fold paper in half, place paper on lap, write name and address on envelope and try and remember it (Mr John Brown, 42 West Street, Bedford).

Ideomotor: Show me how you wave goodbye, Cut with scissors, Brush teeth.

5. **Recent memory** (Recall) (12 points)

Recall: Pictures from language expression (shoe; typewriter; scales; suitcase; barometer; lamp); news in the past week; name and address written on envelope in visuo-spatial praxis section.

6. **Visual memory** (recognition) (6 points)

Recognition from choice of three: Pictures from language expression (shoe; typewriter; scales; suitcase; barometer; lamp).

7. **Remote memory** (9 points)

Recall: Date of First World War; Date of Second World War; Leader of Germans in Second World War; Leader of Russians in Second World War; What was Mae West famous for?; Name of King who abdicated; Current King or Queen; Heir to the throne; Name of Prime Minister.

8. **Attention and calculation** (8 points)

Attention: Count backwards from 20; five serial subtractions of seven from 100 (i.e. 93, 86, 79, 71, 64)

Calculation: Add 10p and 5p; take 15p from £1

9. **Perception** (10 points)

Tactile: Pen, watch.

Visual: Identify pictures of Queen; Pope; objects from unusual angles (spectacles; shoe; purse; cup and saucer; telephone; pipe)

10. **Abstract thinking** (12 points)

Similarities: Apple and banana; shirt and dress; table and chair; plant and animal

Verbal fluency: Name as many animals as possible in 1 minute.

11. **Additional items** included in the original CAMCOG test.

Modified scores for: Counting backwards; verbal fluency; writing name and address; folding papers.

Additional questions: What does this person do (nurse)?, repeat after me “no ifs, ands or buts”.

2.3 Ethical approval.

Ethical guidance and approval was obtained from local regional ethics committees. Written informed consent was obtained from all participants following procedures for obtaining consent from dementia patients.

2.4 Statistical analysis.

Details of procedures for statistical analysis are described in detail in the relevant chapters. Statistics were undertaken using the Minitab package (Minitab version 10.2; 1994). Exact ‘p’ values are reported for the range $0.10 < p > 0.001$. Following the Minitab package, any values of $p < 0.001$ are reported as $p < 0.001$.

Chapter 3:

A comparison of cognitive deficits in AD, DLB, and elderly controls using the Cambridge neuropsychological test automated battery (CANTAB): Methods.

3.1 Introduction.

This chapter describes the methodology employed in a study to compare cognitive function in DLB, AD, and normal elderly controls using the Cambridge Neuropsychological Test Automated Battery (CANTAB).

The CANTAB battery was developed by a research group working at the University of Cambridge to improve comparative assessment of cognition in humans and animals. CANTAB has been used extensively in humans to examine a number of neurological and psychiatric disorders including Alzheimer's disease (Sahakian et al, 1988; 1990; Sahgal et al, 1991); Parkinson's disease (Morris et al, 1986; 1988; Sahakian et al, 1988; 1990; Downes et al, 1989; Owen et al, 1992, 1993); multi system atrophy (Robbins et al, 1992; 1994a); Huntingdon's disease (Lange et al, 1995); schizophrenia (Charlesworth et al, 1993; Elliot et al, 1995); affective disorders (Abas et al, 1990; O'Brien et al, 1993; Moffoot et al, 1994); motor neurone disease (Chari et al, 1996); and senile dementia of the Lewy body type (Sahgal et al, 1992a; 1992b; 1992c; 1995; Galloway et al, 1992).

3.2 Participants.

All participants satisfied the following inclusion criteria:

- 1) age above 65
- 2) no current medication likely to influence test performance
- 3) no concurrent major psychiatric disorder e.g. major depression, epilepsy, alcohol abuse.
- 4) adequate colour vision (Ishihara, 1973)
- 5) adequate visual acuity (able to read font 12 letters)

AD patients (n=8) met NINCDS-ADRDA criteria for the clinical diagnosis of probable AD (McKhann et al, 1984). DLB (n=6) cases met consensus criteria for the diagnosis of probable DLB (McKeith et al, 1996a). Elderly controls (n=10) were screened for cognitive impairment sufficient for a diagnosis of dementia. Participants were assessed at their place of residence.

3.3 Materials and apparatus.

CANTAB version 1.58 for IBM PC and compatibles was installed on a portable microcomputer (Carry I 5320 series fitted with a 655XX VGA flat panel display driver) and presented on a portable LCD screen (Datalux, 195 mm wide by 143 mm high) with a touch sensitive screen (Microtouch) set up to use Com 1 port. For some tests, a non latching , hand operated switch fitted with a light spring for comfortable hand operation was connected to the parallel port of the computer.

The abstract patterns used as stimuli in CANTAB were designed to minimise verbal encoding of the material and are described in detail elsewhere (see Sahakian et al, 1992; Roberts et al, 1993; Robbins et al, 1994b for reviews).

3.4 Statistical Analysis.

Data were analysed using the parametric analysis of variance (ANOVA), with or without transformation (proportional data - arcsine; latencies - logarithmic) according to Winer et al (1991), and post hoc analyses were made using the Newman-Keuls pair-wise comparisons. Data failing to meet assumptions for the use of ANOVA were analysed using the non-parametric Kruskal-Wallis test, and means were compared using the non-parametric Mann-Witney U test. A minimum level of significance of $\alpha=0.05$ was adopted. A trend towards significance is reported for p-values of between 0.1 and 0.05.

3.5 Psychometric assessment.

All participants were tested on the National Adult Reading Test (NART) (Nelson, 1982); the CAMCOG schedule (Roth et al, 1986); the Instrumental Activities of Daily Living (IADL) and the Activities of Daily Living (ADL) schedules (see Ballard et al, 1997b). These tests are described in more detail in the General Methods (Chapter 2).

3.6 Computerised assessment: The CANTAB procedure.

Care was taken to standardise the testing environment. The computer was always set up on a table of comfortable height, in a room in which the curtains were closed and strong overhead lighting was extinguished. Participants sat in a chair about 0.5m from the touch screen. The computer, which was handled only by the experimenter, was placed a short distance away in front of the experimenter. Participants responded only via the touch screen and the hand switch where appropriate. A brief touch screen calibration procedure was undertaken at the beginning of each testing session. All participants attempted the entire CANTAB battery.

The experimenter first explained the nature of each task, and all procedures and response requirements were demonstrated in a number of practice trials. A control check was incorporated to assure the participant had fully understood the requirements of each test, and where necessary instructions were repeated. Details of each of these tests can be obtained in the citations listed below. Testing usually required several visits to complete. Total testing time was approximately 4 hours, but varied according to the individual participant (1.5 hours minimum to 9 hours maximum). Standardised testing instructions supplied by Paul Fray Ltd were applied to all tasks.

The CANTAB package consists of three separate batteries which measure visual memory, attention, and working memory and planning. A test of motor screening

is included at the beginning of each battery. Examples of test stimuli, and detailed descriptions of the tasks included in the CANTAB battery, are given elsewhere (Owen et al, 1993; Sahakian, 1988).

3.6.1 Motor screening.

This task is common to all three CANTAB batteries, and is a measure of motor response speed and accuracy. In this task a series of crosses appear on the screen in pseudo-random locations. The crosses alternatively flash green and pink. Initially a series of three demonstration crosses appear one at the time on the screen. At this stage the experimenter demonstrates to the participant by pointing to the crosses displayed sequentially on the screen. A pause is then introduced by the computer, and depression of the space bar is required to continue. The experimenter indicates to the participant that they must now touch the crosses as they appear on the screen. A further series of 10 crosses is sequentially displayed on the screen and the participant must point to them in turn.

The motor screening test has a dual purpose. Firstly, it serves to familiarise participants with the touch screen. Secondly, measures of latency to respond and pointing accuracy are recorded.

3.6.2 Visual memory battery.

3.6.2.1 Pattern and spatial recognition.

Pattern recognition.

Twelve abstract line patterns were sequentially presented at the centre of the screen. These stimuli were enclosed by a 2.6 x 2.6 cm box outline, and were presented for three seconds each. The participant's task was to remember these patterns. Once the entire list had been presented, and 5 seconds after the final stimulus, 12 pairs of stimuli were sequentially presented side by side. One stimulus in each pair was novel, the other had occurred in the original list; the order of the presentation was the reverse of that earlier. The participant had to

point to the familiar stimulus. Feedback was provided by an Auditory tone, and by the appearance of a tick (for a correct response) or a cross (for an incorrect response). A second list of 12 stimuli, containing novel patterns, was presented soon after testing on the first list had finished. Accuracy (number correct) and latencies were recorded.

Spatial recognition.

In this task participants were sequentially presented a series of five white squares (2.0 x 2.0 cm) which appeared in pseudo-random locations on the screen for a duration of 3 seconds each. Participants are required to remember the location of the five sample stimuli. After a short delay (5 seconds), the recognition phase begins. The participant sees a series of pairs of squares, which includes one square presented in the location visited by a square in the presentation phase, and another square in a novel location. The participant is required to touch the square which is in the location occupied by a square in the presentation phase. Auditory and visual feedback is provided as described above for pattern recognition. All five locations visited in recognition phase are tested in the reverse of the presentation order. This cycle is repeated a total of 4 times, each time using a novel set of five locations. Accuracy (number correct) and latencies were recorded.

3.6.2.2 Simultaneous and Delayed Matching to sample (MTS).

Matching to Sample (MTS) involved the opening of a 3 x 3 cm red box, located at the top centre of the screen, to reveal a sample stimulus (one of a number of abstract rectangular dot patterns involving different arrangements of two components: four types of shape and four colours, measuring approximately 2 cm long by 0.7 cm high). This was followed by the opening of four boxes of the same size, which revealed four different choice stimuli in a row along the screen. One stimulus was always identical in shapes and colours to the sample stimulus, a second differed in shapes, but had the same colour components, the third differed in colours, but not shapes, and the fourth (a distracter) had different shapes and colours. The stimuli positions varied across trials and one (random) quadrant of the stimulus was common to all four stimuli.

In simultaneous matching, the sample stimulus remained on the screen whilst the choice stimuli appeared. Choice stimuli appeared 4.5 seconds after presentation of the sample stimulus. In delayed matching, the sample stimulus appeared for 4.5 seconds, then disappeared, and the choice stimuli were presented 0, 4 or 12 seconds later. When the choice stimuli appeared, participants had to point to the one which resembled the sample. Auditory and visual feedback was provided by the machine. The stimuli remained in the event of an incorrect response, but with a cross superimposed on the incorrect stimuli until a correct response, signalled by a tone and a click, was made.

Different delays (including the simultaneous condition) were programmed in a pseudo-random order, with 10 trials at each delay. The test always began with practice trials on the simultaneous condition, followed by 0 and 12 seconds delay conditions. After half (20) of the total (40) trials were completed, a break was included. Participants were given 2 minutes (or more if requested or required) to rest before the second half of testing was undertaken.

Data pertaining to latency to respond, accuracy, position and type of error were recorded. In this task, three types of error are possible: responding to incorrect shapes but correct colours, incorrect colours but correct shapes, and incorrect shapes and colours (distracter stimulus).

3.6.2.3 Conditional learning: pattern-location paired associates.

In this task, six white boxes (2.7 x 3 cm) appeared in a circle around the screen. These opened for 3 seconds, and in a random manner to reveal one of a number of abstract colour stimuli; they could also be empty. A probe stimulus appeared at the centre of the circle of boxes after all the boxes had been opened, and the participant was required to point to (touch) the box where the probe stimulus had appeared. At first, only one stimulus was hidden in one of the six locations. If a correct response was made, a further replication of the test using a novel stimulus, was presented. An incorrect response resulted in the whole cycle of stimulus

presentation being repeated up to a maximum of 10 cycles in all. At this point the test would terminate. Otherwise, the stimulus set size was increased from 1 to 2, 3, 6, and finally 8 different stimuli (two extra boxes being added to the display on these occasions). A replication was included at set sizes 1, 2, and 3, and error(s) resulted in a repeat of the cycle for up to 10 cycles. Performance was measured in terms of the total number of trials taken to complete the test, cumulated over all the sets and replications; the (maximum) score of 10 was added for each stage not attempted.

3.6.3 Attentional battery.

3.6.3.1 Circle discrimination.

This task requires the participant to discriminate between two (0.6 and 1.8 cm diameter) circles of varying colours. The participant was initially instructed to touch the smaller of the two circles each time it appeared on the screen; after 20 trials, and for a further 20, they were instructed to reverse the rule and touch the larger circle. The stimuli remained on until a response was made, when auditory and visual feedback was given. The number correct and latencies were recorded.

3.6.3.2 Intra- and extra- dimensional (ID/ED) set shifting.

This task assesses the ability of a participant to shift attentional set, either within a particular dimension (intra-dimensional shift; ID), or from one dimension to another (extra-dimensional shift; ED) when required. The protocol required the participant to learn, in a sequential manner, a set of visual discrimination tasks in which one of two stimuli were correct; feedback being provided by the machine. When touched, a correct box turned green and “correct” was presented above the central boxes, whereas when an incorrect box was touched, the box turned red and “incorrect” was displayed above the central boxes. The same feedback was shown for all subsequent trials at all nine stages. The feedback was displayed for 1.5 seconds, and then both stimuli and feedback were cleared from the screen for 1 second before the subsequent trial.

A participant passes through each stage by achieving a criterion of learning (six successive correct responses) at each stage. If at any stage a participant fails to achieve six successive responses within the maximum of 50 trials for each stage, then the task is terminated.

Two artificial dimensions are used in this task: purple filled shapes and abstract white line figures, and the test comprised nine stages presented in the same order. Initially, the participant was presented with two abstract white line figures presented in two of four boxes around the centre of the screen. The abstract white line figures were selected by the experimenter as the first dimension.

i) **Simple discrimination (sd)** the participant was required to learn by trial and error, which of the two (different) line stimuli was 'correct'. The same stimuli were then represented in differing pseudo-randomly selected boxes.

ii) In the second stage, the stimuli remained the same. However, participants must now respond to the previously incorrect stimulus, and ignore the previously correct stimulus; a **simple discrimination reversal (sdR)**.

iii) In the third stage, the second dimension (purple shapes) was introduced. One stimulus of each dimension was paired together to give a compound stimulus in each response box. At this stage the stimulus from each dimension were spatially separated within the response boxes. To respond correctly, participants had to continue responding to the stimulus that was correct for the previous stage; a **compound discrimination (c_d)**. For this and all subsequent stages, stimuli of the different dimensions were paired in a pseudo random fashion with the constraint that the same pairings never occurred for more than three trials in a row.

iv) Stimuli for the fourth stage and above were also compound (they involved stimuli from both dimensions). However, they were no longer spatially distinct, as the white line figure was superimposed on the purple shape. To respond correctly in the fourth stage, participants had to continue responding to the correct stimuli

from the previous two stages. This stage also involved **compound discrimination (cd)**, but for superimposed figures.

v) At the fifth stage, a **compound discrimination reversal (cdR)** occurred. The participant had to respond to the previously incorrect stimulus in the same dimension to obtain a correct response.

vi) To avoid previous experience confounding the results at the subsequent ID and ED shift stages, novel stimuli were introduced at the sixth stage. This stage was an **intra-dimensional shift (IDS)**, which required the participant to discover which of the stimuli (in the same dimension as used in the previous stages) was now the 'correct' one.

vii) This was succeeded by a further reversal at the seventh stage; an **intra-dimensional reversal (IDR)**.

viii) In stage eight, new stimuli were again introduced in both dimensions, but correct responses were only obtained when responding to the correct stimulus which was from the previously incorrect dimension; an **extra-dimensional shift (EDS)**.

ix) In the final stage, contingencies were reversed so that the previously incorrect stimulus of the new dimension became the 'correct' stimulus; an **extra-dimensional reversal (EDR)**.

Outcome measures included: the proportion of participants achieving criterion at each stage; the number of trials to criterion at each stage; and response latencies.

3.6.3.3 Five choice serial reaction time.

This task involved five sequential stages of increasing complexity. This task has three main purposes: firstly to train the participant to use the hand-switch; secondly to test the participants ability to acquire this motor skill; and thirdly, to

act as a simple and choice reaction time task. All stages involved the presentation of a (1.0 cm diameter) yellow dot within a 2.7 cm diameter circular outline.

i) In the first stage, a single circle (diameter 2.7 cm) is permanently present in the centre of the screen and the smaller yellow dot appears for 0.25 seconds in the centre of the circle. The participant is required to accurately touch the screen inside the circular outline. Auditory and visual feedback informs the participant if their response was too quick (i.e. prior to the presentation of the yellow dot), or too slow (i.e. more than five seconds after the presentation of the yellow), or inaccurate (i.e. outside the circle), or if an appropriate response was made. Once the participant has successfully achieved five out of six correct response, or completed a maximum of 18 attempts, the choice reaction time is introduced.

ii) In this stage, a series of five circles (diameter 3.5 cm) are presented in a circle around the centre of the screen. The procedure is similar to that in the first stage except the yellow dot may now appear in any one of the five circles, and the participant must point to the circle in which the yellow dot appeared. Auditory and visual feedback are provided as described above for the first stage. The participant must achieve a criterion of five out of six correct responses, or reach a maximum of 30 attempts before the third stage begins.

iii) The third stage is attempted only if participants have achieved the criterion of five out of six correct responses in the first and second stages. This task introduces participants to the hand switch. A single circle appears in the centre of the screen as in stage one. The participant is required to depress the hand-switch until the yellow dot appears in the centre of the screen. The participant is required to release the hand-switch as soon as possible after the dot appears but is not required to touch the screen. Auditory and visual feedback indicate if the participant correctly released the hand switch, or took too long to release the switch (more than 5 seconds), or released the switch too early (prior to the dot appearing on the screen).

iv) The fourth stage is procedurally the same as the third stage, except that after releasing the hand switch the participant was required to point to the centre of the screen as in stage one.

v) In the fifth and final stage five choice reaction time, 5-CRT), participants are required to hold down a the hand switch until the appearance, for 0.25 seconds, of the stimulus within one of five circular outlines which are arranged in a circle around the centre of the screen. Participants are then required to release the switch and touch the outline within which the dot had appeared as quickly as possible; auditory and visual feedback was provided, and a maximum of 40 trials, depending on performance, was given. The number correct, reaction time (interval between appearance of stimulus and release of switch) and movement time (interval between release of switch and response registration) were recorded.

3.6.3.4 Visual search matching to sample.

This task always directly followed the 5-CRT task described above, and so the participants were familiar with use of the hand switch. The stimuli used were similar to the type described for the MTS task.

The VSMTS task undertaken is dependent on performance in the previous reaction time task. If criterion (five out of six correct responses in all tests completed and within a maximum of 18 trials for simple reaction time tasks and within 40 trials for choice reaction time tasks) was reached, then the VSMTS procedure was employed. If participants failed to reach criterion at any stage then the VSMTS (simple) procedure was employed.

VSMTS: This method allowed participants to determine the pace of the task. Depression of the hand switch opened a central red box (3.0 x 2.7 cm), after a delay of 1 second, to reveal the sample stimulus and 2 seconds later choice stimuli (1, 2, 4, or 8 in number) appeared in the eight surrounding boxes. As for the MTS procedure, one choice stimulus was identical to the sample. The participant was required to hold down the hand switch and, when ready to make their choice, to

release it and point to the choice stimuli selected as quickly as possible. Auditory and visual feedback was provided. In the event of correct response, the trial was complete. If, however, an incorrect response was made, the participant had to continue selecting choice stimuli until the correct choice stimulus was selected and the trial completed. Practice trials involving four examples in order of increasing set size (1, 2, 4 or 8) were given before the 48 test trials (12 at each of the four set sizes, presented in a pseudo-random order). Number of correct responses, reaction and movement time (as in the 5-CRT) were recorded.

VSMTS (simple): This task is similar to the procedure described above for VSMTS except for the following.

- i) The sample stimulus was displayed in a green rather than a red box for the benefit of the experimenter.
- ii) The hand-switch was depressed by the experimenter to reveal the sample stimulus. Thus, movement and reaction times are not distinguished in the VSMTS (simple) task, and a single choice time is recorded.
- iii) The participant was encouraged to maintain their hand in a constant location at the start of trials.

3.6.4 Working memory and planning battery.

3.6.4.1 Spatial span.

This task is a computerised version of the Corsi Block Tapping test (Milner, 1971) using the block layout and sequences of Smirni (1983). Spatial span assesses the participants spatial sequencing ability. Nine boxes (2.2 x 2.2 cm) were presented in the same pseudo random locations on the screen at the beginning of each trial. In the initial presentation phase, a number of boxes sequentially changed colour for a period of 3 seconds, with no delay between each box changing colour. The participant was required to remember the location and sequential order in which the boxes changed colour. Following an Auditory cue (tone) the participant was required to point to the boxes in the same sequence that they had changed colour. During this response sequence, each selected box changed colour for 1 second, and a feedback tone sounded. Whilst a box had changed colour during the response phase, the touchscreen was inactive, and the participant had to wait for the selected box to return to the original white colour before proceeding with the sequence. The initial set involved a sequence of 2 boxes. This was increased by one box each time a sequence was correctly recalled by the participant, up to a maximum of nine boxes. This continued until the participant failed three consecutive trials at any one level. Interference was minimised at the presentation phase by using different colours for adjacent sequences. The outcome measure was calculated as the final level at which the participant successfully recalled at least one sequence.

3.6.4.2 Spatial working memory.

The spatial working memory task determines the participants ability to manipulate, store and mentally segment spatial areas, as well as their ability to form efficient strategies.

For each trial in the spatial working memory task, a number of boxes (2.3 x 2.0 cm) were presented on the screen. Participants were required to search for blue

tokens which are hidden in the boxes and relocate them in a column at the side of the screen. A crucial rule, that a counter would never be found in a square that a counter had already been taken from, was carefully explained to participants.

Participants searched the boxes by touching them in turn to reveal whether there was a “blue counter” hidden in the box. At any one time there was only one token hidden inside one of the boxes. Returning to an empty box already visited within a search is recorded as an error. Once found, the blue token had to be transferred to the column on the right hand side of the screen. The counter then appeared in the ‘counter store’ on the right side of the screen which displayed the number of counters collected to date.

The participant then started a new search for another blue counter which might have been in any of the boxes which so far had not had a blue counter in it. The order of the search is self directed. As every box was used once in each trial to hide a blue token, the number of tokens to be collected corresponded to the number of boxes for each trial. A trial was complete when the number of blue tokens collected was the same as the number of boxes present and the counter store was full. The number of boxes (set size) was gradually increased from 3 to 4 to 6, and finally to 8 boxes. There are four trials at each set size, and set size three was used as practice. The colour and position of the boxes is changed from trial to trial to discourage the use of stereotyped response strategies.

Three types of error are evident in this task. A ‘between search error’ is recorded when a participant returns to a box in which a blue counter had already been found. A ‘within search error’ was recorded when the participant returns to a box opened and shown to be empty earlier in the search. A double error is when a participant returns to a box which was shown to be empty earlier in the search, and the box was one in which a blue counter had already been found. The number of empty boxes visited (excluding any errors) before a token was found was determined by the computer so that each participant received the same degree of feedback prior to finding the first blue counter.

To complete the task in the most efficient way, a search strategy using predetermined search sequences can be developed by the participant. One measure of the use of a search strategy is to record the number of times search sequences started from the same box for each trial in the more difficult 6 and 8 box problems. The total of these scores provides a measure of strategy, with high scores representing efficient search strategies (many searches starting with the same box), and low scores representing poor search strategies (many searches starting with a different box).

3.6.4.3 Tower of London: “Stockings of Cambridge”.

This task assesses higher cognitive functioning, in particular spatial planning and is based on the ‘Tower of Hanoi’ task (Shallice, 1982).

Initially the participant was shown two displays containing three coloured (red, blue and green) balls (3 cm diameter), one display in the top half of the screen and the other in the bottom half of the screen. The upper and lower half of the screen were separated by a line from left to right across the screen. The coloured balls were described to the participant as hanging in ‘socks’ from a beam. There were three socks in both the upper and lower halves of the screen. The leftmost sock could hold three balls, the centre sock could hold two balls, and the rightmost sock could hold only one ball.

On each trial the three balls were placed in predetermined position in both upper and lower displays. The position of the balls in the lower display relative to the position of the balls in the upper display determined the minimum number of moves to complete, and hence the difficulty, of that particular trial. The participant was required to move the red, green, and blue balls in the lower display so that they occupied the equivalent positions to those occupied by the red, green and blue balls in the upper half of the screen.

A ball was moved by first touching it. A tone sounded and the rim of the ball started flashing, to indicate the ball was ‘activated’ and ready to move. A ball

could be ‘deactivated’ by touching it a second time¹. The ball was moved to the desired location by touching that location. The rules of the TL task does not allow balls to be placed high in a pocket when there are no balls beneath it, or for a ball to be moved when there is another ball above it in the same pocket. These ‘illegal’ moves were carefully explained to the participant prior to and, where necessary, during testing. These moves were registered but ignored by the computer.

Participants were instructed to carefully study the position of the balls and to start only when they were confident that they had planned a sequence of moves to solve each trial. Participants were instructed to solve the problem in the minimum number of moves possible. The original positions of the balls in the upper and lower halves of the screen determine the minimum number of moves required to complete a particular trial. The maximum number of moves for a given trial was twice the minimum number of moves. If a participant failed on three problems in a row, the computer terminated testing. There were no time limits for solving problems.

At first it was only necessary to move one ball, but this increased to ‘five move’ problems. There were three practice problems at each of the one and two move stages, and then two problems at each of the three and three move stages. At this point a procedure controlling for motor performance is included, a so called ‘yoked’ condition. The upper display moves one ball at a time, exactly repeating the moves made by the participant during the planning phase, the participant must follow the moves in the upper display by moving the corresponding balls in the lower display. The participant was unaware that the moves being made were the same moves they had previously made whilst attempting to solve the problem.

¹ Unfortunately a programming error meant that when ‘activated’ balls were at the bottom of sock they could not be deactivated. This problem was brought to the attention of the distributor, however, they were unable to rectify the problem, although the problem has been rectified in later versions on CANTAB. This problem was, however, consistent for all participants who completed the Tower of London task.

A second block of two 'two move' (which acted as practice trials) , two 'four move', and four 'five move' problems were undertaken, and then followed by a further 'yoked' motor control section.

The time taken to complete each problem, and the number of moves taken are considered indices of the participant's planning ability. Selection and execution times in the 'yoked' motor control condition provided estimates of motor initiation and execution times. These were subtracted from the total time taken to solve a problem to eliminate the influence of motor confounds.

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Chapter 4:

A comparison of cognitive deficits in AD, DLB, and elderly controls using the Cambridge Neuropsychological Test Automated Battery (CANTAB): Results.

4.1 Non-computerised assessment.

4.1.1 Demographic features of experimental groups.

Data pertaining to age, sex, whether the participant wore glasses, and the age at which participants left full-time education are documented in Table 4.1.

Table 4.1: Demographic data for experimental groups (\pm SEM).

	N, (M:F)	Mean age (\pmSEM) [years]	Glasses Yes / No	Age left full-time education (\pmSEM) [years]
Control	10 (3:7)	73.2 (\pm2.03)	8 : 2	14.7 (\pm0.40)
AD	8 (2:6)	82.8 (\pm0.70)	7 : 1	15.5 (\pm0.85)
DLB	6 (4:2)	70.8 (\pm2.65)	4 : 2	14.2 (\pm0.17)

Analysis indicated that groups were matched for the age at which full-time education was left. The AD group were significantly older than the DLB and control groups ($F_{(2,21)}=10.36$, $p=0.001$), although the control and DLB groups were of similar ages.

4.1.2 Non-computerised psychometric assessment.

Mean scores for estimated pre-morbid IQ (NART IQ), global severity of dementia (total CAMCOG scores), and activities of daily living skills (ADL, IADL) are detailed in Table 4.2. Analyses indicated that groups were matched for estimated pre-morbid IQ (NART IQ), global severity of dementia (total CAMCOG scores), and on activities of daily living skills (ADL, IADL).

Table 4.2: Mean scores for non-computerised psychometric test data (\pm SEM).

	Mean NART IQ (\pmSEM)	Mean total CAMCOG score (\pmSEM)	Mean ADL score (\pmSEM)	Mean IADL score (\pmSEM)
Control (n=10)	113 (\pm1.9)	101.1 (\pm0.53)	N / A	N / A
AD (n=8)	113 (\pm3.3)	67.3 (\pm3.69)	16.9 (\pm1.11)	18.5 (\pm1.67)
DLB (n=6)	107 (\pm4.0)	73.5 (\pm6.69)	17.8 (\pm0.86)	20.6 (\pm2.29)

'N/A' = Not Applicable.

Scores for subsections of the CAMCOG schedule are presented in Table 4.3 and Figure 4.1.

Table 4.3: Mean scores (\pm SEM) for CAMCOG subsections

	<u>Control</u> (n=10)	<u>AD</u> n=8	<u>DLB</u> n=6
Orientation	10.0 (\pm0.00)	4.63 (\pm0.65)	7.7 (\pm0.84)
Language Comprehension	8.7 (\pm0.15)	8.0 (\pm0.38)	8.5 (\pm0.22)
Language Expression	11.5 (\pm0.22)	9.4 (\pm0.78)	10.2 (\pm1.14)
Praxis	14.3 (\pm0.30)	13.1 (\pm0.48)	11.0 (\pm1.48)
Recent Memory	10.5 (\pm0.22)	1.0 (\pm0.76)	5.2 (\pm1.25)
Visual Memory (recognition)	5.9 (\pm0.10)	3.4 (\pm0.60)	4.3 (\pm0.62)
Remote Memory	8.8 (\pm0.13)	4.0 (\pm0.73)	7.0 (\pm1.06)
Attention and Calculation	8.0 (\pm0.00)	6.4 (\pm0.73)	4.2 (\pm0.79)
Perception	9.9 (\pm0.10)	7.6 (\pm0.65)	7.3 (\pm0.67)
Abstract Thinking	11.4 (\pm0.27)	7.5 (\pm0.93)	6.2 (\pm1.25)
Additional Questions	0.9 (\pm0.01)	2.3 (\pm0.25)	2.0 (\pm0.37)
CAMCOG Total Score	101.1 (\pm0.53)	67.3 (\pm3.69)	73.5 (\pm6.69)

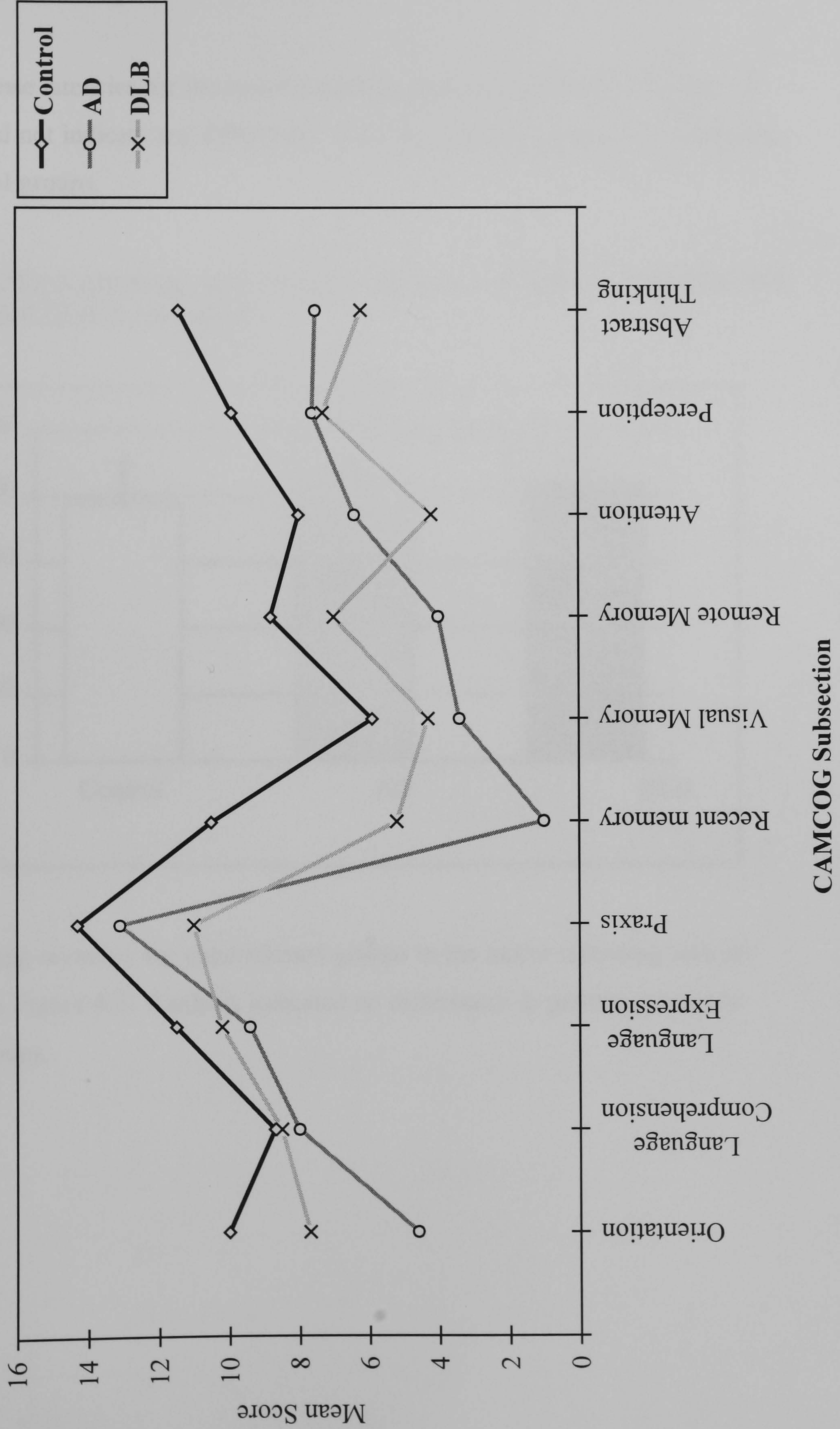
Analysis of data from subsections of the CAMCOG schedule indicated that on the orientation subsection both dementia groups performed worse than controls, and in addition the AD group performed worse than the DLB group ($F_{(2,21)}=29.83$, $p<0.001$). All groups performed equivalently on the language comprehension subsection ($F<1$). In the language expression subsection there was a trend towards a main effect of group ($F_{(2,21)}=2.82$, $p=0.082$) but further pair-wise comparisons revealed no differences between groups on this measure.

Analysis of data from the visuospatial praxis subsection, using one-way ANOVA ($F_{(2,21)}=4.93$, $p=0.018$), revealed the DLB group's performance to be worse than the control group's. The performance of the AD group was not statistically different from either DLB or control groups. Performance in the recent memory recall subsection of the CAMCOG was significantly worse in both dementia groups compared to control, in addition, the AD group performed significantly worse than the DLB group ($F_{(2,21)}=51.24$, $p<0.001$).

In the visual recognition memory subsection both dementia groups performed worse than controls ($F_{(2,21)}=9.56$, $p=0.001$), but there were no statistically significant differences between dementia groups. The remote memory subsection revealed a similar pattern of performance with both dementia groups impaired with respect to controls ($F_{(2,21)}=16.47$, $p<0.001$), but not with respect to each other. Analyses of data from the attention-calculation subsection of the CAMCOG revealed both dementia groups to be impaired with respect to controls, and in addition the DLB group performed worse than the AD group ($F_{(2,21)}=11.92$, $p<0.001$).

Performance in the perception subsection was worse in both dementia groups compared to controls ($F_{(2,21)}=9.34$, $p=0.001$), however, the dementia groups did not differ with respect to each other. Similarly for the abstract subsection both dementia groups were impaired with respect to controls ($F_{(2,21)}=12.73$, $p<0.001$), but not with respect to each other.

Figure 4.1: Mean scores on subsections of the CAMCOG schedule for control (n=10), AD (n=8) and DLB (n=6) groups.

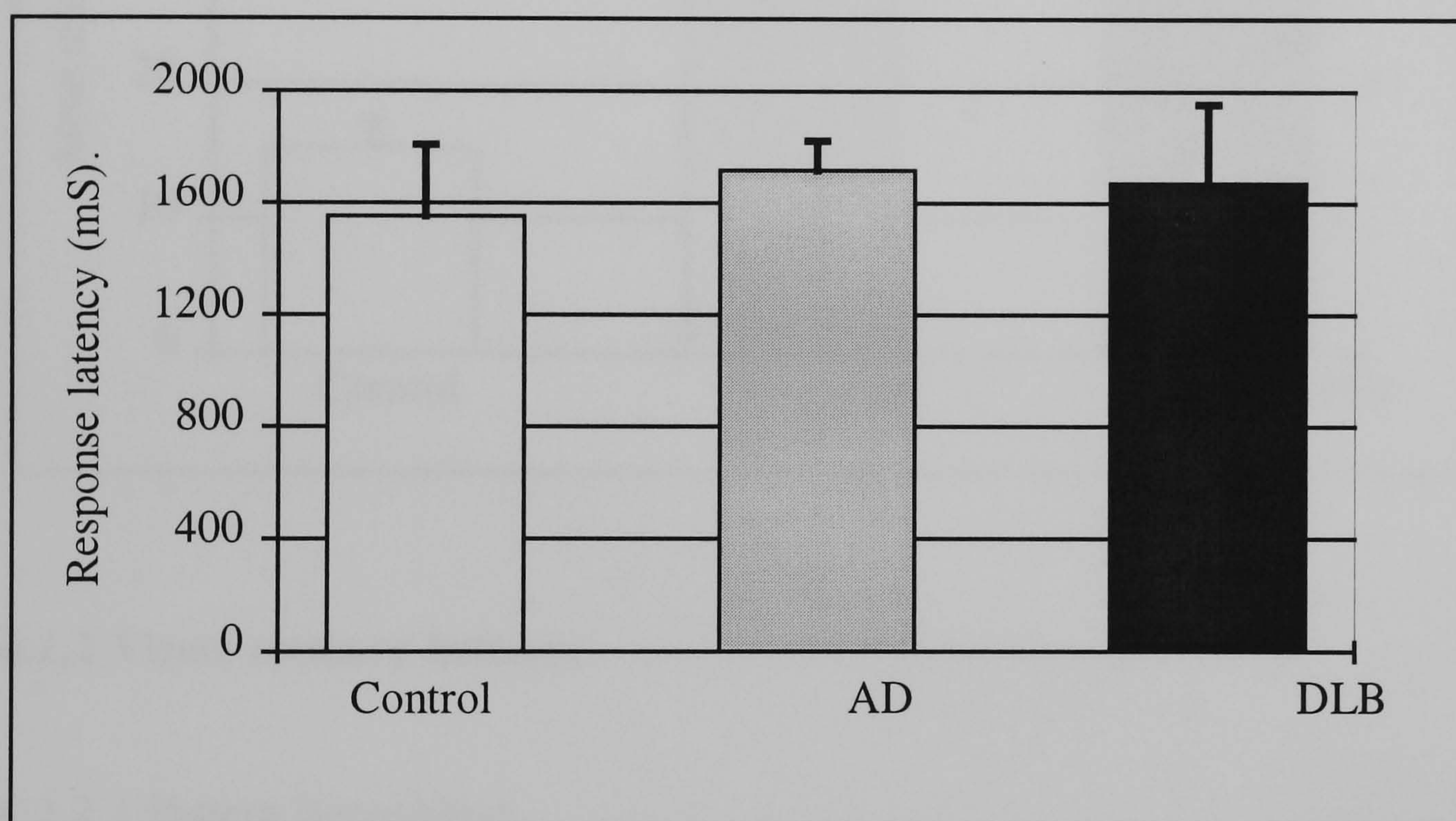


4.2 Computerised CANTAB assessment.

4.2.1 Motor screening.

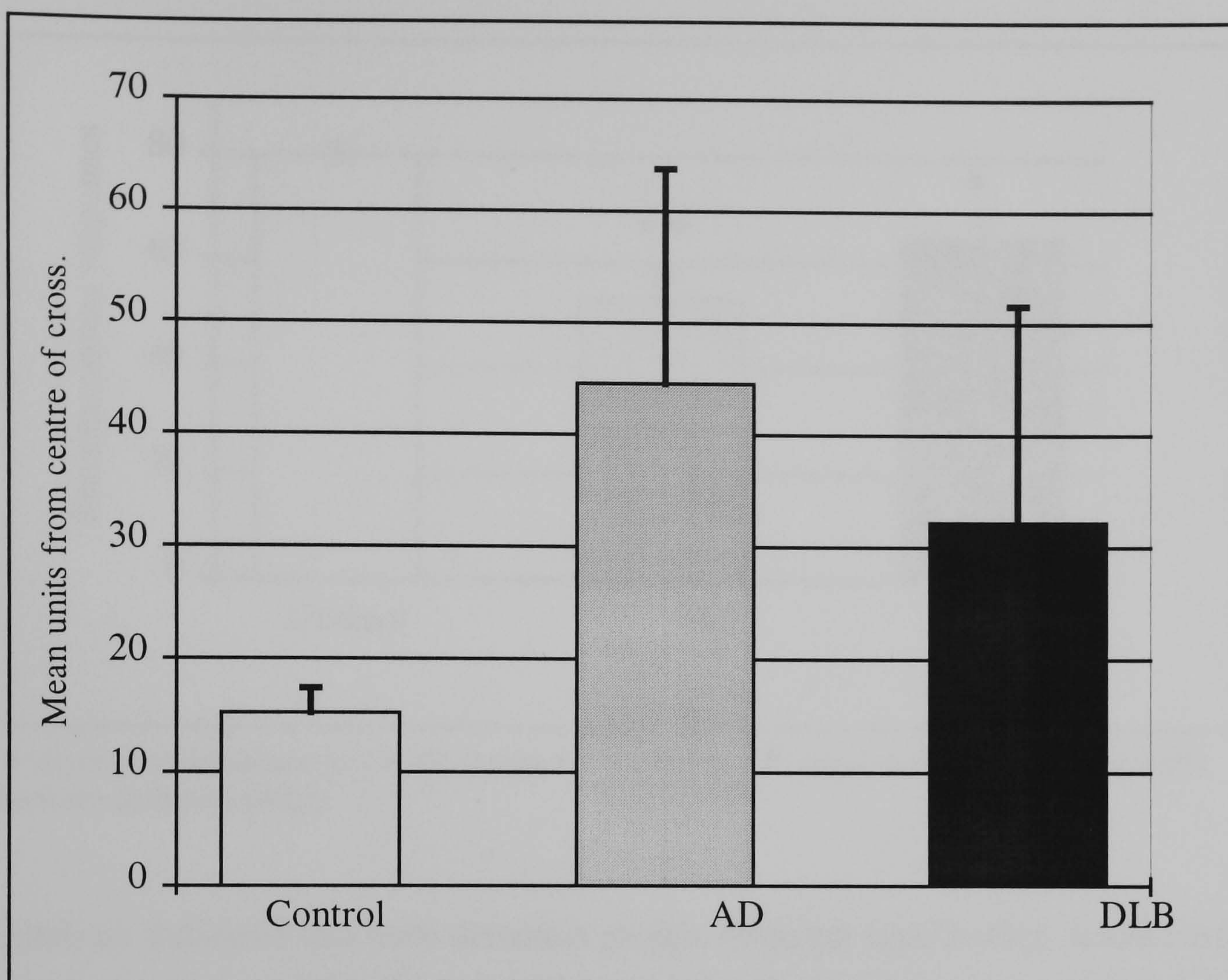
Mean response latencies for the motor screening task are displayed in Figure 4.2. Analyses did not indicate any differences in motor response speed ($F < 1$) between experimental groups.

Figure 4.2: Motor screening: mean response latencies (\pm SEM) for control (n=10), AD (n=8) and DLB (n=6) groups.



Mean pointing accuracy for experimental groups in the motor screening task are displayed in Figure 4.3. Analysis indicated no differences in pointing accuracy between groups.

Figure 4.3: Motor screening: mean accuracy of responses for control (n=10), AD (n=8) and DLB (n=6) groups.



4.2.2 Visual memory battery.

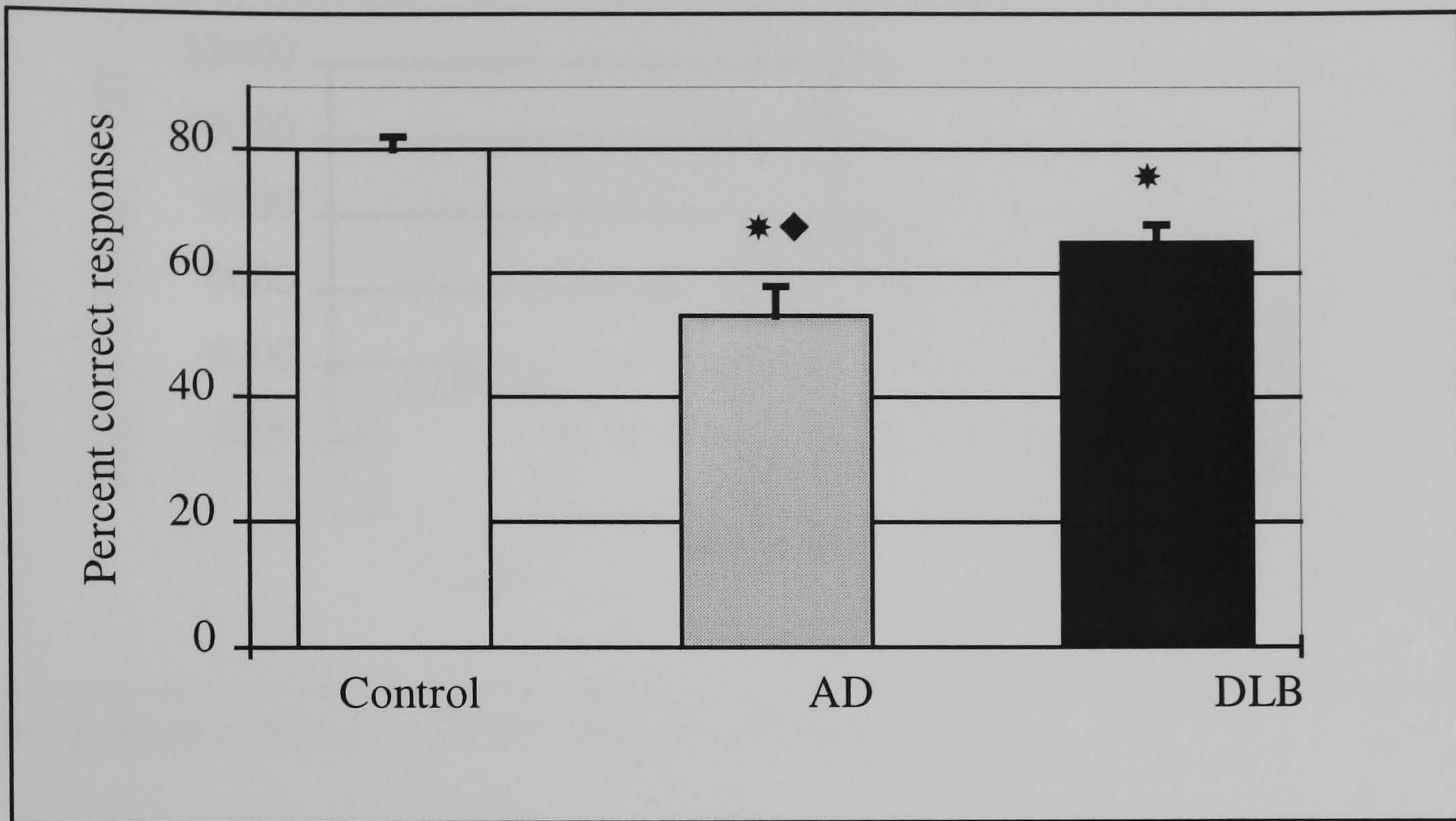
4.2.2.1 Pattern Recognition.

Mean values for percent correct responses and mean reaction times for the pattern recognition task are presented in Table 4.4 and Figures 4.4 and 4.5.

Table 4.4: Pattern recognition: Mean percent correct response (\pm SEM) and response latencies (\pm SEM).

	Mean percent correct responses	Mean response latency (mS)
Control (n=10)	80 (\pm 2.0)	3196 (\pm 365)
AD (n=8)	53 (\pm 4.7)	7711 (\pm 2777)
DLB (n=5)	65 (\pm 2.8)	5493 (\pm 1066)

Figure 4.4: Pattern recognition task: mean percent correct responses (\pm SEM) for control (n=10), AD (n=8) and DLB (n=5) groups.

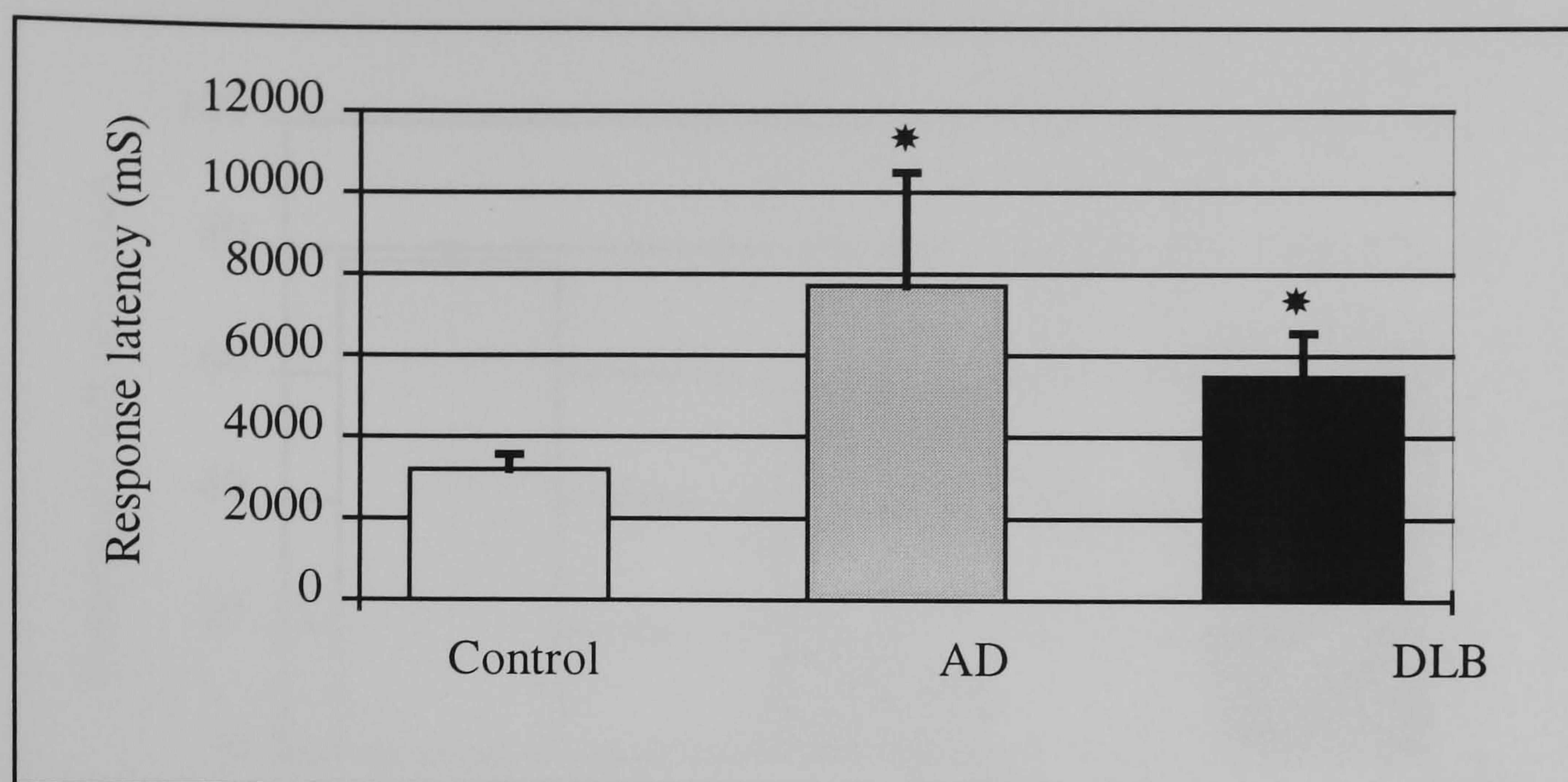


* significant difference ($p < 0.05$) compared to controls; ♦ significant difference ($p < 0.05$) between dementia groups

Analysis indicated that both dementia groups obtained significantly fewer correct responses than controls, and in addition, the AD group performed worse than the DLB group ($F_{(2,20)} = 19.08$, $p < 0.001$). Further analysis of percent correct responses indicated the AD group were responding at chance levels (50% correct responses).

Analysis of response latency data indicated that both dementia groups response latencies were longer than the control group ($F_{(2,20)} = 4.76$, $p = 0.02$), but response latencies for the AD and DLB groups were similar.

Figure 4.5: Pattern recognition task: mean response latencies (\pm SEM) for control (n=10), AD (n=8) and DLB (n=5) groups.



* significant difference ($p < 0.05$) compared to controls

4.2.2.2 Spatial recognition.

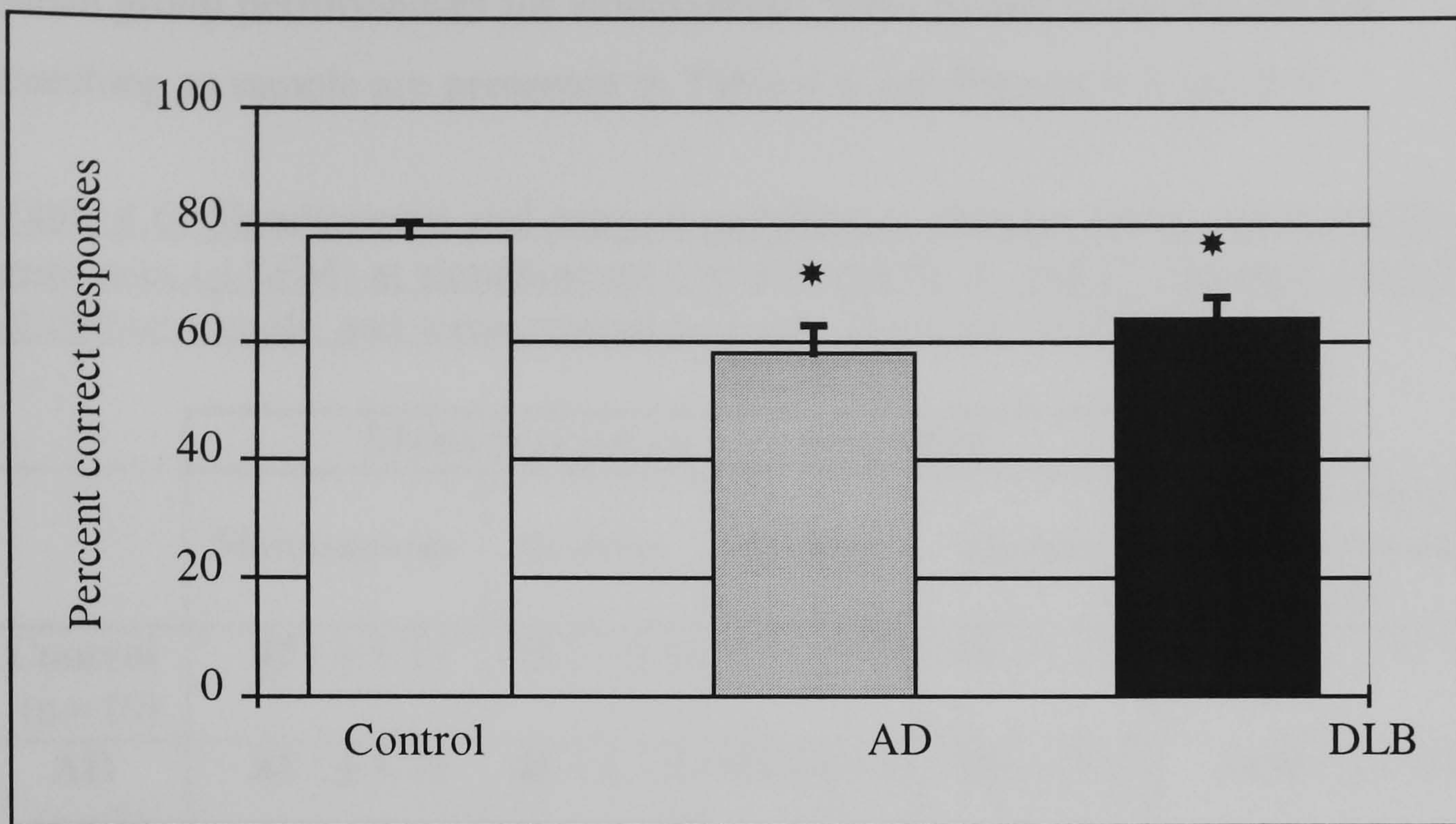
Mean percent correct response data and mean response latencies for the spatial recognition task are displayed in Table 4.5 and Figures 4.6 and 4.7.

Table 4.5: Spatial recognition: Mean percent correct responses (\pm SEM) and response latencies (\pm SEM).

	Mean percent correct responses	Mean response latency (mS)
Control (n=10)	78 (± 2.5)	3006 (± 277)
AD (n=8)	58 (± 4.7)	5101 (± 434)
DLB (n=5)	64 (± 3.7)	5618 (± 724)

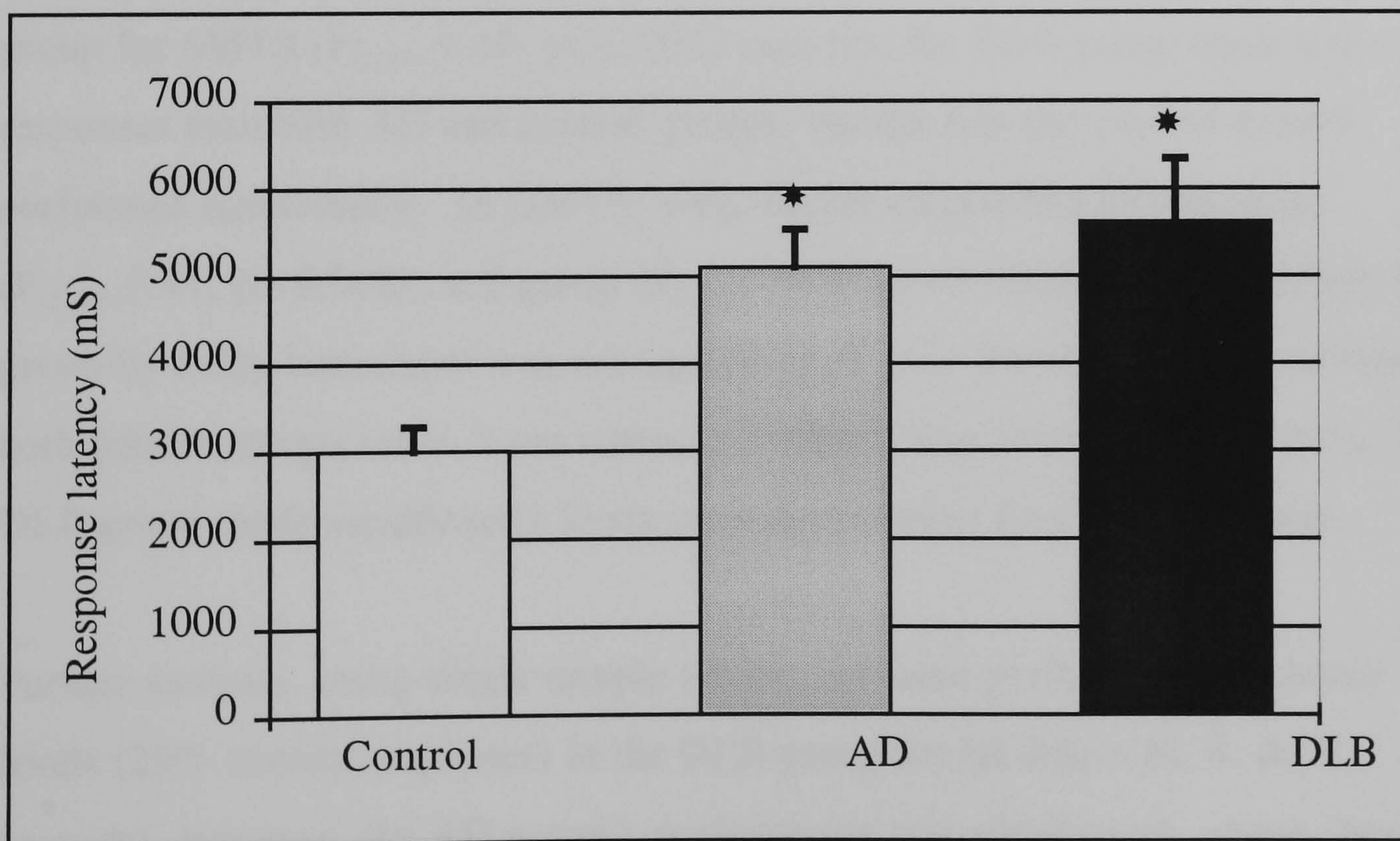
Analysis indicated that both dementia groups made fewer correct responses than the control group ($F_{(2,20)} = 8.96$, $p = 0.002$), but the dementia groups did not differ from each other. Subsequent analysis indicated that the DLB group were performing at above chance ($t = 3.81$, $p = 0.019$), however, the AD groups performance was not significantly better than chance ($t = 1.72$, N.S.).

Figure 4.6: Spatial recognition task: mean percent correct responses (\pm SEM) for control (n=10), AD (n=8) and DLB (n=5) groups.



* significant difference ($p < 0.05$) compared to controls

Figure 4.7: Spatial recognition task: mean response latencies (\pm SEM) for control (n=10), AD (n=8) and DLB (n=5) groups.



* significant difference ($p < 0.05$) compared to controls

Analysis indicated that both dementia groups responded more slowly than the control group ($F_{(2,20)} = 10.95, p = 0.001$), but the dementia groups took an equivalent amount of time to respond.

4.2.2.3 Simultaneous and delayed matching to sample (DMTS).

Mean group performances for simultaneous (SMTS) and delayed (DMTS) matching to sample are presented in Table 4.6 and Figures 4.8 and 4.9.

Table 4.6: Simultaneous and delayed matching to sample: Mean percent correct responses (+SEM) at simultaneous and delayed (0, 4 and 12 seconds) presentation of choice stimuli, and mean overall response latencies (+SEM).

	Mean percent correct responses				Mean overall response latency (mS)
	Simultaneous	0s delay	4s delay	12s delay	
Control (n=10)	83 (± 3.3)	62 (± 2.8)	57 (± 4.6)	56 (± 4.3)	4418 (± 571)
AD (n=7)	81 (± 4.7)	48 (± 7.4)	42 (± 3.2)	35 (± 5.0)	6820 (± 1058)
DLB (n=6)	54 (± 5.6)	39 (± 9.3)	33 (± 4.8)	21 (± 6.4)	8117 (± 1742)

Mean values for percent correct responses from the SMTS task were analysed independently to the DMTS. Analysis of variance revealed a significant effect of group for SMTS ($F_{(2,20)}=4.48$, $p=0.025$) such that the DLB group made less correct responses than both AD and control groups, but the AD and control groups performed equivalently. In DMTS, a significant main effect of both delay ($F_{(2,38)}=5.41$, $p=0.008$), and group ($F_{(2,20)}=13.85$, $p=0.0003$) were described, but the group-by-delay interaction was not significant ($F < 1$). Further analysis revealed both patient groups made fewer correct responses than controls, furthermore the DLB group made significantly fewer correct responses than the AD group.

Further analysis, using single sample t-tests, indicated performance at chance levels (25% correct responses) in the DLB group for all delays (0, 4, & 12 seconds), however, the AD group's performance was significantly above chance for 0 ($t=3.04$, $p=0.023$) and 4 second intervals ($t=5.29$, $p=0.0018$), although at 12 seconds delay the AD group's performance was at chance levels.

Figure 4.8: Mean percent correct for simultaneous, 0, 4, and 12 second delays on the matching to sample task

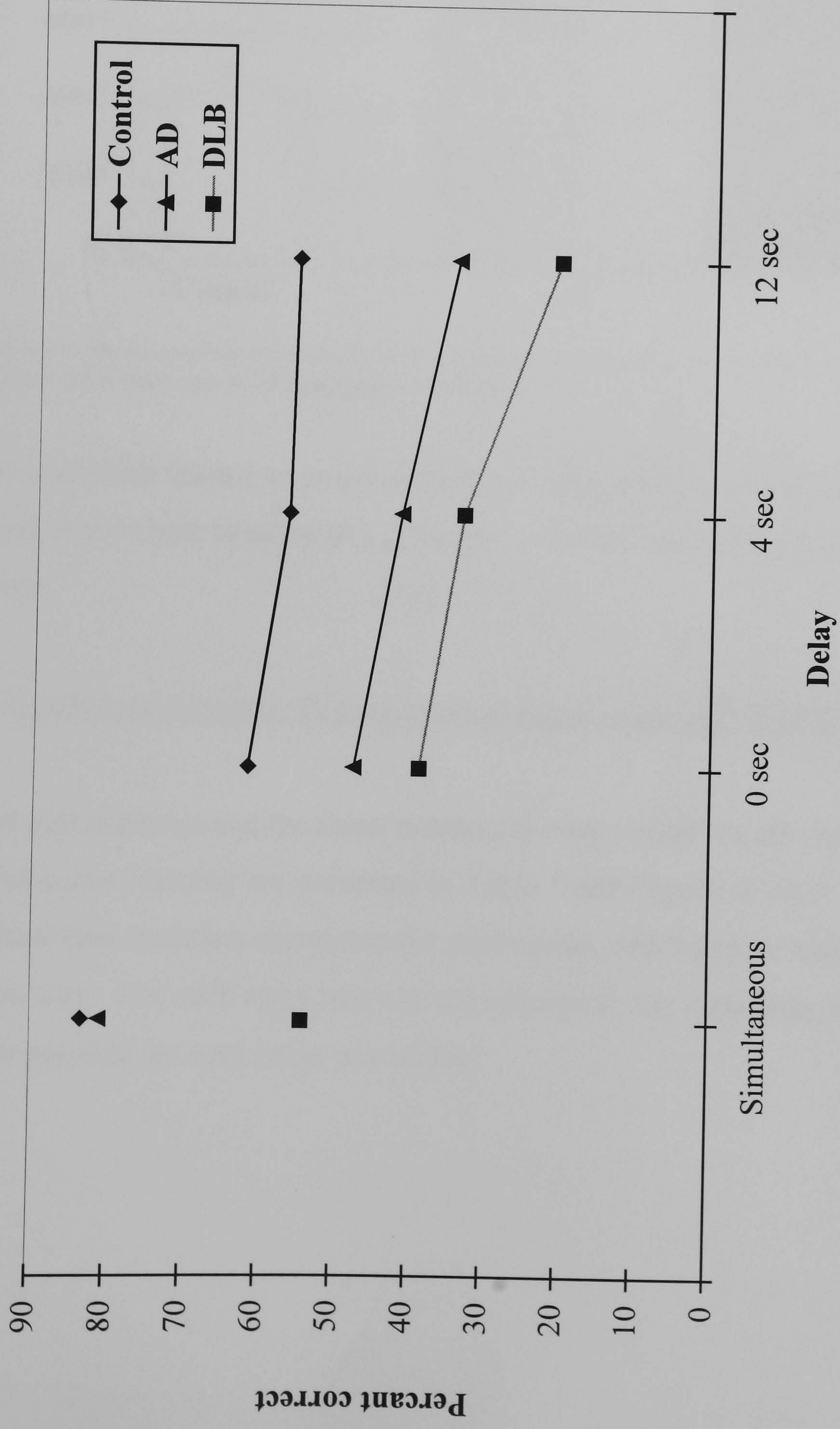
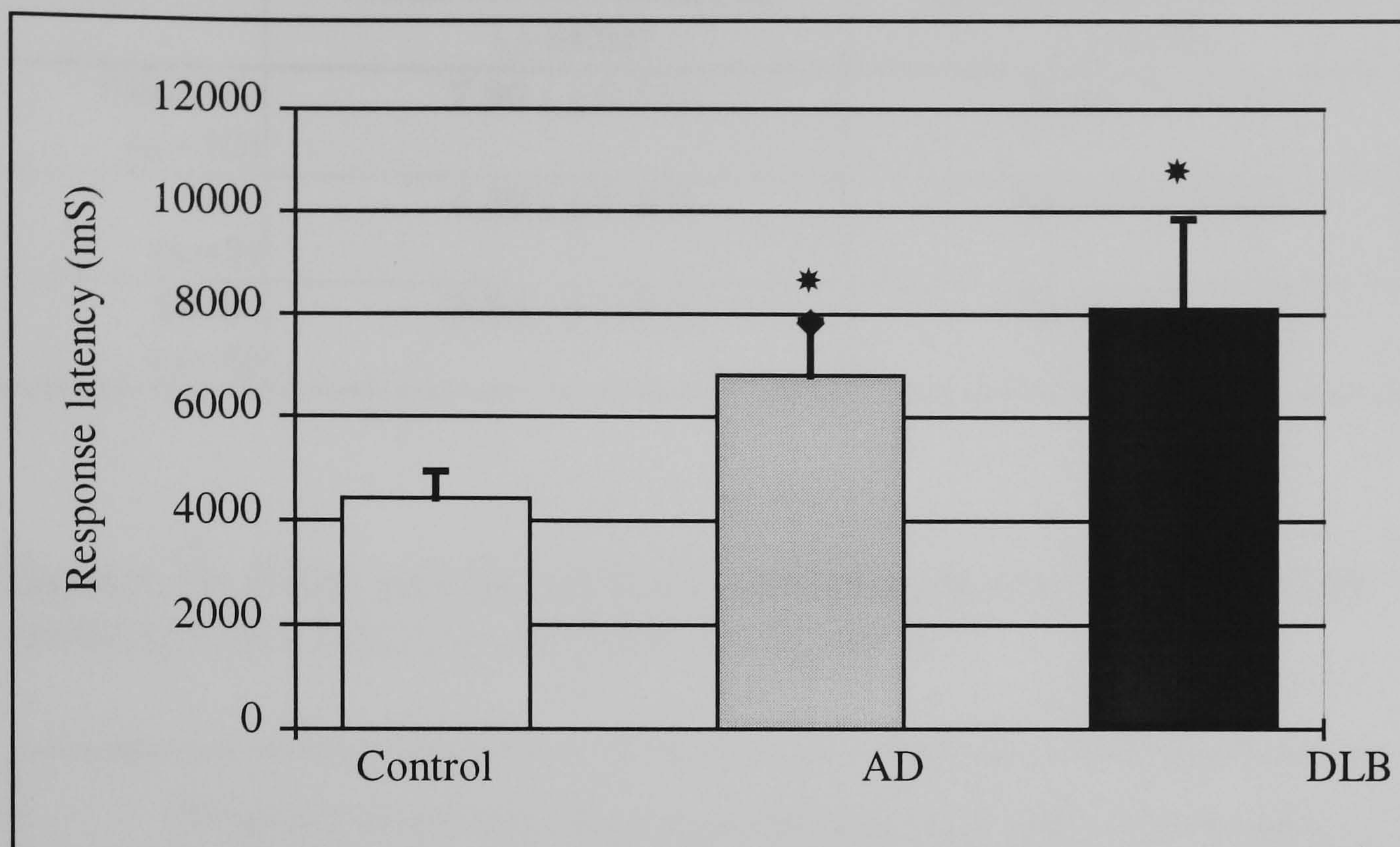


Figure 4.9: Simultaneous and delayed matching to sample: Mean response latencies (+SEM) over all delays for control (n=10), AD (n=7) and DLB (n=6) groups.



* significant difference ($p < 0.05$) compared to controls

The corresponding latency to respond analyses indicated that both patient groups responded slower than controls ($F_{(2,20)}=4.48$, $p=0.025$) but were not different from each other.

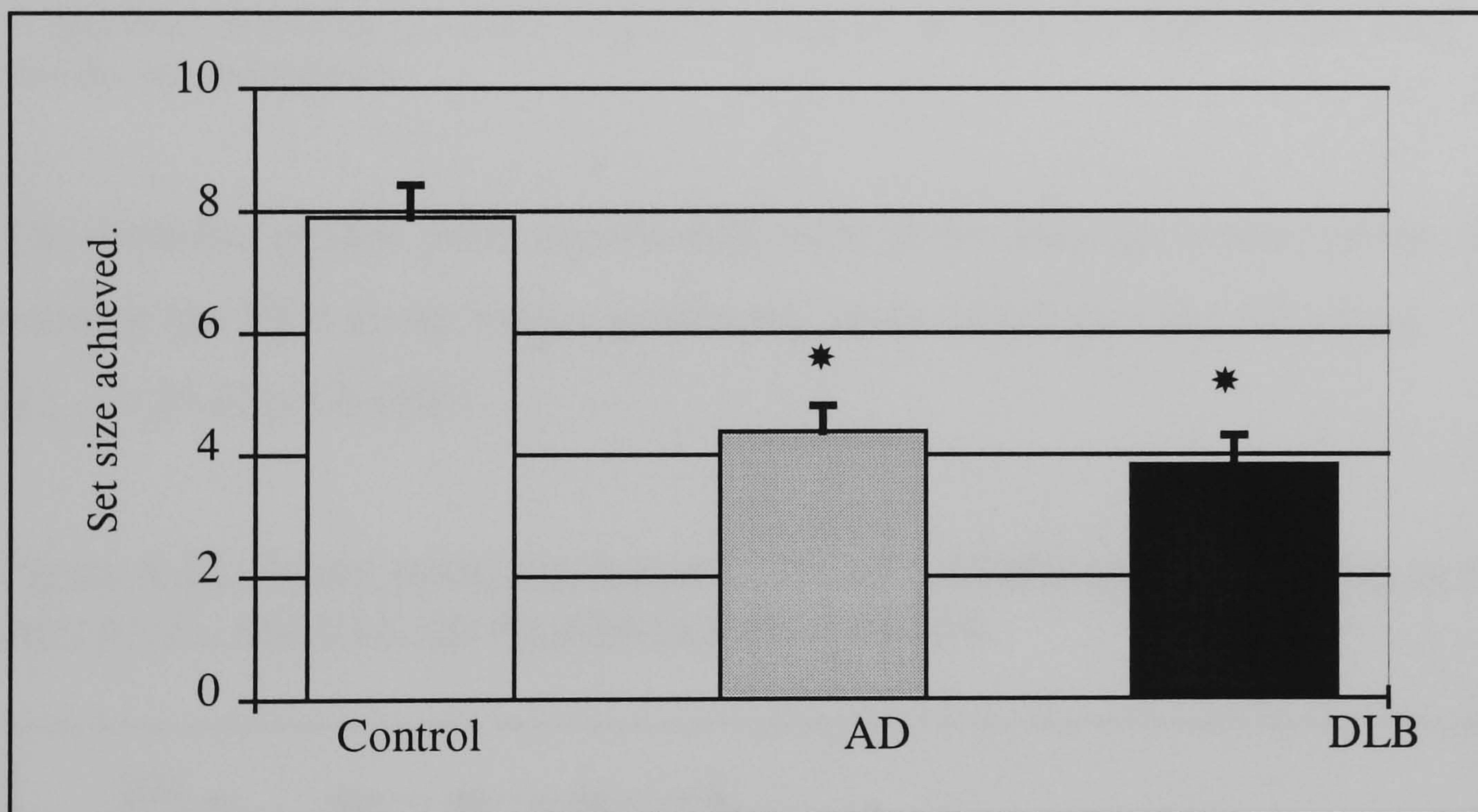
4.2.2.4 Conditional learning: Pattern location paired associates (CLPA).

Mean set size achieved and the mean number of errors made for all trials in the paired associates learning are presented in Table 7 and Figures 4.10, 4.11, and 4.12. These data include a correction for participants who failed to reach the largest set size. For each stage that was not attempted, the maximum number of 10 errors possible for each stage was added.

Table 4.7: Paired associates learning: mean set size achieved (\pm SEM) and mean number of errors (\pm SEM).

	Mean set size achieved (\pm SEM)	Mean number of errors (\pm SEM)
Control (n=10)	7.90 (\pm 0.53)	33.83 (\pm 5.75)
AD (n=8)	4.38 (\pm 0.42)	65.75 (\pm 4.38)
DLB (n=6)	3.83 (\pm 0.48)	79.33 (\pm 1.09)

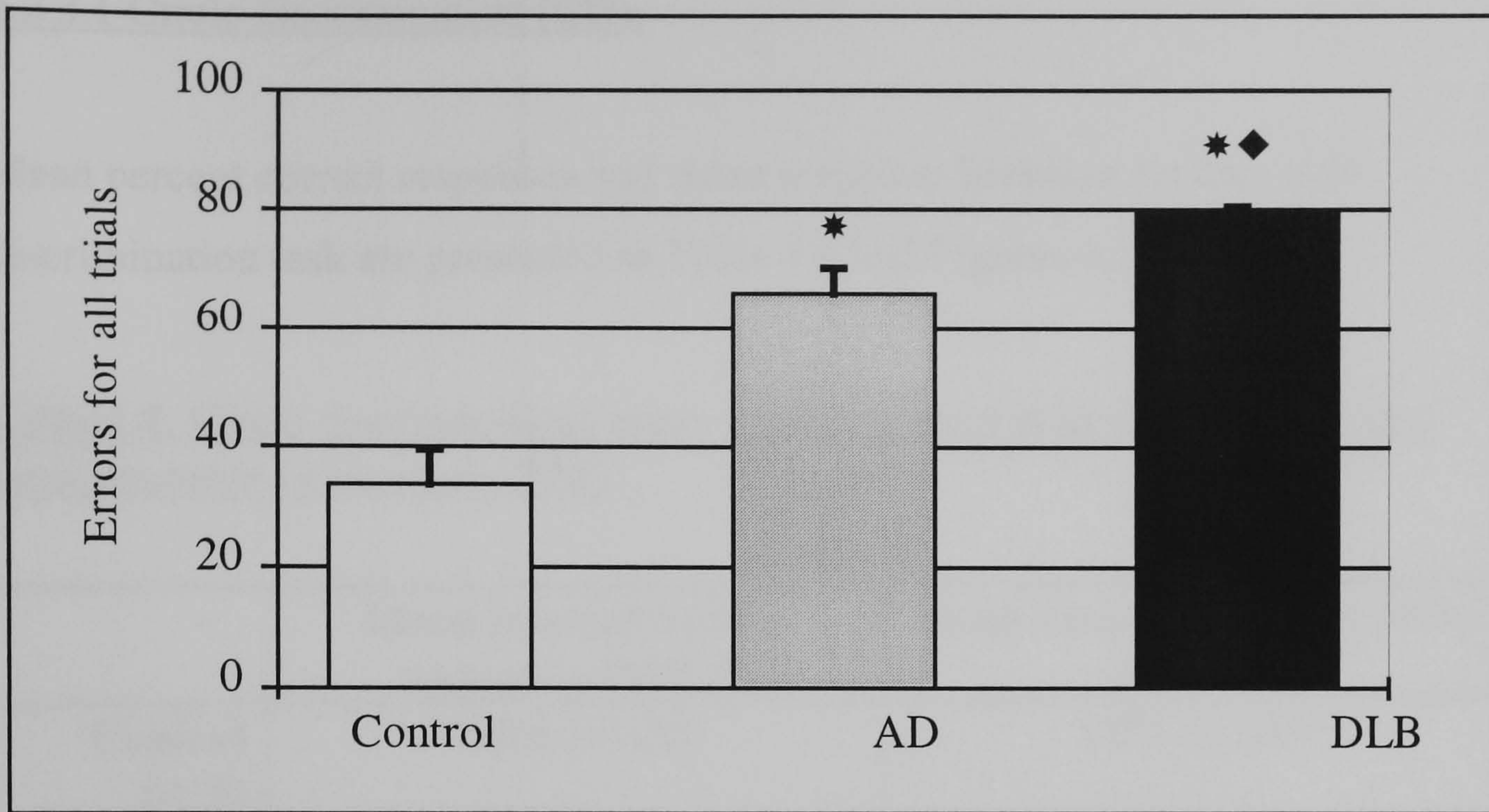
Figure 4.10: Paired associates learning: mean set size achieved (\pm SEM) for control (n=10), AD (n=8) and DLB (n=6) groups.



* significant difference ($p < 0.05$) compared to controls

Analysis indicated that both dementia groups achieved a lower set size than controls ($F_{(2,21)} = 21.03$, $p < 0.001$) but did not differ with respect to each other.

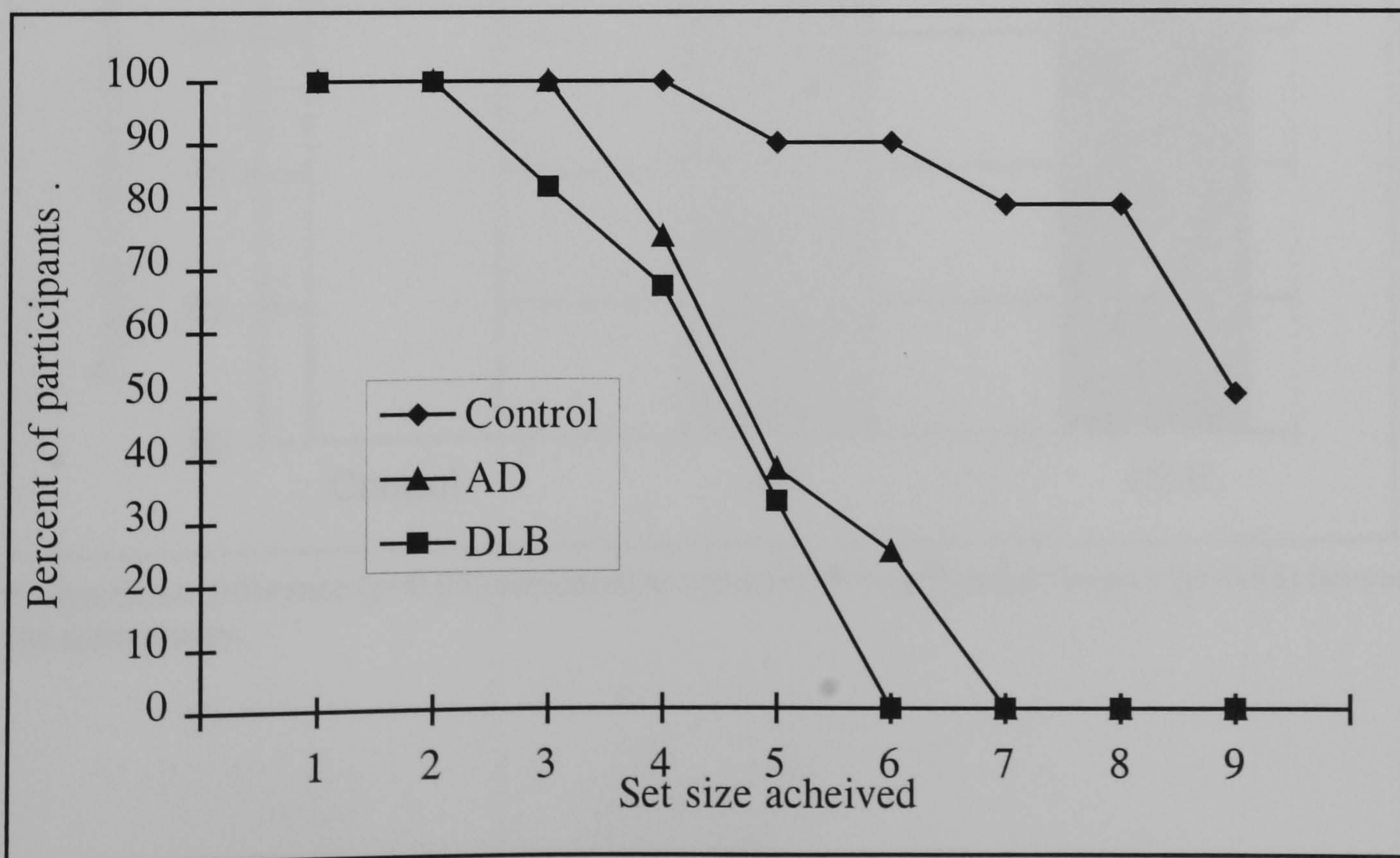
Figure 4.11: Paired associates learning: mean number of errors (+SEM) made in all trials for control (n=10), AD (n=8) and DLB (n=6) groups.



* significant difference ($p < 0.05$) compared to controls; ♦ significant difference ($p < 0.05$) between dementia groups

The dementia groups made significantly more errors than the control group, and in addition the DLB group made significantly more errors than the AD group ($F_{(2,21)} = 23.0, p < 0.001$).

Figure 4.12: Paired associates learning: percent of participants in control (n=10), AD (n=8), and DLB (n=6) achieving each set size.



4.2.3 Attentional Battery.

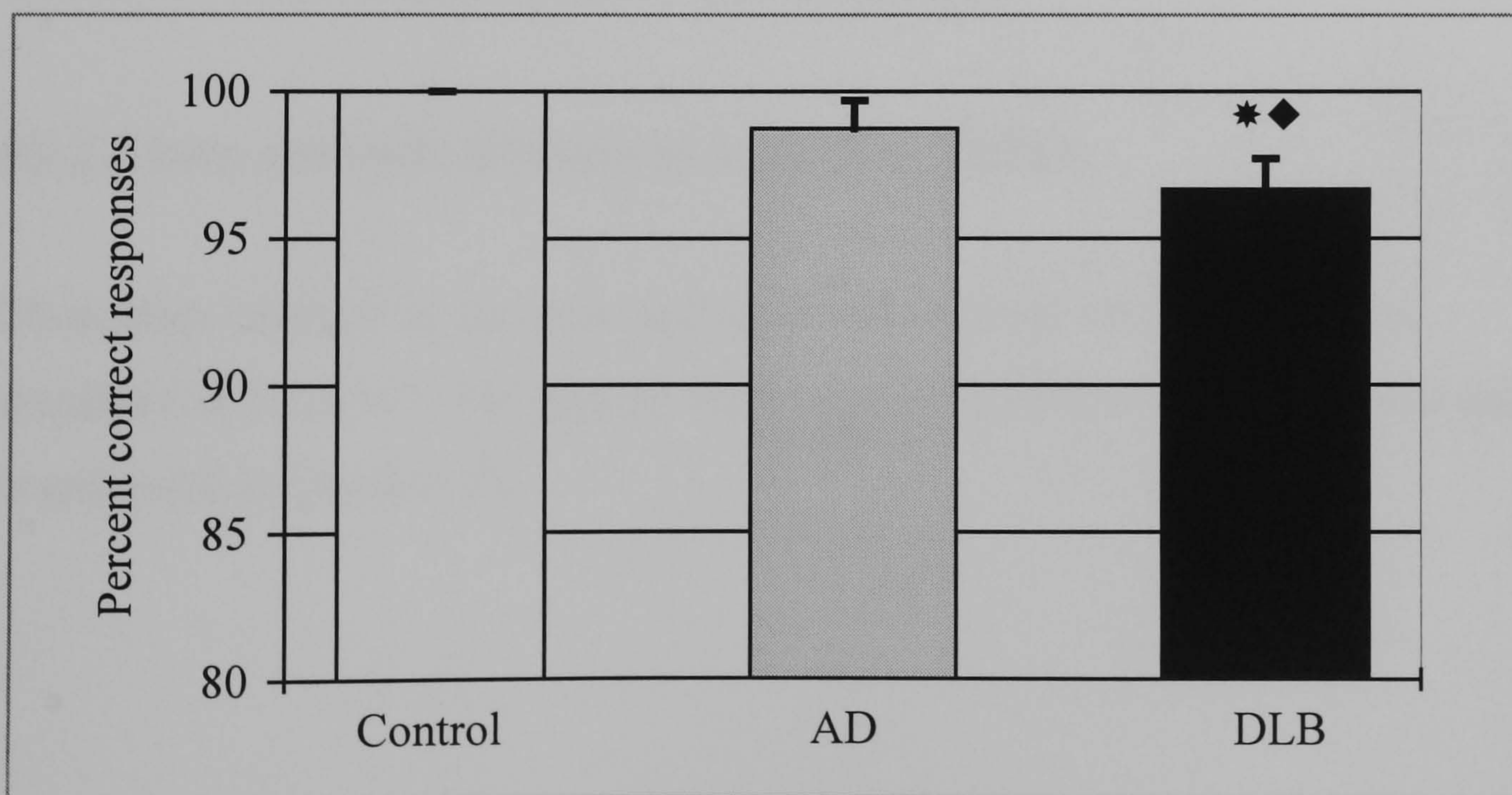
4.2.3.1 Circle discrimination (CD).

Mean percent correct responses and mean response latencies for the circle discrimination task are presented in Table 4.8 and Figures 4.13 and 4.14.

Table 4.8: Circle discrimination: mean percent correct responses (\pm SEM) and mean response latencies (\pm SEM).

	Mean percent correct responses (\pmSEM)	Mean response latency (mS) (\pmSEM)
Control (n=9)	100.0 (\pm0.00)	1231 (\pm202)
AD (n=8)	98.8 (\pm0.95)	1501 (\pm174)
DLB (n=6)	96.7 (\pm1.05)	1874 (\pm624)

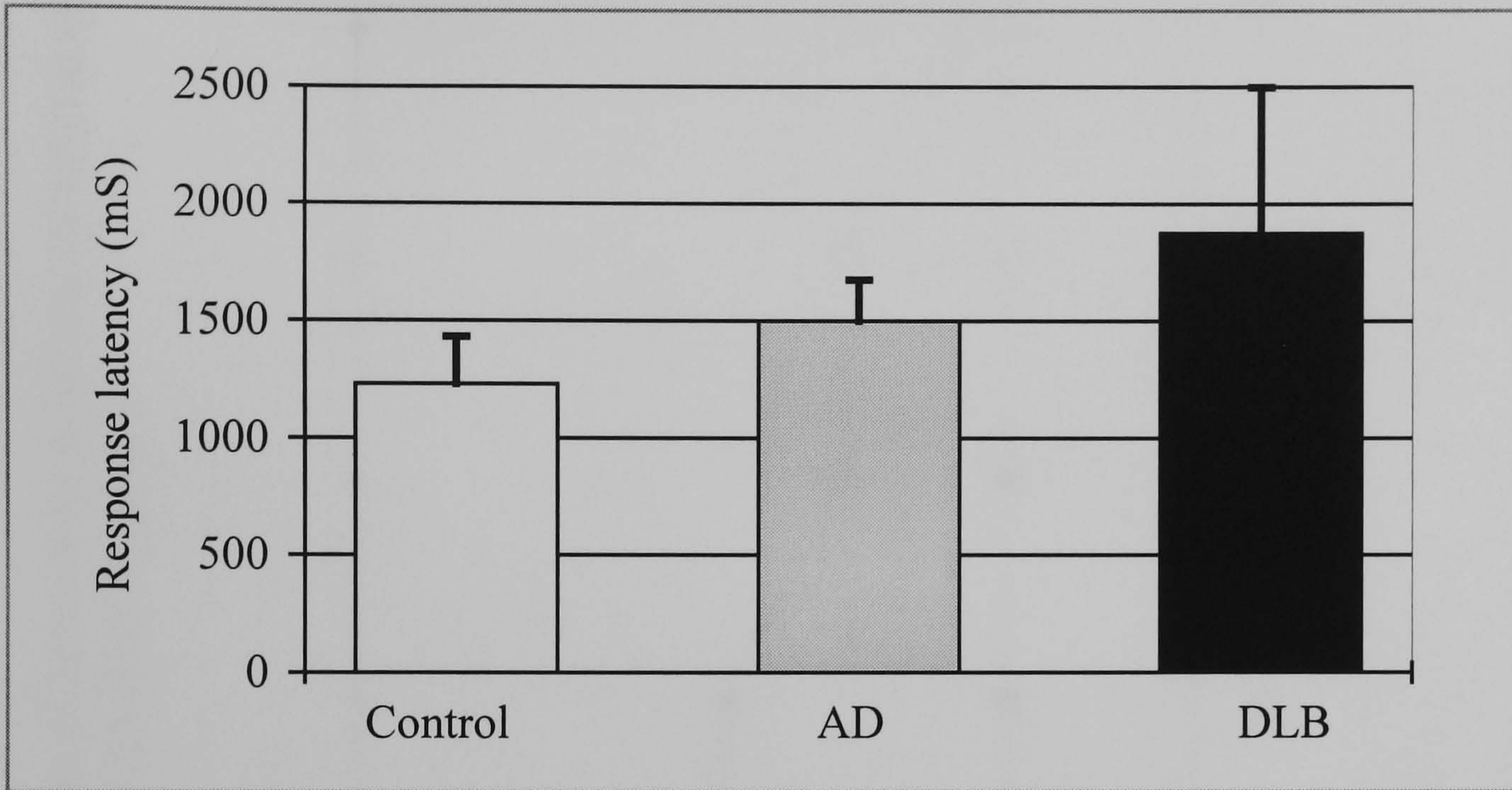
Figure 4.13: Circle discrimination: mean percent correct responses (\pm SEM) for control (n=9), AD (n=8) and DLB (n=6) groups.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

Analysis of variance revealed a significant effect of group for circle discrimination ($F_{(2,20)}=7.91, p=0.003$) such that the DLB group were impaired with respect to both AD and control groups, but AD and control groups performed equivalently.

Figure 4.14: Circle discrimination: mean response latencies (\pm SEM) for control (n=9), AD (n=8) and DLB (n=6) groups.



Analysis of the latency to respond data indicated that there were no significant differences in the speed of response between groups.

4.2.3.2 Intra- and extra- dimensional set shifting (ID/ED).

Mean stage reached in the intra- and extra- dimensional set shifting task is displayed in Table 4.9. The percent achieving criteria for each group at each stage is presented in Figure 4.15.

Figure 4.15: Intra- and extra- dimensional set shifting: percent of participants achieving criterion at each stage for control (n=9), AD (n=8) and DLB (n=5) groups.

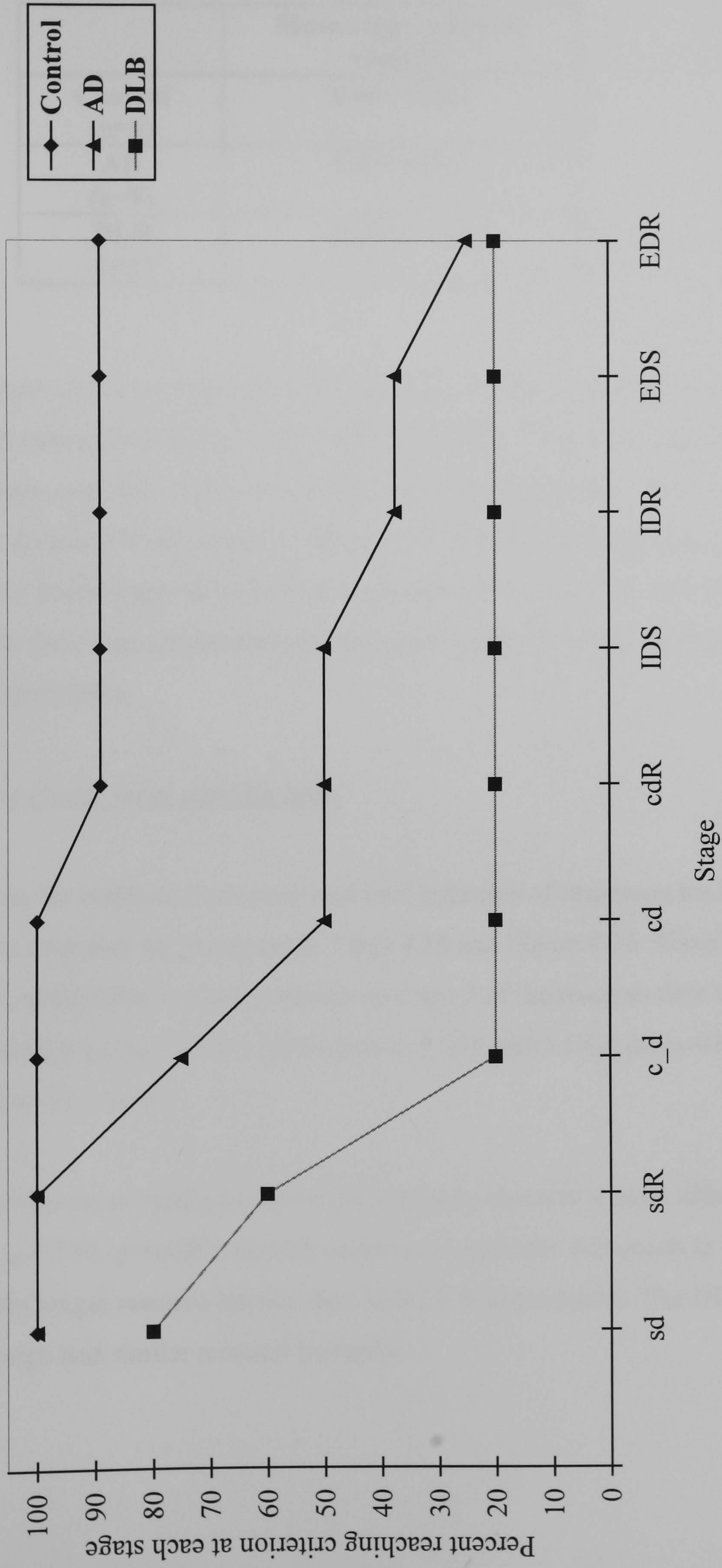


Table 4.9: Intra- and extra- dimensional set shifting: mean stage achieved.

	Mean stage achieved (±SEM)
Control (n=9)	8.44 (±0.56)
AD (n=8)	5.25 (±1.10)
DLB (n=6)	2.80 (±1.59)

All participants achieved criterion in the circle discrimination task (see section 4.1.3.6) indicating their ability to use a rule in making a simple discrimination with feedback, and their ability to change the rule under instruction. Non-parametric Kruskal-Wallis analysis indicated that both dementia groups achieved significantly fewer stages than the control groups ($H=10.23$, $df=2$, $p=0.006$), and additionally there was a trend towards less stages achieved by the DLB than the AD group ($p=0.094$).

4.2.3.3 Five choice serial reaction time.

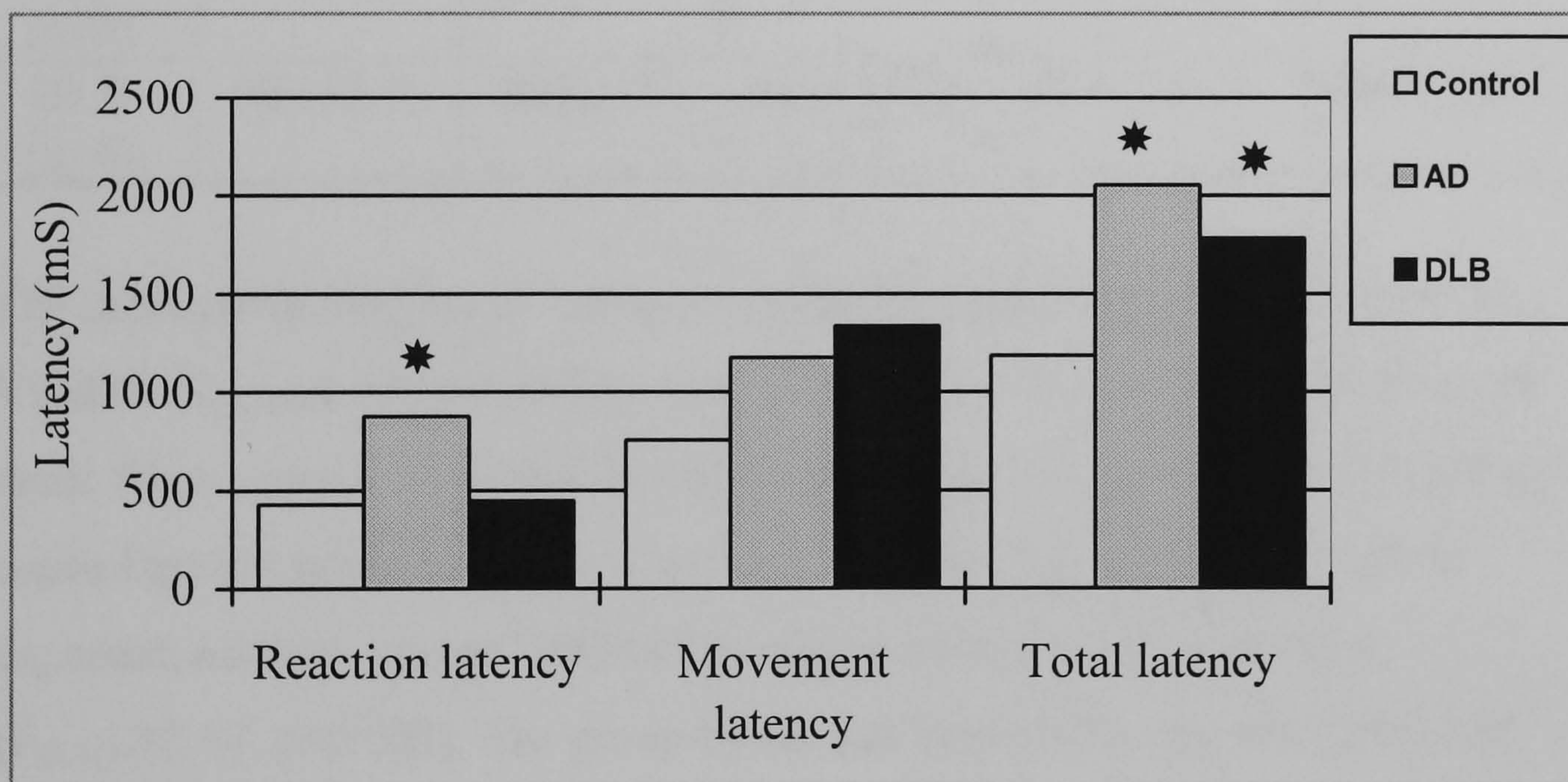
Mean values for reaction, movement and total latencies of responses for level 5 of the reaction time task are presented in Table 4.10 and Figure 4.16. Three DLB and 1 AD participant failed to reach criterion on stage 2 of the reaction time task and hence the data presented are for the 9 control, 7 AD, and 3 DLB cases who completed all five levels.

Analysis of the mean values for the reaction latency revealed a main effect of group ($F_{(2,16)}=7.60$, $p=0.005$). Further analysis revealed the AD group to have a significantly longer reaction latency than both DLB and controls. The DLB and control groups had similar reaction latencies.

Table 4.10: Five choice serial reaction time task (level 5): Mean values (\pm SEM) for reaction, movement and total response latencies for control (n=9), AD (n=7) and DLB (n=3) groups.

	Mean reaction latency (mS)	Mean movement latency (mS)	Mean total latency to respond (mS)
Control	428 (\pm38)	756 (\pm56)	11784 (\pm88)
AD	878 (\pm180)	1175 (\pm200)	2053 (\pm263)
DLB	448 (\pm34)	1336 (\pm285)	1785 (\pm304)

Figure 4.16: Five choice serial reaction time task (level 5): Mean values for reaction, movement and total response latencies for control (n=9), AD (n=7) and DLB (n=3) groups.



* significant difference ($p < 0.05$) compared to controls

The analysis of movement latencies indicated that all groups took a similar amount of time between releasing the non-latching switch and touching the screen. For the total latency to respond, analysis indicated that both dementia groups took longer to respond than the control group. There was no difference in the total response latency between AD and DLB groups.

4.2.3.4 Visual search matching to sample (VSMTS).

Mean group performances for set sizes 1, 2, 4, and 8 are presented in Table 4.11 and Figures 4.17 and 4.18.

Table 4.11: Visual search matching to sample: Mean percent correct responses (\pm SEM) at set sizes 1, 2, 4, and 8 and mean overall response latencies (\pm SEM).

	Mean percent correct				Mean response latency (mS)
	Set size 1	Set size 2	Set size 4	Set size 8	
Control (n=9)	100 (\pm 0.0)	100 (\pm 0.0)	88 (\pm 2.8)	78 (\pm 5.6)	4189 (\pm 649)
AD (n=7)	100 (\pm 0.0)	100 (\pm 0.0)	90 (\pm 5.6)	70 (\pm 4.4)	5901 (\pm 537)
DLB (n=6)	92 (\pm 5.7)	86 (\pm 5.1)	68 (\pm 13.2)	40 (\pm 8.5)	10265 (\pm 3125)

The main group analysis of variance revealed a significant effect of group for VSMTS ($F_{(2,19)}=8.89$, $p=0.0022$). Further analysis revealed that the DLB group made fewer correct responses than both AD and control groups, but the AD and control groups made equivalent numbers of correct responses. As might be expected, all three groups' VSMTS performance depended on set size ($F_{(3,51)}=85.67$, $p<0.001$). The group-by-set size interaction was not significant.

Figure 4.17: Visual search matching to sample: Mean percent correct responses for set sizes 1, 2, 4 and 8 for control (n=9), AD (n=7) and DLB (n=6) groups.

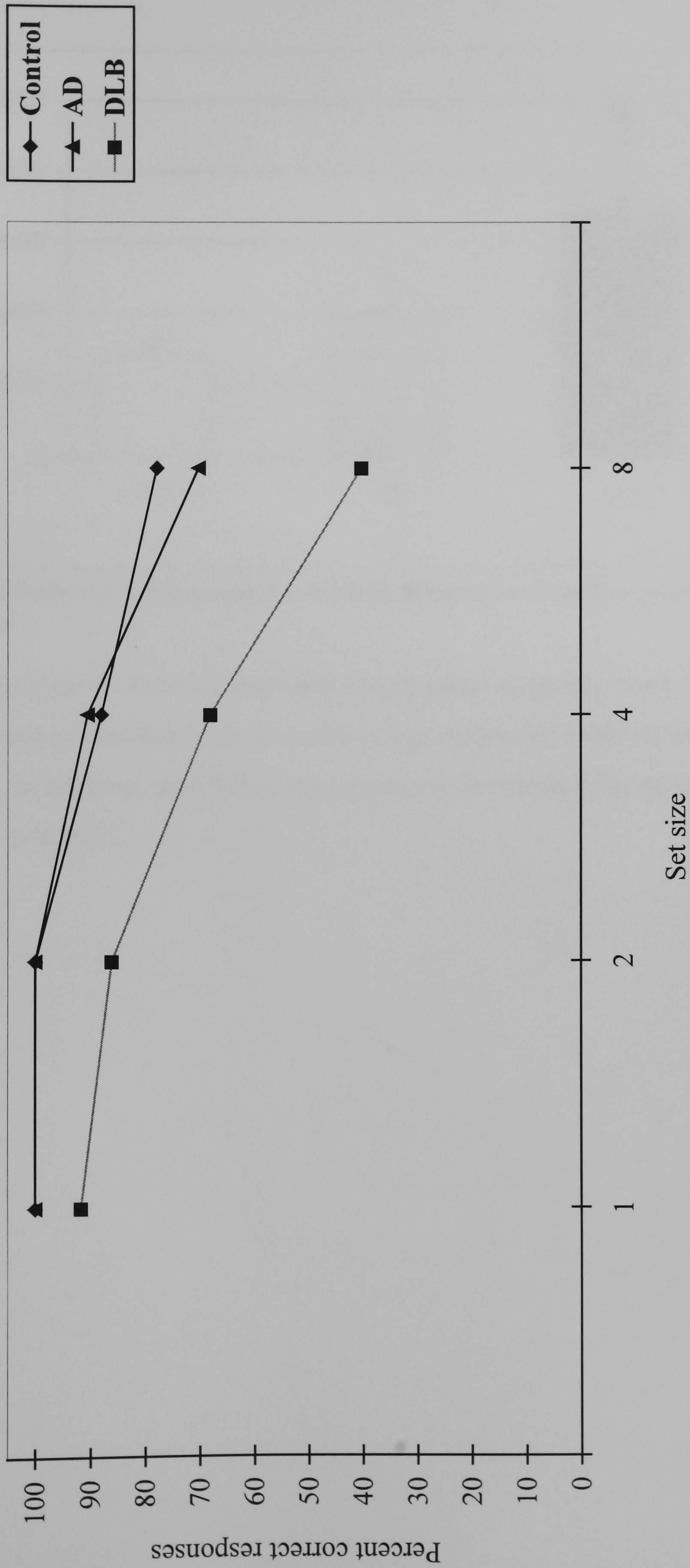
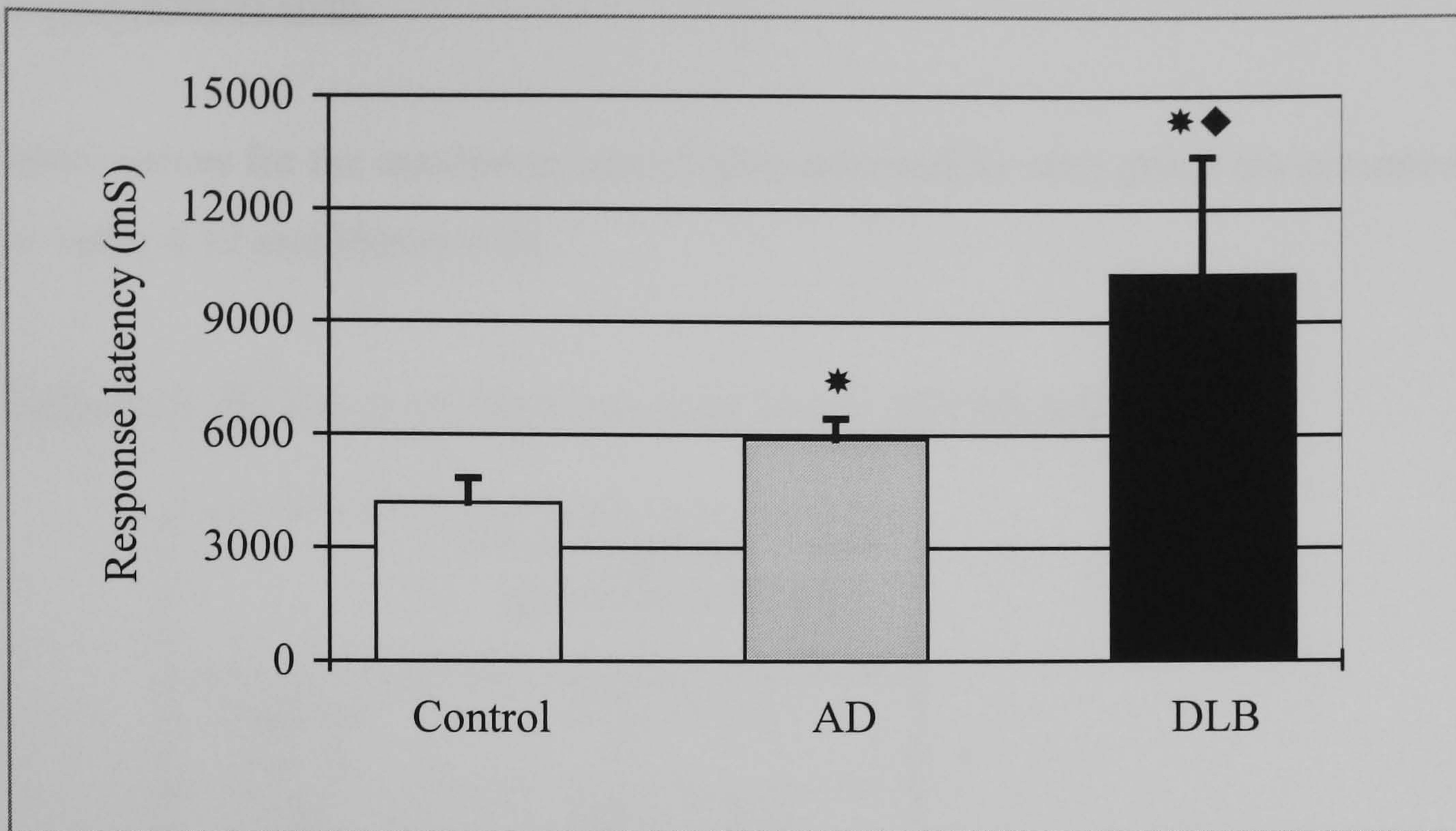


Figure 4.18: Visual search matching to sample: mean response latencies (\pm SEM) for control (n=9), AD (n=7) and DLB (n=6) groups.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

The latency to respond analyses indicated a main effect of group. Upon further analysis it was revealed that both dementia groups responded more slowly than controls and, in addition, the DLB group responded slower than the AD group ($F_{(2,19)}=6.45, p=0.007$).

4.2.4 Working memory and planning battery.

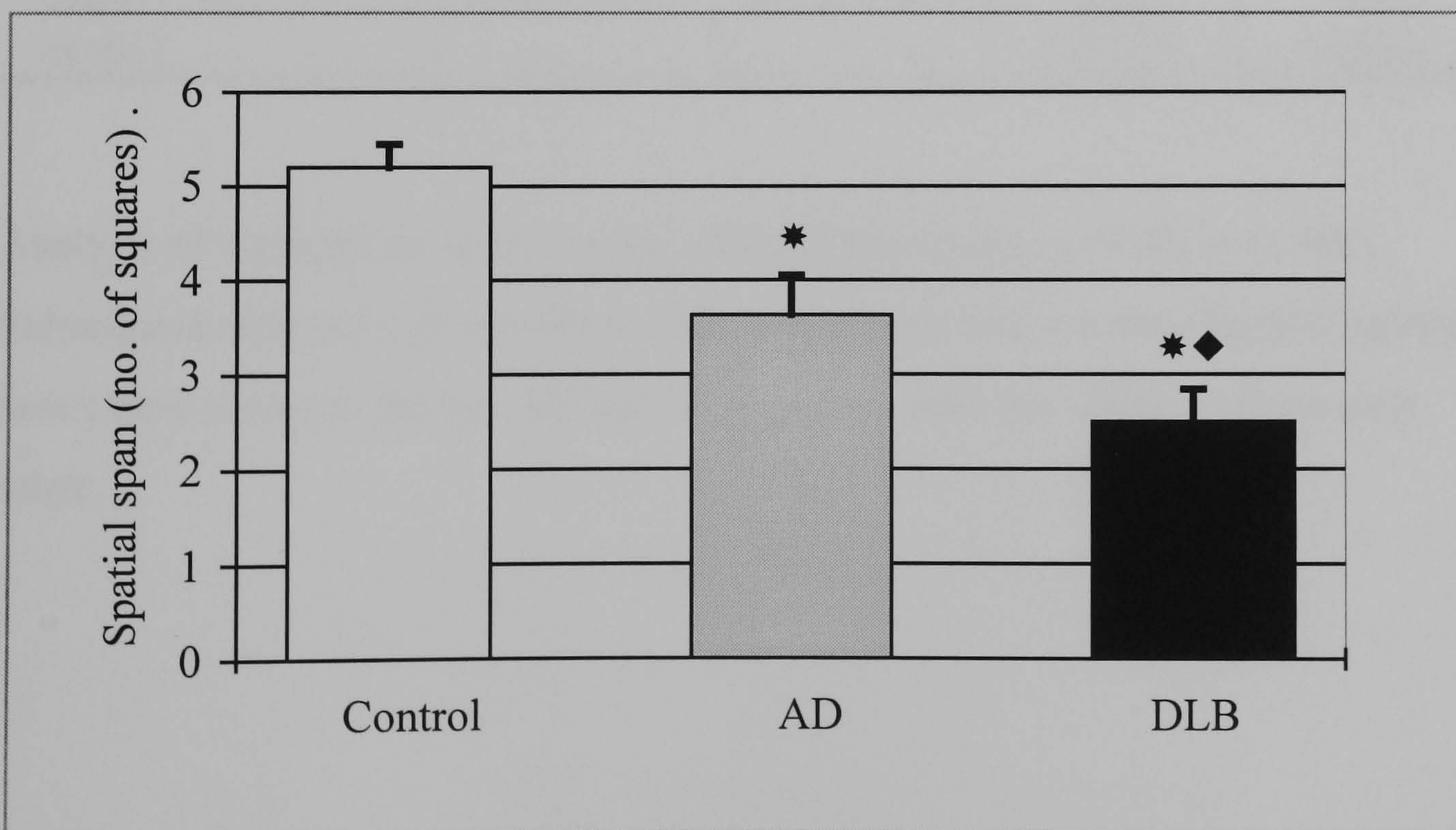
4.2.4.1 Spatial span.

Mean values for the maximum spatial span achieved by each group are presented in Table 4.12 and Figure 4.19.

Table 4.12: Spatial span: mean sequence length (\pm SEM) achieved.

	Mean sequence length achieved (\pm SEM)
Control (n=9)	5.2 (\pm 0.25)
AD (n=8)	3.63 (\pm 0.42)
DLB (n=6)	2.50 (\pm 0.34)

Figure 4.19: Spatial span: mean sequence length achieved (\pm SEM) for control (n=10), AD (n=8) and DLB (n=6) groups.



* significant difference ($p < 0.05$) compared to controls; ♦ significant difference ($p < 0.05$) between dementia groups

Analysis of variance indicated a main effect of group ($F_{(2,22)}=16.1$, $p<0.001$). Further analysis revealed that the spatial span for both dementia groups were significantly shorter than the control group. In addition spatial span for the DLB group was significantly shorter than the spatial span for the AD group.

4.2.4.2 Spatial working memory.

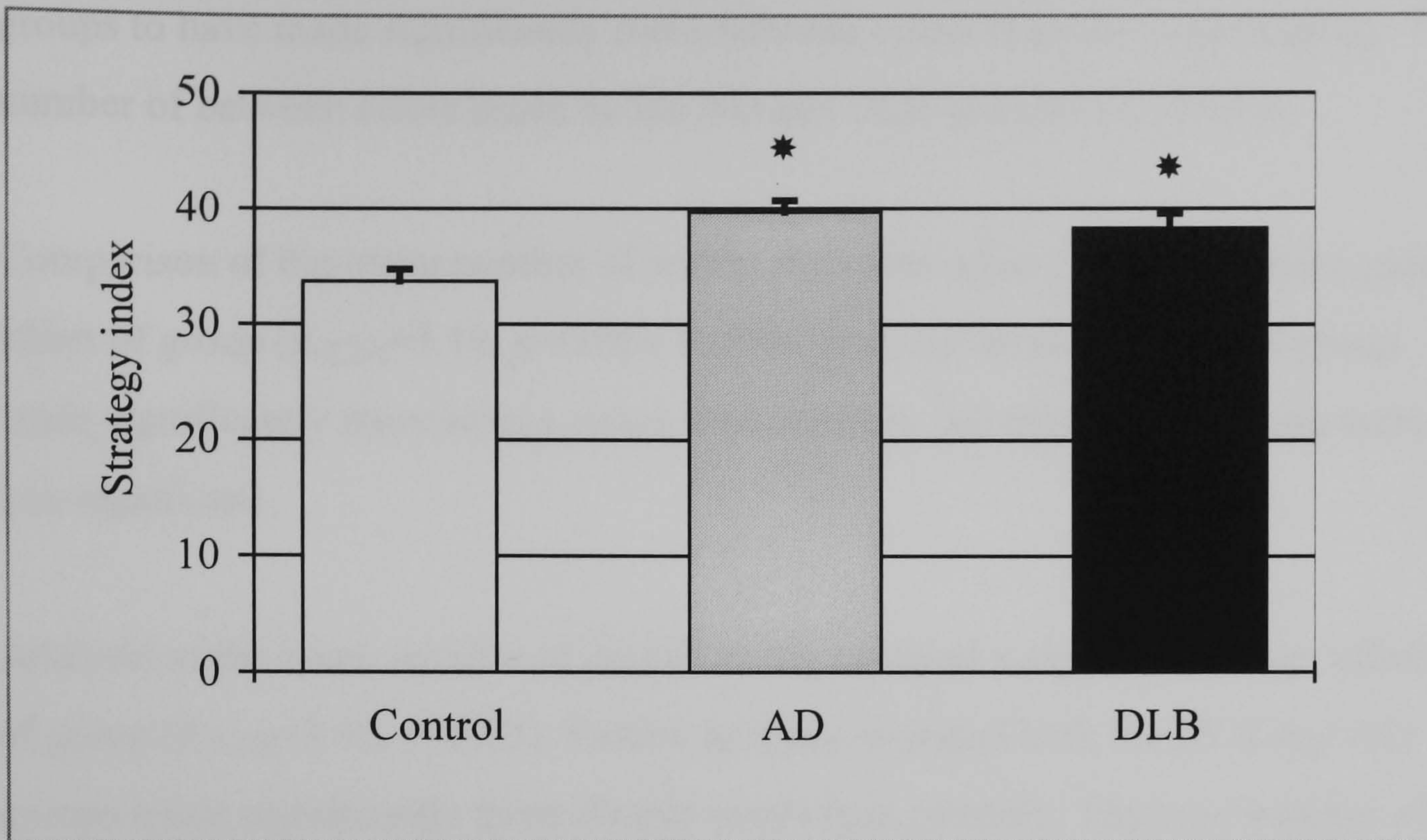
Data for the spatial working memory task is presented for set sizes 6 and 8 only. The strategy index, the total number of between, within and double errors, and the total time to complete levels 6 and 8 is presented in Table 4.13 and Figure 4.20.

Table 4.13: Spatial working memory: mean strategy index (\pm SEM), mean total number of between, within and double errors (\pm SEM) and mean time to complete levels 6 and 8 (\pm SEM).

	Mean strategy index	Mean total between errors	Mean total within errors	Mean total double errors	Mean total response latency (S)
Control (n=10)	33.7 (± 1.07)	32.9 (± 6.39)	0.6 (± 0.31)	1.1 (± 0.46)	517 (± 251)
AD (n=7)	39.7 (± 0.99)	68.6 (± 3.66)	3.14 (± 0.51)	10.4 (± 2.77)	1028 (± 1378)
DLB (n=6)	38.3 (± 1.26)	69.0 (± 5.11)	6.5 (± 3.61)	13.0 (± 7.15)	1592 (± 3034)

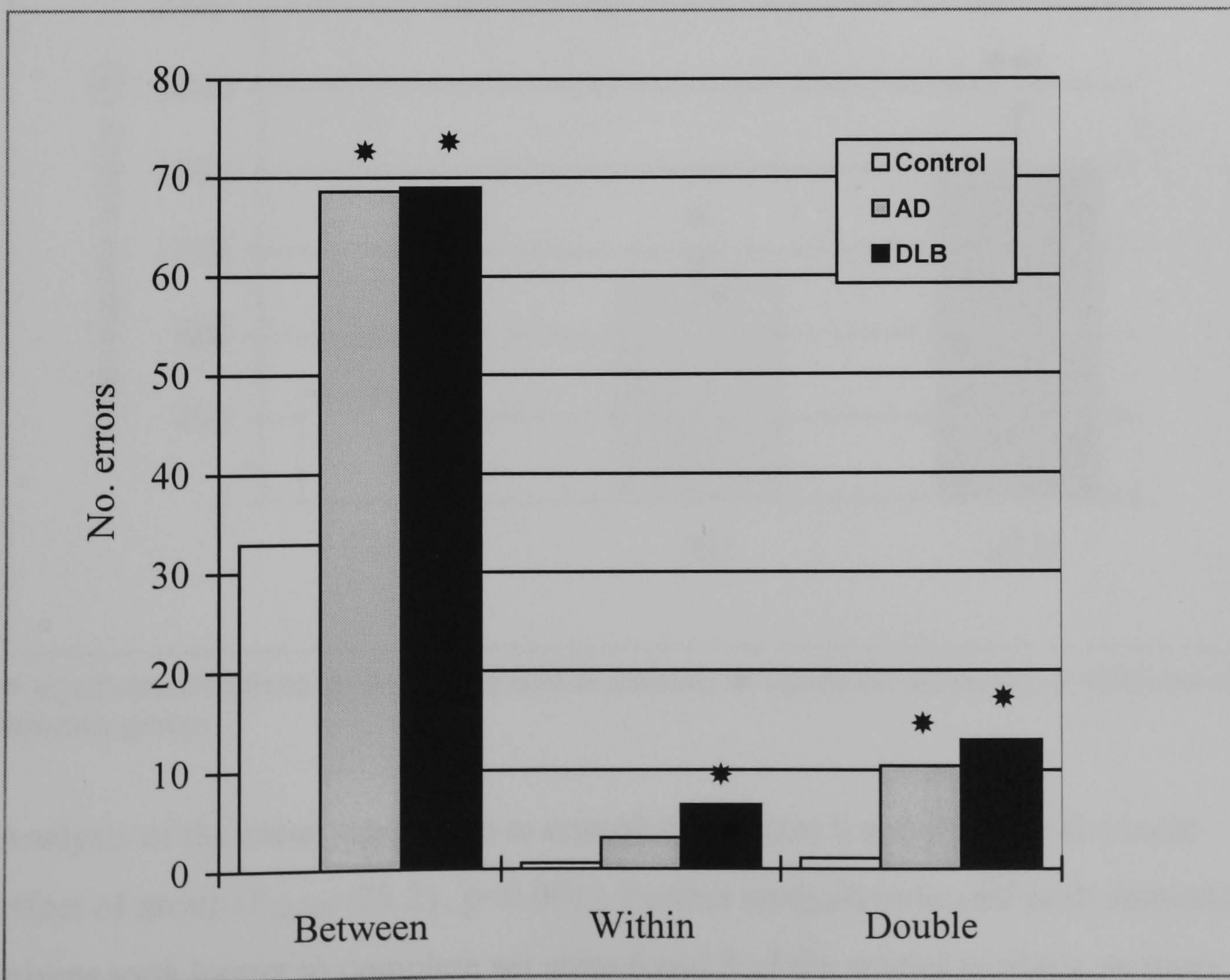
Analysis of variance revealed a main effect of group ($F_{(2,20)}=8.88$, $p=0.002$). Subsequent analysis indicated both dementia groups had a worse (higher) strategy index than controls, but the AD and DLB groups were not different from each other.

Figure 4.20: Spatial working memory: mean strategy indices (\pm SEM) for control (n=10), AD (n=7) and DLB (n=6) groups.



* significant difference ($p < 0.05$) compared to controls

Figure 4.21: Spatial working memory: mean number of between, within, and double errors at set sizes 6 and 8 for control (n=10), AD (n=7) and DLB (n=6) groups.



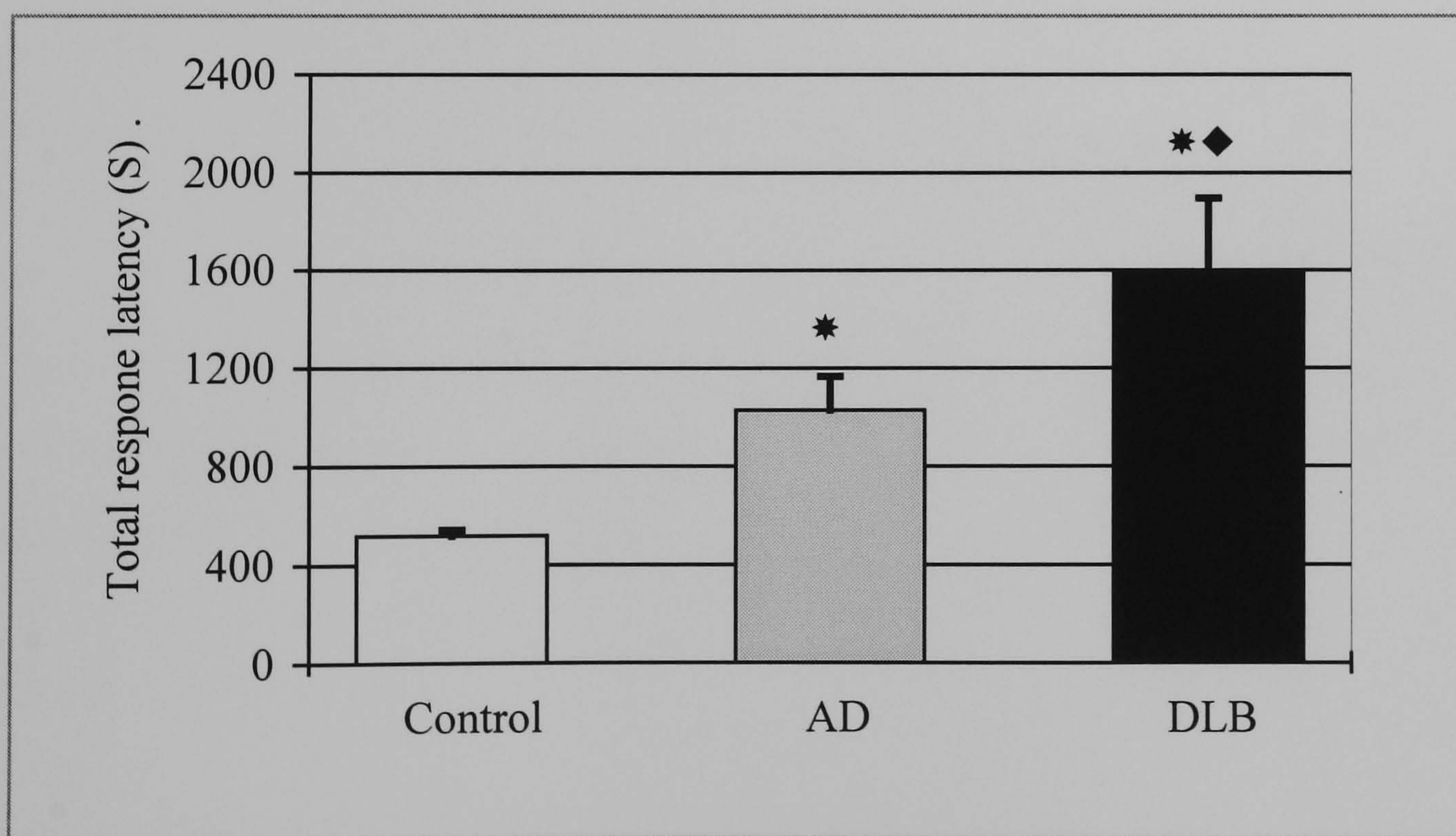
* significant difference ($p < 0.05$) compared to controls

Analysis of the number of between errors revealed a significant main effect of group ($F_{(2,20)}=14.49, p<0.001$). Further analysis revealed both of the dementia groups to have made significantly more between errors than the control group. The number of between errors made by the AD and DLB groups was similar.

Comparison of the mean number of within errors revealed a trend towards a main effect of group ($F_{(2,20)}=3.19, p=0.06$). Further analysis revealed the DLB group made significantly more within errors than controls. All other comparisons were non significant.

Analysis of the mean number of double errors revealed a significant main effect of group ($F_{(2,20)}=3.45, p=0.05$). Further analysis revealed both the DLB and AD groups made significantly more double errors than controls. The total number of double errors were similar for the AD and DLB groups.

Figure 4.22: Spatial working memory: mean total response latencies (seconds) (\pm SEM) at set sizes 6 and 8 for control (n=10), AD (n=7) and DLB (n=6) groups.



* significant difference ($p<0.05$) compared to controls; ♦ significant difference ($p<0.05$) between dementia groups

Analysis of the mean time taken to complete set sizes 6 and 8 revealed a main effect of group ($F_{(2,20)}=25.21, p<0.001$). Further analysis indicated both dementia groups took longer to complete set sizes 6 and 8 of the spatial working memory

task than the control group. In addition the DLB group took longer to complete set sizes 6 and 8 than the AD group.

4.2.4.3 Tower of London.

Analysis was not undertaken on data from the Tower of London task, as only one DLB and three AD cases were able to complete the task.

Chapter 5:

A comparison of cognitive deficits in AD, DLB, and elderly controls using the Cambridge Neuropsychological Test Automated Battery (CANTAB): Discussion.

5.1 Introduction.

This study compared cognition in a cohort of DLB, AD and non-demented elderly controls. In the main, findings from this study replicated those from a series of studies by Sahgal and colleagues (Sahgal et al, 1992a; 1992b; 1992c; 1995; Galloway et al, 1992).

Control, DLB and AD groups were matched for estimated pre-morbid IQ (NART), and the dementia groups were matched for overall level of cognitive impairment (CAMCOG), and measures of daily living skills (ADL, and IADL). Findings from subsections of the CAMCOG are not discussed in detail in this section, as a more substantial comparison is reported in chapters 7 & 8. The AD group were older than both the control and DLB groups. However, the control and DLB groups were of a similar age.

The control group performed significantly better than both dementia groups on practically all indices of performance in the CANTAB battery, thus demonstrating the sensitivity of the CANTAB battery to the neuropsychological deficits associated with dementia, as well as the global nature of the cognitive impairment apparent in dementia.

However, the comparison between the Alzheimer's disease and DLB groups is of primary importance for this study, and this is discussed in more detail in the following sections.

5.2 Individual CANTAB tests: comparison with previous studies and implications of findings.

5.2.1 CANTAB motor screening.

On the motor screening task both AD and DLB groups responded following similar latencies, although both took longer to respond than the control group. Pointing accuracy was equivalent for all groups. The similar response latencies and pointing accuracy on the motor screening task in the Alzheimer's disease and DLB groups suggests that differences observed on other CANTAB tests between the groups, were not due to difficulties in executing the motor components of the tasks.

Galloway et al (1992) also found both SDLT and AD groups to have longer response latencies than the control group, although pointing accuracy in the SDLT group was less accurate than controls (but not the AD group). However, the magnitude of this difference was deemed too small (< 0.5 cm) to adversely affect performance on the CANTAB procedures, because the responses required were to stimuli which are relatively large compared to the observed difference in pointing ability.

Although the motor screening test assesses the ability to respond to tasks requiring relatively simple motor response patterns, the DLB and AD groups may not have demonstrated equivalent motor abilities on tests which required more complex motor response patterns. Typically, DLB patients show neurochemical and neuropathological changes in basal ganglia structures (Langlais et al, 1993; Perry, E. et al, 1993b), which are strongly implicated in the integration, sequencing and execution of complex motor programmes (Marsden, 1982). Further, previous studies have shown DLB patients have problems when complex grapho-motor responses are required (e.g. Gnanalingham et al, 1997; Hansen et al, 1990), although it is difficult to dissociate the motor and cognitive components of these tasks. Thus, although findings from the motor screening task imply equivalent motor abilities in the dementia groups, extrapolation of these findings to tasks

requiring more complex motor response programmes should be made with caution.

5.2.2 CANTAB visual memory battery.

5.2.2.1 Pattern and spatial recognition.

The pattern recognition task is a test of visual recognition memory and is sensitive to temporal lobe damage. The pattern recognition task discriminated the dementia groups, with the DLB recognising more patterns than the DLB group, who actually performed at chance levels. These data suggest less severe impairment of visual pattern recognition memory in the DLB group.

In the study conducted by Galloway et al (1992), AD and SDLT groups showed equivalent impairment on the pattern recognition task. Galloway and colleagues suggested that the failure to dissociate DLB and AD groups on this task may have represented a floor effect for both dementia groups, although analysis supporting this assertion was not reported.

Response latencies for the pattern recognition task were equivalently increased in the dementia groups compared to the control group, and is concordance with the Galloway et al (1992) study. This implies that differences in general responsiveness were not responsible for the inferior accuracy of the AD group compared to the DLB group in the pattern recognition task.

The spatial recognition task assesses the ability to retain spatial information. Both dementia groups showed equivalently impaired performance for percent correct responses. Further analysis indicated that the DLB group performed at above chance levels, whilst the AD group were experiencing floor effects. The floor effects seen in this test may have reduced the power of the test to discriminate dementia groups. Galloway (unpublished thesis) found that the AD and DLB groups responded with similar accuracy, although no analysis of possible floor effects was reported.

The ability to recognise visually presented abstract patterns is relatively more preserved in the DLB group and is in agreement with a number of studies finding less mnemonic impairment in DLB than Alzheimer's disease (e.g. Walker et al, 1997; McKeith et al, 1992c). These findings imply less severe temporal lobe disruption in the DLB group. This assertion is in concordance with neuropathological findings which suggest a smaller burden of pathology in the temporal lobe, and in particular hippocampal structures in DLB than in AD (Dickson et al, 1991).

5.2.2.2 Simultaneous and delayed matching to sample (S/DMTS).

The simultaneous and delayed matching to sample task quantifies the ability to recognise and select a stimulus from an array of 'choice' stimuli in a manner which allows performance to be analysed with respect to delay.

At simultaneous matching the AD and control groups showed similar performance. However, the DLB group made fewer correct responses than both control and AD groups. Simultaneous matching to sample requires the participant to select one of four choice stimuli whilst the 'to be remembered' pattern remains visible to the participant. Thus, simultaneous matching has no mnemonic burden and acts as a measure of problems, such as visuo-perceptual or attentional dysfunction, in completing the task. These data showed that the DLB group were not as able as the control and AD groups to meet the fundamental requirements of the task.

As expected from previous work, introduction of a delay between presentation of the 'to be remembered' and 'choice' stimuli demonstrated a main effect of delay. More interestingly, a main effect of group was also identified, such that the DLB group made fewer correct responses than the AD group, who in turn made fewer correct responses than the control group. Analysis indicated floor effects in the DLB group for all delays, and in the AD group for the longest delay (12 seconds) but not for shorter delays (0 & 4 seconds). The poor performance of the DLB

group must be interpreted with reference to the similarly worse performance of the DLB group in the simultaneous matching task. Task-specific problems identified at simultaneous matching cannot be distinguished from the 'apparent' mnemonic deficits *per se* in the DLB group.

As mentioned above, the AD group were not impaired with respect to the control group at simultaneous matching. The reduced ability of the AD, compared with the control group, to recognise and select the 'to be remembered' pattern with the introduction of increasing delays can therefore be attributed to mnemonic deficits.

Response latencies in the matching to sample task were similarly increased for both dementia groups compared to the control group. Differences in performance in the DMTS task cannot therefore be attributed to a speed - accuracy trade off.

Sahgal et al (1992b) also found the DLB group performed worse than both AD and control groups in the delayed matching to sample task. Unlike the current study, performance at simultaneous matching to sample was similar for all three groups, although means were in a similar pattern to those recorded in the current study. Data for simultaneous matching to sample from the Sahgal et al (1992b) study were subsequently revisited and a trend ($0.1 > p > 0.05$) towards worse performance of the DLB compared to AD and control groups was observed.

These data suggest the S/DMTS test is highly sensitive to cognitive decline in dementia, particularly in DLB. Caution is required, however, in the causal attribution of the particularly poor performance by the DLB group. The non-mnemonic problems associated with the DLB group's performance on this task can only be implied from the interpretation of findings from other tests. For example, pattern recognition was less impaired in DLB than AD groups (see Section 5.2.2.1), which is contrary to the 'apparent' worse mnemonic impairment of the DLB group recorded in the matching to sample task.

The floor effects experienced by both dementia groups in this task indicate a decreased sensitivity of the task to discriminate between the dementia groups. Use

of the DMTS task in future investigations of dementia patients requires a review of task difficulty and the implementation of amendments to make the task easier.

5.2.2.3 Conditional learning: pattern-location paired associates.

On the pattern-location paired associates learning task, the AD and DLB groups achieved set sizes smaller than the control group. However, there was no difference in the set size achieved between dementia groups. The total number of trials to completion (including correction for set sizes not attempted) made for all trials was greater in both dementia groups than controls. Furthermore, the DLB group made more errors overall than the AD group. The ability to retain pattern-location paired associates is similar for both dementia groups. However, the DLB group required more trials to learn these associations than the AD group.

The mean response latencies for the dementia groups were longer than the control group. In addition, the DLB group took longer to respond than the AD group. The combination of longer response latencies and more trials to completion in the DLB compared to AD group, supports an impaired conditional learning ability in the DLB group. Findings from the current study follow a similar pattern to those reported by Galloway et al (1992).

The conditional learning paradigm is similar to a test of object place memory employed by Smith et al (1981), which was demonstrated to be sensitive to right-sided hippocampal damage. The conditional component of learning in the task is also similar to procedures used by Petrides (1985) which are shown to be especially sensitive to frontal lobe damage. Thus, data from the conditional learning task imply relatively greater involvement of frontal and temporal lobe structures in DLB than AD.

However, neuropathological (Dickson et al, 1991) and neuropsychological (see Section 5.2.2.1; Walker et al, 1997) findings suggest less medial temporal lobe involvement in DLB than AD. Furthermore, there may be greater frontal involvement in the poor performance of the DLB group on the conditional

learning paradigm, as dopamine is markedly depleted in the striatum in DLB (Langlais et al, 1993; Perry, E. et al, 1993b). The explanation for this is that the striatum forms an integral part of the intimate circuitry linking the striatum to frontal lobe structures, via parallel, segregated cortico-striatal loops that feed back via the pallidum and thalamus to the frontal cortex (Alexander et al, 1986). Disruption of fronto-striatal circuitry may produce cognitive impairments which are similar to the effects of lesions to the respective targets in the frontal lobe (Owen et al, 1992). It is therefore tempting to speculate that the basis of the poor performance of the DLB group on the conditional learning task may be primarily related to dysfunction of frontal lobe structures and associated circuitry.

5.2.3 CANTAB attentional battery.

5.2.3.1 Circle discrimination.

This simple discrimination task assesses the ability to follow a rule and to switch rules when requested, and acts as screening for the intra / extra-dimensional set shifting task. The DLB group made fewer correct responses than both the control and the AD groups who performed equivalently. Despite making more errors than both AD and control groups, the DLB group responded correctly in 97% of trials. Furthermore, all DLB cases achieved criterion for the subsequent intra / extra-dimensional set shifting task.

5.2.3.2 Intra / extra-dimensional set shifting.

The intra / extra-dimensional (ID/ED) set shifting task assesses complex aspects of attentional ability; requiring the participant to selectively respond to certain stimuli following a rule, and to switch attentional set and follow a novel rule when required. The ID / ED set shifting task is analogous to the Wisconsin card sorting task which, has been shown to be sensitive to dorsolateral frontal lobe lesions (Milner, 1964).

The intra / extra dimensional set shifting task did not discriminate between the dementia groups. However, both dementia groups achieved lower stages than controls. This pattern was similar to that reported by Sahgal et al (1992a) except none of the SDLT cases in the Sahgal et al (1992a) study progressed beyond the IDS stage, one of the DLB cases successfully completed the whole task in this study. Sahgal and colleagues suggest on the basis of these data, and in combination with findings from the visual search matching to sample task, that DLB cases have more severely degenerated fronto-striatal circuitry than the DLB group. This is supported by neuropathological and neurochemical abnormalities described in DLB (Perry, E. et al, 1990a: 1990b; Perry, E. et al, 1992).

In view of the greater fronto-striatal involvement in DLB proposed by Sahgal and colleagues and the similar assertion made in this discussion (see Section 5.2.2.3), it would be predicted that the DLB group would perform less well than the AD group on the ID/ED set-shifting task. However, statistical analysis failed to discriminate the AD and DLB groups in either of the studies to date, although the mean set size achieved by each group was in the predicted order (Control > AD >DLB). A possible explanation for the failure to discriminate AD and DLB groups may be in the design of the tasks. Patients who fail to reach criterion at each stage are automatically excluded from analysis. Thus statistical analysis is restricted to less powerful, non-parametric procedures, which may be of particular interest when small experimental groups are compared.

5.2.3.3 Five choice serial reaction time.

Data from the five choice serial reaction time task indicated that the AD group had longer reaction latencies than both DLB and control groups, who responded following similar latencies. Movement latencies were similar for all groups. Comparison of total response latencies indicated that both dementia groups took longer to respond than controls, but there was no difference between dementia groups.

Of particular note, however, is the finding that only three DLB patients achieved criterion at stage 2 of the task. Statistical analysis was restricted to just 3 DLB cases. Patients who failed to reach criterion at stage two of the task, by definition, responded more slowly and less accurately than those who achieved criterion. There is therefore a strong probability that DLB cases not reaching criterion represent those cases with slow reaction latencies and poor response accuracy.

Hence the results described above are difficult to interpret, as exclusion of cases who found the task difficult in earlier stages (particularly in the DLB group) will selectively sample those cases able to competently perform the task. Thus the differences found on this task should not have too much weight placed upon them.

5.2.3.3 Visual search matching to sample.

The Visual Search Matching to Sample (VSMTS) procedure assesses focal attentional abilities. In the VSMTS task, the DLB group made less correct responses at all set sizes than both AD and control groups, who performed equivalently throughout. The group by set size interaction term was not significant, indicating that increasing set size did not disproportionately affect any particular group. However, response latencies were greater for both dementia groups than controls. In addition the DLB group took longer to respond than the AD group. The DLB group were thus impaired compared to the AD group on both indices of performance in the VSMTS task.

The ‘apparent’ visual focal attention dysfunction in DLB compared to both control and AD groups, is confounded by the finding that the DLB group were impaired even at a set size 1. Set size one acts as a control for task specific problems with the task, such as visuo-perceptual problems or failure to comprehend the task instructions. Thus the poor performance of the DLB group in this task may be mediated by specific difficulties with the VSMTS procedure, such as visuo-perceptual or motor problems, or a basic failure to sustain attention.

Data from the current study partially replicate those of Sahgal et al (1992a), in that both studies found AD and control group performance were similar for all set sizes and the DLB group were impaired at set sizes 4 and 8. Nonetheless, the earlier study did not find any differences between groups at set sizes 1 and 2, which suggested the DLB group were able to perform the VSMTS task. Sahgal and colleagues suggested that qualitative differences exist between the DLB and AD groups in terms of focal attentional ability, and that this was due to damage to fronto-striatal circuitry.

Although the current study also found impairments on the VSMTS task, the more impaired performance of the DLB group at the smallest set size means interpretation of the cognitive basis of poor performance of the DLB group at larger set sizes is equivocal. Notwithstanding the possible contribution of non-mnemonic problems to performance on the VSMTS task, the performance of the DLB group was qualitatively distinct from both AD and control groups.

5.2.4 Working memory and planning battery.

5.2.4.1 Spatial span.

The spatial span task assesses spatial working memory, and is a computerised version of the Corsi block tapping test (Milner, 1971). Both dementia groups achieved shorter spans than the control group, and, in addition, the spatial span for the DLB group was significantly shorter than for the AD group. This suggests that spatial span is relatively more preserved in AD than DLB. However, while Sahgal

et al (1995) found both dementia groups achieved a shorter spatial span than the control group, they also found no difference between AD and DLB groups. These findings are difficult to interpret and require replication with a larger cohort of Alzheimer's disease and DLB patients.

5.2.4.2 Spatial working memory.

On the spatial working memory task, which assesses spatial working memory and requires the application of efficient search strategies for effective completion, both dementia groups had equivalently higher (worse) strategy indices than controls. The number of between and double errors was significantly greater in both dementia groups compared to control, although the number of between errors made by the AD and DLB groups was similar. The DLB group made more within search errors than the AD and control groups who made a similar number of errors, although the number of within search errors was still relatively small. In addition, the DLB group took longer than both AD and control groups to complete the task. The DLB group took three times longer (almost 27 minutes) than the control group, and one and a half times as long as the AD group to complete the task.

These findings, although similar to those reported by Sahgal et al (1995) do not exactly replicate their findings. Sahgal and colleagues found no differences between AD, DLB and control groups with respect to the strategy index employed in this study. A novel index, which focused on within search errors, dissociated dementia groups from the control group, but not from each other. The two strategy indices assessed similar aspects of spatial working memory ability, although the between search index measures the retention of spatial information over a longer delay, and is more susceptible to possible interference from intervening searches.

The types of error made by the different groups reported by Sahgal and colleagues also differs from the present study. The earlier study suggested that the DLB group made more between search errors than the AD group, who also made more

between search errors than the control group. In addition the DLB group made more errors than both AD and control groups.

These data further illustrate that both dementia groups show deficits in spatial working memory. The DLB patients performed significantly worse on one of three measures of performance accuracy than the DLB group, in addition the DLB group were considerably slower than the Alzheimer's disease group.

5.2.4.3 Tower of London.

The Tower of London task proved too difficult for the dementia groups with only one DLB and three AD cases completing the task. Analysis was not undertaken on these cases.

5.3 CANTAB study: General discussion.

This study compared the AD and DLB dementia groups on most tasks from the CANTAB battery and demonstrated distinct profiles of performance for the AD and DLB groups. On the majority of tasks where differences were observed between dementia groups, the performance of the DLB group was more impaired than that of the AD group (simultaneous and delayed matching to sample; conditional paired associates learning; circle discrimination; visual search matching to sample; spatial span; and spatial working memory). However, the DLB group was less impaired than the AD group on the pattern recognition task. In addition, the AD group took longer to release the switch in the five-choice serial reaction time task than the DLB group although data from this task should be interpreted with caution, as only three DLB cases completed the task. Equivalent performance of AD and DLB groups were observed on the motor screening, spatial recognition and intra / extra-dimensional set-shifting tasks.

Comparison of cognitive function using the CANTAB battery has demonstrated a double-dissociation between AD and DLB groups. This strongly implies that DLB

and AD show distinct profiles of cognitive impairment, and that the differences between AD and DLB groups were not attributable to problems with matching populations. Likewise, this pattern of deficits is highly unlikely to be attributable to the observed age differences between groups. Moreover, observed differences between groups, such as an inability to understand task instructions in one group, cannot be attributed to problems which generalise to all tasks. This assertion is further supported by the finding that all groups showed similar language comprehension ability in the CAMCOG schedule.

Nonetheless, certain tasks may be differentially susceptible to cognitive deficits not directly measured by the CANTAB battery. As the pattern recognition and matching to sample tasks both examine short term, non-verbal, visual recognition memory, it might be expected that both groups would perform similarly on these two tasks. However, the DLB group perform better on the pattern recognition task than the AD group, while the opposite was true for the simultaneous / delayed matching to sample task. This apparent discrepancy in findings from tasks which, purport to measure similar aspects of mnemonic function, can possibly be explained by considering specific attributes of the respective tasks. Firstly, the simultaneous / delayed matching to sample test duration is approximately 20 minutes compared to 2/3 minutes required to complete the pattern recognition test. The longer duration of the simultaneous / delayed matching to sample task may adversely affect the DLB group, on the basis that the DLB group may be less able than the AD group to sustain attention as clouding of consciousness and fluctuations in alertness are common in DLB (McKeith et al, 1992c, 1996a). Such an inability to sustain attention for the necessary period required to complete the matching to sample task may represent the non-mnemonic impairment of performance identified at simultaneous matching to sample in the DLB group.

Most of the previous studies investigating mnemonic performance in DLB have identified equivalent (Hansen et al, 1990) or better mnemonic performance in the DLB compared to AD groups (McKeith et al, 1992c; Connor et al, in press; Ballard et al, 1996b; Walker et al, 1997). Less severe impairment of visual recognition memory in DLB was identified using the pattern recognition task (see

Section 5.2.2.1). In view of these findings, the earlier assertion that the worse performance of the DLB group on the simultaneous and delayed matching to sample task is due to task-specific confounds is supported. Moreover, no aspect of cognition stands in isolation, and the interdependence of different cognitive processes has been highlighted.

Performance on the spatial working memory and spatial span tasks (which also examines spatial working memory) was more severely impaired in the DLB group compared to the AD group. However, the DLB and AD groups performed equivalently on the spatial recognition task. Furthermore, the DLB group required more trials to learn visuo-spatial associations in the paired associates learning task, although the DLB group were able to eventually remember similar numbers of paired associates to the AD group. These data strongly suggest that impaired visuo-spatial ability in the DLB group is not due to an inability to store and recognise spatial locations *per se*, but is due to difficulties in learning and manipulating ‘on-line’ visuo-spatial information.

5.3.1 Summary.

The results of this study reveal distinct patterns of impairment in carefully matched patients with DLB and AD. Visual pattern recognition memory appears to be relatively preserved in DLB, whilst visuo-spatial working, but not recognition, memory is more disrupted in the DLB group. In addition, matching to sample procedures with and without a mnemonic burden have demonstrated qualitatively distinct performance in the DLB group, although non-mnemonic deficits appear, at least, to contribute to the observed poor performance.

The double-dissociation, between the neuropsychological performance of the dementia groups on subtests of the CANTAB battery, support previous studies suggesting that DLB cases represent a subgroup of dementia patients which may be distinguished from AD patients by neuropsychological assessment.

Chapter 6:

A comparative study of cognitive performance in DLB, AD, and elderly controls using the Cognitive Drug Research Computerised Assessment Battery (CDR): Methods.

6.1 Introduction.

This chapter describes the methods for a comparative study of cognitive performance in a large cohort of DLB, AD, and elderly controls using the Cognitive Drug Research (CDR) Computerised Assessment Battery.

The CDR battery of tests was originally designed to provide an instrument that could be used to detect alterations in the efficiency of cognitive functioning in various participant and patient groups. The aim was to provide sensitive, reliable and precise measures of the effect of pharmaceutical compounds upon cognitive and motor function using tests of human performance. The CDR system has been widely used by groups throughout Europe and North America to study a wide variety of compounds and clinical populations. Examples of the research relevant to the present thesis include: the effects of scopolamine on human cognitive function (Wesnes et al, 1988a; 1988b); the reversal of the effect of scopolamine on cognitive performance (Wesnes et al, 1987; 1990a; 1990b; 1991); smoking and nicotine administration (Parrot et al, 1989; 1990; 1992); Alzheimer's disease (Mohr et al, 1996; Goa et al, 1997); and Huntingdon's disease (Mohr et al, 1996).

6.2 Participants.

See General Methods section (Chapter 2) for details of recruitment and standardised assessment of cases.

Participants included 26 elderly controls, 46 AD patients (24 probable AD, 22 possible AD) diagnosed according to NINCDS-ARDRA criteria

(McKhann et al, 1984), and 24 DLB patients (20 probable DLB, 4 possible DLB) diagnosed according to consensus criteria (McKeith et al, 1996a). All participants attempted the entire battery of tests, although some, more severely demented cases, were unable to complete the whole battery. The number of participants completing each CDR task is outlined in the relevant sections.

6.3 Materials and apparatus.

The CDR battery was installed on a portable microcomputer (Carry I 5320 series) and presented on a portable LCD screen (Datalux, 195 mm wide by 143 mm high) as previously described (see Section 3.3). Participant responses were recorded via modules containing two non-latching buttons, one marked 'NO' and the other 'YES', connected to the games port of the computer.

Data from each participant was stored on two floppy discs with coded participant identification details as well as on the hard drive of the portable microcomputer. The experimenter was not able to access these data.

6.4 Procedures.

6.4.1 Non-computerised psychometric assessment.

The following psychometric tests were administered to all participants: the National Adult Reading Test (NART) (Nelson, 1982); the CAMCOG schedule (Roth et al, 1986); and the Cornell Depression Scale (Alexopoulos et al, 1988). These tests are described in detail in the General Methods section (Chapter 2). Patient groups also underwent a standardised psychiatric evaluation, as described in the General methods section.

6.4.2 Computerised assessment using the CDR battery.

A version of the CDR battery specially designed for use in an elderly or demented population was employed in this study, which included a selection of tasks from the CDR Computerised Cognitive Assessment System. The CDR battery was administered at the place of residence of the participant. Procedures outlined in the General Methods section were employed to minimise any changes in testing environment.

A log book of performance was completed for each participant, which included details of any unusual occurrences during testing, such as: pausing tests if the participant became distracted, confused or distressed; the use of thumbs (rather than their index fingers) on the response module. The log was subsequently used in the interpretation of data points unrepresentative of a participant's performance.

Prior to cognitive assessment, participants were introduced to the computer screen and response module. The computer automatically requests that the experimenter depress both buttons in turn on the response module to ensure the response module is functioning correctly before testing can begin.

All participants received training on the use of the response module, and the following instructions were given:

“You will be communicating with the computer by using the two buttons in front of you. The left, black button is the ‘NO’ button and you should place your left index finger on this button. The right, red button is the ‘YES’ button and you should place your right index finger on this button”

If the participant was unable to place their fingers (or thumbs) on the buttons due to physical disability, a note was made in the log book. In these exceptional circumstances the response module was operated by the experimenter and response latencies disregarded. Only one participant was unable to use the response module. Participants were trained in the use of the response module by

completing the choice reaction time (CRT) task (see Section 6.4.2.7), but without emphasising the need for rapid responding. All data from this practice CRT were disregarded. If after initial training, the participant was not able to utilise the response box correctly, the practice choice reaction time task was repeated. Appropriate use of the response buttons was monitored by the experimenter throughout the assessment session.

When the participant was able to competently use the response buttons, the test session began.

If the participant's attention wandered from the screen (with the exception of during the digit vigilance task; see Section 6.4.2.6), the task was paused by pressing the 'ENTER' key. When the participants attention was again focused on the screen, the task was resumed with the stimulus that was on the screen prior to pausing the task. This event was recorded in the log book.

6.4.2.1 Word presentation.

The following instructions were read to each participants:

“A series of 12 words will appear on the screen, one at a time. Please read aloud, with me, each word as it appears on the screen. Try to remember the words as you will be asked to recognise them later on.”

The word presentation was then initiated by the experimenter, and 12 words were serially presented on the monitor at the rate of 1 every 3 seconds. The words remained on the screen for 2.5 seconds and there was a pause of 0.5 seconds between words.

The word list was composed of 5 AA words (frequency of 100 or over per million), 3 A words (frequency of between 50 and 100 per million) and four words of relatively high frequency. The list was balanced to have approximately the same fairly high overall imaginability and consisted of seven 1 syllable words,

four 2 syllable words, and 1 three syllable word. Asking the participant to read each word aloud ensured the participant was attending to the stimuli.

6.4.2.2 Immediate word recognition.

This task measures the ability to store and retrieve verbal information, being a measure of episodic secondary verbal recognition memory. The immediate word recognition task directly followed the presentation of the ‘to be remembered’ words. The following instructions were read to each participant:

“You will again see a list of words one at a time on the screen. For each word, if you think that it is one of those you have just seen, you should press the ‘YES’ button as quickly as you can, but if you do not remember seeing the word just now, you should press the ‘NO’ button as quickly as you can”

The experimenter stressed the importance of making the decision and response as quickly as possible, but not at the expense of making errors. The task was subsequently initiated by the experimenter and 24 words were presented. Twelve of the words presented were from the list presented in ‘word presentation’. These were represented in a random order and interspersed with 12 novel distracter words. The list of 12 novel words were created in the same manner as described above (Section 6.4.2.1).

Although equal numbers of original and novel words were presented, participants were only informed that they would see ‘some of the words originally presented’. This eliminated ongoing feedback about memory performance to reduce stress and improve participant compliance. Participants responded ‘YES’ / ‘NO’, to indicate whether they remembered seeing each word in the original list. The words remained on the screen until the participant responded.

Participants had to respond within a window of between 0.25 seconds and 30 seconds for the response to be recorded. Responses made outside this window were disregarded and the word presented prior to the response was represented.

Following a response from the participant there was a 1 second pause prior to presentation of the subsequent word.

6.4.2.3 Picture presentation.

The following instructions were read to each participant:

“A series of 14 pictures will appear on the screen, one at a time. Please look at each picture carefully as it appears and try and remember as many as you can. We will come back to them a little later on.”

The picture presentation was then initiated by the experimenter. A series of 14 pictures were presented on the monitor at the rate of 1 every 4 seconds for the participant to remember. Each picture remained on the screen for 3 seconds and was followed by a 1 second pause, prior to presentation of the next picture.

The fourteen pictures consisted of one each of the following categories: animals; buildings; food; general transport; household items; interiors; jewellery; kitchen items; landscapes; outside items; road transport; sport; tools; toys.

6.4.2.4 Face presentation.

The following instructions were read to each participant:

“A series of 14 pictures of people’s faces will appear on the screen, one at a time. Please look at each face carefully as it appears and try and remember as many as you can. We will come back to them a little later on.”

The face presentation was then initiated by the experimenter. A series of 14 faces were sequentially presented on the monitor at the rate of 1 every 4 seconds for the participant to remember. Each face remained on the screen for 3 seconds and was followed by a pause of 1 second prior to presentation of the next face. The faces

presented were balanced for sex, age group and backdrop (either a brick wall or an open landscape).

6.4.2.5 Simple Reaction Time (SRT).

This task measures reaction time and assesses the participant's ability to concentrate on the screen, and the speed of reaction to an expected event.

The experimenter instructed the participant to place their right index finger on the 'YES' response key, and remove their left finger from the 'NO' response key. All participants were then given the following instructions:

“Every time you see the word ‘YES’ on the screen, you should press the ‘YES’ button as quickly as possible”

The experimenter stressed the importance of making the response as quickly as possible. The SRT task was then initiated by the experimenter pressing the 'ENTER' key. A series of 20 stimuli ('YES') were presented on the screen with a random and varying inter-stimulus interval of between 1 second and 2.5 seconds. Subsequent trials were only presented following a response to the previous trial. The participant had to respond within the window of 0.1 seconds and 30 seconds for the data to be recorded.

6.4.2.6 Digit vigilance.

This task assesses the ability to sustain an attentional focus and ignore distraction. The experimenter instructed the participant to place their right index finger on the 'YES' response key, and remove their left finger from the 'NO' response key. All participants received the following instructions:

“A number will appear on the right hand side of the screen and then remain there.”

The experimenter then pressed the 'ENTER' key to initiate the presentation of the target digit. A target digit was pseudo-randomly selected and displayed on the right of the monitor screen for the whole duration of the task. The experimenter then gave the following instructions:

“A series of numbers will appear, one at a time, in the middle of the screen. Every time the number in the middle is the same as the number on the right, press the 'YES' button as quickly as possible.”

Once the experimenter was certain the participant had understood the task requirements, the digit vigilance task proper was initiated by the experimenter pressing the 'ENTER' key. A series of 90 digits was serially presented in the centre of the screen at the rate of 80 per minute. Each digit remained on the screen for 0.7 seconds and there was a gap of 0.05 seconds between each digit. The participant was required to press the 'YES' button every time the digit in the series matched the target digit on the right hand side of the screen. There were 15 target digits to be detected in the rapidly changing digits.

As this task measured sustained attentional capability, the task was *not* paused if the participant's attention wandered. If, however, it was apparent the participant had failed to understand the task requirements, the task was terminated and re-started, following further instruction from the experimenter.

6.4.2.7 Choice Reaction Time (CRT).

The choice reaction time task assesses the participant's alertness and ability to concentrate on the screen, as for the simple reaction time task. In addition, the choice reaction time task requires a further element of information processing to enable the participant to identify and select the correct response.

All participants received the following instructions:

“Either the word ‘YES’ or the word ‘NO’ will appear on the screen. Every time you see the word ‘YES’ you should press the ‘YES’ button as quickly as possible. Every time you see the word ‘NO’ you should press the ‘NO’ button as quickly as possible.”

The importance of responding as quickly as possible, but without making errors, was stressed. Once the experimenter was confident the participant had fully understood the instructions, the ‘ENTER’ key was pressed to initiate testing. Twenty stimuli (either the word ‘YES’ or the word ‘NO’) were presented on the screen with a random and varying inter-stimulus interval of between 1 second and 2.5 seconds. The stimuli remained on the screen until the participant responded. The participant had to respond within the window of between 0.15 seconds and 30 seconds for the response to be recorded.

6.4.2.8 Spatial working memory.

This task assesses the ability to temporarily retain and manipulate spatial information.

The following instructions were given to all participants:

“A picture of a house will appear on the screen with nine windows. Four of the windows will be lit and five will be dark. Please try to remember the position of the lit windows”

The experimenter stressed the importance of making the decision and response as quickly as possible, but not at the expense of making errors. The experimenter initiated the spatial memory task. A picture of a house appeared, which remained on the screen for 10 seconds. Four of the nine windows in the house were lit. The participant was required to remember the position of the lit windows. Which four of the nine windows were lit was selected randomly, with the limitation that a combination of the four corner windows was impossible. The following instructions were then given:

“You will see a series of houses appear on the screen one at a time. Each house will have just one window lit. If the window that is lit is one of the four that was lit in the original house you should press the ‘YES’ button as quickly as you can, but if the window was not lit in the original house you should press the ‘NO’ button as quickly as you can”

This was followed by 18 presentations of the house with only one window lit, and the participant was required to indicate whether the lit window was one of the four windows lit in the original presentation. There was a gap of 1 second between the participant’s response and presentation of the next house. The participant had to respond within a time frame of between 0.25 seconds and 30 seconds for the data to be valid. The participant recorded their response by pressing the 'YES' or 'NO' response button as appropriate.

6.4.2.9 Numeric working memory.

The task assesses the ability to hold information ‘on line’ and to rapidly manipulate this information.

The following instructions were given to all participants:

“Please try to remember the three numbers that will now come on the screen one at a time. Say each number aloud to help you remember it.”

The experimenter then pressed the ‘ENTER’ key twice to initiate the display of three pseudo randomly selected numbers. Each number was displayed for 1.15 seconds with a gap of 0.5 seconds between each digit. The experimenter then asked the participant to recite the numbers to ensure they had been remembered. If the participant failed to correctly recite the three numbers, they were represented. Contingent upon the participant correctly reciting the three words, the following instructions were given:

“Now for each number which appears on the screen, you should press the ‘YES’ button if it is one of the numbers you are remembering, and you should press the ‘NO’ button if it is any other number.”

The experimenter stressed the importance of making the decision and response as quickly as possible, but not at the expense of making errors. Once the experimenter was confident the participant had fully understood the instructions, and again verified that the participant could remember the three target numbers, the ‘ENTER’ key was pressed to initiate the next stage of the task. The participant was required to respond to 18 serially presented probe digits. The digits remained on the screen until the participant responded. The participant had to respond with a time frame of 0.25 seconds and 30 seconds for the data to be valid. There was a gap of 0.5 seconds between the participant’s response and the presentation of the next number. The three target digits appeared 3 times each. The participant

recorded their response by pressing the 'YES' or 'NO' response button as appropriate.

6.4.2.10 Delayed word recognition.

This task measures the ability to store and retrieve verbal information, being a measure of cued secondary verbal memory. The delayed word recognition task was presented to the participant approximately thirty minutes after presentation of the 'to be remembered' words. The interval between word presentation and recognition phases depended on the time taken to complete intervening tasks and any breaks requested by the participant.

The following instructions were given to each participant:

“You will again see a list of words one at a time on the screen. For each word, if you think that it is one of those you have just seen, you should press the ‘YES’ button as quickly as you can, but if you do not remember seeing the word just now, you should press the ‘NO’ button as quickly as you can”

The procedure for the delayed word recognition task are the same as for immediate verbal recognition except that the 12 distracter words were drawn from a new list formulated as described previously (see Section 6.4.2.2).

6.4.2.11 Delayed picture recognition.

This task assesses the ability to store and retrieve pictorial information from secondary memory. The delayed picture recognition task was presented to the participant approximately thirty five minutes after presentation of the 'to be remembered' pictures. The interval between picture presentation and recognition phases depended on the time taken to complete intervening tasks and any breaks requested by the participant.

The following instructions were given to each participant:

“Now you are going to see some pictures one at a time on the screen. For each picture, if you think it is one of those you saw earlier and tried to remember, you should press the ‘YES’ button as quickly as you can, but if you do not think that you saw it earlier, you should press the ‘NO’ button as quickly as you can.”

The experimenter stressed the importance of making the decision and response as quickly as possible, but not at the expense of making errors. Once the experimenter was confident the participant had fully understood the task, the ‘ENTER’ key was pressed to initiate testing. Twenty eight pictures were presented containing the original 14 shown in picture presentation (see Section 6.4.2.3) and 14 novel exemplars, one from each of the categories previously described. The two pictures presented from the same category (picture pairings) were relatively distinct (e.g. in the animal category the pairing might be a dog and a horse). The pictures were ordered so that pairings were not shown one after the other. The pictures remained on the screen until the participant made a response and there was a gap of 1 second before the subsequent picture was presented. The window within which participants had to respond was 0.25 seconds to 30 seconds for the data to be valid. Participants responded ‘YES’ / ‘NO’, to indicate whether they remembered seeing each picture in the original list.

The participant was only told that they would see some of the pictures originally presented. This eliminated ongoing feedback about memory performance to reduce stress and improve participant compliance.

6.4.2.12 Delayed face recognition.

This task assesses the ability to store and retrieve pictorial representations of human faces from secondary memory. The delayed face recognition task was presented to the participant approximately forty minutes after presentation of the ‘to be remembered’ faces. The interval between face presentation and recognition phases depended on the time taken to complete intervening tasks and any breaks requested by the participant.

The following instructions were given to each participant:

“Now you are going to see some pictures of faces one at a time on the screen. For each face, if you think it is one of those you saw earlier and tried to remember, you should press the ‘YES’ button as quickly as you can, but if you do not think that you saw it earlier, you should press the ‘NO’ button as quickly as you can.”

The experimenter stressed the importance of making the decision and response as quickly as possible, but not at the expense of making errors. Once the experimenter was confident the participant had fully understood the task, the ‘ENTER’ key was pressed to initiate testing. Twenty faces were presented containing the original 12 shown in face presentation (see Section 6.4.2.4) and 12 novel exemplars made up as previously described. The faces were paired for age, sex and backdrop, and were ordered so that pairings were not shown one after the other. The faces remained on the screen until the participant made a response and there was a gap of 1 second before the subsequent picture was presented. The window within which participants had to respond was 0.25 seconds to 30 seconds for the data to be valid. Participants responded ‘YES’ / ‘NO’, to indicate whether they saw each picture in the original list.

6.4.2.13 Critical Flicker Fusion (CFF).

This task is an indirect psychophysical measure of arousal and attention which determines the frequency at which a participants are able to distinguish a flickering light from a steady light.

The task is sensitive to variables such as the distance between the participant and the CFF box and background illumination. However, attempts were made to minimise variations of these variables. The participant was seated approximately 50 cm from the screen, and the special CFF box was mounted on top of the screen. The CFF box was attached to the parallel port of the computer and had two orange light emitting diodes on the front panel.

The CFF consists of two sections: an initial titration phase followed by the test phase. The initial titration phase establishes a preliminary frequency, using ascending and descending trials.

The participant was instructed to place a single index finger on one of the buttons. Prior to the ascending titration phase, the following instructions were presented on the screen and read aloud by the experimenter:

“In a moment the lights will start to flicker slowly and will start to flicker faster and faster until you can no longer see them flickering. Please press the button when you can no longer see the lights flickering.”

There followed three ascending titration trials. Upon completion the following instructions were presented on the screen and read aloud by the experimenter:

“In a moment the lights will come on steadily. After a short while the lights will start to flicker. Please press the button as soon as you see the lights flicker”

There followed three descending titration trials. The mean frequency at which the participant was able to distinguish a flickering light from a steady light was established by averaging frequencies from all 6 titration trials. This preliminary frequency of the test phase was set at this value. Prior to commencing the test phase, the following instructions were presented on the screen and read aloud by the experimenter:

“Both lights will come on for a short period. One of the lights will be steady and the other will be flickering. Please press the response key which corresponds to the light which was flickering. If you are unsure about which light was flickering just guess.”

The participant was instructed to place both index fingers on the corresponding response buttons. The test phase was then initiated by the experimenter. The two

lights then came on, one of which was a steady light, and the other was flickering at the frequency determined in the titration phase. Whether the flickering light was on the left or the right or the left hand side was determined randomly. The frequency of the flickering light increased by 1 Hz if the participant responded correctly three times in a row. The frequency decreased by 1 Hz if the participant made one incorrect response. There was a gap of 2 seconds between the response of the participant and the subsequent trial.

There were 15 trials to establish the final critical flicker fusion frequency. Reaction time was not recorded for this task, but a response had to be made within the time window of 0.1 seconds to 30 seconds for the response to be recorded.

6.4.2.14 Summary tables of CDR tests: main and secondary outcome measures.

Table 6.1: The CDR battery: tasks and the associated cognitive states and processes assessed

<u>Task</u>	<u>Cognitive States and Processes Assessed</u>
	Attention
Simple reaction time	<ul style="list-style-type: none"> Alertness, power of concentration, primary stage of information processing, motor speed.
Choice reaction time	<ul style="list-style-type: none"> Alertness, power of concentration, primary stage of information processing, motor speed, stimulus discrimination, response organisation.
Digit vigilance	<ul style="list-style-type: none"> Intensive vigilance, ability to ignore distraction.
Critical Flicker Fusion Frequency (CFF)	<ul style="list-style-type: none"> Correlated with alertness and attention, though not itself a direct measure of either.
	Working memory
Digit scanning (numeric working memory)	<ul style="list-style-type: none"> Sub-vocal rehearsal of digit sequences. Articulatory loop sub-system of working memory.
Spatial working memory	<ul style="list-style-type: none"> Ability to temporarily retain spatial information. Visuo-Spatial sub-loop of working memory.
	Secondary memory
Word recognition	<ul style="list-style-type: none"> Ability (speed and sensitivity) to discriminate novel from previously presented words. Episodic secondary verbal recognition.
Picture recognition	<ul style="list-style-type: none"> Ability to discriminate novel from previously presented pictorial information. Episodic secondary non-verbal visual recognition.
Face recognition	<ul style="list-style-type: none"> Ability to discriminate novel from previously presented faces. Episodic secondary face recognition.

Table 6.2: The CDR battery: primary and secondary outcome measures

Task	Primary Measure	Secondary Measure
Immediate word recognition	Recognition sensitivity (SI) Recognition speed (mS)	
Simple reaction time	Speed (mS)	
Digit vigilance	Speed (mS) Percentage of targets detected	False alarms
Choice reaction time	Speed (mS)	Accuracy (%)
Spatial working memory	Scanning sensitivity (SI) Scanning speed (mS)	
Numeric working memory	Scanning sensitivity (SI) Scanning speed (mS)	
Delayed word recognition	Recognition sensitivity (SI) Recognition speed (mS)	
Picture recognition	Recognition sensitivity (SI) Recognition speed (mS)	
Face recognition	Recognition sensitivity (SI) Recognition speed (mS)	
Critical flicker fusion	CFF threshold (Hz)	

Primary variables are variables that, if affected, reflect upon the overall efficiency of the performance of the task. Secondary variables are those which, if affected, will not in themselves reflect on the actual ability to perform the task, but will be important in modulating the interpretation of any changes in the primary variables.

6.5 Statistical procedures.

Data were analysed using the parametric analysis of variance (ANOVA), with or without transformation (proportional data - arcsine; latencies - logarithmic) according to Winer et al (1991), and post hoc analyses were made using the Newman-Keuls pair-wise comparison. A minimum level of significance of $\alpha=0.05$ was adopted. A trend towards significance is reported for p-values of between 0.1 and 0.05.

A signal detection theory index of sensitivity is used for several tasks (see Table 6.2). This non-parametric index (SI) is calculated from formulae presented by Frey & Colliver (1973) and combines the accuracy scores from the original and novel information. The index ranges from 1 (total sensitivity) to -1, with zero representing an absence of sensitivity that is equivalent to chance performance. The sensitivity index was chosen for several reasons. Firstly, the index combines into a single measure the ability to recognise previously presented information and the ability to discriminate this from novel information. Secondly, the index prevents erroneous conclusions about performance based on changes to only one measure. Thirdly, this methodology reduces the total number of variables to be analysed which helps the overall statistical power.

Chapter 7:

A comparative study of cognitive performance in DLB, AD, and elderly controls using the Cognitive Drug Research Computerised Assessment Battery (CDR): Results.

7.1 Intra-group comparison of probable versus possible diagnoses for AD and DLB.

To establish whether probable and possible cases within the AD and DLB groups could be considered as similar, comparisons of demographic variables and neuropsychological deficits were made. Two-sample t-tests were used to compare probable and possible AD cases, and probable and possible DLB cases.

Demographic features and primary outcome measures from the psychometric analyses (age, NART IQ, total CAMCOG score, and all primary outcome measures from the CDR assessment battery) were considered. A summary of findings is presented in Tables 7.1 and 7.2.

The possible and probable AD categories were matched for age, estimated pre-morbid IQ, and overall level of cognitive impairment using the CAMCOG.

Analysis of the main outcome measures for the CDR battery indicated there were no differences in performance between possible and probable AD groups.

Analysis indicated no differences between possible and probable DLB diagnostic categories for age and on measures of estimated pre-morbid IQ (NART) and overall degree of cognitive impairment (CAMCOG). Analysis of performance on all the main outcome measures for the CDR assessment battery indicated no significant differences between possible and probable diagnostic groups. Trends towards significance were, however, demonstrated for several measures of response latencies. There was a trend towards significantly longer reaction times for the probable than the possible DLB groups on immediate word recognition ($t=-2.03$, $p=0.08$), delayed word recognition ($t=-2.09$, $p=0.08$), delayed picture recognition ($t=-2.06$, $p=0.09$), and delayed face recognition ($t=-1.99$, $p=0.08$).

Table 7.1: Comparative analysis of possible and probable diagnostic categories for AD for age and primary outcome measures of neuropsychological performance (\pm SEM).

	Possible AD (n=22)	Probable AD (n=24)	2-sample t-test
Age	78.2 (\pm 1.84)	81.8 (\pm 0.35)	N.S..
NART pre-morbid IQ	109.0 (\pm 1.64)	112.3 (\pm 1.67)	N.S..
CAMCOG total score	65.9 (\pm 3.16)	60.83 (\pm 3.54)	N.S..
Immediate word recognition			
Sensitivity index	0.40 (\pm 0.06)	0.32 (\pm 0.37)	N.S..
Reaction latency (mS)	3265 (\pm 410)	3664 (\pm 526)	N.S..
Simple reaction time (mS)	680 (\pm 85)	674 (\pm 63)	N.S..
Number vigilance			
Accuracy (% targets detected)	79.1 (\pm 5.86)	89.7 (\pm 3.21)	N.S..
Reaction latency (mS)	622 (\pm 27)	622 (\pm 21)	N.S..
Choice reaction time			
Response latency (mS)	802 (\pm 63)	727 (\pm 32)	N.S..
Accuracy (% correct)	94.0 (\pm 1.61)	95 (\pm 1.55)	N.S.
Cognitive reaction time (mS)	193 (\pm 49)	126 (\pm 26)	N.S.
Spatial memory			
Sensitivity index	0.15 (\pm 0.07)	0.14 (\pm 0.07)	N.S.
Reaction latency (mS)	2789 (\pm 239)	3546 (\pm 595)	N.S.
Memory scanning			
Sensitivity index	0.77 (\pm 0.06)	0.69 (\pm 0.08)	N.S.
Reaction latency (mS)	1891 (\pm 281)	2231 (\pm 361)	N.S.
Delayed word recognition			
Sensitivity index	0.31 (\pm 0.08)	0.24 (\pm 0.08)	N.S.
Reaction latency (mS)	2461 (\pm 312)	2521 (\pm 511)	N.S.
Delayed picture recognition			
Sensitivity index	0.39 (\pm 0.07)	0.37 (\pm 0.06)	N.S.
Reaction latency (mS)	2672 (\pm 395)	2723 (\pm 268)	N.S.
Delayed face recognition			
Sensitivity index	0.36 (\pm 0.07)	0.28 (\pm 0.06)	N.S.
Reaction latency (mS)	2218 (\pm 231)	2603 (\pm 286)	N.S.
Critical flicker frequency (Hz)	33.5 (\pm 0.96)	34.2 (\pm 1.58)	N.S.

Table 7.2: Comparative analysis of possible and probable DLB cases on age and primary outcome measures (\pm SEM) of neuropsychological performance.

	Possible DLB (n=4)	Probable DLB (n=20)	2-sample t-test
Age	80.0 (\pm 2.38)	77.1 (\pm 1.78)	N.S.
NART pre-morbid IQ	108.5 (\pm 1.71)	109.2 (\pm 1.77)	N.S.
CAMCOG total score	73.8 (\pm 7.41)	59.35 (\pm 4.13)	N.S.
Immediate word recognition Sensitivity index Reaction latency (mS)	0.47 (\pm 0.13) 1845 (\pm 292)	0.38 (\pm 0.13) 3382 (\pm 528)	N.S. (t=-2.03, p=0.08)
Simple reaction time (mS)	1017 (\pm 314)	1131 (\pm 164)	N.S.
Number vigilance Accuracy (% targets detected) Reaction latency (mS)	73.3 (\pm 18.9) 607 (\pm 37)	57.3 (\pm 7.85) 656 (\pm 31)	N.S. N.S.
Choice reaction time Response latency (mS) Accuracy (% correct)	904 (\pm 204) 95.0 (\pm 3.54)	1803 (\pm 350) 88.2 (\pm 4.24)	N.S. N.S.
Cognitive reaction time (mS)	33 (\pm 22)	652 (\pm 255)	(t=-2.29, p=0.07)
Spatial memory Sensitivity index Reaction latency (mS)	0.15 (\pm 0.14) 3707 (\pm 1303)	0.06 (\pm 0.08) 3523 (\pm 527)	N.S. N.S.
Memory scanning Sensitivity index Reaction latency (mS)	0.84 (\pm 0.08) 2533 (\pm 1251)	0.66 (\pm 0.08) 2846 (\pm 477)	N.S. N.S.
Delayed word recognition Sensitivity index Reaction latency (mS)	0.49 (\pm 0.19) 1624 (\pm 366)	0.41 (\pm 0.06) 2991 (\pm 486)	N.S. (t=-2.09, p=0.08)
Delayed picture recognition Sensitivity index Reaction latency (mS)	0.38 (\pm 0.13) 1735 (\pm 382)	0.35 (\pm 0.08) 3524 (\pm 522)	N.S. (t=-2.06, p=0.09)
Delayed face recognition Sensitivity index Reaction latency (mS)	0.28 (\pm 0.16) 1634 (\pm 253)	0.30 (\pm 0.09) 3153 (\pm 648)	N.S. (t=-1.99, p=0.08)
Critical flicker frequency (Hz)	33.5 (\pm 0.96)	34.2 (\pm 1.58)	N.S.

In summary, there were no statistically significant differences between the probable and possible diagnostic categories on any measures undertaken. All subsequent analyses compare generic AD and DLB groups, and do not distinguish possible and probable diagnostic cases.

7.2 Comparison of cognitive function in AD, DLB and elderly controls using the CDR assessment battery.

7.2.1 Demographic features of experimental groups.

Data pertaining to age, sex, handedness, whether the participant wore glasses and age of education are documented in Table 7.3.

Table 7.3: Demographic data for control, AD and DLB groups.

	N (M : F)	Mean Age (years) (±SEM)	Handedness right / left	Glasses Yes / No	Mean years of education (±SEM)
Control	26 (8:18)	74.5 (±1.51)	26: 0	24 : 2	15.0 (±0.37)
AD	46 (18:28)	80.1 (±1.08)	45:1	43:3	15.3 (±0.38)
DLB	24 (13:11)	77.5 (±1.53)	23:1	22:2	14.2 (±0.10)

Analysis of variance indicated that the AD group were significantly older than controls ($F_{(2,93)}=4.72$, $p=0.01$), however, there was no age difference between AD and DLB groups, or between DLB and control groups. All groups were matched for the age at which full time education was left.

7.2.2 Non-computerised psychometric assessment.

Mean scores for estimated pre-morbid IQ (NART), global severity of dementia (total CAMCOG scores), and activities of daily living skills (ADL, IADL) are detailed in Table 7.4.

Table 7.4: Mean scores for psychometric test data for control, AD and DLB groups.

	Mean NART IQ (±SEM)	Mean total CAMCOG score (±SEM)	Mean ADL score (±SEM)	Mean IADL score (±SEM)
Control (n=26)	114.9 (±1.3)	99.4 (±0.86)	N / A	N / A
AD (n=46)	110.4 (±1.2)	62.8 (±2.27)	17.3 (±0.45)	21.4 (±0.92)
DLB (n=24)	109.2 (±1.4)	62.4 (±4.00)	16.2 (±0.77)	22.13 (±1.19)

N/A = not available

The dementia groups were matched for estimated pre-morbid IQ using the NART, however, both dementia groups had lower estimated pre-morbid IQs than the control group ($F_{(2,93)}=4.45$, $p=0.01$). Similarly, the dementia groups were matched for overall level of cognitive impairment, but as would be expected both AD and DLB groups showed significantly greater global impairment of cognitive function than the control group ($F_{(2,93)}=59.66$, $p<0.001$). Comparison of daily living skills revealed dementia groups were matched for both ADL and IADL measures.

Mean scores for subsections of the CAMCOG schedule are presented in Table 7.5 and Figure 7.1.

Analyses of data from subsections of the CAMCOG schedule indicated that on the orientation subsection both dementia groups performed worse than controls ($F_{(2,93)}=35.7$, $p<0.001$), but AD and DLB groups performed equivalently. A similar pattern of performance was observed for the language comprehension subsection ($F_{(2,93)}=7.0$, $p=0.001$), and language expression subsection ($F_{(2,93)}=11.42$, $p<0.001$).

Analysis of data from the visuo-spatial praxis subsection revealed that the DLB group performed worse than both control and AD groups, furthermore the performance of the AD group was worse than controls ($F_{(2,93)}=30.59$, $p<0.001$).

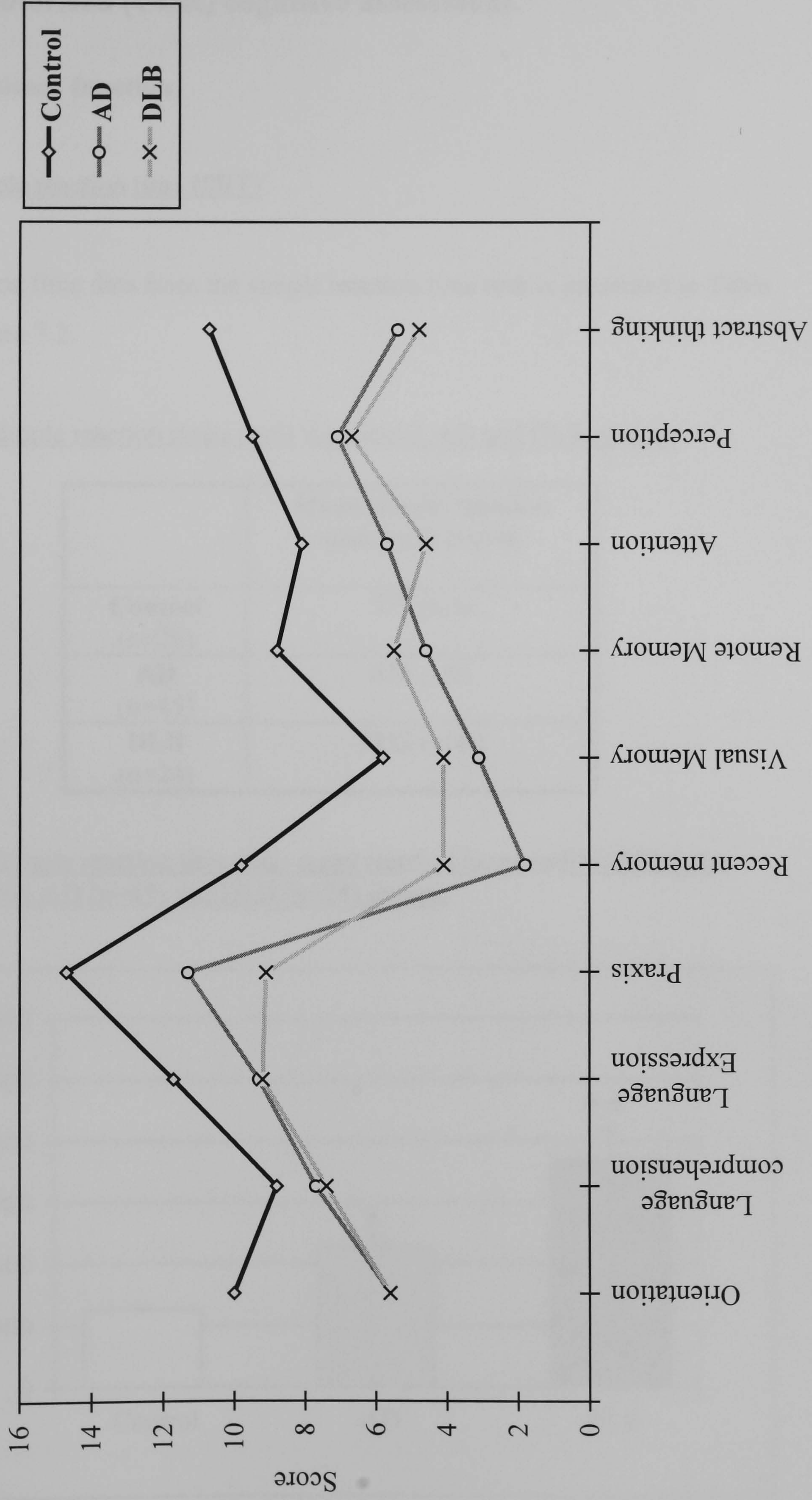
Table 7.5: Mean scores (\pm SEM) for control, AD and DLB groups on subsections of the CAMCOG schedule.

	Control (n=26)	AD (n=46)	DLB (n=24)
Orientation	10.0 (\pm 0.04)	5.6 (\pm 0.35)	5.6 (\pm 0.62)
Language Comprehension	8.8 (\pm 0.08)	7.7 (\pm 0.21)	7.4 (\pm 0.40)
Language Expression	11.7 (\pm 0.12)	9.3 (\pm 0.33)	9.2 (\pm 0.60)
Praxis	14.7 (\pm 0.13)	11.3 (\pm 0.37)	9.1 (\pm 0.76)
Recent Memory	9.8 (\pm 0.33)	1.8 (\pm 0.37)	4.1 (\pm 0.64)
Visual Memory (recognition)	5.8 (\pm 0.08)	3.1 (\pm 0.31)	4.1 (\pm 0.37)
Remote Memory	8.8 (\pm 0.08)	4.6 (\pm 0.37)	5.5 (\pm 0.56)
Attention and Calculation	8.1 (\pm 0.09)	5.7 (\pm 0.39)	4.6 (\pm 0.56)
Perception	9.5 (\pm 0.19)	7.1 (\pm 0.27)	6.7 (\pm 0.36)
Abstract Thinking	10.7 (\pm 0.27)	5.4 (\pm 0.48)	4.8 (\pm 0.65)
CAMCOG Total Score	99.4 (\pm 0.86)	62.8 (\pm 2.27)	62.4 (\pm 4.00)

Performance in the recent memory recall subsection of the CAMCOG was significantly worse in both dementia groups compared to control, in addition the AD group performed significantly worse than the DLB group ($F_{(2,93)}=85.69$, $p < 0.001$). In the visual recognition memory subsection both dementia groups performed worse than controls, however, the AD group performed worse than the DLB group ($F_{(2,93)}=19.84$, $p < 0.001$).

In the remote memory subsection both dementia groups were impaired with respect to controls ($F_{(2,93)}=30.79$, $p < 0.001$), but not with respect to each other. Analyses of data from the attention-calculation subsection of the CAMCOG revealed both dementia groups to be impaired with respect to controls ($F_{(2,93)}=15.24$, $p < 0.001$), but AD and DLB groups were not impaired with respect to each other. Performance in the perception subsection was worse in both dementia groups than the control group ($F_{(2,93)}=23.54$, $p < 0.001$), however, the dementia groups did not differ with respect to each other. Similarly for the abstract subsection both dementia groups were impaired with respect to controls ($F_{(2,93)}=35.67$, $p < 0.001$), but not with respect to each other.

Figure 7.1: Mean scores on subsections of the CAMCOG schedule for control (n=26), AD (n=46) and DLB (n=24) groups.



7.3 Computerised (CDR) cognitive assessment.

7.3.1 Attentional function

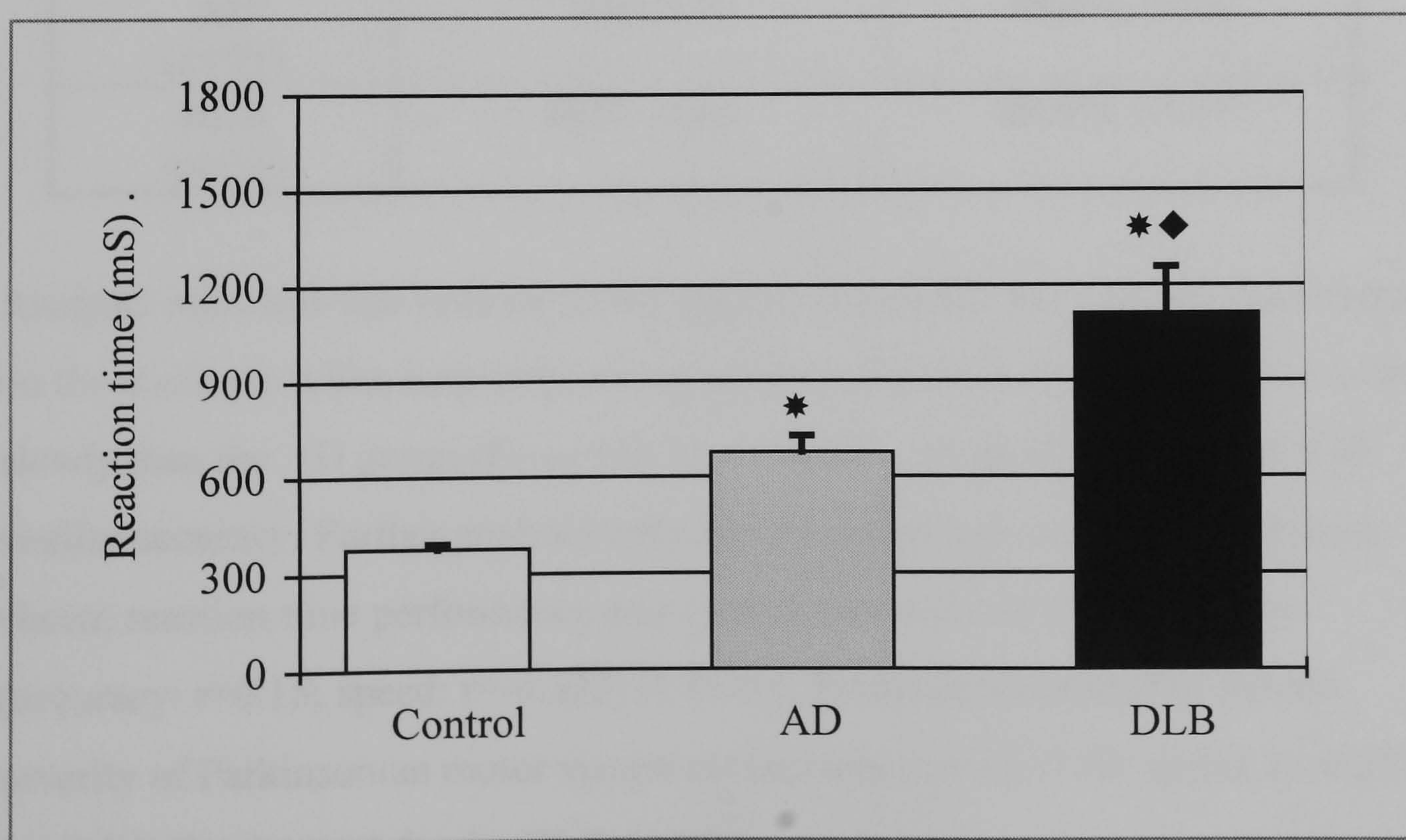
7.3.1.1 Simple reaction time (SRT)

Mean reaction time data from the simple reaction time task is presented in Table 7.6 and Figure 7.2.

Table 7.6: Simple reaction times (mS) for control, AD and DLB groups.

	Mean simple reaction time (mS) (\pm SEM)
Control (n=26)	377 (\pm 15)
AD (n=45)	676 (\pm 51)
DLB (n=24)	1112 (\pm 144)

Figure 7.2: Simple reaction time task: mean reaction times (mS) (\pm SEM) for control (n=26), AD (n=45) and DLB (n=24) groups.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

Analysis revealed both dementia groups to react more slowly on the simple reaction time task, in addition the DLB group reacted more slowly than the AD group ($F(2,92)=28.00$, $p<0.001$). Further analysis indicated no significant correlation between simple reaction times and clinical measures (Unified Parkinson's Disease Rating Scale; UPDRS) of motor slowing ($r=-0.24$) (UPDRS Bradykinesia score) or overall severity of Parkinsonian motor symptoms ($r=-0.01$) (UPDRS Total score) for the DLB group.

7.3.1.2 Choice reaction time (CRT).

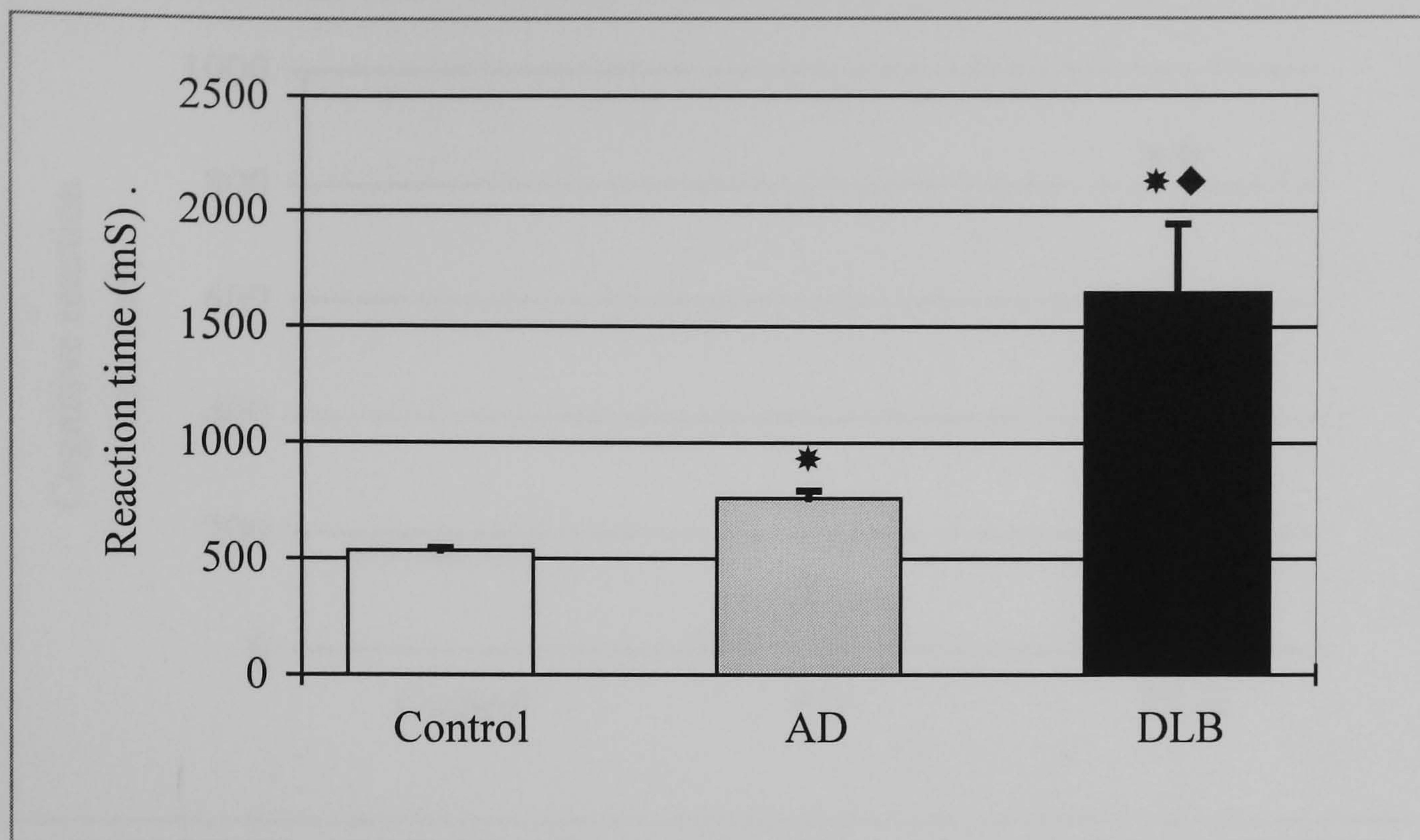
Data concerning accuracy and response latency for the choice reaction time task are presented in Table 7.7 and Figures 7.3.

Table 7.7: Choice reaction time: mean reaction times (mS) and accuracy (% correct) for control, AD and DLB groups.

	Mean choice reaction time (mS) (\pm SEM)	Mean accuracy of responses (% correct) (\pm SEM)
Control (n=26)	534 (\pm 12)	95.8% (\pm 0.72)
AD (n=45)	760 (\pm 33)	94.6% (\pm 1.1)
DLB (n=23)	1647 (\pm 298)	89.4% (\pm 3.57)

Analysis indicated that both dementia groups responded more slowly than controls on the choice reaction time task, and in addition the DLB group responded more slowly than the AD group ($F(2,91)=30.32$, $p<0.001$). All groups responded with similar accuracy. Further analysis indicated no significant correlation between choice reaction time performance and clinical measures of motor slowing (accuracy: $r=0.15$; speed: $r=-0.325$) (UPDRS Bradykinesia score) or overall severity of Parkinsonian motor symptoms (accuracy: $r=-0.20$; speed: $r=-0.27$) (UPDRS Total score) for the DLB group.

Figure 7.3: Choice reaction time task: mean reaction time (mS) (\pm SEM) for control (n=26), AD (n=45) and DLB (n=23) groups.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

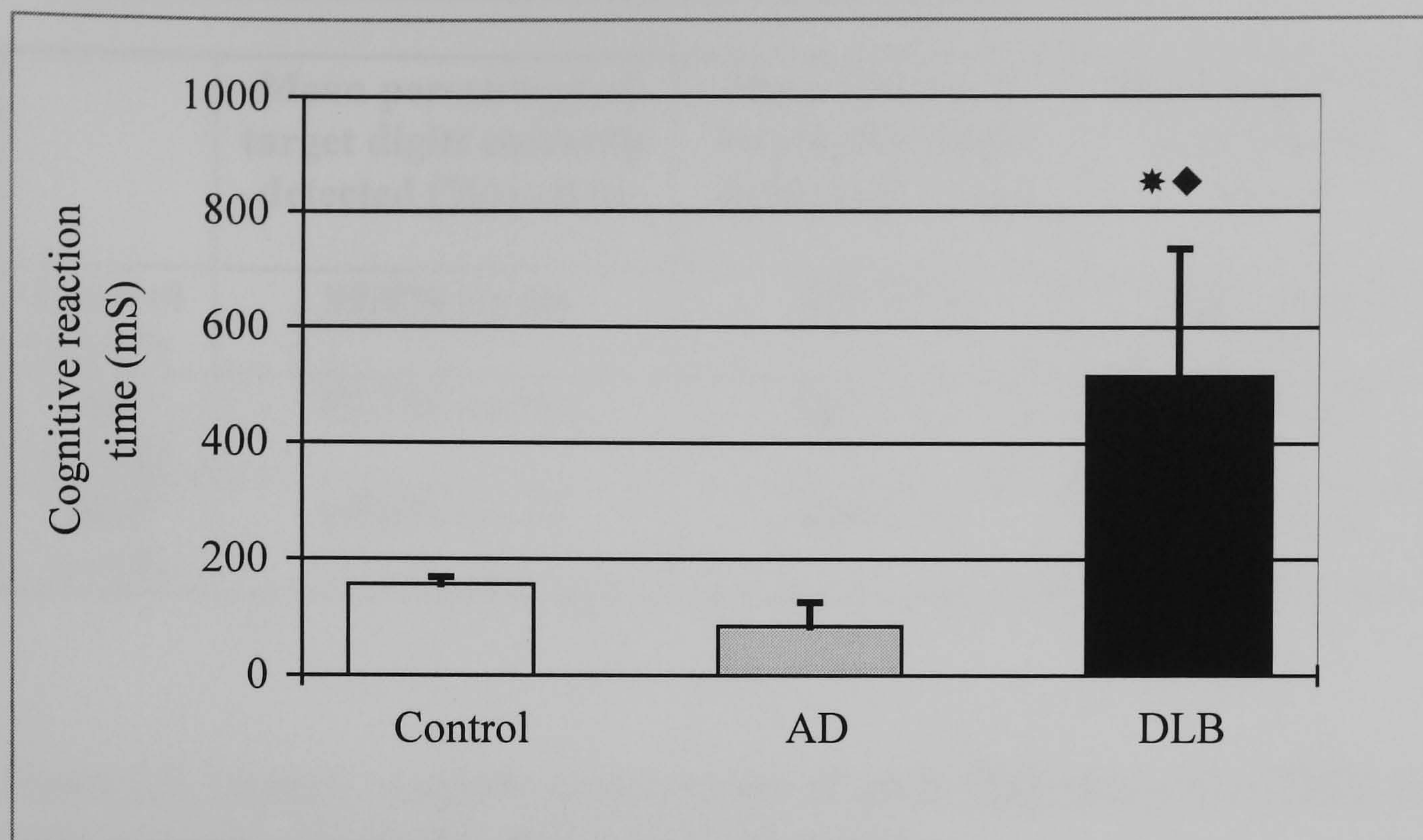
7.1.3.3 Cognitive reaction time.

Cognitive reaction time provides a measure of speed of cognitive processing and were calculated by deducting simple reaction times from corresponding choice reaction times. Mean cognitive reaction times are presented in Table 7.8 and Figure 7.4.

Table 7.8: Cognitive reaction times (mS) for control, AD and DLB groups.

	Mean cognitive reaction time (mS) (\pmSEM)
Control (n=26)	157 (\pm12)
AD (n=45)	156 (\pm26)
DLB (n=23)	544 (\pm216)

Figure 7.4: Mean cognitive reaction time (mS) (\pm SEM) for control (n=26), AD (n=45) and DLB (n=23) groups.



* significant difference ($p < 0.05$) compared to controls; ♦ significant difference ($p < 0.05$) between dementia groups

Some of the cognitive reaction times were negative values. All negative values were assigned a value of 0 mS. Analysis indicated that cognitive reaction times for the DLB group were significantly greater than both control and AD, and in addition the cognitive reaction times for the control group were longer than the AD group ($F_{(2,92)}=25.98$, $p < 0.001$).

7.1.3.4 Number vigilance.

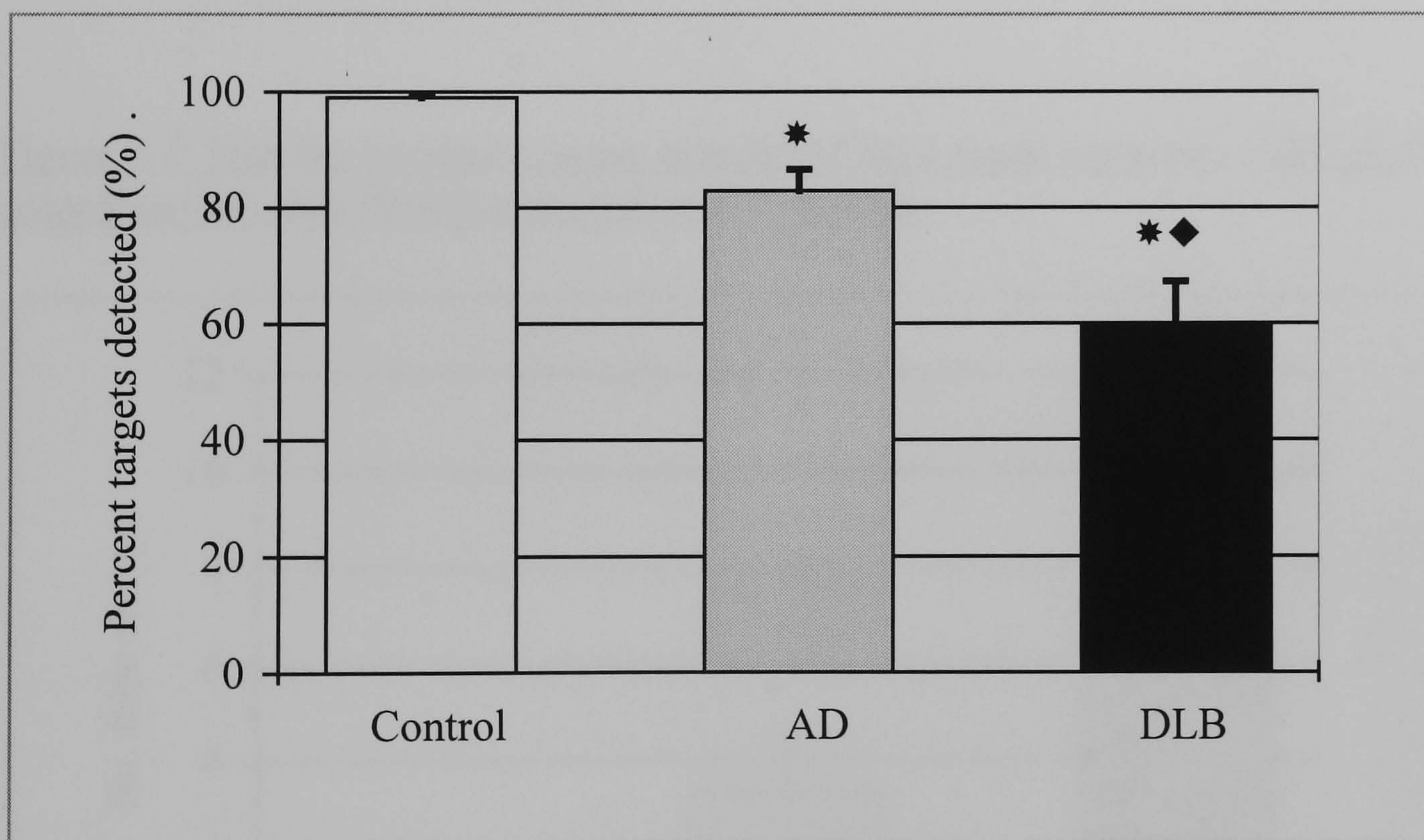
Data pertaining to the number vigilance task are described in Table 7.9 and Figures 7.5, 7.6 and 7.7.

Both dementia groups detected significantly fewer target digits than controls, and furthermore, the DLB group detected fewer target digits than the AD group ($F_{(2,93)}=16.30$, $p < 0.001$). Further analysis indicated no significant correlation between the number of target digits correctly identified and clinical measures (Unified Parkinson's Disease Rating Scale; UPDRS) of motor slowing ($r=-0.25$) UPDRS Bradykinesia score) or overall severity of Parkinsonian motor symptoms ($r=-0.25$) (UPDRS Total score) for the DLB group.

Table 7.9: Number vigilance: mean accuracy scores, response latencies and number of false alarms for control, AD and DLB groups.

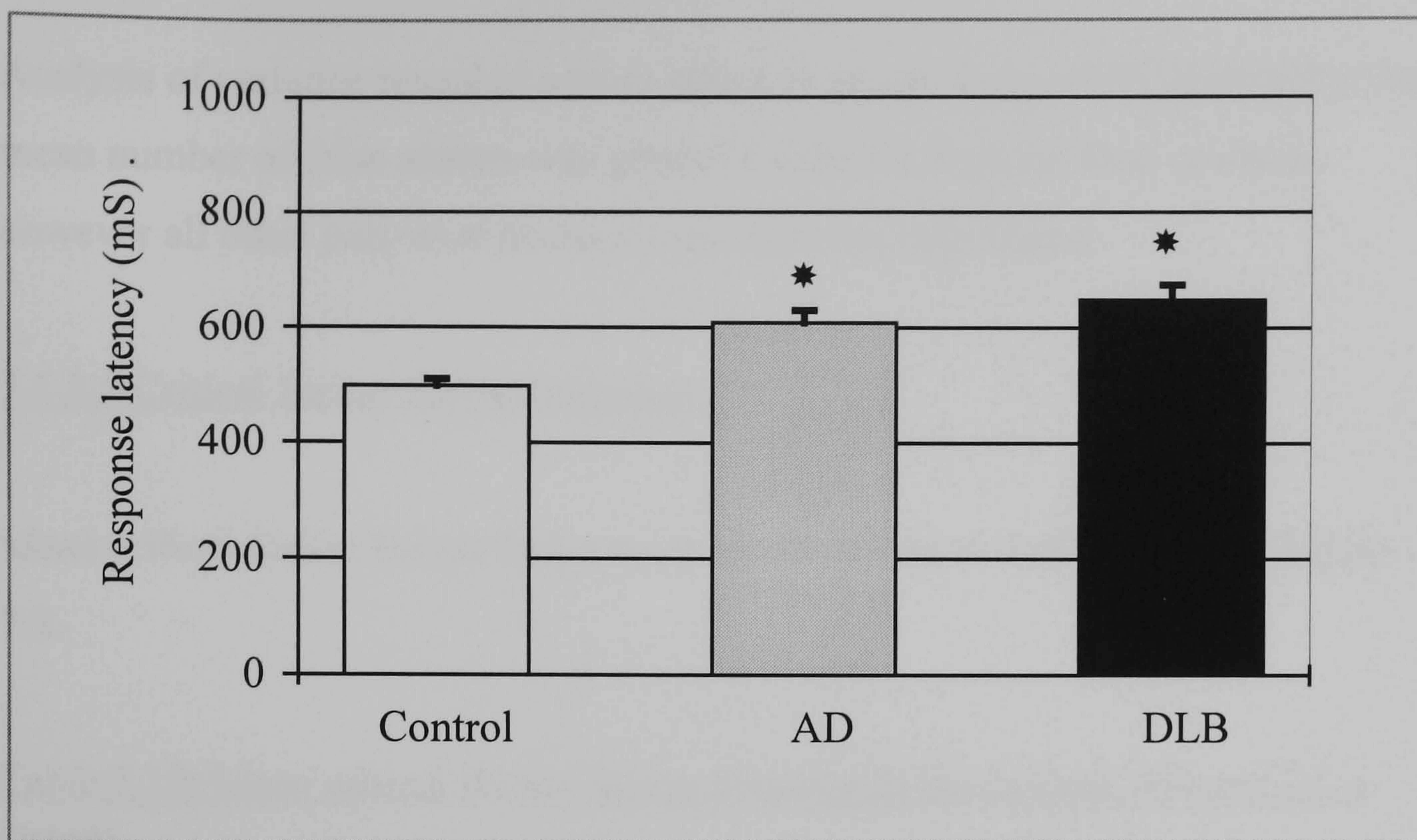
	Mean percentage of target digits correctly detected (%) (\pm SEM)	Mean latency to respond to target digits(mS) (\pm SEM)	Mean number of false alarms (\pm SEM)
Control (n=26)	99.0% (\pm 0.48)	498 (\pm 11)	0.35 (\pm 0.15)
AD (n=46)	82.9% (\pm 3.70)	609 (\pm 21)	3.39 (\pm 1.12)
DLB (n=24)	60.0% (\pm 7.19)	648 (\pm 27)	7.21 (\pm 2.30)

Figure 7.5: Number vigilance: mean percent of target digits detected (\pm SEM) for control (n=26), AD (n=46) and DLB (n=24) groups.



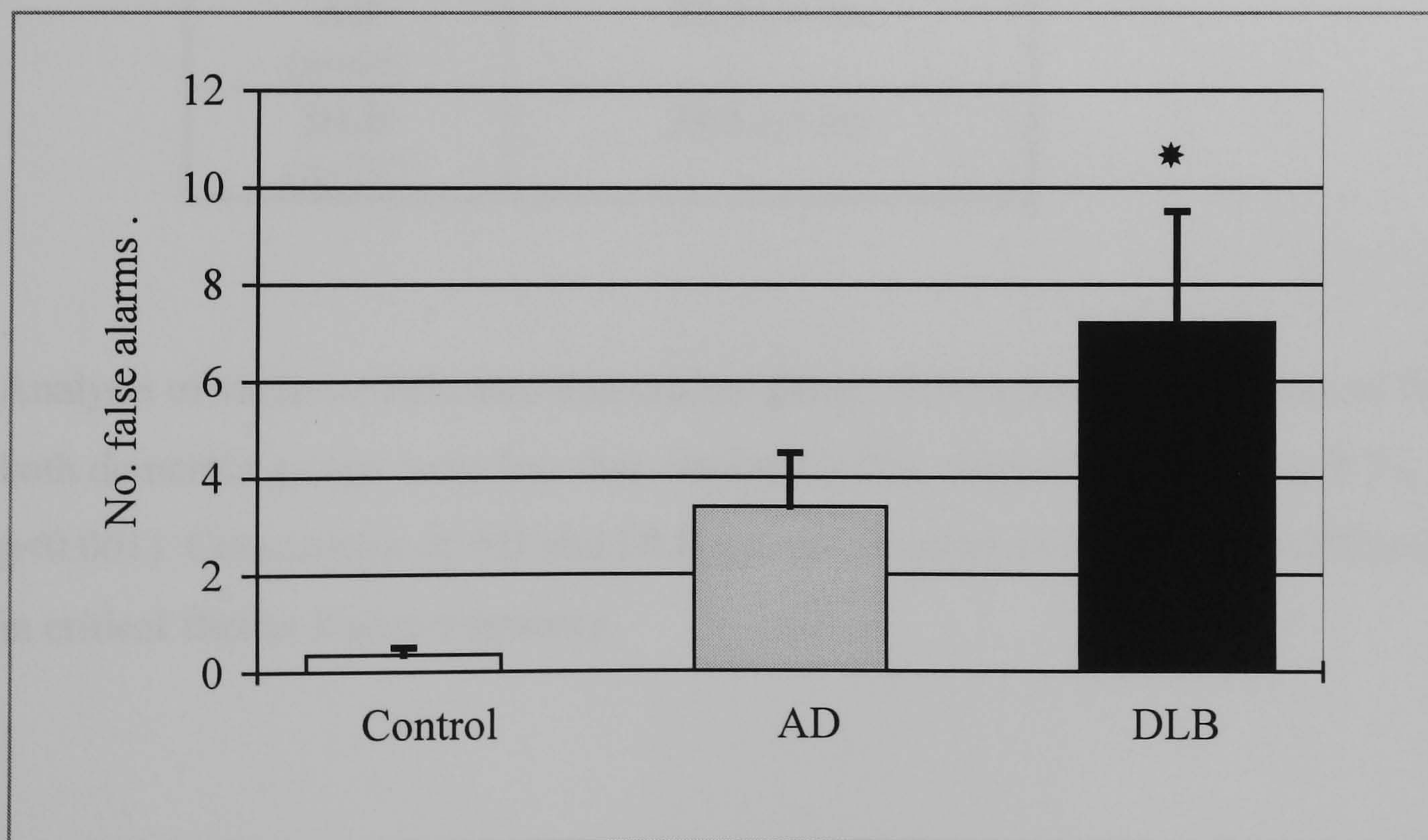
* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

Figure 7.6: Number vigilance: mean response latencies for correctly detected target digits (\pm SEM) for control (n=26), AD (n=46) and DLB (n=24) groups.



* significant difference ($p < 0.05$) compared to controls

Figure 7.7: Number vigilance: mean number of false alarm responses (\pm SEM) for control (n=26), AD (n=46) and DLB (n=24) groups.



* significant difference ($p < 0.05$) compared to controls

Response latencies are described for responses to correctly detected target digits only. Mean response times for all groups were within the requisite 1.25-second response window. Both dementia groups responded more slowly than the control

group ($F_{(2,93)}=15.97$, $p<0.001$), however, there was no difference in response latency between AD and DLB groups.

Analysis of variance revealed a main effect of group ($F_{(2,93)}=4.93$, $p=0.009$). The mean number of false alarms was greater for the DLB group than controls, however all other pair-wise comparisons were non-significant.

7.1.3.5 Critical flicker fusion frequency.

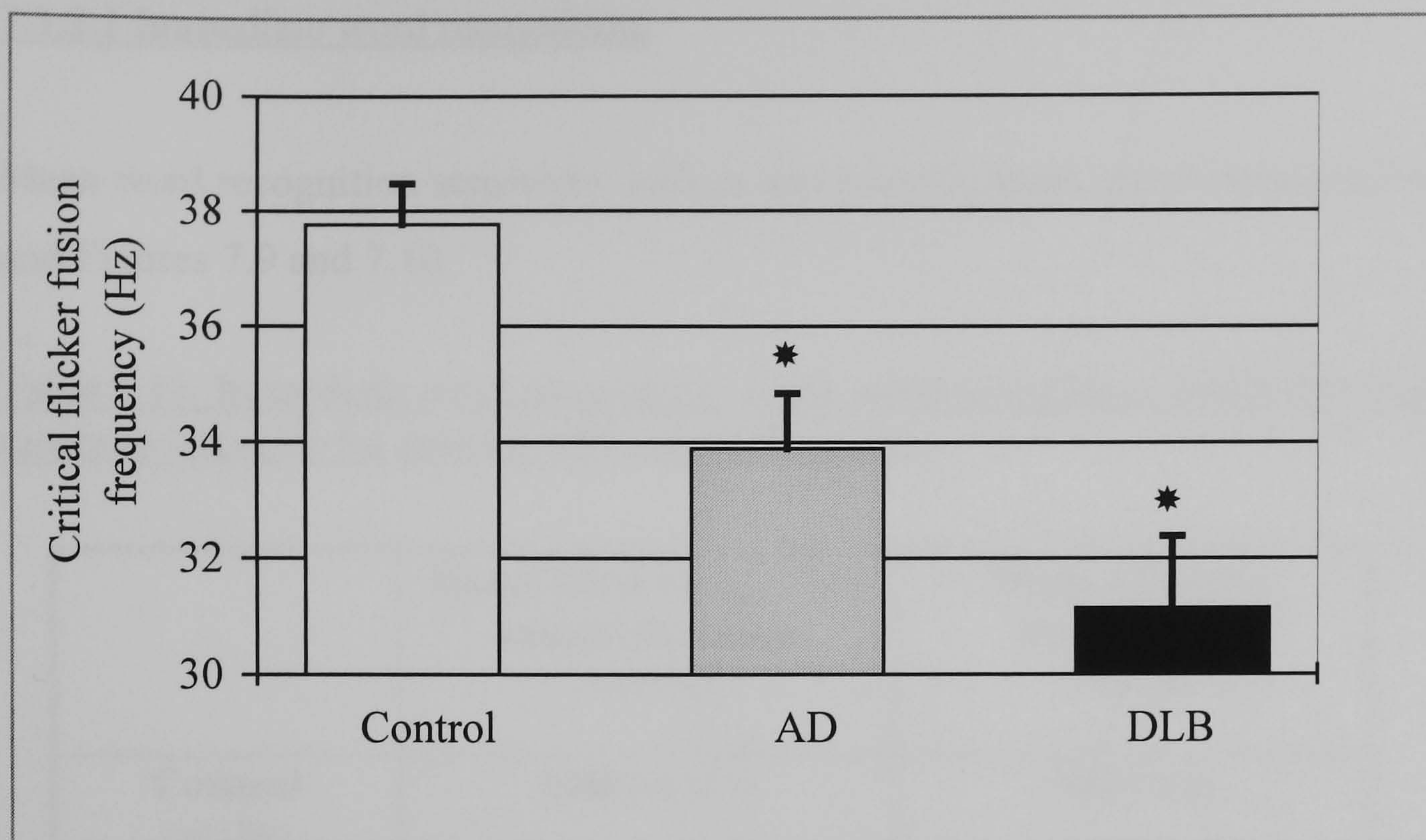
Mean critical flicker fusion frequencies are described in Table 7.10 and Figure 7.8.

Table 7.10: Mean critical flicker fusion frequencies for control, AD and DLB groups.

	Mean critical flicker fusion frequency (Hz) (\pm SEM)
Control (n=25)	37.8 (± 0.71)
AD (n=44)	33.9 (± 0.96)
DLB (n=21)	31.1 (± 1.24)

Analysis of variance indicated that critical flicker fusion frequencies obtained for both dementia groups were less than obtained by the control group ($F_{(2,89)}=8.37$, $p<0.001$). Comparison of AD and DLB groups revealed no significant difference in critical flicker fusion frequency.

Figure 7.8: Mean critical flicker fusion frequencies (\pm SEM) for control (n=25), AD (n=44) and DLB (n=23) groups.



* significant difference ($p < 0.05$) compared to controls

7.3.2 Secondary memory.

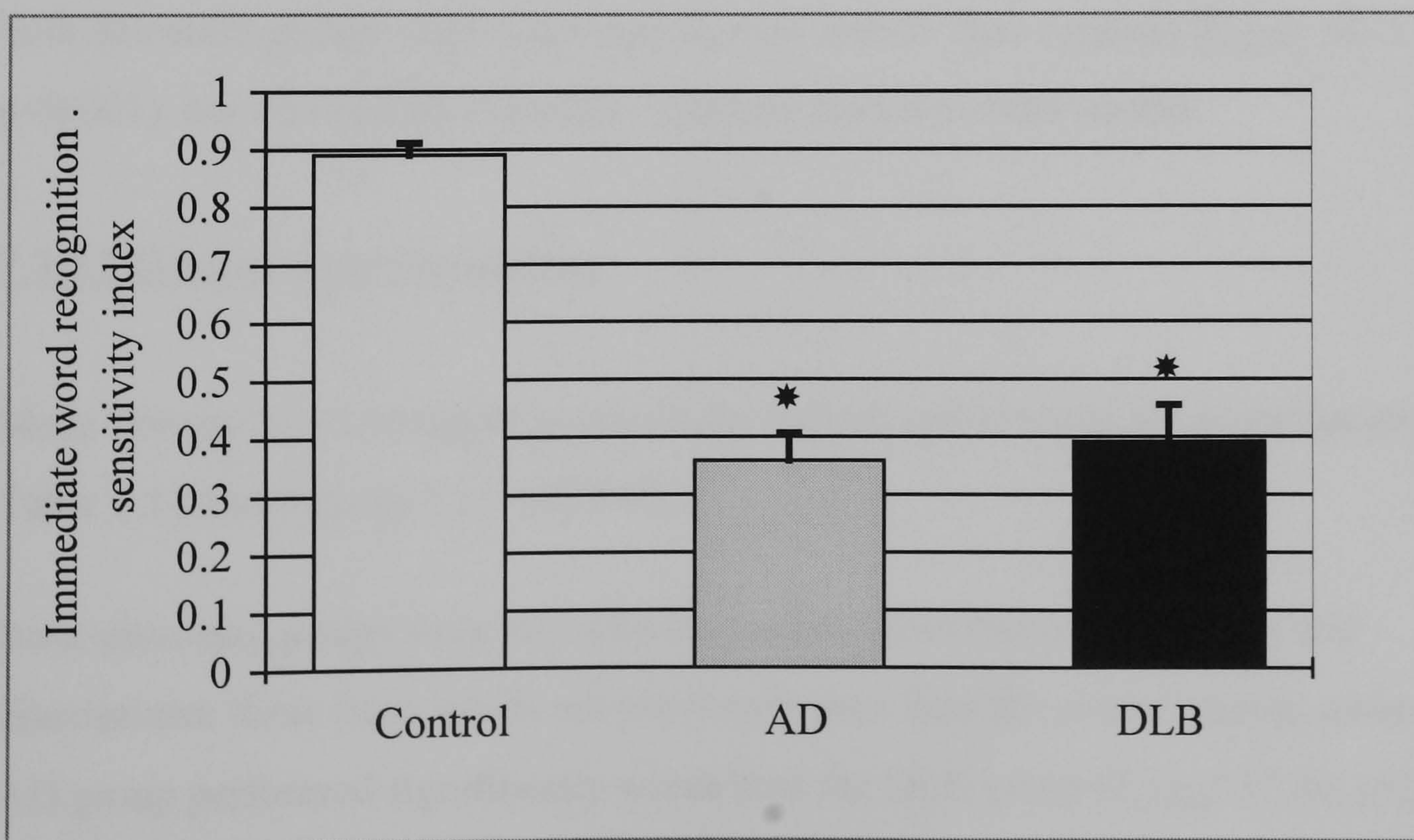
7.3.2.1 Immediate word recognition.

Mean word recognition sensitivity indices and reaction times are presented in Table 7.11 and Figures 7.9 and 7.10.

Table 7.11: Immediate word recognition: mean word recognition sensitivity index and response latencies for control, AD and DLB groups.

	Mean word recognition sensitivity index (\pm SEM)	Mean response latency (mS) (\pm SEM)
Control (n=26)	0.89 (\pm 0.021)	902 (\pm 28)
AD (n=46)	0.36 (\pm 0.047)	3482 (\pm 340)
DLB (n=24)	0.39 (\pm 0.064)	3126 (\pm 456)

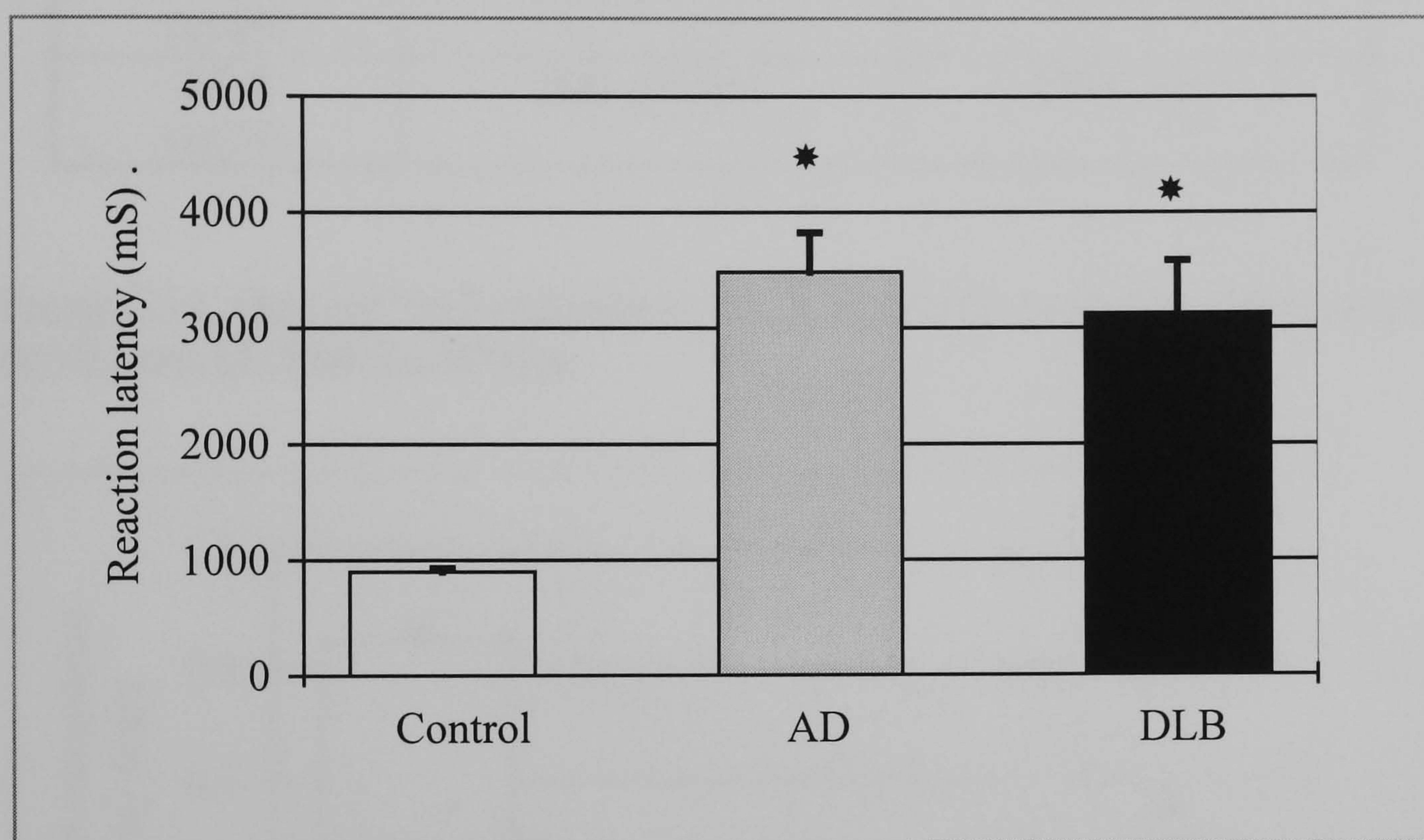
Figure 7.9: Immediate word recognition: mean sensitivity index for control (n=26), AD (n=46) and DLB (n=24) groups.



* significant difference ($p < 0.05$) compared to controls

Analyses of variance indicated that both dementia groups were less able to recognise previously seen words and discriminate these from words not previously seen than the control group ($F_{(2,93)}=33.58$, $p<0.001$), but dementia groups performed equivalently.

Figure 7.10: Immediate word recognition: mean reaction latencies (mS) (\pm SEM) for control (n=26), AD (n=46) and DLB (n=24) groups.



* significant difference ($p<0.05$) compared to controls

Analysis of reaction latencies for the immediate word recognition task indicated that both dementia groups responded significantly slower than controls ($F_{(2,93)}=40.15$, $p<0.001$), but AD and DLB groups' response latencies were similar.

7.3.2.2 Delayed word recognition.

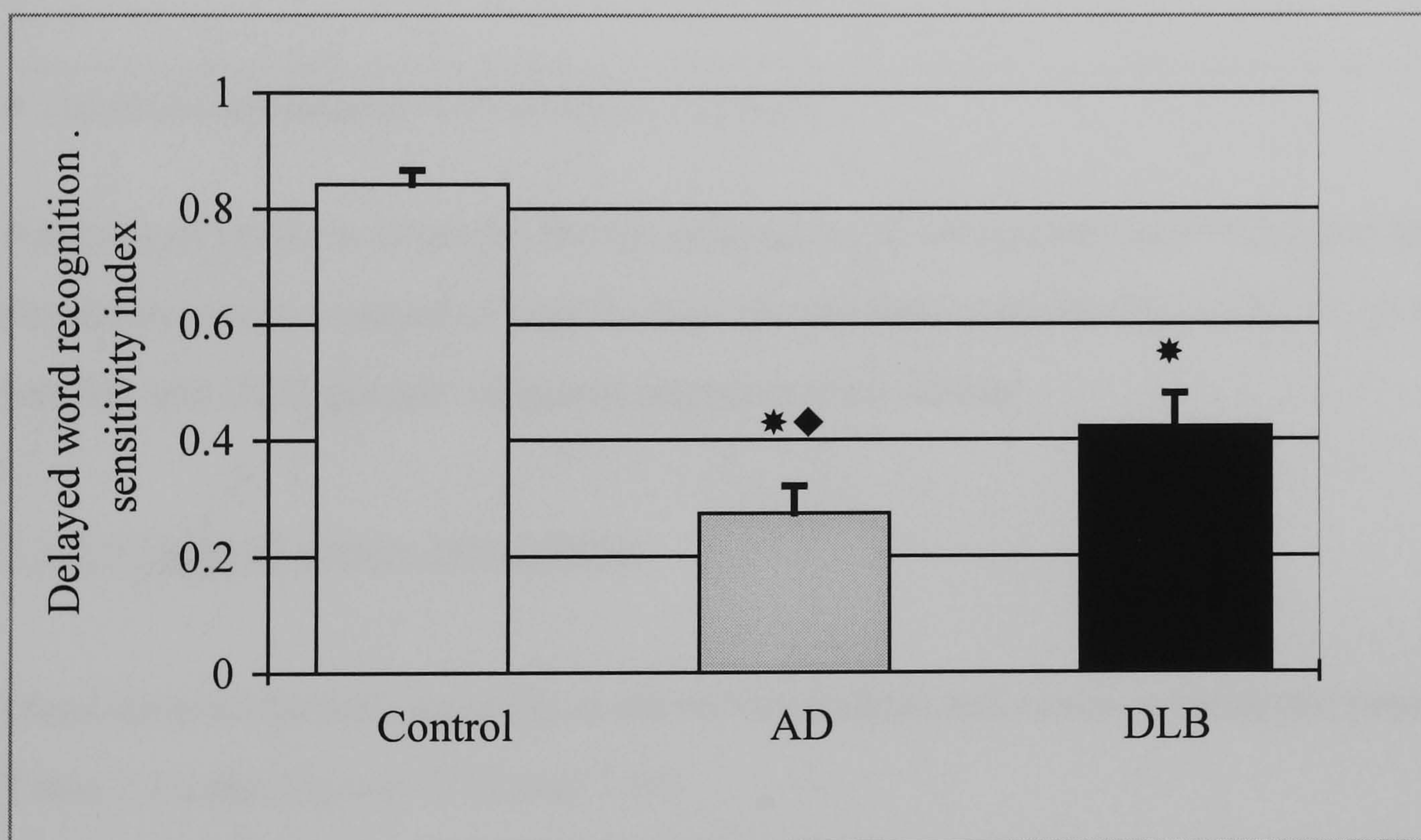
Mean delayed word recognition sensitivity indices and reaction times are presented in Table 7.12 and Figures 7.11 and 7.12.

Both dementia groups were less able to recognise previously seen words and discriminate these from words not previously seen than the control group, moreover, the AD group performed significantly worse than the DLB group ($F_{(2,92)}=37.50$, $p<0.001$).

Table 7.12: Delayed word recognition: mean word recognition sensitivity index and response latencies for control, AD and DLB groups.

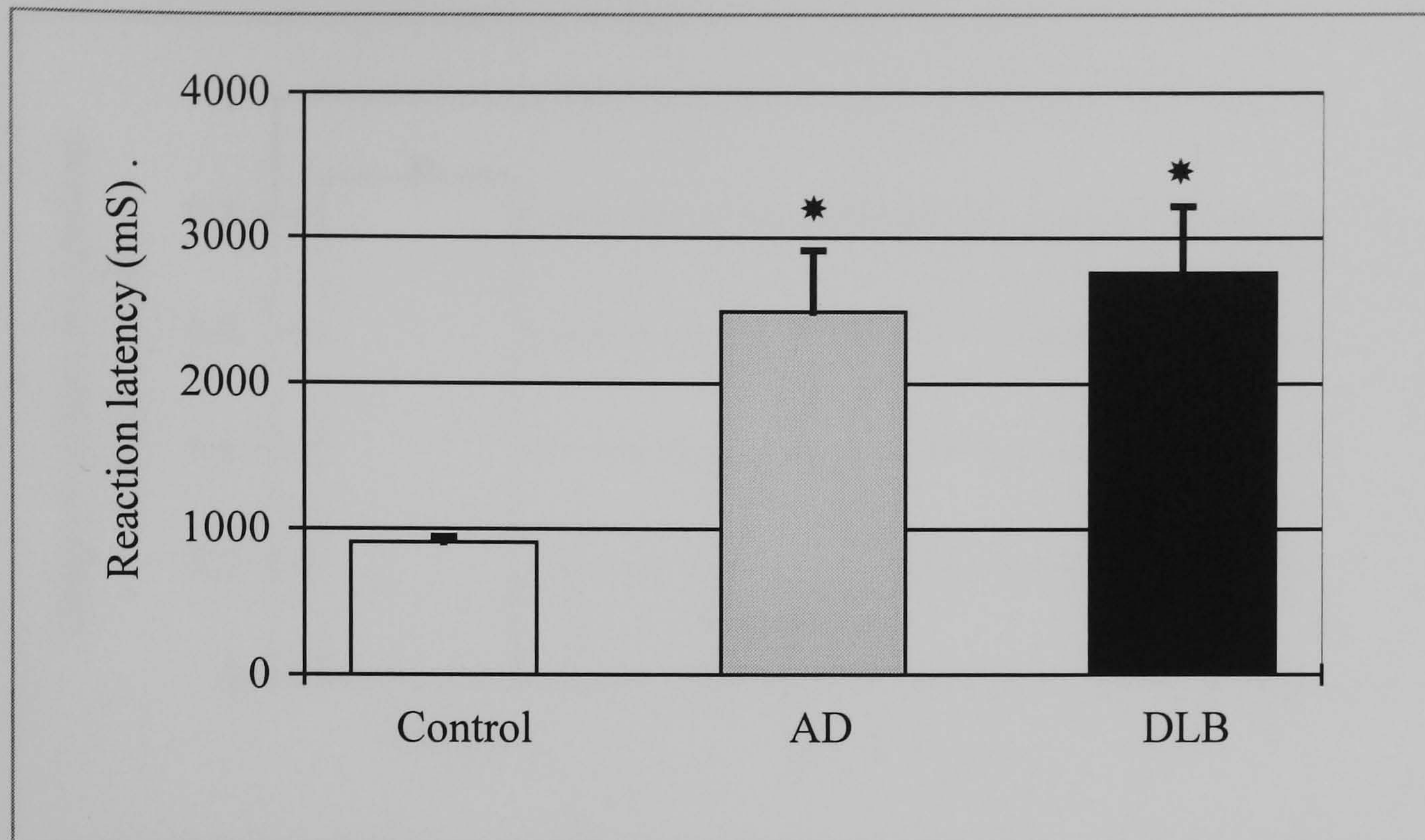
	Mean word recognition sensitivity index (\pmSEM)	Mean response latency (mS) (\pmSEM)
Control (n=26)	0.84 (\pm 0.025)	908 (\pm 35)
AD (n=45)	0.27 (\pm 0.047)	2493 (\pm 306)
DLB (n=24)	0.42 (\pm 0.057)	2763 (\pm 421)

Figure 7.11: Delayed word recognition: mean sensitivity index for control (n=26), AD (n=45) and DLB (n=24) groups.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia group

Figure 7.12: Delayed word recognition: mean reaction latencies (mS) (\pm SEM) for control (n=26), AD (n=45) and DLB (n=24) groups.



* significant difference ($p < 0.05$) compared to controls

Analysis of reaction latencies for the delayed word recognition task indicated that both dementia groups responded significantly slower than controls ($F_{(2,92)} = 33.11$, $p < 0.001$), but AD and DLB groups' response latencies were similar.

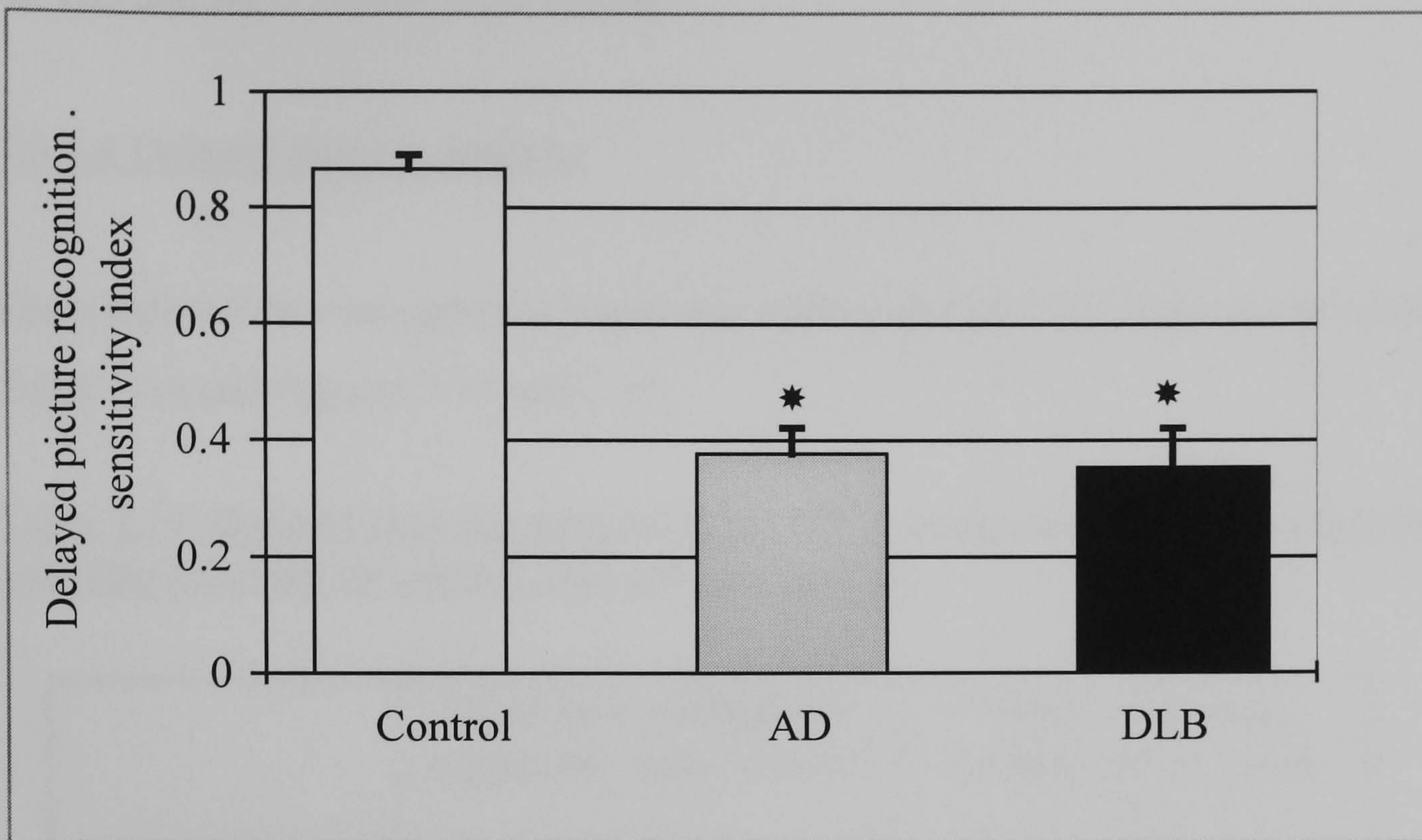
7.3.2.3 Delayed picture recognition.

Mean delayed picture recognition sensitivity indices and reaction times are presented in Table 7.13 and Figures 7.13 and 7.14.

Table 7.13: Delayed picture recognition: mean picture recognition sensitivity index and response latencies for control, AD and DLB groups.

	Mean picture recognition sensitivity index (\pm SEM)	Mean response latency (mS) (\pm SEM)
Control (n=26)	0.87 (± 0.025)	978 (± 35)
AD (n=44)	0.38 (± 0.044)	2700 (± 229)
DLB (n=24)	0.35 (± 0.067)	3001 (± 452)

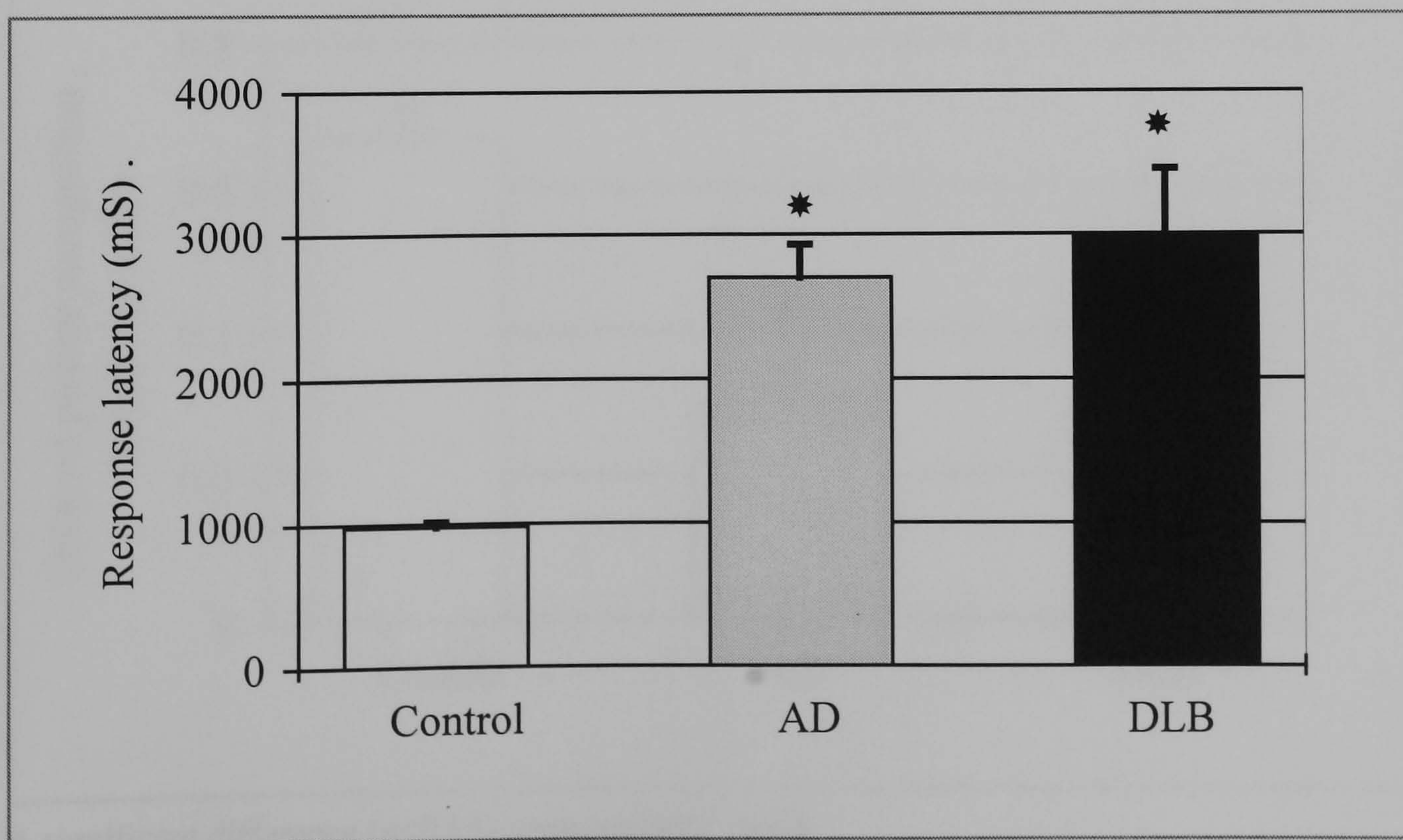
Figure 7.13: Delayed picture recognition: mean sensitivity index for control (n=26), AD (n=44) and DLB (n=24) groups.



* significant difference ($p < 0.05$) compared to controls

Analysis of recognition sensitivity indices indicated both dementia groups were less able than the control group to recognise previously seen pictures and distinguish these from novel exemplars ($F_{(2,91)}=32.12, p < 0.001$). The AD and DLB groups had similar recognition sensitivity indices on the delayed picture recognition task.

Figure 7.14: Delayed picture recognition: mean response latencies (mS) (\pm SEM) for control (n=26), AD (n=44) and DLB (n=24) groups.



* significant difference ($p < 0.05$) compared to controls

Response latencies for the delayed picture recognition task were significantly greater for both dementia groups than controls ($F_{(2,91)}=38.61, p<0.001$), although response latencies for AD and DLB groups were similar.

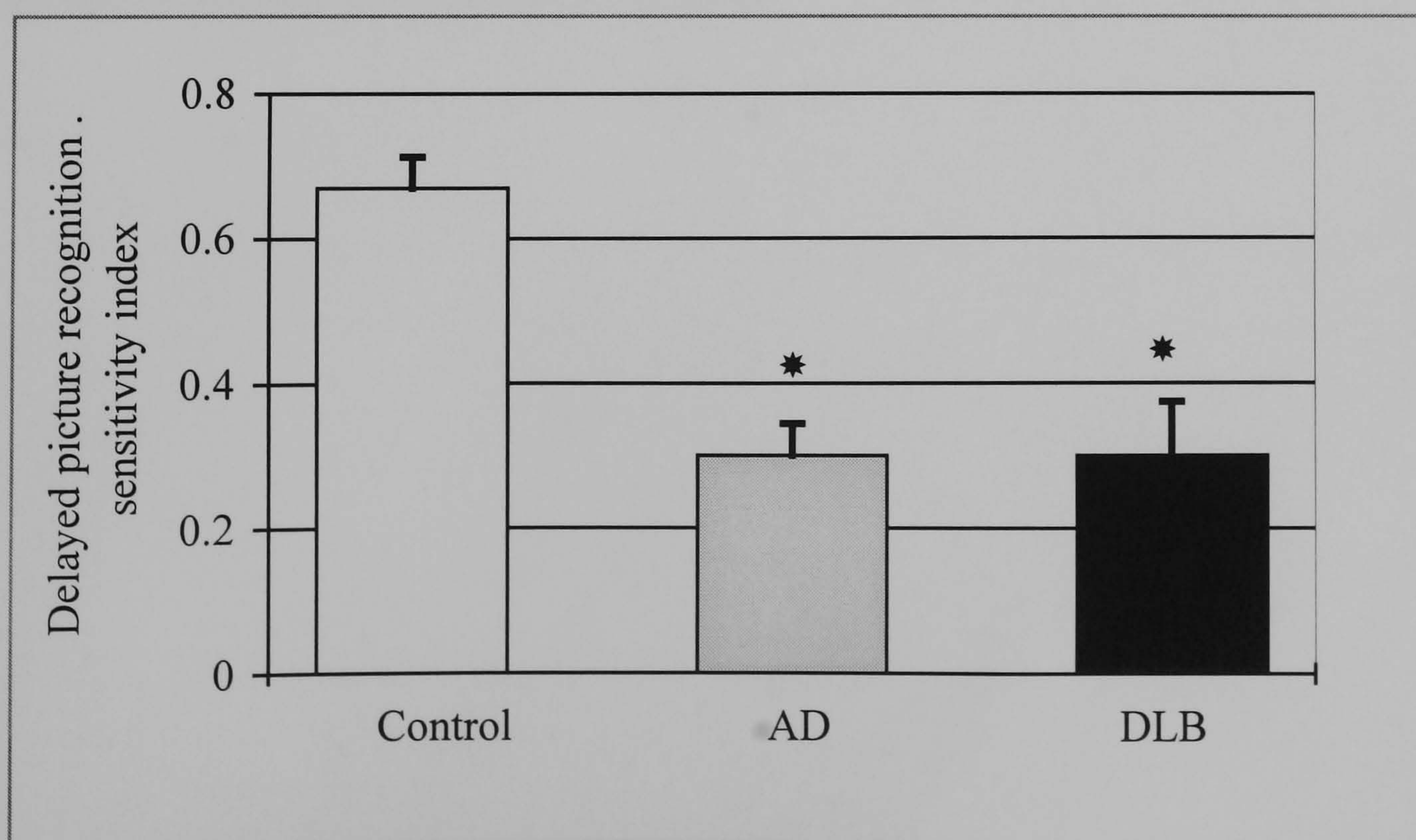
7.3.2.4 Delayed face recognition.

Mean delayed face recognition sensitivity indices and reaction times are presented in Table 7.14 and Figures 7.15 and 7.16.

Table 7.14: Delayed face recognition: mean face recognition sensitivity index and response latencies for control, AD and DLB groups.

	Mean face recognition sensitivity index (\pmSEM)	Mean response latency (mS) (\pmSEM)
Control (n=26)	0.67 (\pm 0.043)	978 (\pm 35)
AD (n=44)	0.30 (\pm 0.044)	2451 (\pm 263)
DLB (n=22)	0.30 (\pm 0.074)	2877 (\pm 544)

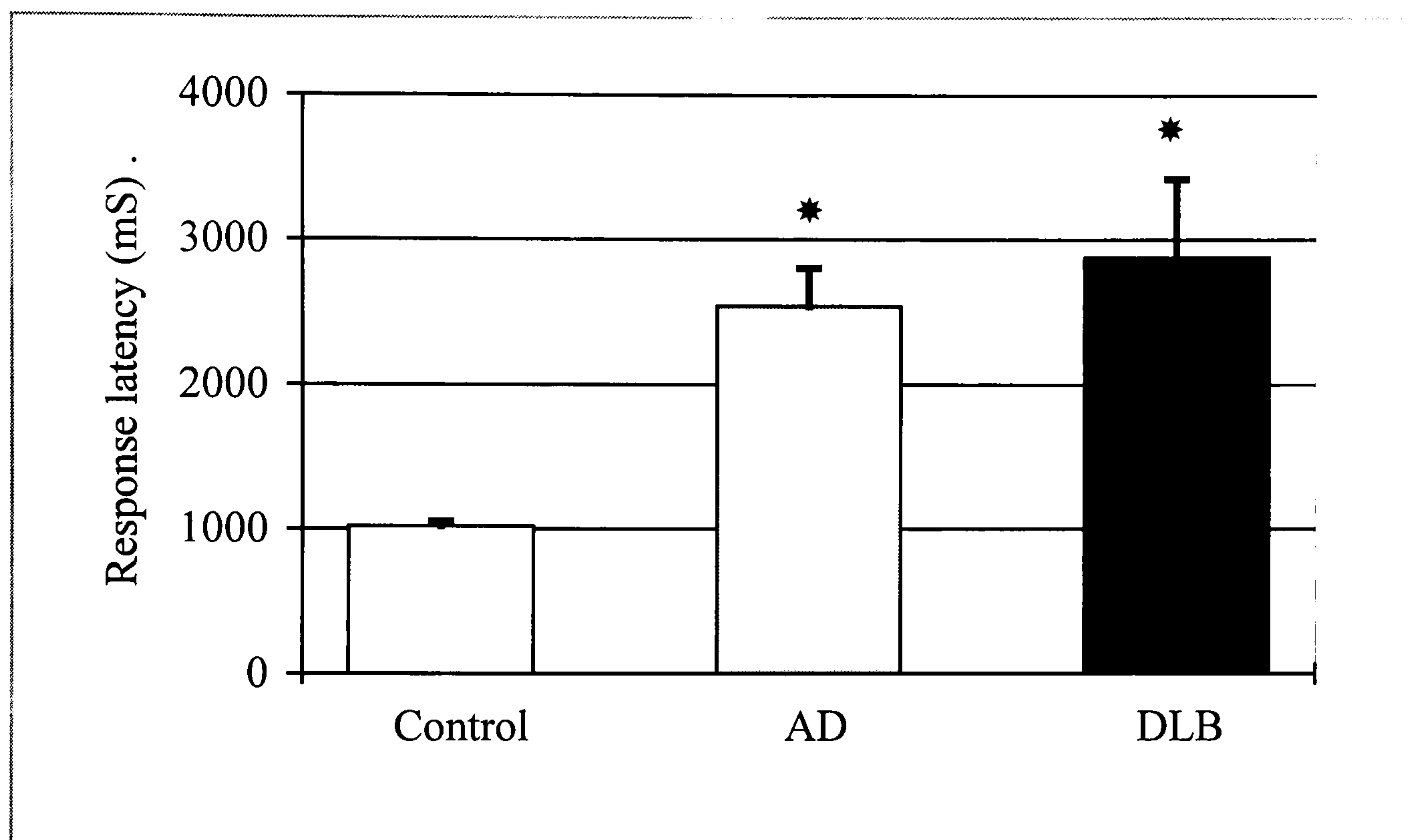
Figure 7.15: Delayed face recognition: mean sensitivity index for control (n=26), AD (n=44) and DLB (n=22) groups.



* significant difference ($p<0.05$) compared to controls

Both dementia groups were less able than the control group to recognise previously seen faces and distinguish these from novel exemplars ($F_{(2,89)}=15.84, p<0.001$), but AD and DLB groups performed similarly on the delayed face recognition task.

Figure 7.16: Delayed face recognition: mean response latencies (mS) (\pm SEM) for control (n=26), AD (n=44) and DLB (n=22) groups.



* significant difference ($p<0.05$) compared to controls

Both dementia groups took significantly longer to respond in the delayed face recognition task than the control group ($F_{(2,89)}=25.96, p<0.001$), but AD and DLB groups responded with equivalent latencies.

7.3.3 Working memory.

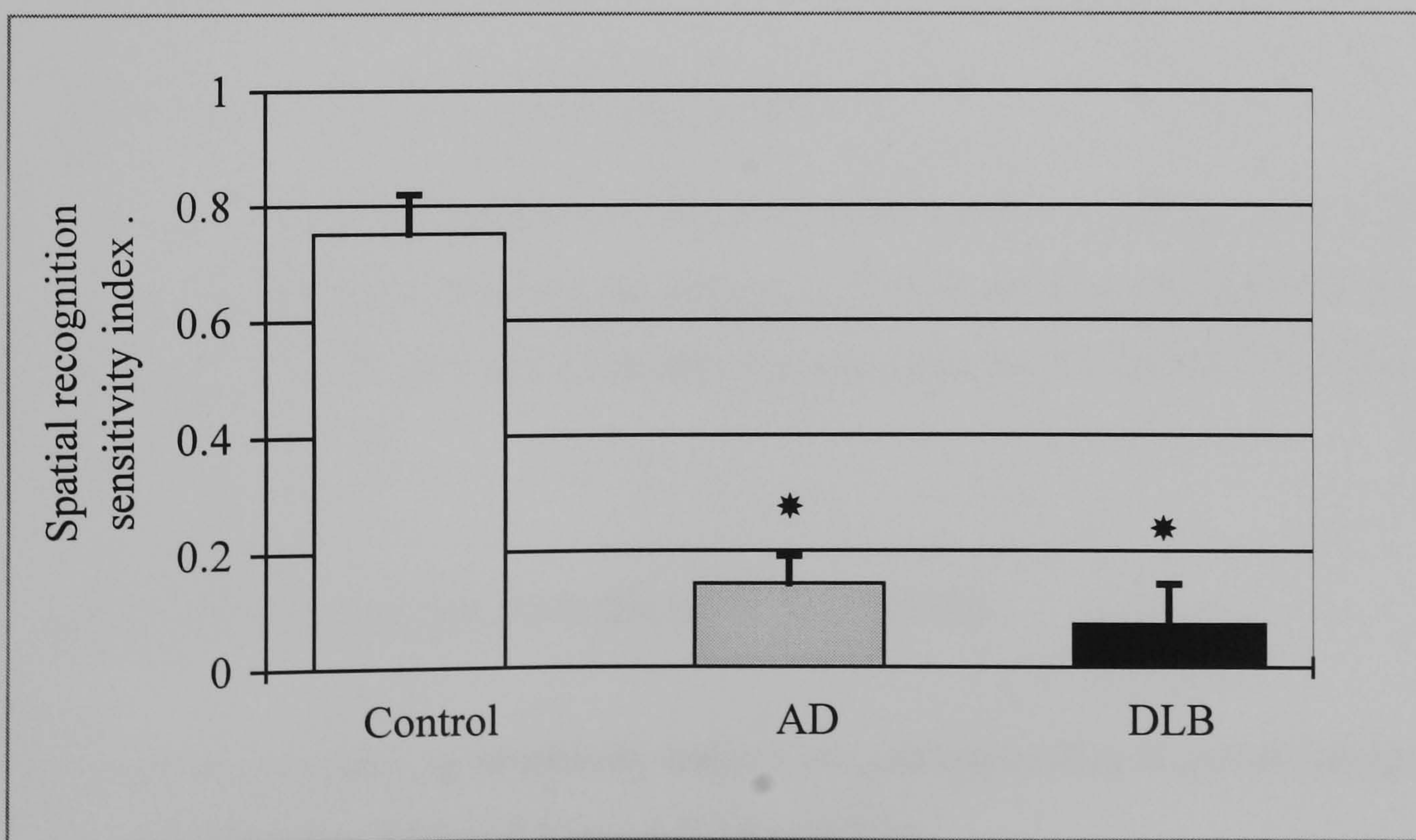
7.3.3.1 Spatial working memory.

Mean spatial working memory sensitivity indices and response latencies are presented in Table 7.15 and Figures 7.17 and 7.18.

Table 7.15: Spatial working memory: mean spatial recognition sensitivity index and response latencies for control, AD and DLB groups.

	Mean spatial recognition sensitivity index (\pm SEM)	Mean response latency (mS) (\pm SEM)
Control (n=26)	0.75 (\pm 0.068)	1276 (\pm 70)
AD (n=45)	0.14 (\pm 0.047)	3655 (\pm 443)
DLB (n=22)	0.07 (\pm 0.069)	3557 (\pm 478)

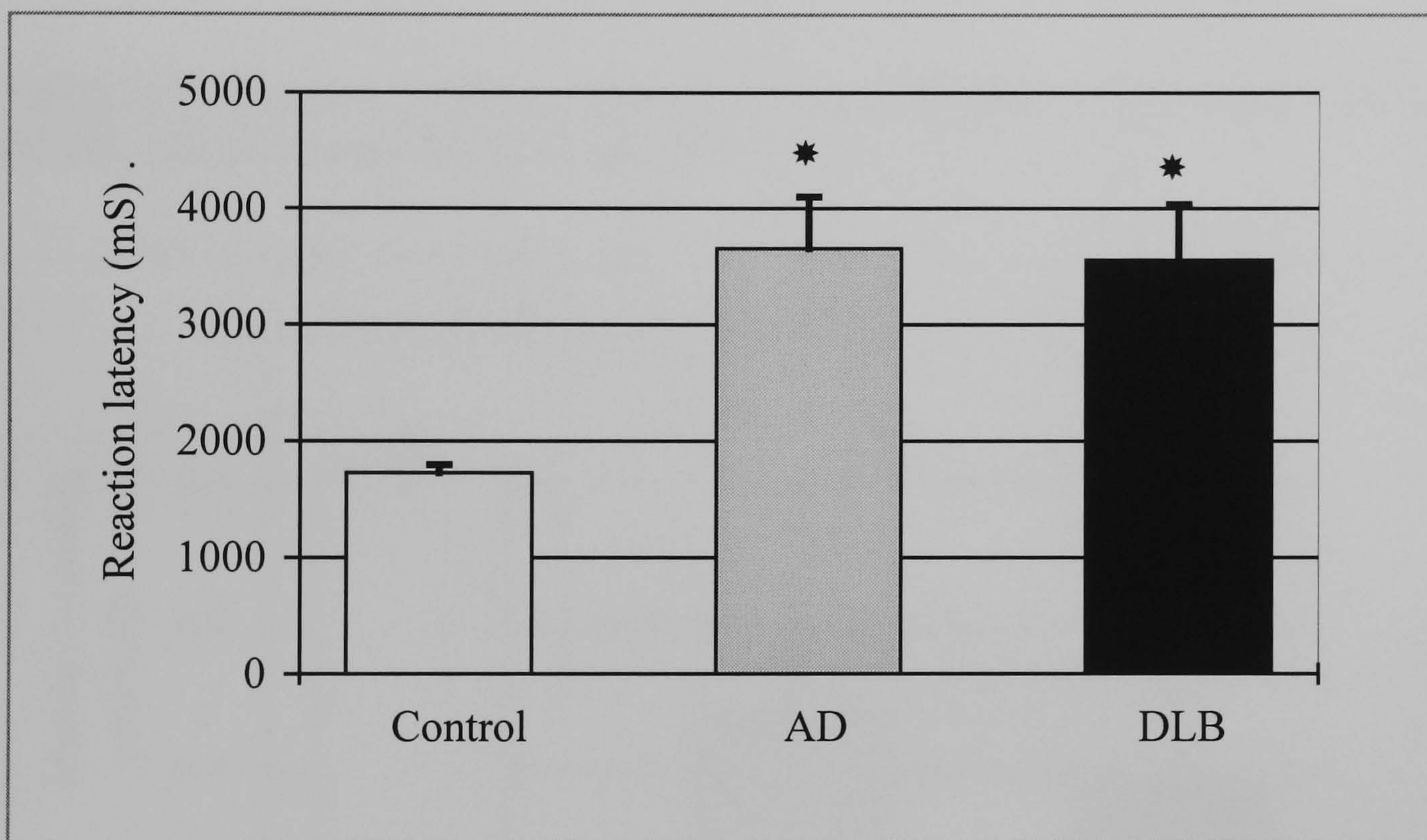
Figure 7.17: Spatial working memory: mean spatial recognition sensitivity index for control (n=26), AD (n=45) and DLB (n=22) groups.



* significant difference ($p < 0.05$) compared to controls

Both dementia groups were less able than the control group to recognise previously presented spatial locations and distinguish these from novel exemplars ($F_{(2,90)}=35.02$, $p<0.001$), but AD and DLB groups performed similarly on the spatial working memory task. Further post hoc analysis comparing the performance of each dementia groups performance to chance performance (sensitivity index of 0) indicated that although the AD group was performing above chance level ($t=3.02$, $p=0.002$), the DLB group was not performing above chance levels ($t=1.06$, n.s.).

Figure 7.18: Spatial working memory: mean reaction latencies (mS) (\pm SEM) for control (n=26), AD (n=45) and DLB (n=22) groups.



* significant difference ($p<0.05$) compared to controls

Analysis indicated that response latencies for both dementia groups on the spatial working memory task were significantly greater than reaction latencies for the control group ($F_{(2,90)}=28.77$, $p<0.001$), but the response latencies for AD and DLB groups were similar.

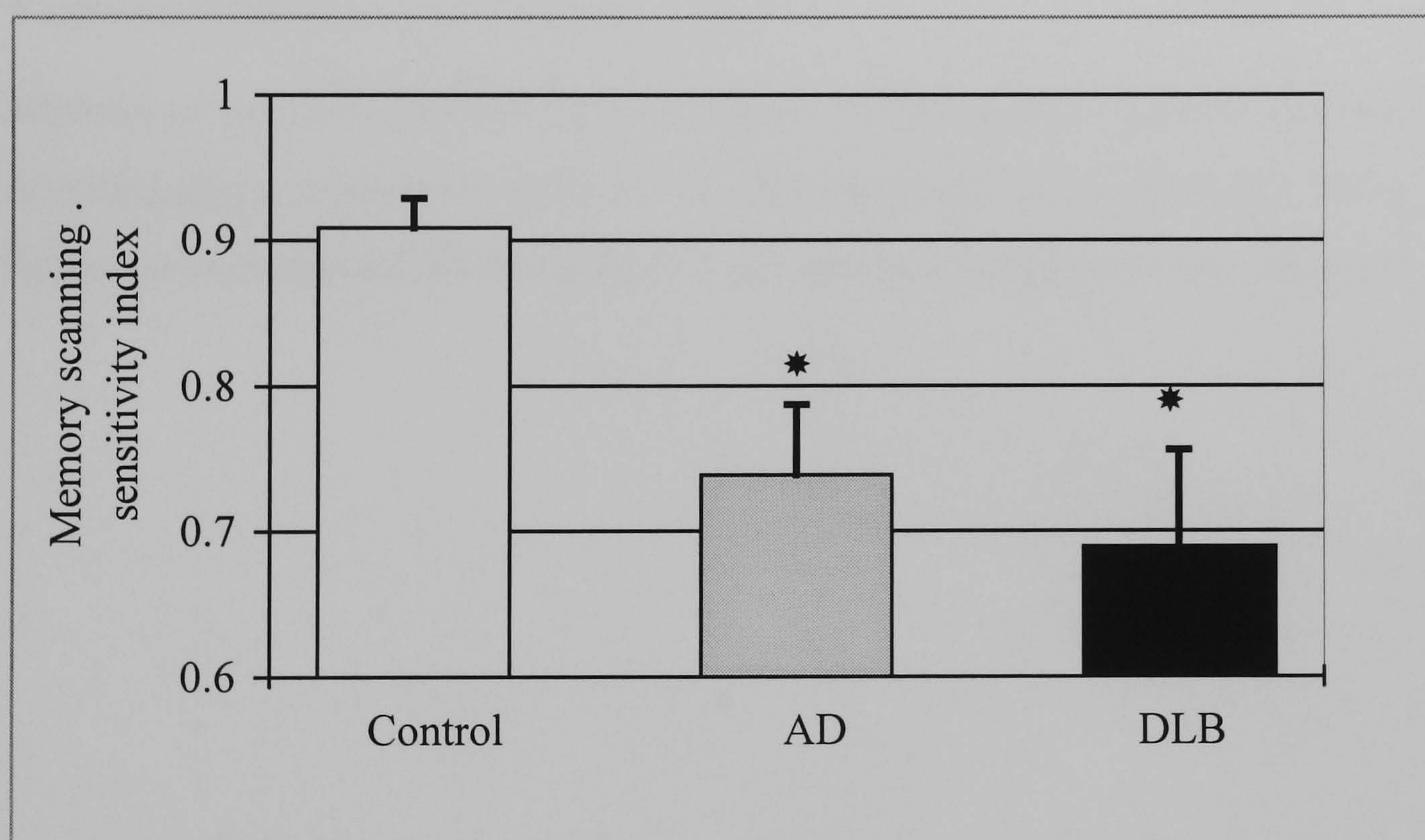
7.3.3.2 Memory scanning (numeric working memory).

Mean memory scanning sensitivity indices and corresponding response latencies are presented in Table 7.16 and Figures 7.19 and 7.20.

Table 7.16: Memory scanning: mean memory scanning sensitivity indices and response latencies for control, AD and DLB groups.

	Mean spatial recognition sensitivity index (±SEM)	Mean response latency (mS) (±SEM)
Control (n=26)	0.91 (±0.020)	805 (±32)
AD (n=45)	0.74 (±0.047)	2072 (±232)
DLB (n=22)	0.69 (±0.067)	2789 (±438)

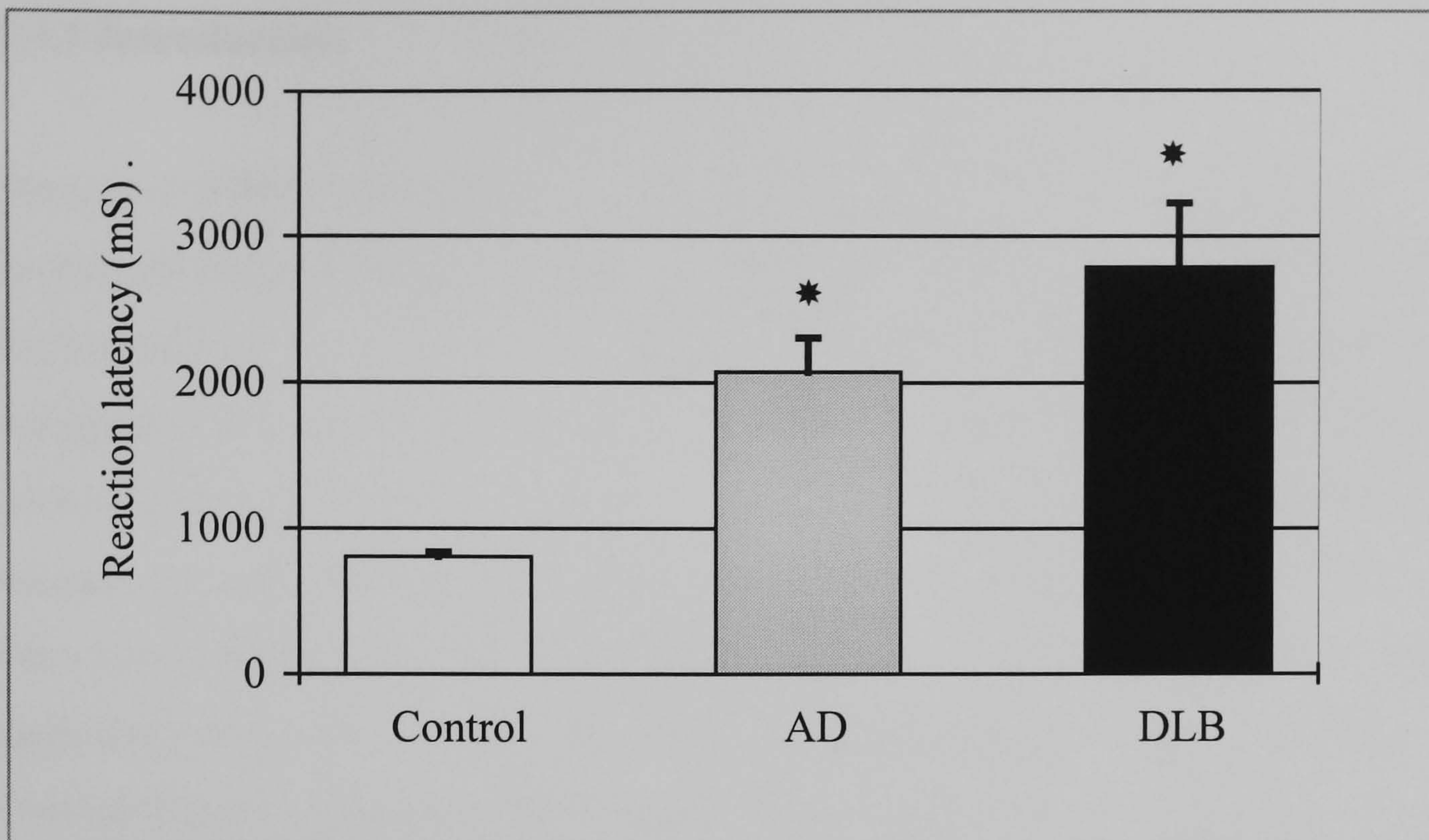
Figure 7.19: Memory scanning: mean memory scanning sensitivity indices for control (n=26), AD (n=45) and DLB (n=22) groups.



* significant difference ($p < 0.05$) compared to controls

Comparison of sensitivity indices for the memory scanning task indicated that both dementia groups were less able to discriminate the target and non-target numbers than controls ($F_{(2,90)}=4.42$, $p=0.015$), but there was no difference between AD and DLB groups.

Figure 7.20: Memory scanning: mean reaction latencies (mS) (\pm SEM) for control (n=26), AD (n=45) and DLB (n=22) groups.



* significant difference ($p < 0.05$) compared to controls

Analysis of response latencies for the memory scanning task indicated that both dementia groups responded more slowly than controls ($F_{(2,90)}=26.69$, $p < 0.001$). Response latencies for the AD and DLB groups was not significantly different.

7.4 Comparative analysis of cognitive function in hallucinating and non-hallucinating DLB groups, AD and controls.

7.4.1 Introduction

Perry et al (1990; 1994) have demonstrated that neocortical ChAT is more profoundly reduced for DLB cases with hallucinations (80% reduction) compared to DLB cases without hallucinations (50% reduction). An analysis was undertaken comparing DLB cases with and without persistent visual hallucinations to elderly controls and the AD group. McShane et al (1995; 1996) have demonstrated that patients with persistent rather than fleeting visual hallucinations are more likely to have Lewy body pathology, and that persistent hallucinations are less likely to be associated with poor eyesight. The dementia with Lewy body cases were hence divided into two subgroups based on the clinical identification of persistent visual hallucinations (VH) into a group with persistent visual hallucinations (DLB+VH) and a group without persistent visual hallucinations (DLB-VH).

The DLB+VH and the DLB-VH groups were compared to control and AD groups using single factor analysis of variance on transformed data as appropriate (Winer et al, 1991). Data analysed included demographic features as well as the primary outcome measures from the psychometric analyses (NART pre-morbid IQ, total CAMCOG score for overall cognitive impairment, and primary outcome measures from the CDR assessment battery). In the following presentation of statistical findings, figures are not drawn to illustrate findings when differences exist only between the control and three dementia groups. Where findings indicate significant differences between dementia groups these findings are illustrated in more detail.

7.4.2 Comparison of demographic features and non-computerised psychometric assessment in control, AD, DLB-VH, and DLB+VH groups.

Details of group means for age, mean estimated pre-morbid IQ (NART) and overall severity of cognitive impairment are described in Table 7.17. All four groups were matched for age and estimated pre-morbid IQ (NART). As expected, the control group showed less severe overall cognitive impairment as measured by the CAMCOG schedule than all dementia groups ($F_{(3,92)}=38.55, p<0.001$), although there were no differences in degree of overall cognitive impairment between the dementia groups.

Table 7.17: Comparative analysis of age, estimated pre-morbid IQ (NART), and overall severity of dementia (CAMCOG) in elderly controls, AD and DLB groups with (DLB+VH) and without (DLB-VH) clinically identified persistent visual hallucinations respectively.

	Control (n=26)	AD (n=46)	DLB-VH (n=10)	DLB+VH (n=14)	One-way ANOVA
Age	74.5 (±1.5)	80.1 (±1.1)	79.1 (±2.8)	76.4 (±1.8)	$F_{(3,92)}=3.39, p=0.02$
NART pre-morbid IQ	114.9 (±1.3)	110.4 (±1.2)	108.6 (±1.1)	109.2 (±1.3)	$F_{(3,92)}=2.99, p=0.04$
CAMCOG total score	99.4 (±0.9)	62.8 (±2.24)	65.2 (±5.8)	59.3 (±5.0)	$F_{(3,92)}=38.55, p<0.001$

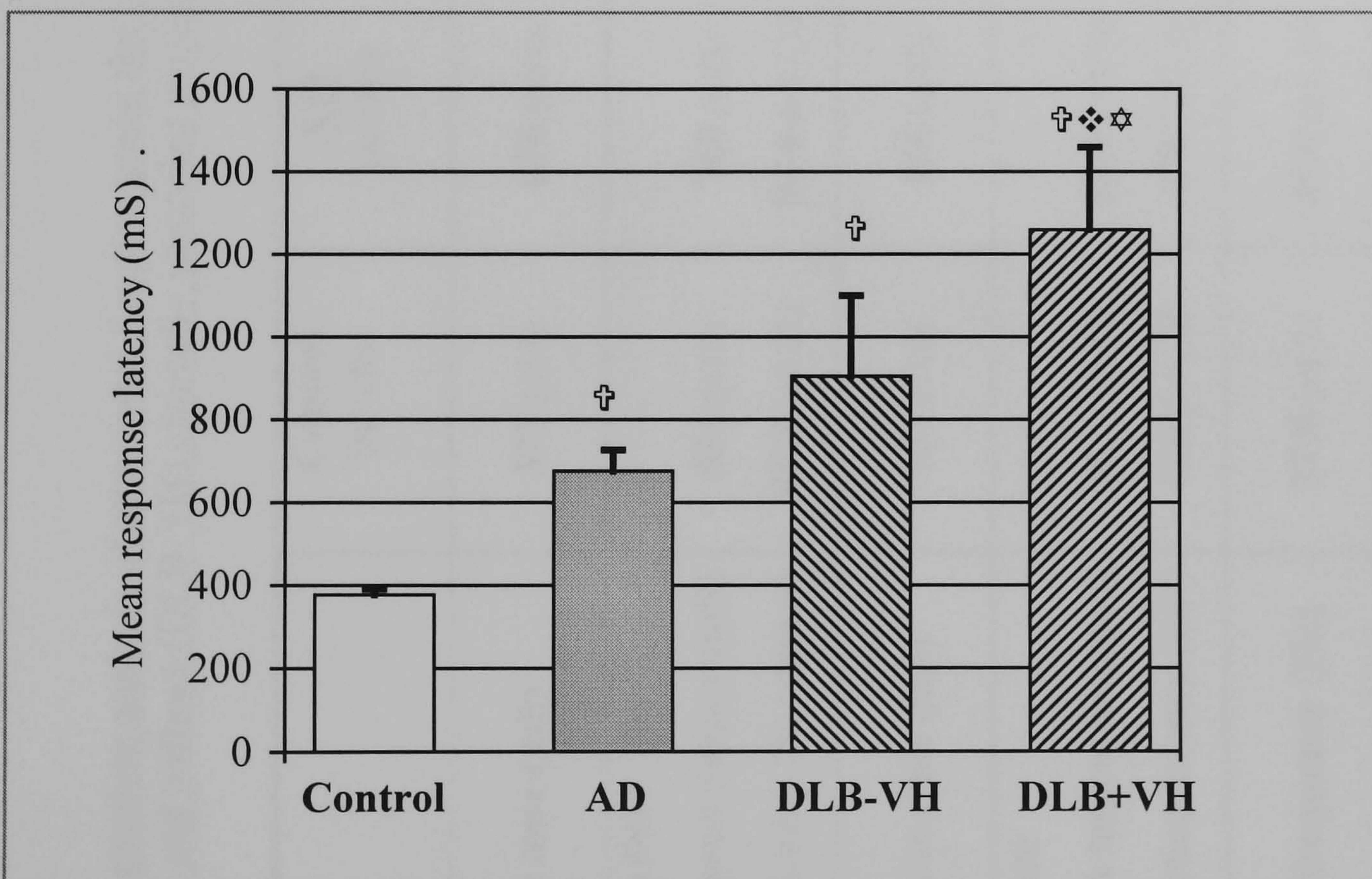
7.4.3 Attentional function.

Performance indices for tests of the computerised tests of attentional function are detailed in Table 7.18 and Figures 7.20, 7.21, and 7.22.

7.4.3.1 Simple reaction time (SRT).

Analysis indicated that all three dementia groups took longer to respond than controls on the simple reaction time task ($F_{(3,91)}=20.12$, $p<0.001$). In addition the DLB+VH group took longer to respond than both the AD and DLB-VH groups, although response latencies for the AD and DLB-VH groups were not significantly different.

Figure 7.21: Simple reaction time: mean response latencies (\pm SEM) for controls (n=26), AD (n=45), DLB-VH (n=10), and DLB+VH (n=14) groups.



- † significant difference ($p<0.05$) compared to controls
- ❖ significant difference ($p<0.05$) compared to AD
- ☆ significant difference ($p<0.05$) compared to DLB-VH

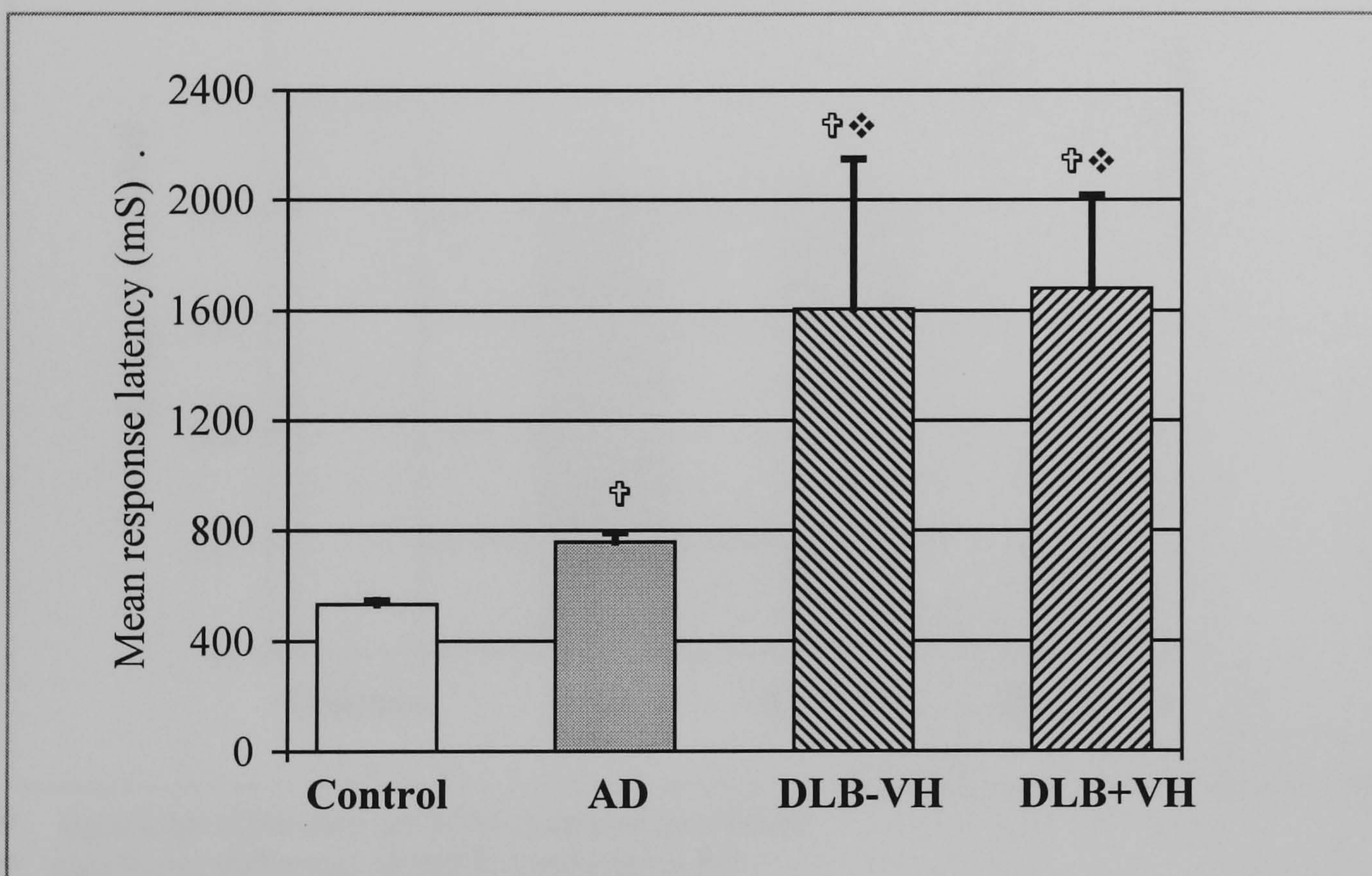
Table 7.18: Comparative analysis of attentional function using the CDR assessment battery for elderly controls, AD, and DLB groups with (DLB+VH) and without (DLB-VH) clinically identified persistent visual hallucinations.

	Control (n=26)	AD (n=46)	DLB-VH (n=10)	DLB+VH (n=14)	One-way ANOVA
Simple reaction time (mS)	377 (±15)	676 (±51)	905 (±194)	1259 (±200)	$F_{(3,91)}=20.12, p<0.001$
Choice reaction time					
Response latency (mS)	534 (±12)	760 (±33)	1604 (±547)	1680 (±340)	$F_{(3,90)}=20.42, p<0.001$
Accuracy (% correct)	95.8 (±0.72)	94.6 (±1.11)	95.0 (±2.11)	85.0 (±5.94)	F<1, N.S.
Cognitive reaction time (mS)	157 (±12)	156 (±27)	713 (±445)	414 (±183)	$F_{(3,90)}=2.75, p=0.05$
Number vigilance					
Accuracy (% targets detected)	98.9 (±0.48)	82.9 (±3.75)	84.7 (±8.20)	42.4 (±8.14)	$F_{(3,91)}=18.78, p<0.001$
Reaction latency (mS)	498 (±11.2)	609 (±21.2)	649 (±32)	647 (±41)	$F_{(3,91)}=10.57, p<0.001$
Critical flicker frequency (Hz)	37.8 (±0.71)	35.9 (±2.25)	32.4 (±1.85)	31.0 (±1.73)	F<1, N.S.

7.4.3.2 Choice reaction time (CRT).

Accuracy of responses in the choice reaction time task was similar for all groups (see Table 7.18). Response latencies for the reaction time task were significantly greater for all dementia groups than the control group. Furthermore, both DLB-VH and DLB+VH groups responded significantly slower than the AD group ($F_{(3,90)}=20.42, p<0.001$), although the response latencies did not differ for the two DLB groups.

Figure 7.22: Choice reaction time: mean response latencies (\pm SEM) for controls (n=26), AD (n=45), DLB-VH (n=10), and DLB+VH (n=13) groups.



† significant difference ($p<0.05$) compared to controls

❖ significant difference ($p<0.05$) compared to AD

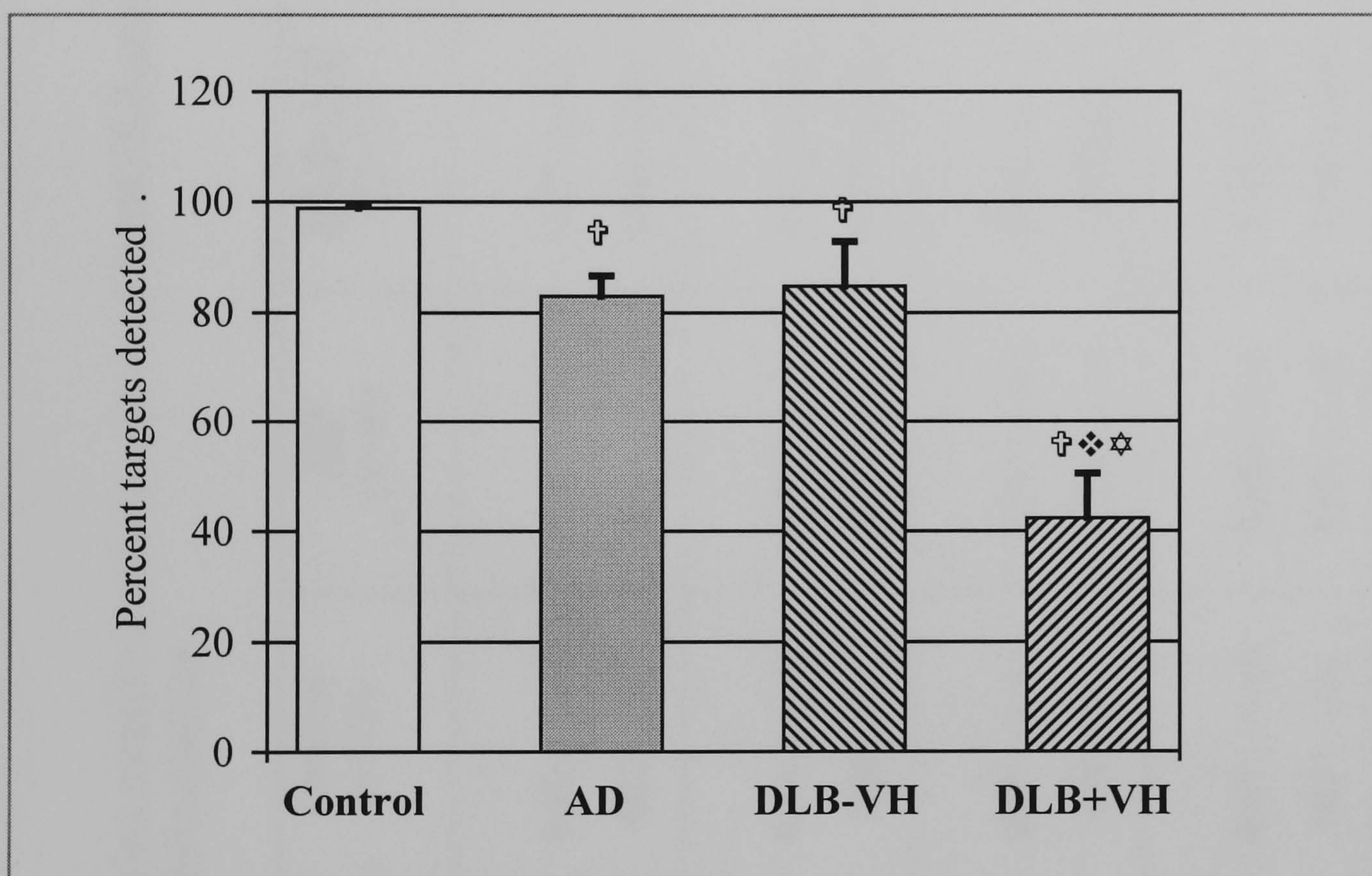
7.4.3.3 Cognitive reaction time

Analysis indicated a main effect of group for cognitive reaction times ($F_{(3,90)}=2.75, p=0.05$), however, subsequent analyses indicated no significant differences between groups.

7.4.3.4 Digit vigilance task.

The percentage of targets digits detected in the number vigilance task was greater in the control group than all of the dementia groups ($F_{(3,91)}=18.78$, $p<0.001$). In addition, the percentage of target digits detected was less in the DLB+VH group than in the DLB-VH and AD group, although the DLB-VH and AD group performed equivalently.

Figure 7.23: Digit vigilance task: mean percent of target digits detected (\pm SEM) for control (n=26), AD (n=45), DLB-VH (n=10), and DLB+VH (n=14) groups.



- † significant difference ($p<0.05$) compared to controls
- ♦ significant difference ($p<0.05$) compared to AD
- ☆ significant difference ($p<0.05$) compared to DLB-VH

Response latencies for the number vigilance task were greater in all of the dementia groups than the control group ($F_{(3,91)}=10.57$, $p<0.001$), however, there were no differences in response latencies between dementia groups. All group means for response latencies were within the 1250 mS response window for the digit vigilance task (see Table 7.18).

7.3.4.5 Critical flicker fusion.

Analysis indicated no group differences on the critical flicker fusion task.

Table 7.19: Comparative analysis of secondary memory in elderly controls, AD and DLB groups with (DLB+VH) and without (DLB-VH) clinically identified persistent visual hallucinations.

	Control (n=26)	AD (n=46)	DLB-VH (n=10)	DLB+VH (n=14)	One-way ANOVA
Immediate word recognition					
Sensitivity index	0.89 (±0.02)	0.36 (±0.05)	0.37 (±0.12)	0.41 (±0.07)	$F_{(3,92)}=22.72, p<0.001$
Reaction latency (mS)	902 (±28)	3482 (±340)	2866 (±846)	3311 (±521)	$F_{(3,92)}=30.15, p<0.001$
Delayed word recognition					
Sensitivity index	0.84 (±0.03)	0.27 (±0.05)	0.41 (±0.09)	0.43 (±0.07)	$F_{(3,91)}=11.80, p<0.001$
Reaction latency (mS)	908 (±35)	2493 (±306)	1971 (±311)	3330 (±655)	$F_{(3,91)}=34.85, p<0.001$
Delayed picture recognition					
Sensitivity index	0.87 (±0.02)	0.38 (±0.04)	0.46 (±0.11)	0.28 (±0.08)	$F_{(3,90)}=22.72, p<0.001$
Reaction latency (mS)	978 (±35)	2700 (±229)	1945 (±218)	3756 (±701)	$F_{(3,90)}=30.15, p<0.001$
Delayed face recognition					
Sensitivity index	0.67 (±0.04)	0.30 (±0.04)	0.42 (±0.10)	0.20 (±0.10)	$F_{(3,90)}=11.80, p<0.001$
Reaction latency (mS)	1017 (±35)	2451 (±263)	1947 (±283)	3652 (±928)	$F_{(3,90)}=34.85, p<0.001$

7.4.4 Secondary memory.

Data pertaining to group performance in the CDR secondary memory tests is detailed in Table 7.19, and Figures 7.24, 7.25, and 7.26.

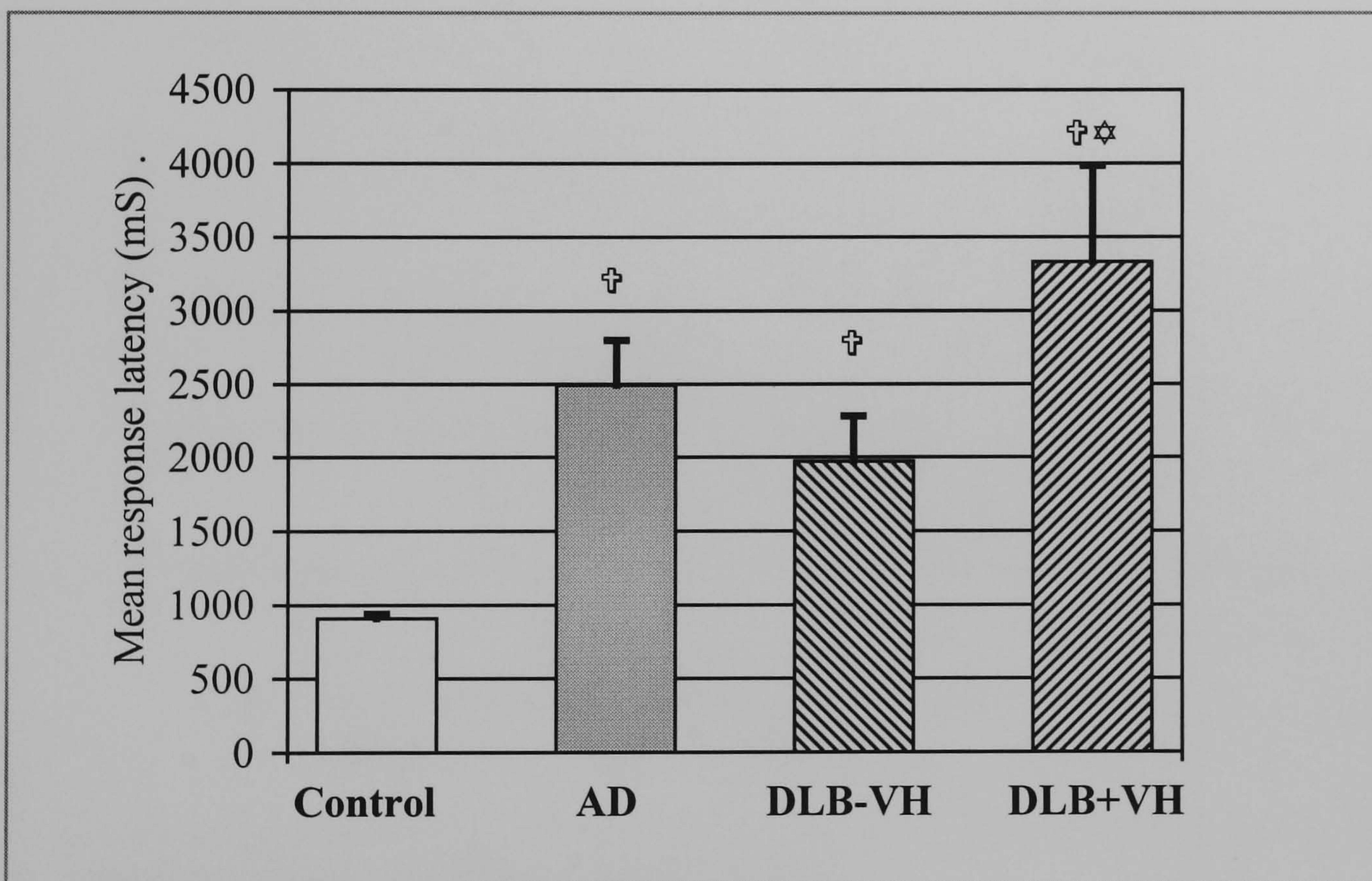
7.4.4.1 Immediate word recognition.

In the immediate word recognition task all dementia groups were less able than controls to discriminate between previously seen words and novel distracter words ($F_{(3,92)}=22.06$, $p<0.001$). There were, however, no differences in recognition sensitivity indices between the AD, DLB-VH and DLB+VH groups. A similar pattern of performance was observed for responses latencies in the immediate word recognition task, all patient groups took longer to respond than controls ($F_{(3,92)}=27.09$, $p<0.001$) but there were no differences between dementia groups.

7.4.4.2 Delayed word recognition.

Analysis of sensitivity indices for the delayed word recognition task revealed the control group's discrimination between previously seen words and novel exemplars was significantly better than all of the dementia groups ($F_{(3,91)}=24.87$, $p<0.001$), however there were no differences between the dementia groups. Response latencies for the control group were significantly greater for all dementia groups than controls ($F_{(3,91)}=24.67$, $p=0.001$). Furthermore, the DLB+VH group took longer to respond than the DLB-VH group. All other comparisons were non-significant.

Figure 7.24: Delayed word recognition: mean response latencies (\pm SEM) for control (n=26), AD (n=45), DLB-VH (n=10), and DLB+VH (n=14) groups.

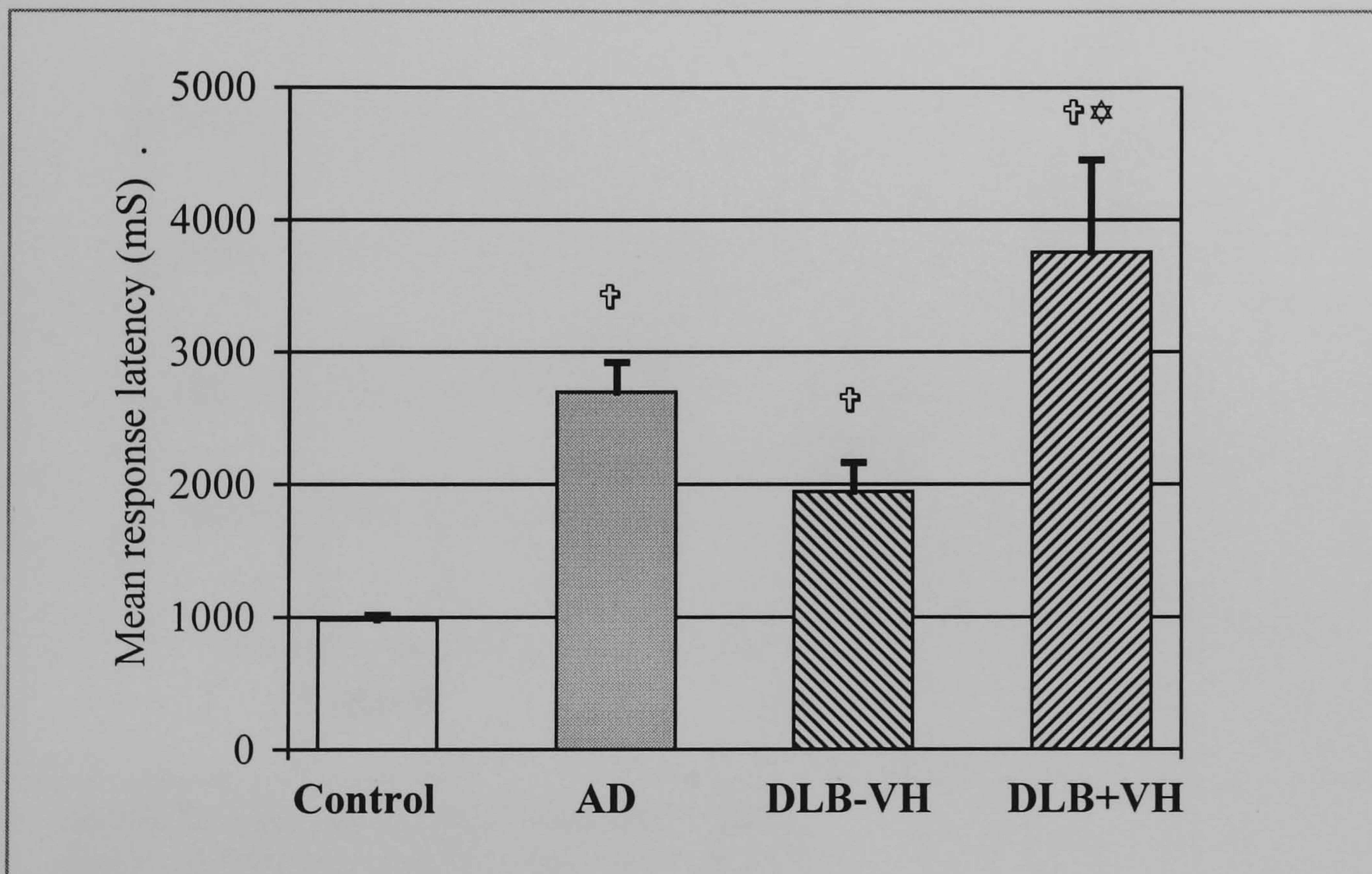


- † significant difference ($p<0.05$) compared to controls
- ☆ significant difference ($p<0.05$) compared to DLB-VH

7.4.4.3 Delayed picture recognition.

The sensitivity index for the control group was significantly greater than for all dementia groups ($F_{(3,90)}=22.72, p<0.001$), however pair-wise comparisons indicated no significant difference between dementia groups. Response latencies for the control group were shorter than the response latencies for all three dementia groups ($F_{(3,90)}=30.15, p<0.001$). In addition, the DLB+VH group took longer to respond than the DLB-VH group. All other comparisons between dementia groups failed to reach significance.

Figure 7.25: Delayed picture recognition: mean response latencies (\pm SEM) for control (n=26), AD (n=44), DLB-VH (n=10), and DLB+VH (n=14) groups.



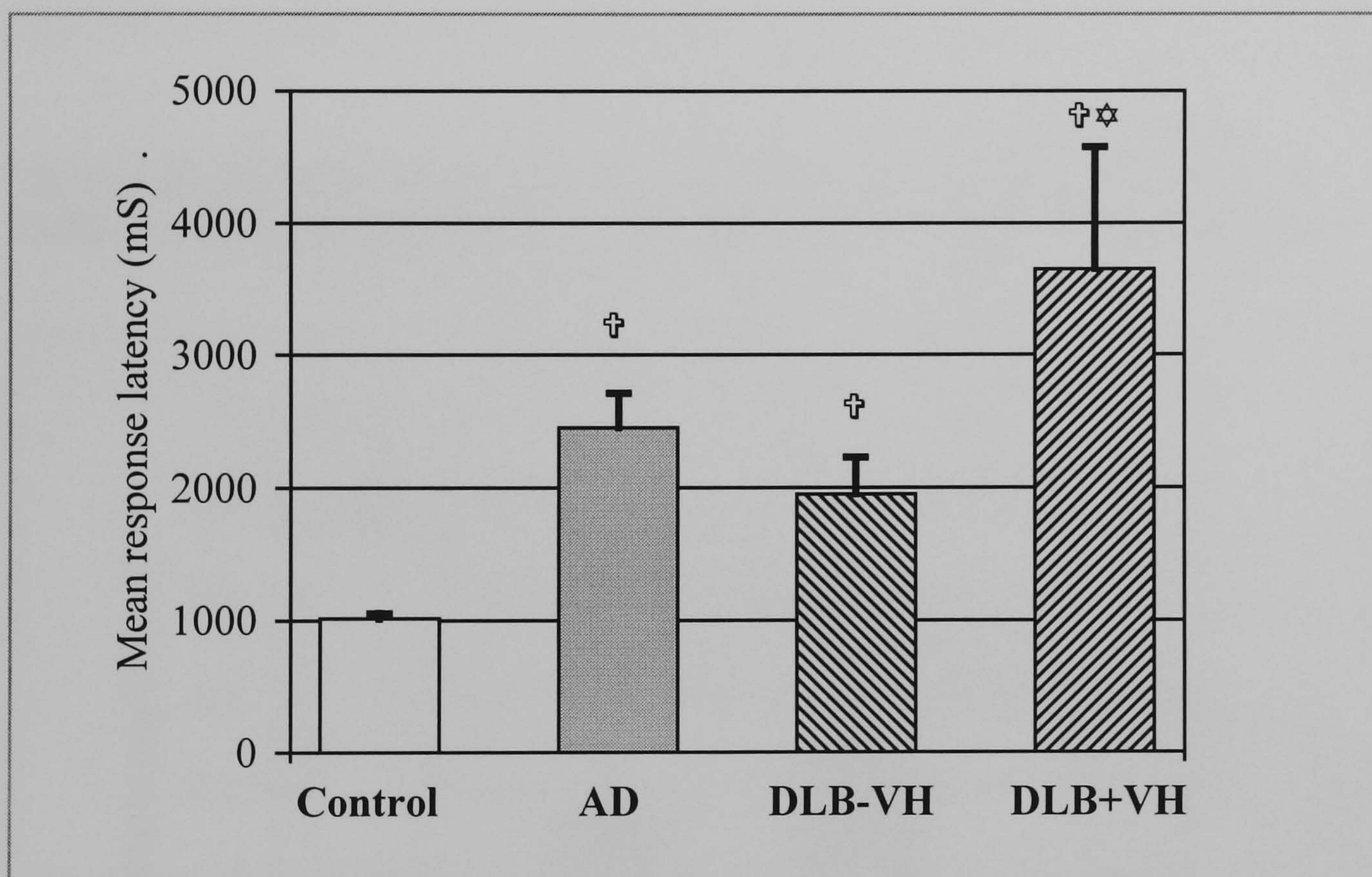
† = significant difference ($p<0.05$) compared to controls

☆ = significant difference ($p<0.05$) compared to DLB-VH

7.4.4.4 Delayed face recognition.

On the delayed face recognition task, all dementia group's sensitivity indices were less than controls ($F_{(3,88)}=11.80, p<0.001$), although there were no differences between the dementia groups. Analysis of response latencies indicated a similar pattern to that seen for delayed word and picture recognition. The DLB+VH group took significantly longer to respond than the DLB-VH group, but all other comparisons between dementia groups were non-significant.

Figure 7.26: Delayed face recognition: mean response latencies (\pm SEM) for control (n=26), AD (n=44), DLB-VH (n=10), and DLB+VH (n=12) groups.



† significant difference ($p<0.05$) compared to controls

☆ significant difference ($p<0.05$) compared to DLB-VH

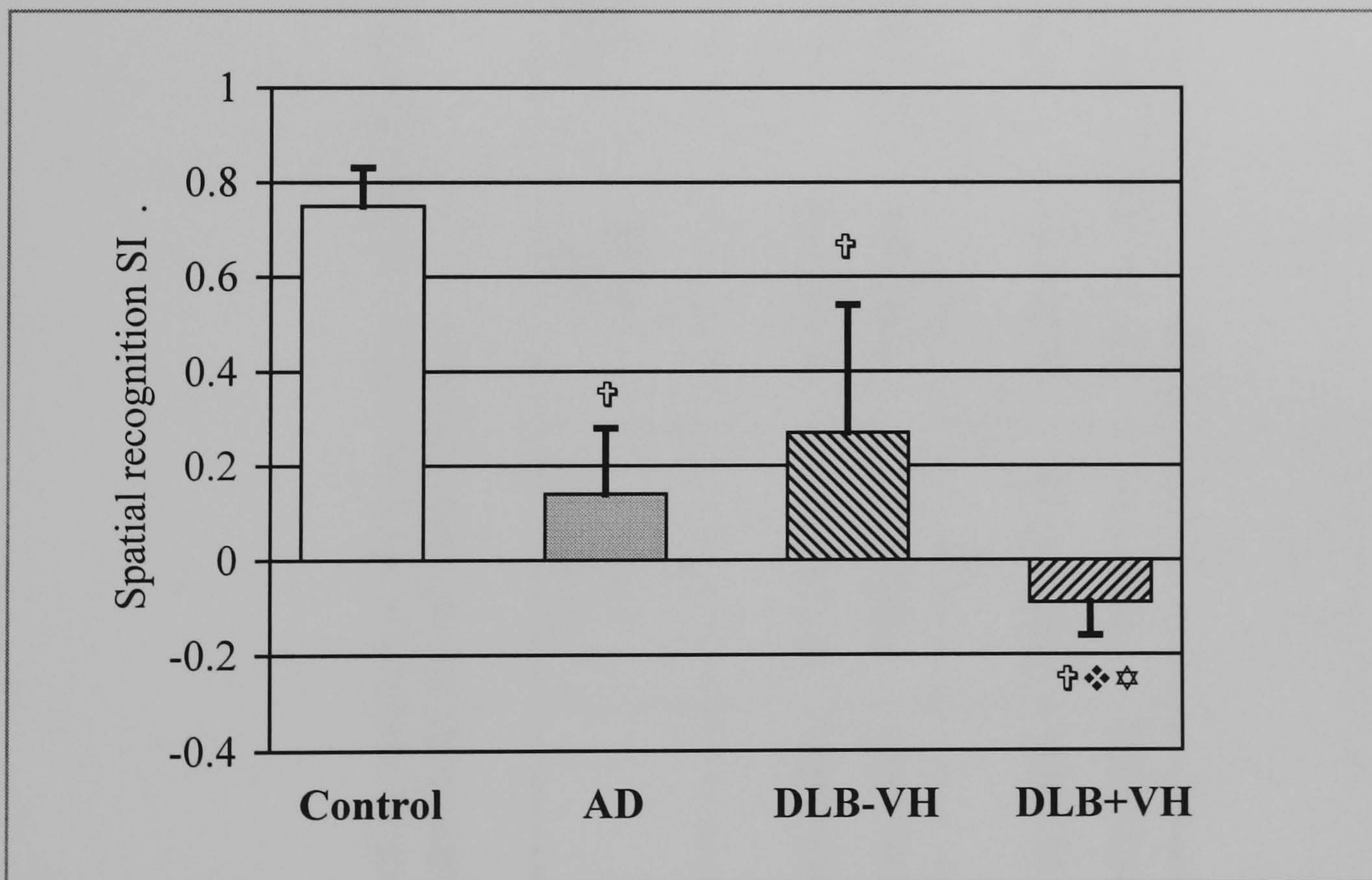
7.4.5 Working memory.

Data pertaining to group performance in the CDR working memory tasks are presented in Table 7.20.

7.4.5.1 Spatial working memory.

The control group was better able than all three dementia groups to discriminate previously seen locations from novel exemplars ($F_{(3,89)}=27.29, p<0.001$). In addition, the DLB+VH group had a significantly lower mean spatial memory sensitivity index than the DLB-VH and AD group. The sensitivity indices for the DLB-VH and AD groups were similar (see Figure 7.26).

Figure 7.26: Spatial working memory: mean sensitivity indices (\pm SEM) for controls (n=26), AD (n=45), DLB-VH (n=10), and DLB+VH (n=12) groups.



† significant difference ($p<0.05$) compared to controls; † significant difference ($p<0.05$) compared to AD; ☆ significant difference ($p<0.05$) compared to DLB-VH

Sensitivity indices for each of the dementia groups were compared to chance performance (sensitivity index = 0.0) using single sample t-tests. Performance significantly above chance was observed for both the AD ($t=3.03, p=0.004$) and

Table 7.20: Comparative analysis of working memory in elderly controls, AD and DLB groups with (DLB+VH) and without (DLB-VH) clinically identified persistent visual hallucinations.

	Control (n=26)	AD (n=46)	DLB-VH (n=10)	DLB+VH (n=14)	One-way ANOVA
Spatial memory					
Sensitivity index	0.75 (±0.08)	0.14 (±0.05)	0.27 (±0.10)	-0.09 (±0.07)	F_(3,89)=27.29, p<0.001
Reaction latency (mS)	1276 (±242)	3655 (±443)	3456 (±885)	3641 (±514)	F_(3,89)=16.46, p<0.001
Memory scanning					
Sensitivity index	0.91 (±0.08)	0.74 (±0.05)	0.72 (±0.16)	0.67 (±0.36)	F_(3,89)=2.98, p=0.036
Reaction latency (mS)	805 (±32)	2072 (±232)	2472 (±692)	3053 (±576)	F_(3,89)=18.36, p<0.001

DLB-VH ($t=2.67$, $p=0.03$) groups, however, the DLB+VH group did not perform at above chance levels.

Analysis of the response latencies for indicated that all dementia groups responded significantly slower than controls ($F_{(3,89)}=16.46$, $p<0.001$), however, all three dementia groups responded following similar latencies.

7.4.5.2 Numeric working memory.

Comparison of group sensitivity indices failed to discriminate between any of the groups. Analysis of response latencies indicated that all dementia groups responded slower than controls ($F_{(3,89)}=16.46$, $p<0.001$), however response latencies for all three dementia groups were similar.

7.5 Additional comparisons of groups based on clinical symptoms.

Additional comparisons were intended between dementia cases with and without major depression, however, a paucity of cases with clinically diagnosed major depression (AD $n=4$; DLB $n=3$) precluded such a comparison on statistical grounds.

Furthermore, intended investigations to establish the relationship between clinically identifiable fluctuating cognitive impairment and cognitive function in DLB cases also proved statistically non-viable. The clinical identification of fluctuating impairment was made in all but one of the DLB cases in the cohort for this study.

Chapter 8:

A comparative study of cognitive performance in DLB, AD, and elderly controls using the Cognitive Drug Research Computerised Assessment Battery (CDR): Discussion

8.1 Introduction.

This body of work is the largest prospective comparison of DLB, AD and control groups to date. Intra-group comparison of probable and possible diagnostic categories indicated no differences in cognitive performance in either AD or DLB groups. Subsequent comparative analysis of controls with pooled (i.e. both probable and possible categories) AD and DLB groups demonstrated impairment in the dementia groups in all areas of cognitive function examined.

The AD and DLB groups, who were carefully matched for global severity of cognitive impairment, showed distinct profiles of differences in performance on several measures of cognitive function. The DLB group showed particularly poor attentional function and relatively, preserved delayed verbal recognition memory compared to the AD group. Such a double dissociation of AD and DLB groups on tests of attentional and mnemonic function further support DLB as a form of dementia with a profile of cognitive impairment distinct from AD.

Similar performance in the two dementia groups was observed on a number of measures. Although impaired on both tests of working memory compared to controls, numeric working memory was relatively preserved in both dementia groups compared to visuo-spatial working memory. Further, immediate word recognition, as well as secondary pictorial and face recognition memory, were markedly impaired in both dementia groups, though the analysis failed to distinguish between them.

A comparison of controls, AD and DLB groups with persistent visual hallucinations (DLB+VH) and without (DLB-VH) persistent visual hallucinations

found both DLB groups to be distinct from the AD group. Furthermore, the DLB+VH group showed a distinct profile of impairment from the DLB-VH group. The number of hallucinating AD patients was too small (n=4) to allow useful comparison with non-hallucinating AD patients.

Many, but not all, of the differences described between DLB and AD groups may be associated with the presence of visual hallucinations in the DLB group. The DLB+VH group showed particularly poor attentional function, demonstrated by poor performance on the simple reaction time and digit vigilance tasks. Although similar sensitivity indices were seen for all dementia groups on all delayed secondary memory tasks, the DLB+VH group showed longer response latencies. The DLB+VH group performed at chance level and worse than both the AD and DLB-VH groups on the spatial working memory task. All groups showed similar performance on the numeric working memory task.

These data suggest that hallucinations and poor cognitive function co-exist and might be produced by a common underlying mechanism such as particularly reduced cholinergic function in the DLB+VH group. The DLB group without persistent visual hallucinations also showed a profile of cognitive impairment distinct from the AD group, but a statistically significant difference was found only on a single task (choice reaction time).

8.2 The comparative neuropsychology of DLB and AD

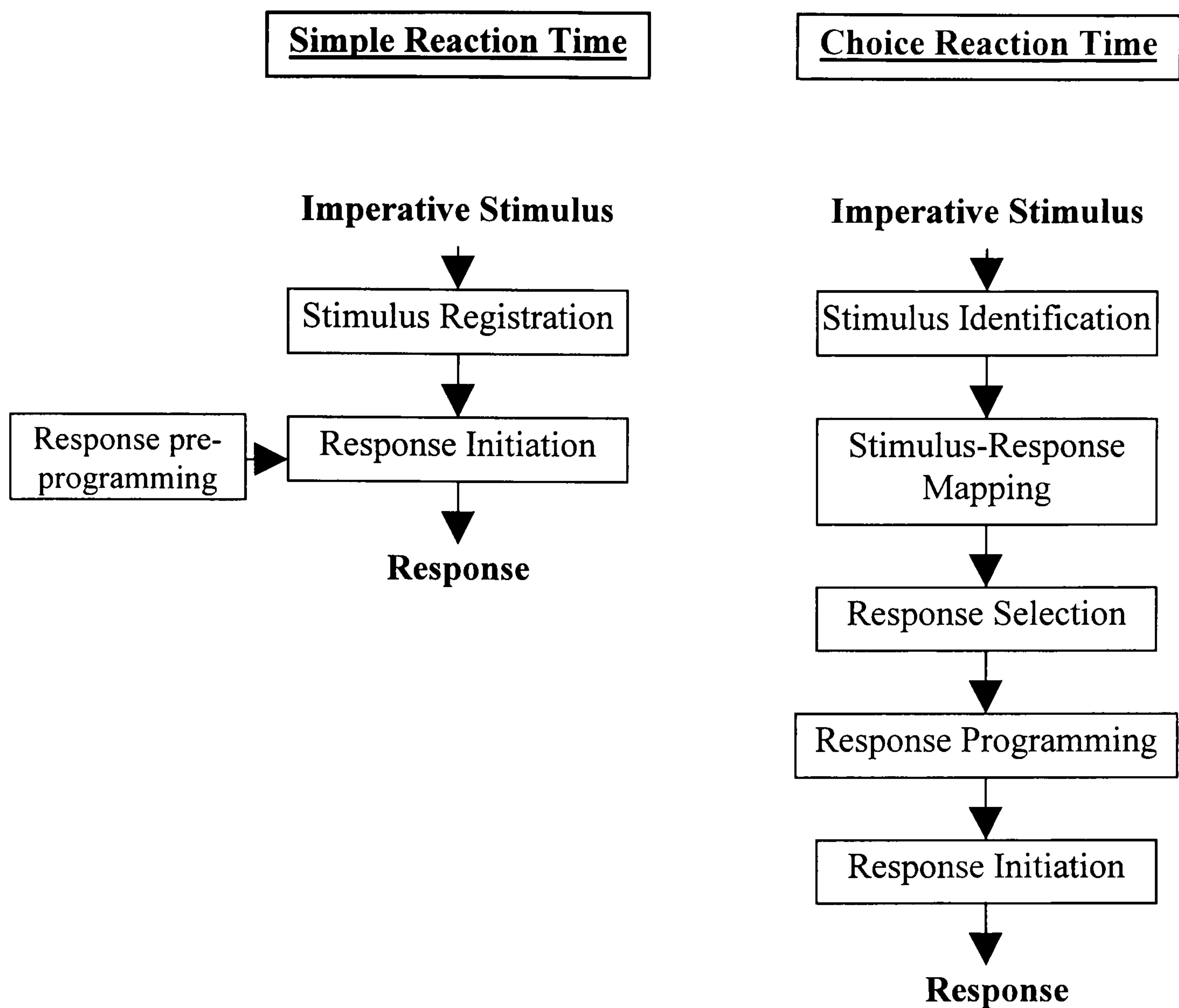
8.2.1 Attentional deficits in AD and DLB.

8.2.1.1 Simple and choice reaction times.

Many studies investigating 'intensive' aspects of attention (alertness and power of concentration) have employed reaction times as an index of available processing resources. Although it is possible to have relatively specific or restricted deficits in selective attention, any disruption of the intensive components will inevitably exert more widespread detrimental effects upon information-processing.

Simple reaction time, as its name implies, invokes relatively elementary information-processing skills, and is also procedurally comparatively simple. Performance on the simple reaction time task is contingent on a number of factors, including: motor response speed (neural conduction velocity, and effector and muscular response); exteroceptor operations; and the central stimulus-response integration. The stimulus-response integration requires attentional components, such as the ability to develop and maintain an appropriate state of readiness to respond to the stimulus. In simple reaction time tasks the stimuli and response are the same on every trial, so identification and encoding of the response are not required. The participant can, therefore, pre-programme the response, which only needs to be initiated when the imperative stimulus is registered. Choice reaction time also involves all of the underlying components of simple reaction time, but requires additional central processing. The participant must, additionally, discriminate stimuli and make contingent responses. This prevents pre-programming of responses possible in simple reaction time. Cognitive models of uncued simple and choice reaction time are shown in Figure 8.1.

Figure 8.1: Cognitive processing involved in uncued simple and choice reaction time tasks adapted from Jahanshahi et al (1992a).



Simple reaction times were markedly slower in both dementia groups than controls. In addition, the DLB group responded more slowly than the Alzheimer's disease group. A similar pattern of performance was observed in the choice reaction time task in which response latencies were in the order: control < AD < DLB. All groups responded with similar accuracy on the choice reaction time task.

The relationship between the simple and choice response latencies and clinical measures of motor impairment in the DLB and AD groups were investigated using correlational analysis. There were no significant correlations between clinical measures of motor impairment (bradykinesia score and overall Unified Parkinson's Disease Rating Scale score) and measures of performance on the

reaction time tasks (response latencies SRT + CRT) or accuracy (choice reaction time). Previous studies have demonstrated that the short ballistic finger movements that constitute responses in the CDR reaction time tasks are easily pre-programmed (Klapp, 1975; Bloxham et al, 1984). Thus, the increased response latencies in the DLB group, particularly on the simple reaction time task, is unlikely to reflect an inability to pre-programme the simple motor response required.

Studies investigating simple and choice reaction time in PD patients have generally described simple reaction times of around 500 milli-seconds, although numerous studies have failed to discriminate PD and control groups on measures of simple and choice reaction time (Jahanshahi et al, 1992a; 1992b; Pate et al, 1994). The response latencies of the non-demented PD patients (~500 milli-seconds), with similar motor difficulties to the DLB group, are noticeably shorter than those observed for the DLB group (~1150 milli-seconds) investigated in this study. This provides further support for the assertion that motor disability is unable to account for the markedly increased response latencies of the DLB group in the simple and choice reaction time tasks.

The lack of association between reaction times and clinical measures of motor impairment in DLB, and the longer simple reaction times observed in the DLB group compared to previous studies investigating PD patients with similar motor difficulties, suggest that the particularly poor performance of the DLB group be a consequence of disruption of intensive aspects of attentional function. This would appear to be a predominant feature of the cognitive impairment associated with DLB.

8.2.1.2 Cognitive reaction time.

The measure of cognitive reaction time described in this study represents the mean differences between simple and choice reaction times. Cognitive reaction time is a means of studying the information-processing requirements distinguishing these tasks, whilst controlling for perceptuo-motor dysfunction. Based on the cognitive

model proposed by Jahanshahi et al (1992a), cognitive reaction time is comprised of the time taken between registration of a stimulus and its identification, the mapping of stimuli to the appropriate responses, and the selection and programming of the contingent response.

Cognitive reaction time was not increased in the AD group compared to controls. However, there is a marked increase in the cognitive reaction time of the DLB group. This suggests that 'central processing' speed in the DLB group is slower than in the AD and control groups. Slowing of central processing speed may reflect difficulties in any one of the individual cognitive processes which distinguish simple and choice reaction time. Equally, the slowed cognitive reaction time may reflect a general slowing of processing speed (bradyphrenia), which is apparent for all of the components of cognitive reaction time.

Bradyphrenia is a generic term describing slowing of thought processes and describes similar slowing of information-processing to the increased cognitive reaction times described in this study. Numerous studies have demonstrated bradyphrenia in PD (e.g. Cummings, 1986; Pate et al, 1994), although these findings are not equivocal (e.g. Bloxham et al, 1987). Wesnes (1996) found cognitive reaction time in AD to be similar to controls in a large comparative study. Data from the current study support similar cognitive reaction times in AD and control groups. Furthermore, Wesnes et al (1996) demonstrated no increase in cognitive reaction time in normal young controls who were administered doses of scopolamine sufficient to induce a broad range of cognitive impairment in other cognitive domains. It is therefore possible that the slowed cognitive reaction time in the DLB group is not principally related to cholinergic dysfunction, and may be due to the other fundamental neurochemical abnormality in DLB, namely depletion of dopaminergic nigro-striatal cells.

8.2.1.3 Sustained attention in DLB.

The digit vigilance task in the CDR battery is similar to the Continuous Performance test originally developed by Rosvold et al (1956). This test requires the participant to sustain intensive attentional resources on a task over a relatively short period of time. The DLB group showed marked impairments compared to AD and control groups; the DLB patients being unable to sustain intensive attentional resources for the duration of this relatively brief vigilance test.

This is the first study to directly assess sustained attention in DLB. Previous work (e.g. McKeith et al, 1992c, 1996a) has identified fluctuation and idiopathic clouding of consciousness as a prominent feature of DLB. This has been included in diagnostic criteria as a feature supportive of a diagnosis of DLB. The DLB group's problems in sustaining attention may represent a neuropsychological quantification of the gross fluctuations and idiopathic clouding of consciousness observed in DLB.

To elucidate the causality of observed deficits on the digit vigilance task, the possibility that motor impairments contribute to the poor performance must be considered. To correctly identify target digits in the digit vigilance task, participants must respond within 1.25 seconds of the target digit presentation. Thus, slow responses might contribute to the poor digit vigilance performance in the DLB group. This notion might be supported by the observation that the number of false alarm responses was significantly greater in the DLB than control group. However, the number of false alarms made by the DLB and AD groups was not statistically different.

Examination of false alarms made by the DLB group revealed that 31% of the false alarms were made between two correctly detected target digits and cannot be attributed to slow responses. The remaining 69% of the false alarms made by the DLB group were not made between successive, correctly detected target digits. It is possible that these false alarms were due to slow motor responses, to the preceding target digits, which were outside the 1.25 second response window.

However, the CDR system allows calculation of the time elapsed between presentation of the last target digit and each false alarm. For false alarms not occurring between two successive correctly detected target digits, the mean time elapsed between the presentation of the previous target digit and the false alarms was 4.62 (± 4.74) seconds. This is considerably greater than the 1.25 second response window and, therefore the increased number of false alarms observed in the DLB group does not appear to reflect an inability to make a response within the requisite time.

During testing, the experimenter remarked that some DLB cases made repeated stereotypical pressing responses during the digit vigilance task following response to a target digit. This observation, although not quantitative, suggests the basis of the observed increased false alarm rate in the DLB group was stereotypical response patterns rather than slow motor responses.

Poor performance on the digit vigilance task might conceivably be due to problems in understanding and retaining task instructions throughout the duration of the task. However, the DLB group showed similar language comprehension skills to the AD group on the CAMCOG schedule, and were able to complete other CDR tasks of similar or greater complexity with equivalent or better performance than the AD group. Furthermore, during testing the experimenter frequently observed DLB patients missing, but subsequently correctly identifying, target digits throughout the course of the digit vigilance task. These observations imply that problems in understanding and retaining the task instructions are unlikely to be major confounds of performance on the digit vigilance task.

Both neuropsychological and clinical observations strongly suggest, therefore, that DLB patients have great difficulty sustaining attentional resources. Previous studies have investigated the neurochemical basis of sustained attention.

Numerous studies on the effect of the administration of scopolamine have demonstrated linear dose-dependent deficits in the ability to sustain attention (Broks et al, 1988; Parrott, 1986; Wesnes et al, 1983a). These deficits have been shown to be due to the central, rather than peripheral, effects of scopolamine.

Administration of methoscopolamine, which has similar peripheral attributes to scopolamine but is unable to cross the blood brain barrier, failed to reproduce the deficits associated with centrally acting scopolamine. Furthermore, nicotine has been shown to improve sustained attention in scopolamine induced cognitive impairment (Wesnes et al, 1984). Nicotine has also been shown to improve vigilance performance in AD patients (Sahakian et al, 1989).

The involvement of the cholinergic system in attentional function is well documented (Broks et al, 1988; Parrott, 1986; Wesnes et al, 1983a). The combination of particularly compromised cholinergic function and poor sustained attention performance are consistent with the assertion that disruption of cholinergic nuclei and pathways contributes significantly to the reduced ability to sustain visual attention in the DLB group.

8.2.2 Secondary memory in AD and DLB.

The disruption of memory function in dementia has been extensively demonstrated by the present study. The marked impairment of secondary verbal and pictorial recognition memory further characterises this mnemonic impairment as a prominent feature in AD and DLB. Secondary memory tests assess the ability to retain information over a period of time without constant rehearsal of this information.

Both AD and DLB groups showed a similar degree of impairment on recognition sensitivity indices and measures of response latencies for immediate word recognition as well as delayed picture and face recognition tasks. The DLB group, however, discriminated previously seen words from novel exemplars more successfully than the AD group in the delayed word recognition task, without a concomitant increase in the latency to respond.

The DLB group also demonstrated less impairment than the AD group on the recent memory and visual recognition memory subsections of the CAMCOG schedule. Although there is undoubtedly marked mnemonic impairment in the

DLB group, performance on several tasks assessing memory function suggest the mnemonic impairment in DLB to be less severe than in AD.

Equivalent or better mnemonic function in DLB than AD has been reported by numerous researchers using a variety of tasks. McKeith et al (1992c) found SDLT cases were less impaired on a test of free recall. Förstl et al (1993) found equivalent impairment of AD and LBV cases on a global score of memory from the CAMCOG schedule. Hansen et al (1990) showed equivalent performance of matched AD and LBV groups on tests of semantic and episodic secondary memory. The same group of researchers showed more severe mnemonic impairment in a group of 23 AD cases than in 23 matched LBV cases on some memory subscales of the Mattis Dementia Rating scale (DRS). Samuel et al (1995) also compared cognitive function in LBV and AD using the Mattis DRS, but failed to replicate the less severe mnemonic deficit in DLB. Sahgal and colleagues reported equivalent performance of SDLT and AD groups on a test of pattern recognition memory, and more impaired performance of the SDLT group on a matching to sample procedure, although, as previously discussed, performance on the matching to sample task may reflect non-specific difficulties in the DLB group with matching to sample procedures.

Ballard et al (1996b) compared AD and SDLT groups using the CAMCOG schedule and demonstrated similar performance on most tests of mnemonic function, although the DLB group were less impaired on the recent memory subscale. Walker et al (1997) found LBD patients were less impaired on the recent memory recall subsection of the CAMCOG.

Mnemonic function does not, however, operate in isolation from other aspects of cognitive function. Intact attention is an essential prerequisite for the efficient execution of all information-processing operations. The role of attentional dysfunction in the genesis of mnemonic impairment in AD, and particularly DLB, is an important consideration when comparing these groups. This study has described attentional impairment in both dementia groups, though the DLB group show particularly reduced attentional capabilities. Although observed secondary

memory impairments are associated with both attentional and mnemonic deficits in both AD and DLB groups, the relative contribution of these cognitive domains may be different in DLB and Alzheimer's disease. It is possible that attentional deficits are more consequential in the genesis of the mnemonic impairment seen in DLB.

The demonstration, by numerous authors, that mnemonic impairment is less severe in DLB than AD is consistent with the neuropathology of these disorders. The memory deficits associated with AD have been strongly linked to neuropathological burden in the medial temporal lobe. In particular, the hippocampus, entorhinal cortex and parahippocampal gyrus (Braak et al, 1991) are thought to underlie memory consolidation. Studies investigating pathological burden in these areas in AD and DLB have demonstrated that ubiquitin-immunoreactive dystrophic neurites are often present in the CA2/CA3 region of the hippocampus in DLB (Dickson et al, 1991). However, the senile plaque and neurofibrillary tangle burden is less in DLB than AD. The hippocampus and related structures are generally thought to be less damaged in DLB than in AD (Salmon et al, 1996).

It is therefore possible that differences in hippocampal pathological burden underlie the relative preservation of secondary memory function in DLB compared to AD, described in this and other studies. Nevertheless, the problems of isolating circumscribed brain areas in patients with diffuse damage, and the uncertain causal link between neuropathological burden and functional abilities are recognised.

8.2.3 Working memory in AD and DLB.

The term working memory is used here to describe the storage and manipulation of small amounts of information for relatively short periods. In the present context, working memory is interchangeable with the term ‘short-term memory’. The term is used in a more restricted fashion than it might be employed in other disciplines, for many of whom it can refer to the retention of information over periods of minutes, hours, days, or even weeks; which would be categorised as secondary memory in the present study.

The current study investigated two aspects of working memory, specifically numeric and spatial working memory. The AD and DLB groups were impaired on both measures of performance (sensitivity index and speed) on both tests of working memory, though, the dementia groups did not show different performance on either task. On the spatial working memory task, the DLB group did not perform above chance levels, suggesting possible floor effects in this group. Floor effects may have reduced the sensitivity of the spatial working memory test to discriminate AD and DLB groups.

Few previous studies have directly assessed working memory in DLB patients. Hansen et al, 1990 reported LBV cases had reduced digit-span compared to AD cases. The digit-span subtest requires participants to repeat a random series of digits in the same (digit-span forward) or the reverse (digit-span backwards) order of presentation. However, digit-span forwards and digit-span reverse have different working memory loads. Digit-span forwards requires little manipulation of information, whereas digit-span reverse requires substantial working memory effort to rearrange the digits. If DLB cases do, indeed, have lowered working memory resources compared to controls, as is suggested by Hansen et al (1990), it might be expected that DLB cases would show a specific deficit in digit-span backwards compared to the AD group. Hansen et al (1990) do not distinguish digit-span forwards and backwards. However, Gnanalingham et al (1997) described performance on the digit-span forwards and backwards, and found neither measure discriminated AD and LBD groups. These data are in

concordance with findings from the current study, which suggest numeric working memory is equivalently impaired in the two dementia groups.

The visuo-spatial praxis section of the CAMCOG has discriminated AD and DLB groups in both the current and previous studies (Walker et al, 1997). The visuo-spatial praxis subsection undoubtedly involves aspects of spatial working memory. However, other aspects of cognitive, and especially motor, function confound a direct comparison with performance on the CDR spatial working memory task.

Comparison of numeric and spatial working memory performance suggests that numeric working memory may be relatively preserved in both dementia groups, compared to spatial working memory. The confounding effect of task difficulty on this comparison can be eliminated by directly relating AD and DLB to control group performance. In the numeric working memory task, the AD and DLB group's recognition sensitivity indices were 81% and 76% of control values respectively. In the spatial working memory task, the AD and DLB group's sensitivity indices were 19% and 9% of control values respectively. Response latencies were increased in both numeric working memory (AD=257% and DLB=346% of control group) and spatial working memory (AD=286% and DLB=279% of control group).

These data support the notion that numeric working memory ability is relatively preserved compared to spatial working memory ability in both AD and DLB. Both tasks are similar in terms of the responses required: the number of pieces of information to be remembered (3 digits and 4 spatial locations); and the number (nine) of possible locations / numbers from which 'to be remembered' information must be selected. In view of these findings, AD and DLB groups have greater difficulty on tasks assessing spatial compared to numeric information. In addition, these findings further the considerable evidence for the separation of visual and verbal working memory systems (Baddeley, 1991).

In summary, findings from the current and previous studies suggest that working memory declines in dementia. Spatial working memory appears to be more

sensitive than numeric working memory to the changes associated with AD and DLB. Neither spatial or numeric working memory discriminated between AD and DLB groups although this is possibly due to floor effects, especially in the spatial working memory task.

8.2.4 Summary.

A double dissociation has been described between AD and DLB dementia groups on tests assessing attentional and secondary word recognition memory. This further confirms the neuropsychological distinction of these dementing disorders. This study is the first to assess sustained attention and speed of information processing in these groups. The importance of including the assessment of attentional function in neuropsychological and pharmaceutical studies of dementia patients has been demonstrated. The assessment of attentional function has previously received limited regard in dementia (Hart et al, 1994). The study also highlights the need to assess diverse aspects of cognition in dementia patients to avoid misinterpretation of aspects of cognitive dysfunction studied in isolation.

8.3 Visual hallucinations and cognitive function in dementia with Lewy bodies.

Visual hallucinations (fleeting and persistent) are observed in the majority (93%) (Ballard et al, 1997b) of DLB cases and are an important diagnostic consideration (McKeith et al, 1992c; 1996a). Persistent visual hallucinations, starting within three years of the onset of dementia, are strongly associated with cortical Lewy bodies (McShane et al, 1995). In addition, neurochemical analysis has demonstrated that hallucinating DLB cases show more profoundly (80% reduction) depleted choline acetyltransferase levels compared to non-hallucinating DLB cases (50% reduction). Non-hallucinating DLB cases show a similar reduction in choline acetyltransferase activity to that observed in AD (Perry et al, 1990a: 1990b).

This study compared neuropsychological deficits in hallucinating (DLB+VH) and non-hallucinating (DLB-VH) DLB cases with Alzheimer's disease, who were matched for global severity of cognitive impairment. A strong association between the presence of persistent visual hallucinations and the profile of cognitive impairment in the DLB group was observed. The DLB+VH group showed worse performance on two tasks assessing attentional function (simple reaction time and digit vigilance) than the DLB-VH group, whose performance was similar to the AD group. On the spatial working memory task, the DLB+VH group performed at chance levels, and had a significantly lower sensitivity index than the DLB-VH and AD groups who performed equivalently. Similar response latencies were observed for both DLB groups on the choice reaction time task. Response latencies were significantly longer than those recorded for the AD group.

Measures of secondary memory failed to discriminate the dementia groups when sensitivity indices were compared. Comparison of response latencies, however, revealed the DLB+VH group took longer to respond on the delayed word, picture and face recognition tasks than the DLB-VH group and AD group, who responded following similar latencies.

The four groups were not significantly different on several indices of performance, namely: choice reaction time accuracy; numeric working memory; and cognitive reaction time.

Thus, the DLB-VH group had a profile of cognitive impairment similar to the AD. Nonetheless, choice reaction time response latencies discriminated the AD and the DLB-VH group. The DLB+VH group showed a profile of cognitive impairment which was markedly different from both AD and DLB-VH groups. The neurochemical basis of these differences are discussed in more detail in the General Discussion (see Chapter 12).

The current study compared 10 non-hallucinating and 14 hallucinating DLB cases, which represents a prevalence rate of 60% for persistent visual hallucinations in the DLB group under investigation. The prevalence rate of visual hallucinations reported in Newcastle has previously been reported as 80% (McKeith et al, 1992c). More recently, Ballard et al (1997b) also reported that 80% of DLB cases experienced persistent visual hallucinations. The prevalence of persistent visual hallucinations in the DLB cohort reported in this study appears somewhat less (60%) than the population from which the participants were recruited.

Several possible explanations for this possible selection bias exist. Firstly, the DLB+VH group demonstrated worse performance than the DLB-VH group on all, but one, measure of performance. Thus, hallucinating DLB cases may be less able to usefully complete neuropsychological investigation, as a consequence of the more severe cognitive impairment associated with the presence of persistent visual hallucinations. Secondly, hallucinating DLB cases are, by definition, behaviourally disturbed. The behavioural and emotional stress associated with visual hallucinations may have precluded some DLB+VH cases from completing the neuropsychological evaluation.

8.3.1 Summary.

This is the first study to examine the relationship between the presence of persistent visual hallucinations and cognitive function. Distinct profiles of cognitive impairment have been described in matched DLB+VH, DLB-VH, and AD groups. The neuropsychological implications of differing patterns of neurochemical and neuropathological changes in these groups is addressed in detail in the General Discussion (see Chapter 12).

Chapter 9:

A comparative study of cognitive decline over one year in DLB, AD, and elderly controls using the Cognitive Drug Research Computerised Assessment Battery (CDR): Methods.

9.1 Introduction.

This chapter describes the methods for a comparative study of cognitive decline in a cohort of DLB, AD, and elderly controls using the Cognitive Drug Research Computerised Assessment Battery (CDR). All participants included in the 1 year follow-up analysis were part of the initial cohort described in Chapter 6.

9.2 Participants.

See general methods (Chapter 2) for details of recruitment and standardised assessment of cases.

All participants in the initial cross sectional cohort were considered for follow-up cognitive testing. The cases reported are those, which, have undergone repeat cognitive testing at one year. A number of participants from the original cohort did not undergo a follow-up assessment due to death, physical ill health, or because they had become too demented or refused to partake in further testing. Furthermore, 27 participants who underwent assessment in the original cross-sectional study have not (to date) been approached for follow-up assessment as 12 months have not elapsed since baseline assessment.

Participants who underwent a follow-up cognitive assessment included 18 elderly controls, 20 AD patients, and 10 DLB patients. A number of these cases did not complete the entire test battery. The number of participants completing each CDR task is outlined in the appropriate sections.

9.3 Procedures.

9.3.1 Non-computerised psychometric assessment.

Non-computerised psychometric assessment (NART, CAMCOG) were carried out at baseline only and are as previously described (see Section 6.4.1.).

9.3.2 Computerised assessment using the CDR battery.

At 1 year follow-up, all participants were tested using a parallel form of the CDR battery used at baseline assessment. The parallel CDR battery used novel stimuli for all tests except the simple and choice reaction time tasks. The follow-up assessment using the CDR battery was otherwise as previously described (see Section 6.4.2).

9.4 Statistical procedures.

Indices of performance in the follow-up CDR assessment were as previously described (see Section 6.5).

Group means for baseline matching measures (age, estimated pre-morbid IQ, overall CAMCOG score) were compared using one-way analysis of variance and Newman-Keuls post-hoc pair-wise comparisons.

Group means for baseline and follow-up scores on the primary outcome measures of the CDR assessment were compared using two-way analysis of variance with repeated measures in one factor. Diagnostic group (control , AD, & DLB) was the between subjects factor, and CDR assessments at baseline and one year were the repeated measure. Newman-Keuls post-hoc pair-wise comparisons were applied when significant effects were described. Analysis of means were employed when significant interaction terms were found. Percentage decline compared to baseline scores over the one year period are also described.

Chapter 10:

A comparative study of cognitive decline over one year in DLB, AD, and elderly controls using the Cognitive Drug Research Computerised Assessment Battery (CDR): Results

10.1 Comparison of baseline demographic features and non-computerised psychometric assessment in control, AD and DLB groups.

Details of group means, and a summary of statistical analyses, for age, mean estimated pre-morbid IQ (NART), and overall severity of cognitive impairment (CAMCOG total score) are presented in Table 10.1. These assessments were used for matching procedures only and were not repeated at the one year follow-up assessment.

Table 10.1: Comparative analysis of age (\pm SEM), estimated pre-morbid IQ (NART) (\pm SEM) and overall severity of dementia (CAMCOG total score) (\pm SEM) at baseline for control, AD and DLB groups.

	Control (n=18)	AD (n=20)	DLB (n=10)	One-way ANOVA
Age	74.8 (\pm 1.84)	79.3 (\pm 1.48)	78.4 (\pm 2.15)	N.S
NART pre-morbid IQ	115.7 (\pm 1.5)	111.6 (\pm 1.3)	109.7 (\pm 1.3)	F_(2,45)=2.84, p=0.07
CAMCOG total score	102.3 (\pm 0.83)	66.8 (\pm 2.88)	59.6 (\pm 4.61)	F_(2,45)=16.54, p<0.001

All diagnostic groups were matched for age. Analysis indicated that for estimated pre-morbid IQ (NART) a trend towards a main effect of group was observed. Which further analysis indicated to be due to the control group having higher estimated pre-morbid mean IQ than the DLB group. The AD and control group

did not differ for estimated pre-morbid IQ. The control group showed less overall cognitive impairment than both dementia groups ($F_{(2,45)}=16.54$, $p<0.001$), though the dementia groups did not differ with respect to each other.

The mean duration between baseline and follow-up assessments is presented in Table 10.2. Analysis indicated there were no differences between groups for the time elapsed between baseline and follow-up assessments.

Table 10.2: Comparative analysis of mean time elapsed (days) (\pm SEM) between baseline and follow-up assessments for control, AD and DLB groups.

	Control (n=18)	<u>AD</u> (n=20)	<u>DLB</u> (n=10)	<u>One-way</u> <u>ANOVA</u>
Time elapsed between baseline and follow-up assessment (days)	378 (± 8)	379 (± 6)	371 (± 4)	N.S

10.2 Computerised (CDR) cognitive assessment.

All outcome measures and statistical analyses for this longitudinal investigation are reported in tabular form. To further illustrate findings, data is also presented in figures where significant between group, between visit, or interaction terms are described.

10.2.1 Attentional function.

10.2.1.1 Simple reaction time.

Group means for response latencies at baseline and 1 year follow-up as well as the percentage change between baseline and 1 year follow-up are presented in Table 10.3 and in Figure 10.1. A summary of statistical analysis using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons is presented in Table 10.4.

Table 10.3: Simple reaction time: mean response latencies (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups..

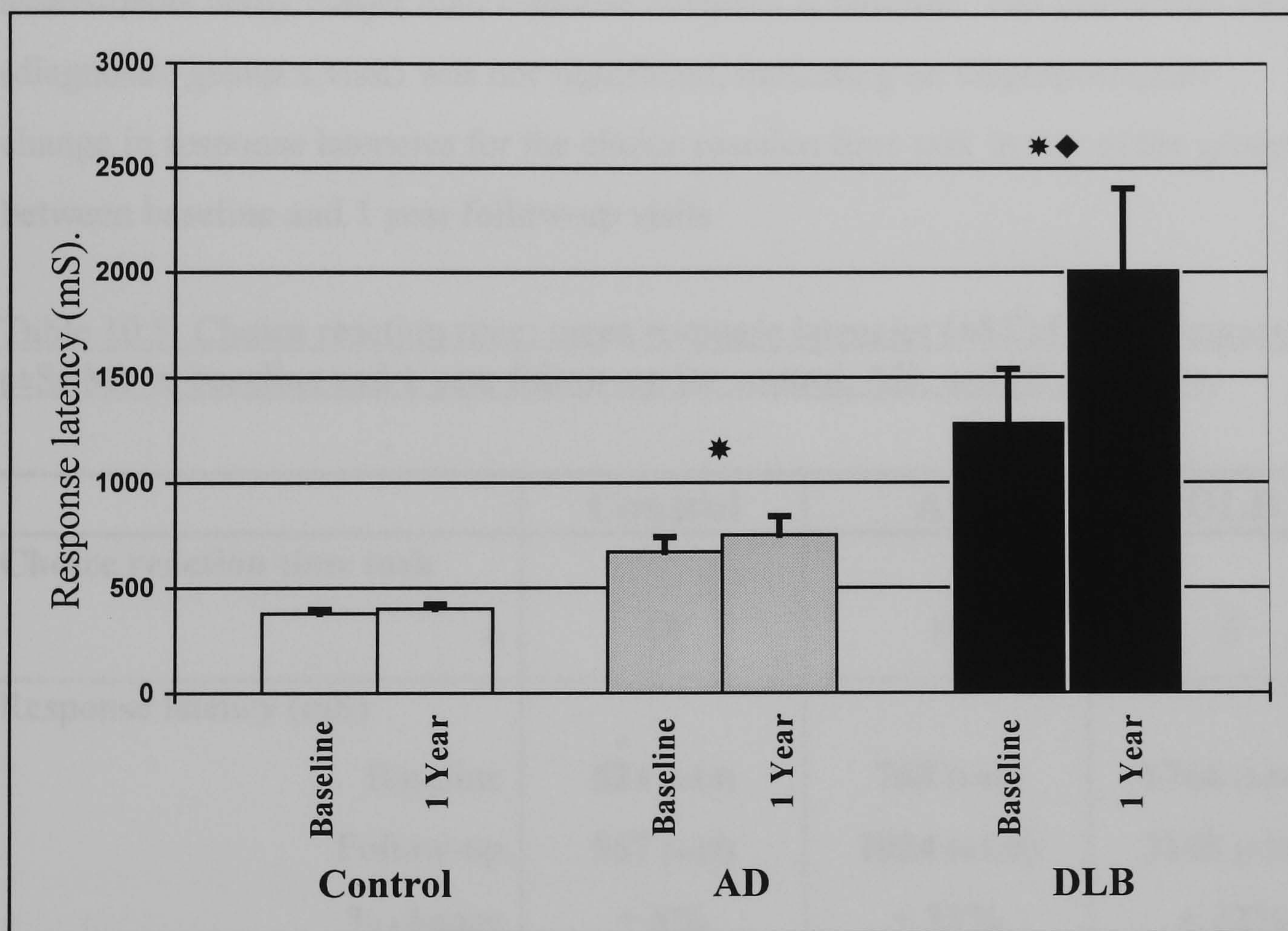
	Control	AD	DLB
Simple reaction time (mS)			
n	18	19	8
Baseline	379 (\pm18)	670 (\pm71)	1294 (\pm243)
Follow-up	400 (\pm21)	751 (\pm88)	2022 (\pm382)
% change	+ 6%	+ 12%	+ 56%

Table 10.4: Simple reaction time task: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis (p<0.05)
Diagnostic group	$F_{(2,42)}=50.3, p<0.001$	Control < AD < DLB
Visit	$F_{(1,42)}=6.0, p=0.019$	Baseline < Follow-up
Diagnostic group x Visit	N.S.	-

Analysis indicated a main effect of group ($F_{(2,42)}=50.3, p<0.001$). Subsequent pairwise comparisons showed group means for simple reaction times were in the order: control < AD < DLB. In addition, a main effect of visit was found ($F_{(1,42)}=6.0, p=0.019$), which was shown to be due to reaction times for follow-up assessments being longer than reaction times for the baseline assessment. The interaction term (diagnostic group x visit) was not significant, indicating there was no disproportionate decline in any of the groups between baseline and 1 year follow-up visits.

Figure 10.1: Simple reaction time task: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=19) and DLB (n=8) groups at baseline and 1 year follow-up assessment.



* significant difference ($p<0.05$) compared to controls; ♦ significant difference ($p<0.05$) between dementia groups

10.2.1.2 Choice reaction time.

Group means for response latencies and accuracy at baseline and 1 year follow-up as well as the percentage change between baseline and 1 year follow-up are presented in Table 10.5 and Figure 10.2. A summary of statistical analysis using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons is presented in Tables 10.6 and 10.7.

Analysis indicated a main effect of group ($F_{(2,40)}=44.0$, $p<0.001$). Subsequent analysis indicated group means for choice reaction time response latencies were in the order: control < AD < DLB. A main effect of visit was found ($F_{(1,40)}=7.2$, $p=0.011$), which was shown to be due to response latencies for follow-up assessments being longer than response latencies at baseline. The interaction term (diagnostic group x visit) was not significant, indicating no disproportionate change in response latencies for the choice reaction time task in any of the groups between baseline and 1 year follow-up visits.

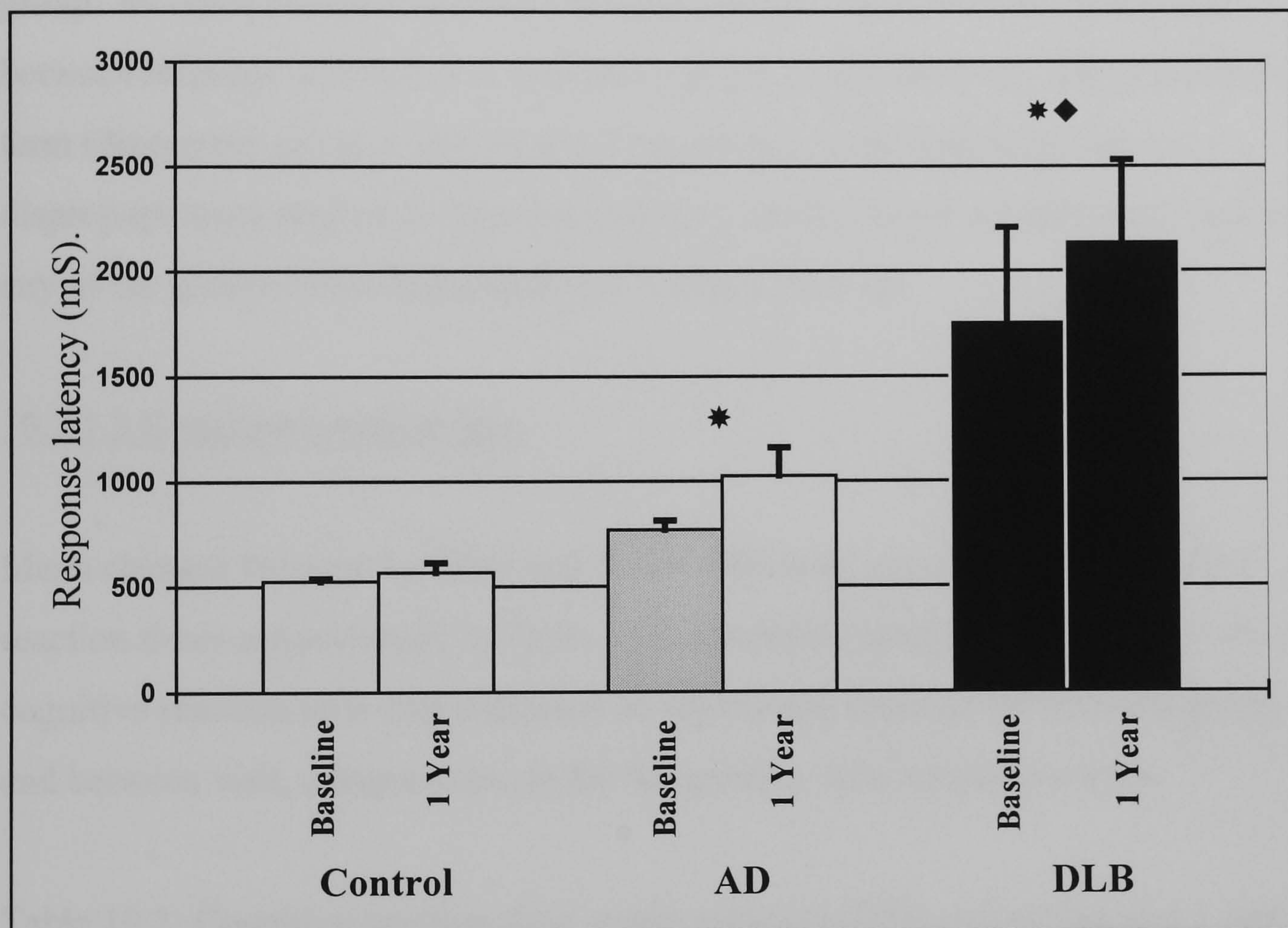
Table 10.5: Choice reaction time: mean response latencies (\pm SEM) and accuracy (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups.

	Control	AD	DLB
Choice reaction time task			
n	18	18	5
Response latency (mS)			
Baseline	524 (\pm14)	768 (\pm44)	1766 (\pm441)
Follow-up	567 (\pm45)	1024 (\pm135)	2148 (\pm382)
% change	+ 8%	+ 33%	+ 22%
Accuracy (% correct)			
Baseline	96.1 (\pm0.86)	91.7 (\pm2.36)	91.0 (\pm1.87)
Follow-up	98.1 (\pm0.59)	94.4 (\pm1.51)	84.0 (\pm6.60)
% change	+ 2%	+ 3%	- 8%

Table 10.6: Choice reaction time: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis (p<0.05)
Diagnostic group	$F_{(2,40)}=44.0, p<0.001$	Control < AD < DLB
Visit	$F_{(1,40)}=7.2, p=0.011$	Baseline < follow-up
Diagnostic group x Visit	N.S.	-

Figure 10.2: Choice reaction time task: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=18) and DLB (n=5) groups at baseline and 1 year follow-up.



* significant difference (p<0.05) compared to controls; ◆ significant difference (p<0.05) between dementia groups

Table 10.7: Choice reaction time: summary of ANOVA for response accuracy.

Source of variance	ANOVA summary	Newman-Keuls analysis (p<0.05)
Diagnostic group	$F_{(2,40)}=6.9, p=0.003$	DLB < control DLB \equiv AD Control \equiv AD
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

Analysis indicated a main effect of group ($F_{(2,40)}=6.9, p=0.003$). Subsequent analysis indicated the DLB group were responding less accurately than the control group. All other comparisons were non-significant. There were no differences between response accuracies at baseline and at 1 year follow-up. The interaction term (diagnostic group x visit) was not significant, indicating there was no disproportionate decline in response accuracy for the choice reaction time task in any of the groups between baseline and 1 year follow-up.

10.2.1.3 Cognitive reaction time.

Mean changes between baseline and 1 year follow-up assessment for cognitive reaction times are presented in Table 10.8. Statistical analysis (see Table 10.9) of cognitive reaction time data indicated no significant findings for between group, and between visit, comparisons, or for the group x visit interaction term.

Table 10.8: Cognitive reaction time: mean values (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups.

	Control	AD	DLB
Cognitive reaction time (mS)			
n	18	19	6
Baseline	145 (\pm 12)	183 (\pm 46)	765 (\pm 504)
Follow-up	167 (\pm 37)	283 (\pm 92)	645 (\pm 160)
% change	+ 15%	+ 55%	- 16%

Table 10.9: Cognitive reaction time: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis (p<0.05)
Diagnostic group	N.S.	-
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

10.2.1.4 Digit vigilance.

Group means in the digit vigilance task primary outcome measures at baseline and 1 year follow-up, as well as the percentage change between baseline and 1 year follow-up are presented in Table 10.10 and Figures 10.3 and 10.4. A summary of statistical analysis using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons is presented in Tables 10.11 and 10.12.

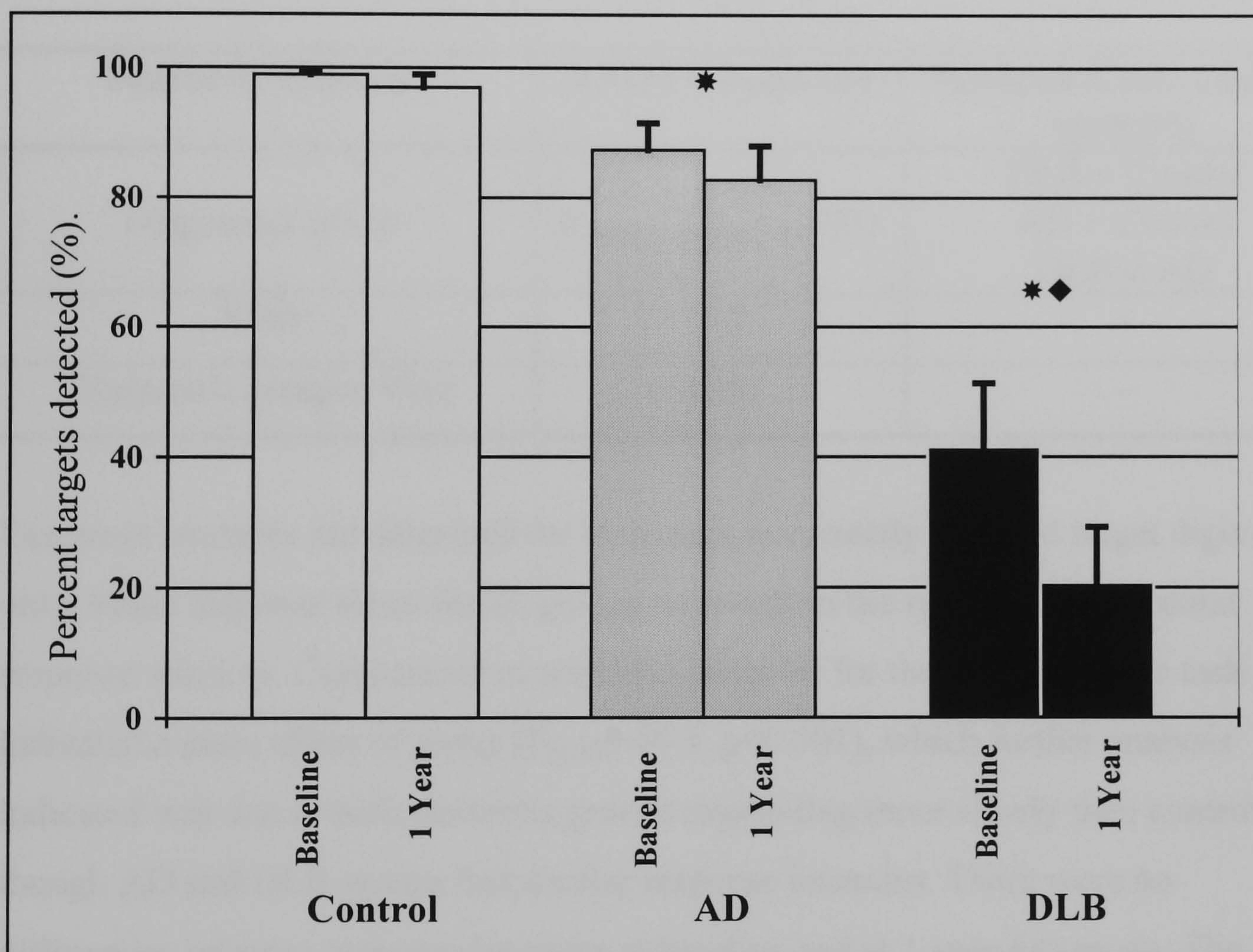
Table 10.10: Digit vigilance: percent of target digits correctly identified (\pm SEM) and response latencies (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups.

	Control	AD	DLB
Digit vigilance			
n	18	19	9
Target digits identified (% correct)			
Baseline	98.9 (\pm0.60)	87.4 (\pm4.17)	41.5 (\pm9.80)
Follow-up	97.0 (\pm1.96)	82.8 (\pm5.21)	20.7 (\pm8.57)
% change	- 2%	- 5%	- 50%
Response latency (mS)			
Baseline	496 (\pm15)	627 (\pm22)	698 (\pm44)
Follow-up	516 (\pm14)	621 (\pm30)	525 (\pm100)
% change	+ 4%	- 1%	- 25%

Table 10.11: Digit vigilance: summary of ANOVA for percent of target digits correctly identified.

Source of variance	ANOVA summary	Newman-Keuls analysis (p<0.05)
Diagnostic group	$F_{(2,43)}=65.2, p<0.001$	Control > AD > DLB
Visit	$F_{(1,43)}=9.9, p=0.003$	Baseline > follow-up
Diagnostic group x Visit	$F_{(2,43)}=4.5, p=0.017$	-

Figure 10.3: Digit vigilance: mean percent of target digits correctly identified (\pm SEM) for control (n=18), AD (n=19) and DLB (n=9) groups at baseline and 1 year follow-up.



* significant difference (p<0.05) compared to controls; ♦ significant difference (p<0.05) between dementia groups

Analysis indicated a main effect of group ($F_{(2,43)}=65.2, p<0.001$). Subsequent pairwise comparisons indicated that group means for the percent of target digits correctly identified were in the order: control < AD < DLB. A main effect of visit was also demonstrated ($F_{(1,43)}=9.9, p=0.003$), which was shown to be due to the

percent of target digits correctly identified at baseline being greater than at 1 year follow-up.

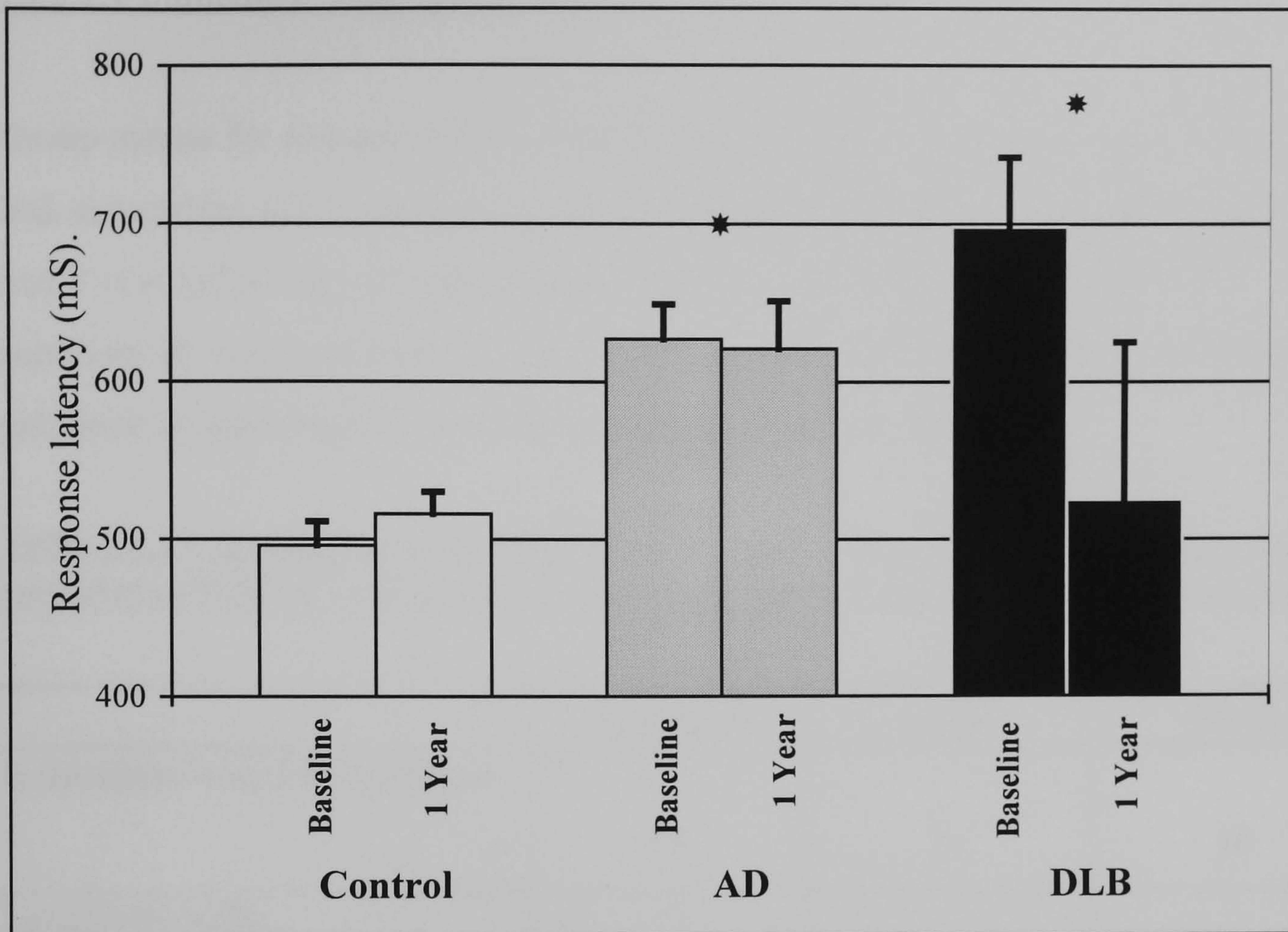
The interaction term (diagnostic group x visit) was significant ($F_{(1,43)}=4.5$, $p=0.017$), indicating disproportionate change in the percent of target digits correctly identified by experimental groups between baseline and 1 year follow-up visits. Post-hoc, analysis of means indicated that the percent of target digits correctly detected by the control and AD groups at baseline and follow-up did not differ. However, the DLB group correctly detected fewer target digits at follow-up than at baseline ($F_{(1,43)}=18.013$, $p<0.001$).

Table 10.12: Digit vigilance task: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p<0.05$)
Diagnostic group	$F_{(2,43)}=10.3$, $p<0.001$	DLB > Control AD > Control DLB \equiv AD
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

Response latencies are described for responses to correctly detected target digits only. Mean response times for all groups were within the requisite 1.25 second response window. Comparison of response latencies for the digit vigilance task indicated a main effect of group ($F_{(2,43)}=10.3$, $p<0.001$), which further analysis indicated was due to both dementia groups responding more slowly than controls, though AD and DLB groups had similar response latencies. There were no differences between response latencies at baseline and at 1 year follow-up. The interaction term (diagnostic group x visit) was not significant.

Figure 10.4: Digit vigilance: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=19) and DLB (n=9) groups at baseline and 1 year follow-up.



* significant difference ($p < 0.05$) compared to controls

10.2.2 Secondary memory.

10.2.2.1 Immediate word recognition.

Group means for primary indices of performance in the immediate word recognition task at baseline and 1 year follow-up, as well as the percentage change between baseline and 1 year follow-up, are presented in Table 10.13 and Figures 10.5 and 10.6. A summary of statistical analysis, using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons, is presented in Tables 10.14 and 10.15.

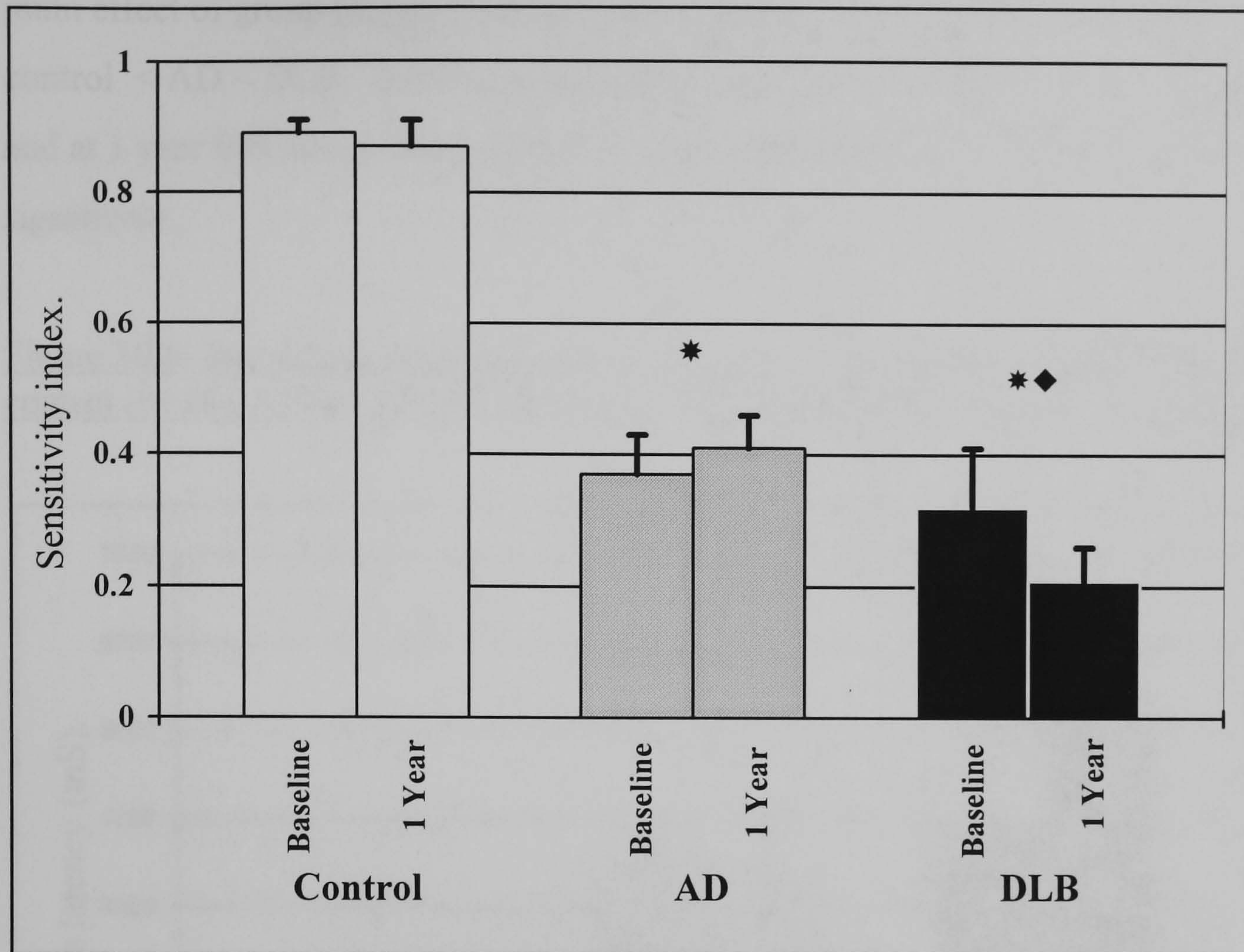
Table 10.13: Immediate word recognition: sensitivity indices (\pm SEM) and response latencies (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups..

	Control	AD	DLB
Immediate word recognition			
n	18	21	10
Sensitivity index			
Baseline	0.89 (\pm0.02)	0.37 (\pm0.06)	0.32 (\pm0.09)
Follow-up	0.87 (\pm0.03)	0.41 (\pm0.05)	0.21 (\pm0.05)
% change	- 2%	+ 11%	- 34%
Response latency (mS)			
Baseline	876 (\pm32)	3518 (\pm528)	3979 (\pm949)
Follow-up	985 (\pm114)	3330 (\pm567)	5432 (\pm874)
% change	+ 12%	- 5%	- 36%

Table 10.14: Immediate word recognition: summary of ANOVA for recognition sensitivity index.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,46)}=65.4, p < 0.001$	Control > AD > DLB
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

Figure 10.5: Immediate word recognition: mean sensitivity indices (\pm SEM) for control (n=18), AD (n=21) and DLB (n=10) groups at baseline and 1 year follow-up.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

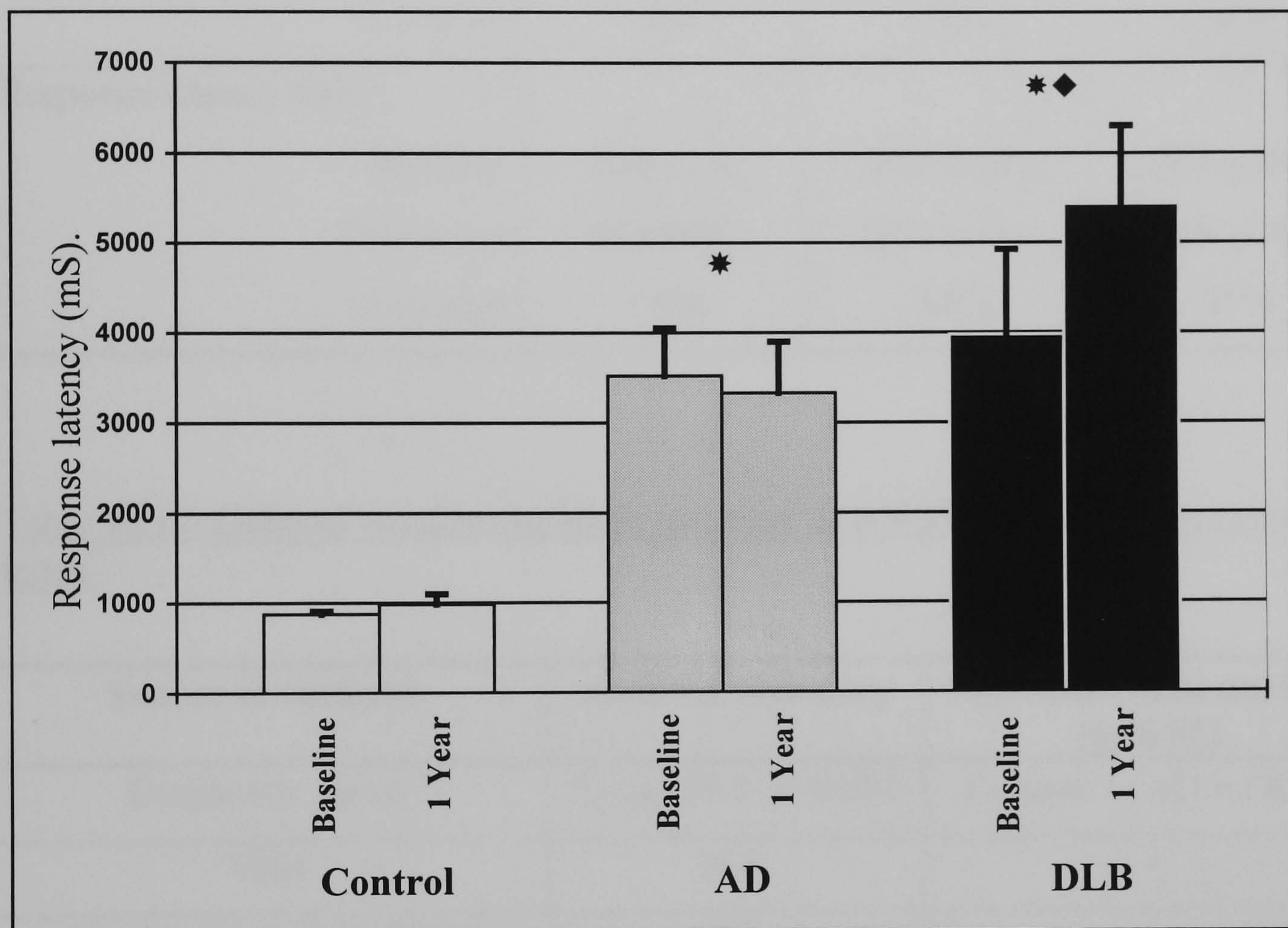
Analysis of sensitivity indices for the immediate word recognition task indicated a main effect of group ($F_{(2,46)}=65.4, p < 0.001$). Group means for immediate word recognition sensitivity indices were in the order: control > AD > DLB. There were no differences in sensitivity indices between baseline and 1 year follow-up visits. The interaction term (diagnostic group x visit) was non-significant.

Table 10.15: Immediate word recognition: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,46)}=51.4, p < 0.001$	Control < AD < DLB
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

Comparison of response latencies for the immediate word recognition task indicated a main effect of group ($F_{(2,46)}=51.4, p<0.001$). Response latencies were in the order: control < AD < DLB. There were no differences between response latencies at baseline and at 1 year follow-up. The interaction term (diagnostic group x visit) was not significant.

Figure 10.6: Immediate word recognition: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=21) and DLB (n=10) groups at baseline and 1 year follow-up.



* significant difference ($p<0.05$) compared to controls; ◆ significant difference ($p<0.05$) between dementia groups

10.2.2.2 Delayed word recognition.

Group means for primary indices of performance in the delayed word recognition task at baseline and 1 year follow-up, as well as the percentage change between baseline and 1 year follow-up, are presented in Table 10.16 and Figures 10.7 and 10.8. A summary of statistical analysis, using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons, is presented in Tables 10.17 and 10.18.

Table 10.16: Delayed word recognition: sensitivity indices (\pm SEM) and response latencies (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups.

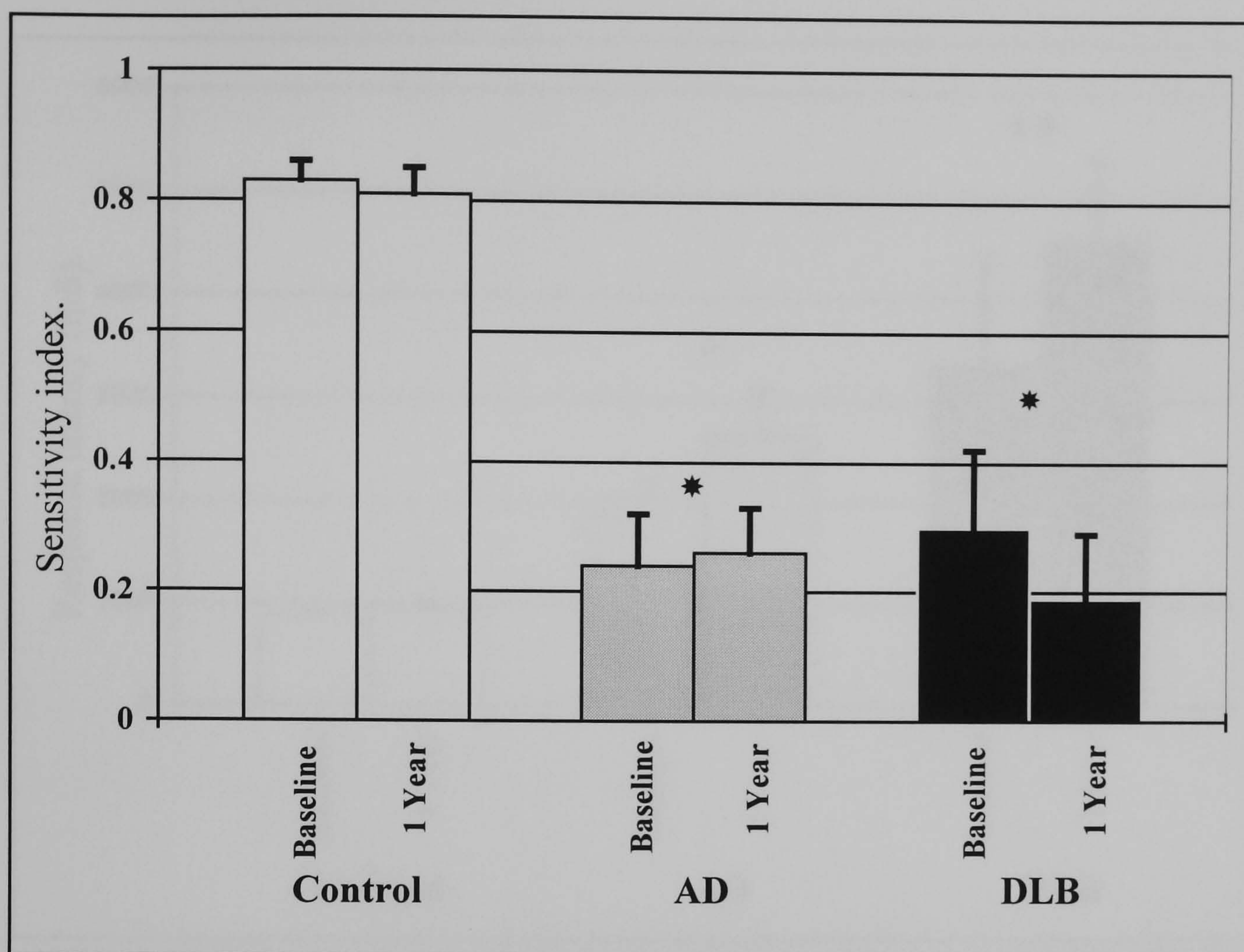
	Control	AD	DLB
Delayed word recognition			
n	18	20	8
Sensitivity index			
Baseline	0.83 (\pm 0.03)	0.24 (\pm 0.08)	0.30 (\pm 0.12)
Follow-up	0.81 (\pm 0.04)	0.26 (\pm 0.07)	0.19 (\pm 0.10)
% change	- 2%	+ 8%	- 32%
Response latency (mS)			
Baseline	864 (\pm 34)	2051 (\pm 197)	3383 (\pm 1069)
Follow-up	944 (\pm 81)	2671 (\pm 441)	4614 (\pm 757)
% change	+ 9%	- 32%	- 37%

Table 10.17: Delayed word recognition: summary of ANOVA for recognition sensitivity index.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,43)}=54.5, p < 0.001$	Control > (AD \equiv DLB)
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

In the delayed word recognition task, analysis of recognition sensitivity indices indicated a main effect of group ($F_{(2,43)}=54.5, p < 0.001$). Both dementia groups scored lower sensitivity indices than the control group, but were similar to each other. There were no differences in sensitivity indices between baseline and 1 year follow-up visits. The interaction term (diagnostic group x visit) was not significant.

Figure 10.7: Delayed word recognition: mean sensitivity indices (\pm SEM) for control (n=18), AD (n=20) and DLB (n=8) groups at baseline and 1 year follow-up.



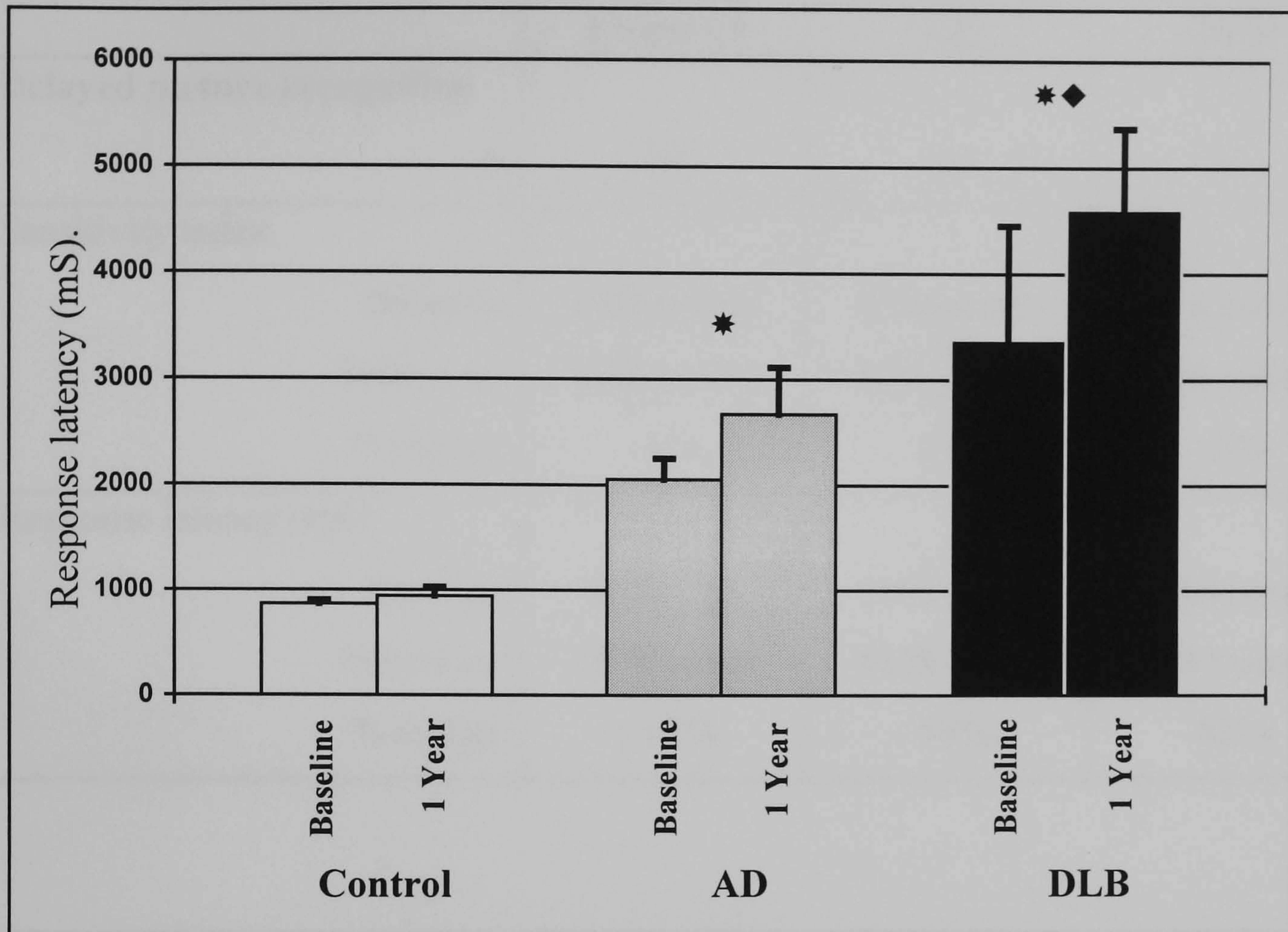
* significant difference ($p < 0.05$) compared to controls

Table 10.18: Delayed word recognition: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,43)}=45.7, p < 0.001$	Control < AD < DLB
Visit	$F_{(1,43)}=6.9, p=0.011$	Baseline < Control
Diagnostic group x Visit	N.S.	-

Comparison of response latencies for the delayed word recognition task indicated a main effect of group ($F_{(2,43)}=45.7, p < 0.001$). Response latencies were in the order: control < AD < DLB. Response latencies at baseline were shorter than response latencies at 1 year follow-up ($F_{(2,43)}=6.9, p=0.011$). The interaction term (diagnostic group x visit) was not significant.

Figure 10.8: Delayed word recognition: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=20) and DLB (n=8) groups at baseline and 1 year follow-up.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

10.2.2.3 Delayed picture recognition.

Group means for the primary indices of performance in the delayed picture recognition task at baseline and 1 year follow-up, and the percentage change between baseline and 1 year follow-up, are presented in Table 10.19 and Figures 10.9 and 10.10. A summary of statistical analysis, using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons, is presented in Tables 10.20 and 10.21.

Table 10.19: Delayed picture recognition: sensitivity indices (\pm SEM) and response latencies (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups.

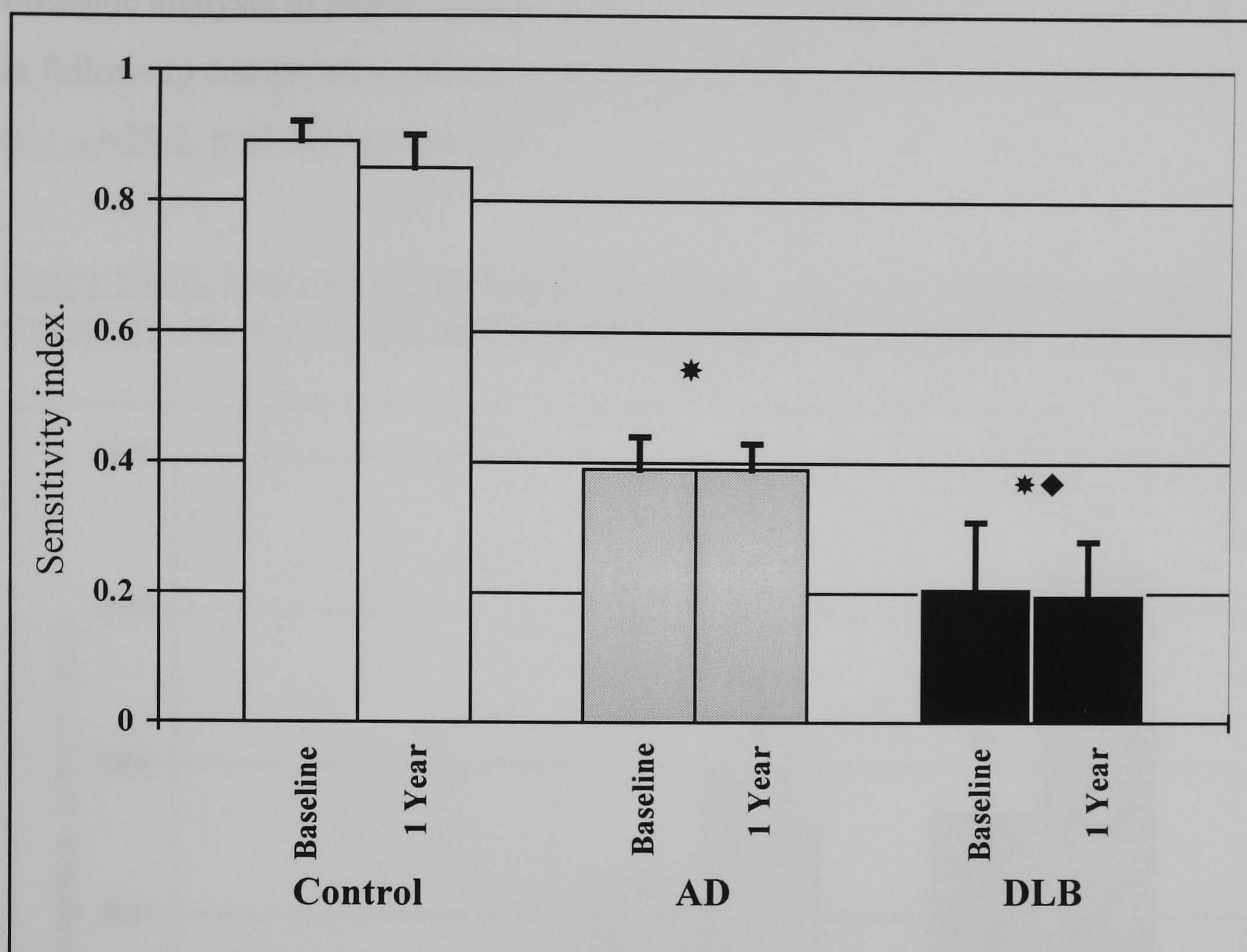
	Control	AD	DLB
Delayed picture recognition			
n	18	20	9
Sensitivity index			
Baseline	0.89 (\pm0.03)	0.39 (\pm0.05)	0.21 (\pm0.10)
Follow-up	0.85 (\pm0.05)	0.39 (\pm0.04)	0.20 (\pm0.08)
% change	- 4%	0%	- 5%
Response latency (mS)			
Baseline	962 (\pm39)	2486 (\pm210)	3414 (\pm941)
Follow-up	1078 (\pm102)	4328 (\pm720)	6553 (\pm858)
% change	+ 12%	- 74%	-92%

Table 10.20: Delayed picture recognition: summary of ANOVA for recognition sensitivity index.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,44)}=58.7, p < 0.001$	Control > AD > DLB
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

Analysis of recognition sensitivity indices for the delayed picture recognition task indicated a main effect of group ($F_{(2,44)}=58.7, p < 0.001$). Mean sensitivity indices were in the following order: control > AD > DLB. There were no differences in sensitivity indices between baseline and 1 year follow-up visits. The interaction term (diagnostic group x visit) was non-significant.

Figure 10.9: Delayed picture recognition: mean sensitivity indices (\pm SEM) for control (n=18), AD (n=20) and DLB (n=9) groups at baseline and 1 year follow-up.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

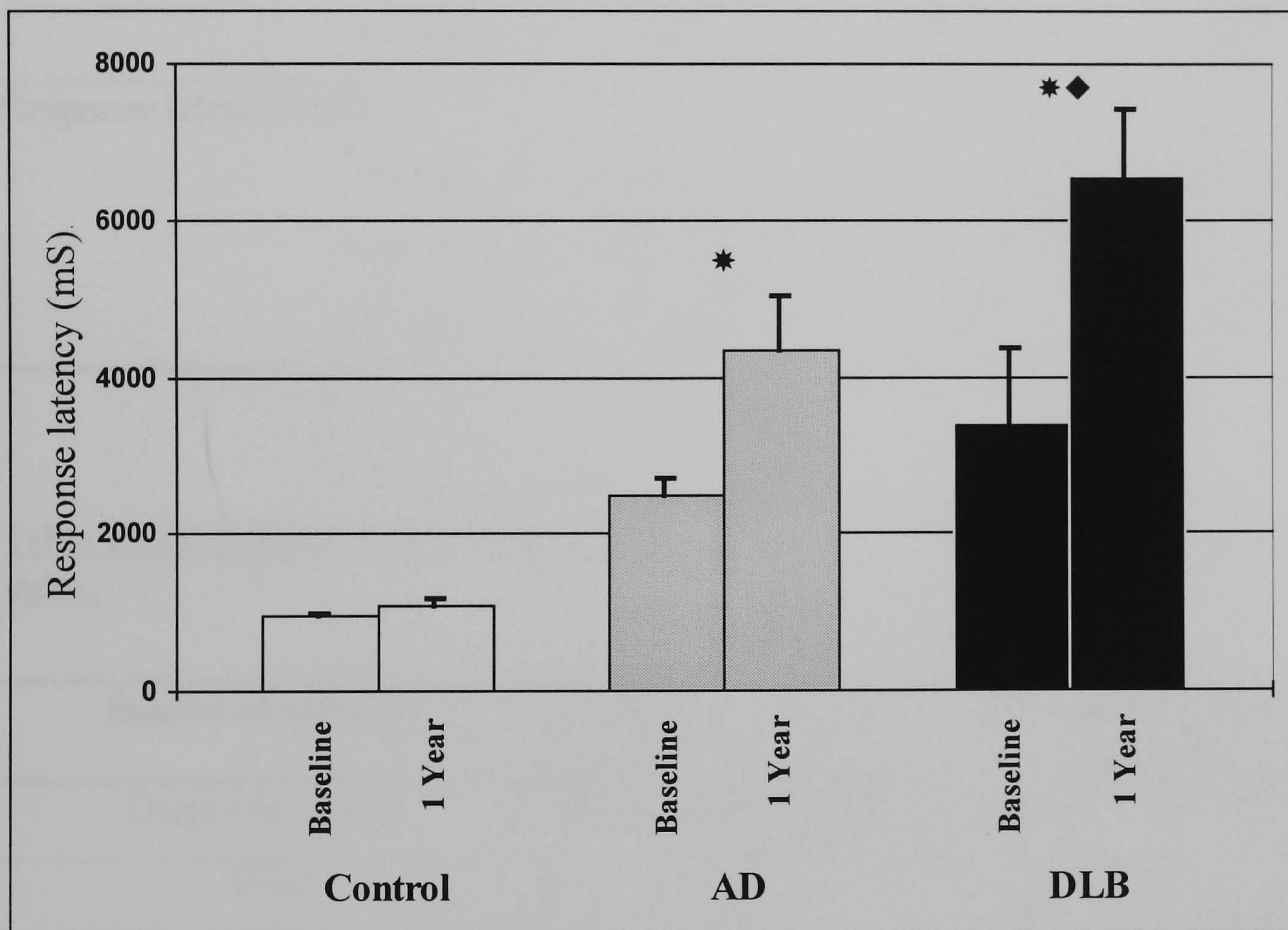
Table 10.21: Delayed picture recognition: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,44)} = 68.7, p < 0.001$	Control < AD < DLB
Visit	$F_{(1,44)} = 24.3, p < 0.001$	Baseline < Control
Diagnostic group x Visit	$F_{(2,44)} = 6.0, p = 0.005$	-

Comparison of response latencies for the delayed picture recognition task indicated a main effect of group ($F_{(2,44)} = 68.7, p < 0.001$). Response latencies were in the order: control < AD < DLB. Response latencies at baseline were shorter than response latencies at 1 year follow-up ($F_{(1,44)} = 24.3, p < 0.001$).

Analysis of response latencies for the group x visit interaction indicated disproportionate changes between visits in the different groups ($F_{(2,44)}=6.0, p=0.005$). Post-hoc analysis of means indicated that response latencies were significantly increased at follow-up compared to baseline for both AD ($F_{(1,44)}=7.0, p=0.011$) and DLB ($F_{(1,44)}=29.2, p<0.001$) groups.

Figure 10.10: Delayed picture recognition: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=20) and DLB (n=9) groups at baseline and 1 year follow-up.



* significant difference ($p<0.05$) compared to controls; ◆ significant difference ($p<0.05$) between dementia groups

10.2.2.4 Delayed face recognition.

Group means for the primary indices of performance in the delayed face recognition task at baseline and 1 year follow-up, and the percentage change between baseline and 1 year follow-up, are presented in Table 10.22 and Figures 10.11 and 10.12. A summary of statistical analysis, using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons, is presented in Tables 10.23 and 10.24.

Table 10.22: Delayed face recognition: sensitivity indices (\pm SEM) and response latencies (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups.

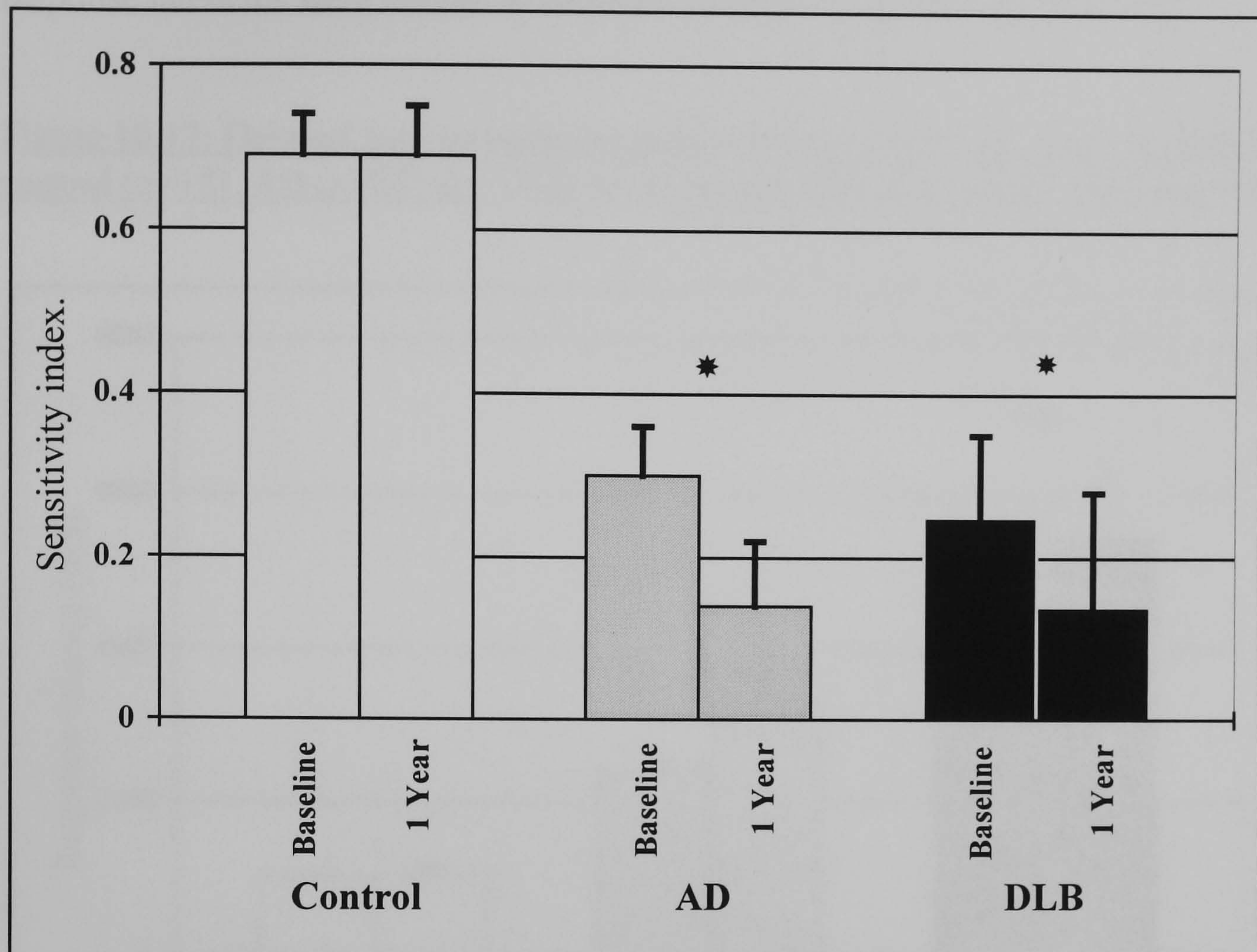
	Control	AD	DLB
Delayed face recognition			
n	18	20	8
Sensitivity index			
Baseline	0.69 (\pm 0.05)	0.30 (\pm 0.06)	0.25 (\pm 0.10)
Follow-up	0.69 (\pm 0.06)	0.14 (\pm 0.08)	0.14 (\pm 0.14)
% change	- 0%	- 53%	- 44%
Response latency (mS)			
Baseline	1012 (\pm 44)	2419 (\pm 251)	3710 (\pm 1277)
Follow-up	1065 (\pm 99)	3365 (\pm 587)	5489 (\pm 910)
% change	+ 5%	+ 39%	+ 48%

Table 10.23: Delayed face recognition: summary of ANOVA for recognition sensitivity index.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,43)}=25.9, p < 0.001$	Control > (AD \equiv DLB)
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

Analysis of recognition sensitivity indices for the delayed face recognition task indicated a main effect of group ($F_{(2,43)}=25.9, p < 0.001$). Recognition indices were smaller for the control than both dementia groups, although the DLB and AD groups had similar sensitivity indices. There were no differences in delayed face recognition sensitivity indices between baseline and 1 year follow-up visits. The interaction term (diagnostic group x visit) was non-significant.

Figure 10.11: Delayed face recognition: mean sensitivity indices (\pm SEM) for control (n=18), AD (n=20) and DLB (n=8) groups at baseline and 1 year follow-up.



* significant difference ($p < 0.05$) compared to controls

Table 10.24: Delayed face recognition: summary of ANOVA for response latencies.

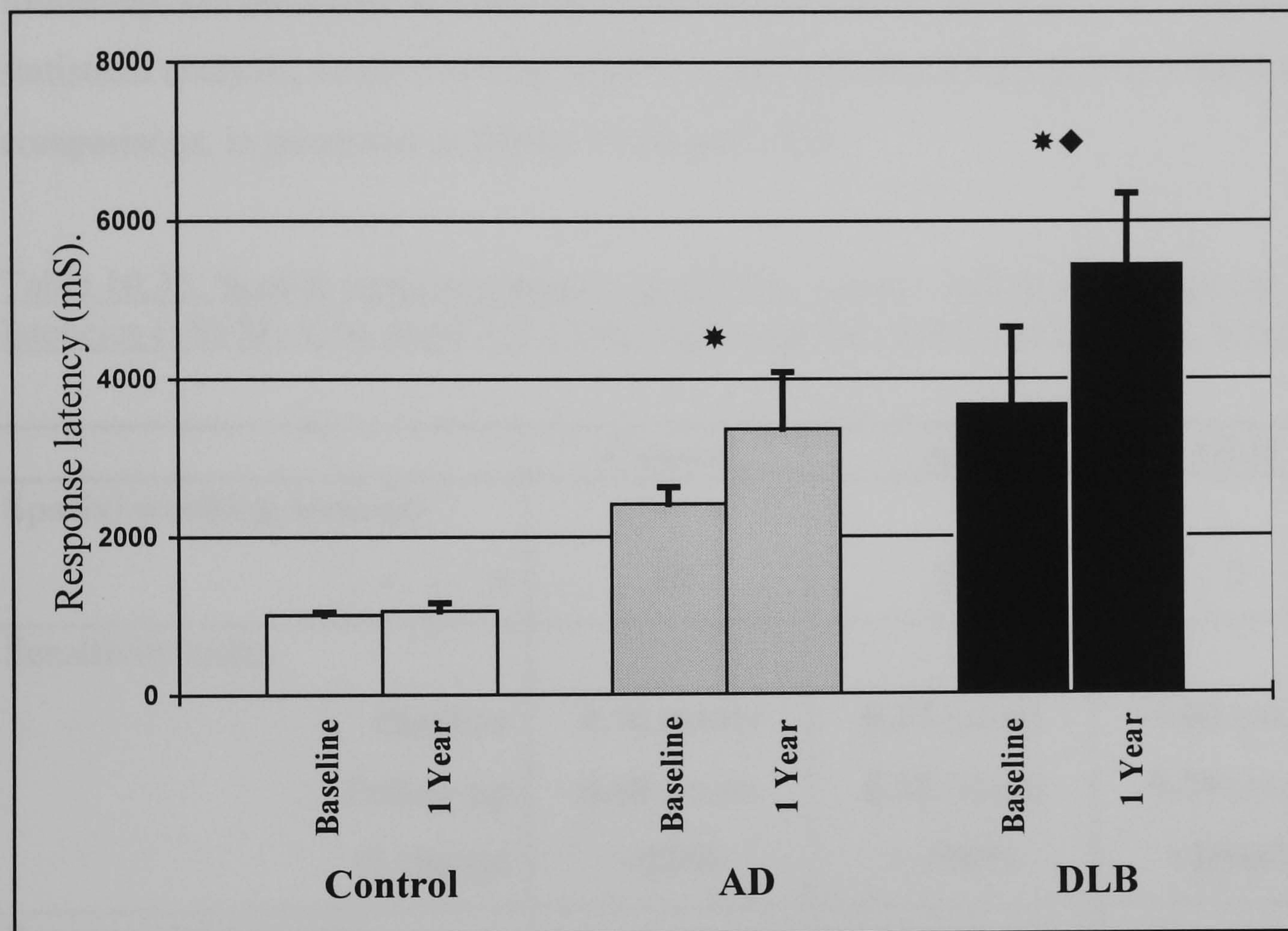
Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,43)}=52.2, p < 0.001$	Control < AD < DLB
Visit	$F_{(1,43)}=8.4, p = 0.006$	Baseline < Control
Diagnostic group x Visit	$F_{(2,43)}=3.3, p = 0.044$	-

In the delayed face recognition task, comparison of response latencies indicated a main effect of group ($F_{(2,43)}=52.2, p < 0.001$). Response latencies were in the order: control < AD < DLB. Response latencies at baseline were shorter than response latencies at 1 year follow-up ($F_{(1,43)}=8.4, p = 0.006$).

Analysis of response latencies for the group x visit interaction indicated disproportionate changes between visits in the different groups ($F_{(2,43)}=3.3, p = 0.044$).

Post-hoc analysis of means indicated that response latencies were significantly increased at follow-up compared to baseline for the DLB ($F_{(1,43)}=11.9, p=0.002$) group, however, response latencies were similar at baseline and follow-up for the AD group.

Figure 10.12: Delayed face recognition: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=20) and DLB (n=8) groups at baseline and 1 year follow-up.



* significant difference ($p<0.05$) compared to controls; ♦ significant difference ($p<0.05$) between dementia groups

10.2.3 Working memory.

10.2.3.1 Spatial working memory.

Group means for the primary indices of performance in the spatial working memory task at baseline and 1 year follow-up, and the percentage change between baseline and 1 year follow-up, are presented in Table 10.25 and Figures 10.13 and 10.14. A summary of statistical analysis, using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons, is presented in Tables 10.26 and 10.27.

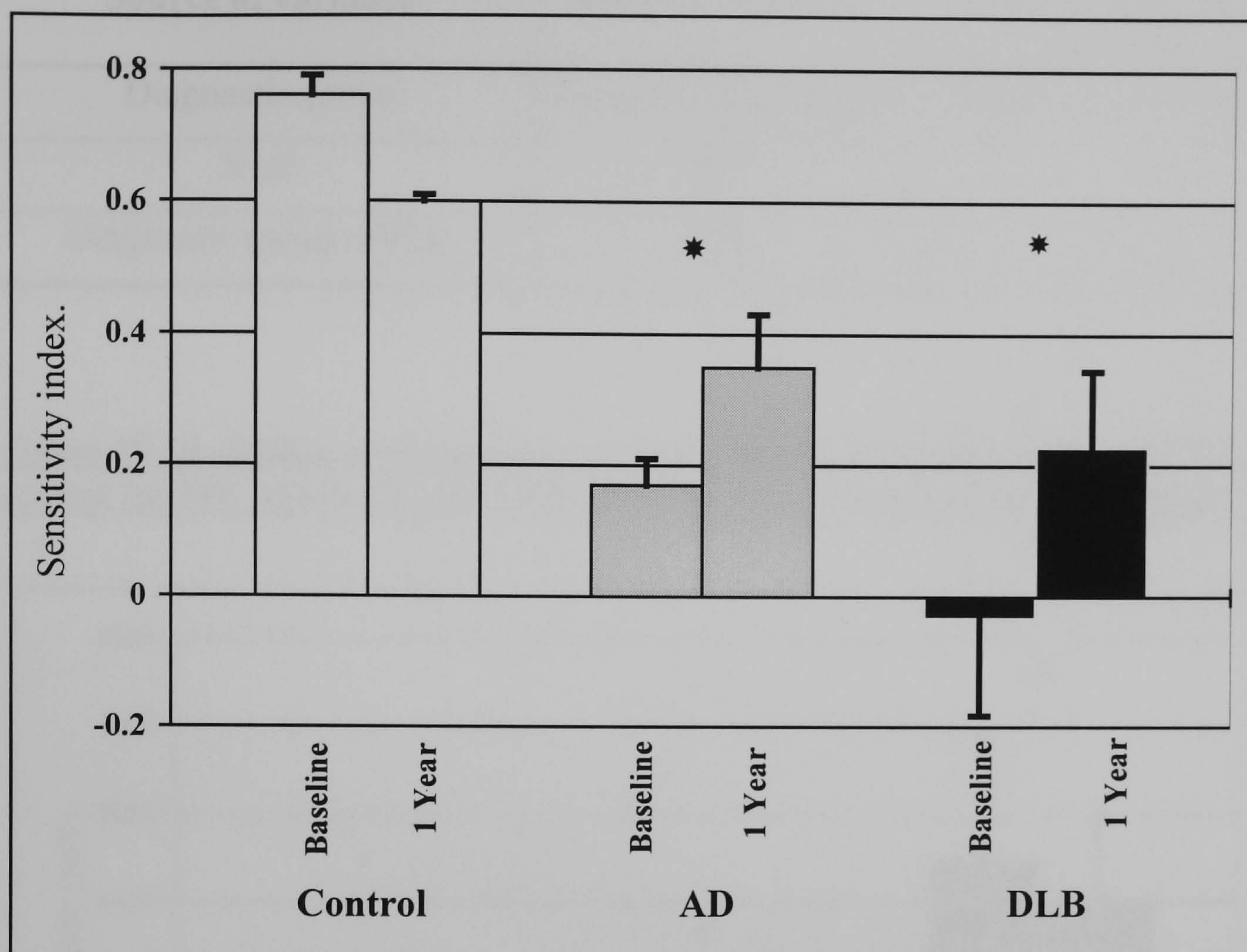
Table 10.25: Spatial working memory: sensitivity indices (\pm SEM) and response latencies (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups.

	Control	AD	DLB
Spatial working memory			
n	18	18	5
Sensitivity index			
Baseline	0.76 (\pm 0.08)	0.17 (\pm 0.08)	-0.03 (\pm 0.15)
Follow-up	0.60 (\pm 0.08)	0.35 (\pm 0.08)	0.29 (\pm 0.12)
% change	- 21%	+ 100%	+1066%
Response latency (ms)			
Baseline	1420 (\pm 253)	2630 (\pm 310)	4518 (\pm 1403)
Follow-up	1751 (\pm 416)	2861 (\pm 484)	4044 (\pm 894)
% change	+ 23%	+ 9%	+ 10%

Table 10.26: Spatial working memory: summary of ANOVA for recognition sensitivity index.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,39)}=10.7, p=0.002$	Control > (AD \equiv DLB)
Visit	N.S.	-
Diagnostic group x Visit	$F_{(2,39)}=3.7, p=0.034$	-

Figure 10.13: Spatial working memory: mean sensitivity indices (\pm SEM) for control (n=18), AD (n=18) and DLB (n=5) groups at baseline and 1 year follow-up.



* significant difference ($p < 0.05$) compared to controls

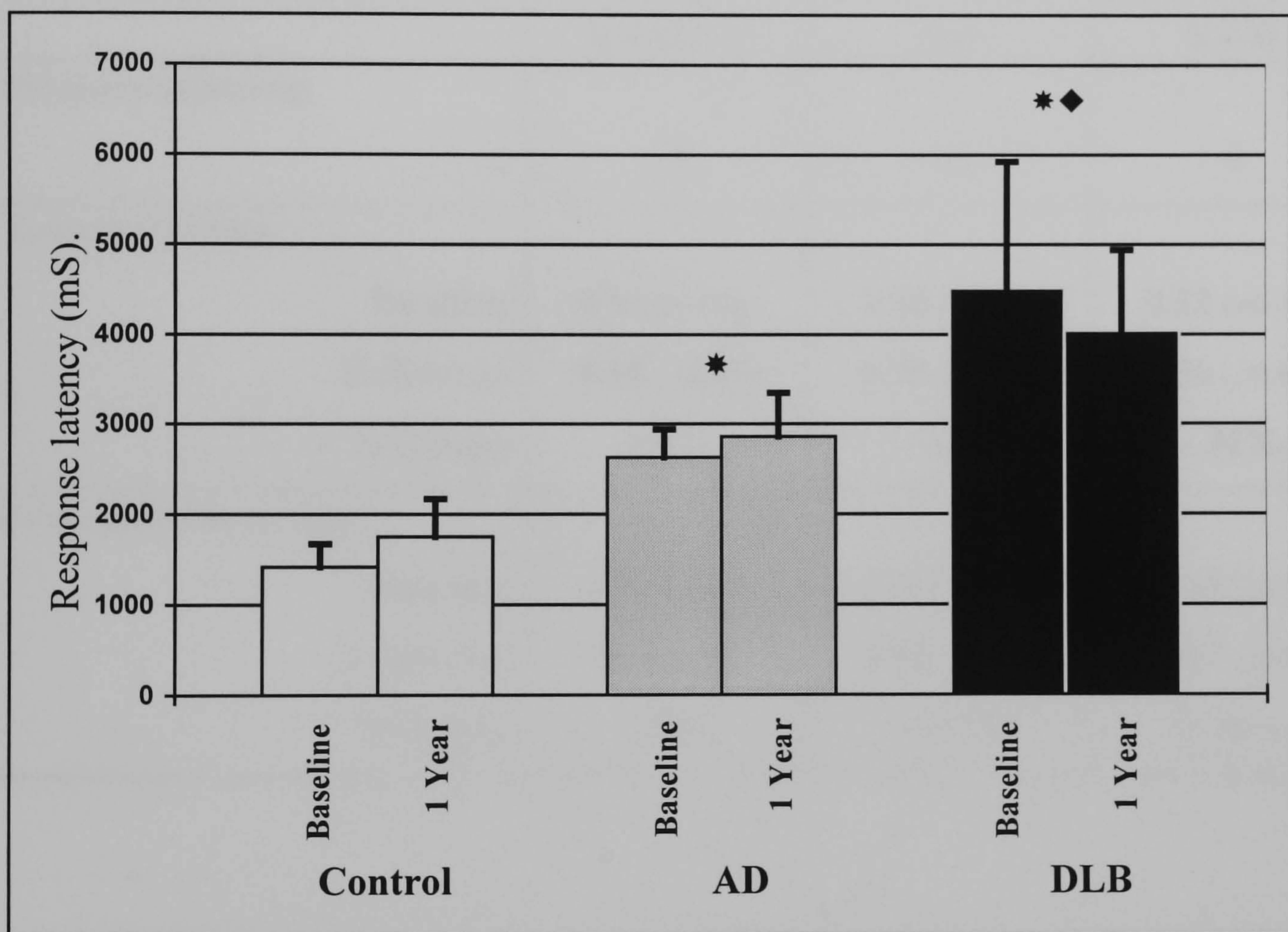
Analysis of sensitivity indices for the spatial working memory task indicated a main effect of group ($F_{(2,39)}=10.7$, $p=0.002$). The dementia groups performed equivalently, but significantly worse than the control group.

There was no overall difference in performance between baseline and 1 year follow-up visits. However, the interaction term (diagnostic group x visit) indicated disproportionate changes in groups between visits for the spatial working memory task ($F_{(2,39)}=3.7$, $p=0.034$). Post-hoc, analysis of means indicated that recognition sensitivity indices were improved at follow-up compared to baseline for both AD ($F_{(1,39)}=2.99$, $p=0.088$) and DLB groups ($F_{(1,39)}=99.6$, $p=0.004$).

Table 10.27: Spatial working memory: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis (p<0.05)
Diagnostic group	$F_{(2,39)}=12.2, p<0.001$	Control < AD < DLB
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

Figure 10.14: Spatial working memory: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=18) and DLB (n=5) groups at baseline and 1 year follow-up.



* significant difference (p<0.05) compared to controls; ◆ significant difference (p<0.05) between dementia groups

Comparison of response latencies for the spatial working memory task indicated a main effect of group ($F_{(2,39)}=12.2, p<0.001$). Response latencies were in the order: control < AD < DLB. Comparison of response latencies at baseline and 1 year follow-up indicated no differences between baseline and 1 year follow-up. Analysis of response latencies for the group x visit interaction indicated no significant interaction.

10.2.3.2 Memory scanning (numeric working memory).

Group means for the primary indices of performance in the numeric working memory task at baseline and 1 year follow-up, and the percentage change between baseline and 1 year follow-up, are presented in Table 10.28 and Figures 10.15 and 10.16. A summary of statistical analysis, using two-way ANOVA and Newman-Keuls post-hoc pair-wise comparisons, is presented in Tables 10.29 and 10.30.

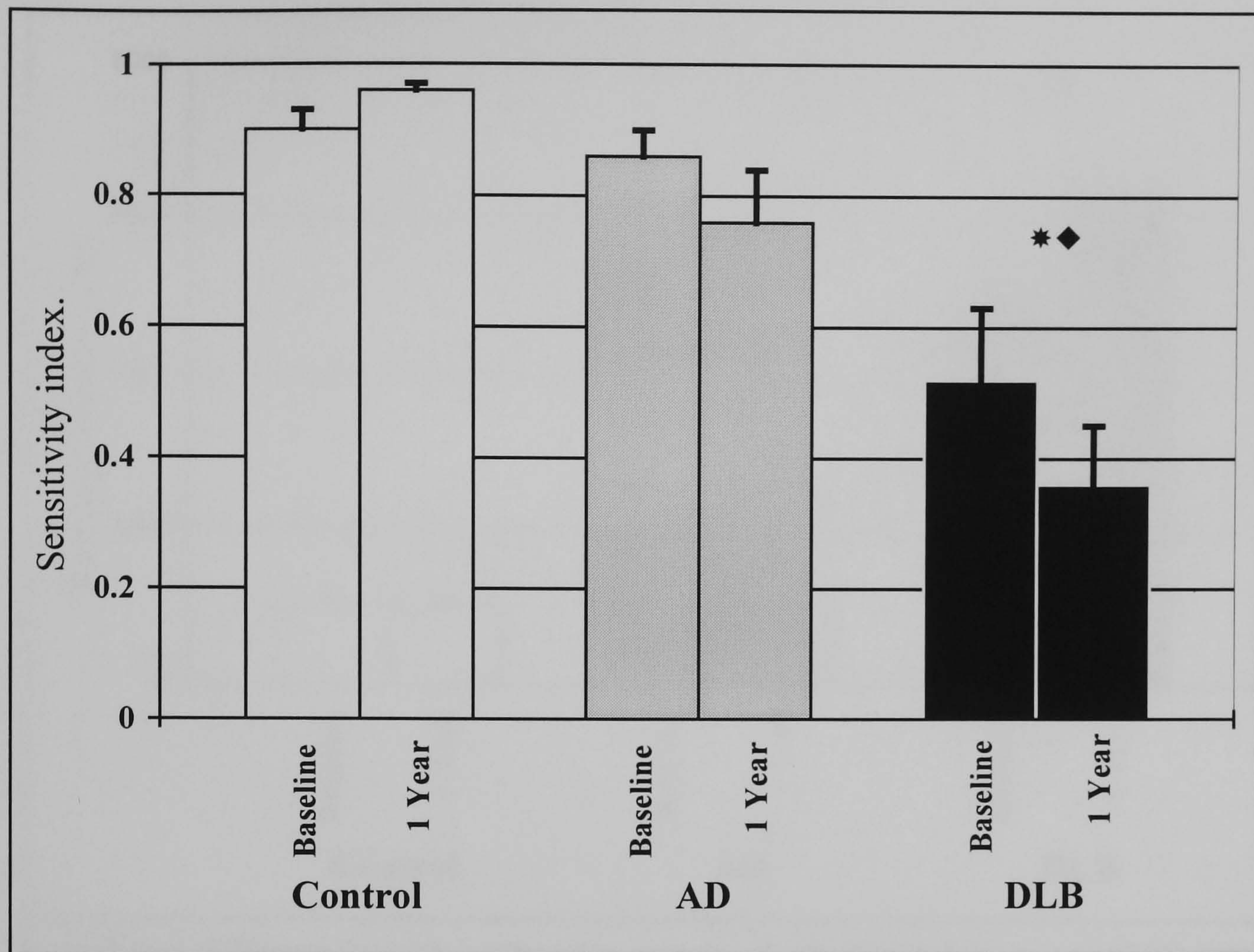
Table 10.28: Memory scanning: sensitivity indices (\pm SEM) and response latencies (\pm SEM) at baseline and 1 year follow-up for control, AD, and DLB groups.

	Control	AD	DLB
Memory scanning			
n	18	18	6
Sensitivity index			
Baseline	0.90 (\pm 0.03)	0.86 (\pm 0.06)	0.52 (\pm 0.11)
Follow-up	0.96 (\pm 0.02)	0.76 (\pm 0.08)	0.36 (\pm 0.09)
% change	+ 6%	- 12%	- 31%
Response latency (ms)			
Baseline	787 (\pm 32)	1501 (\pm 126)	3766 (\pm 858)
Follow-up	831 (\pm 76)	1941 (\pm 468)	4917 (\pm 849)
% change	+ 6%	+ 29%	+ 30%

Table 10.29: Memory scanning: summary of ANOVA for recognition sensitivity index.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,39)}=27.1, p < 0.001$	(Control \equiv AD) > DLB
Visit	N.S.	-
Diagnostic group x Visit	N.S.	-

Figure 10.15: Memory scanning: mean sensitivity indices (\pm SEM) for control (n=18), AD (n=18) and DLB (n=6) groups at baseline and 1 year follow-up.



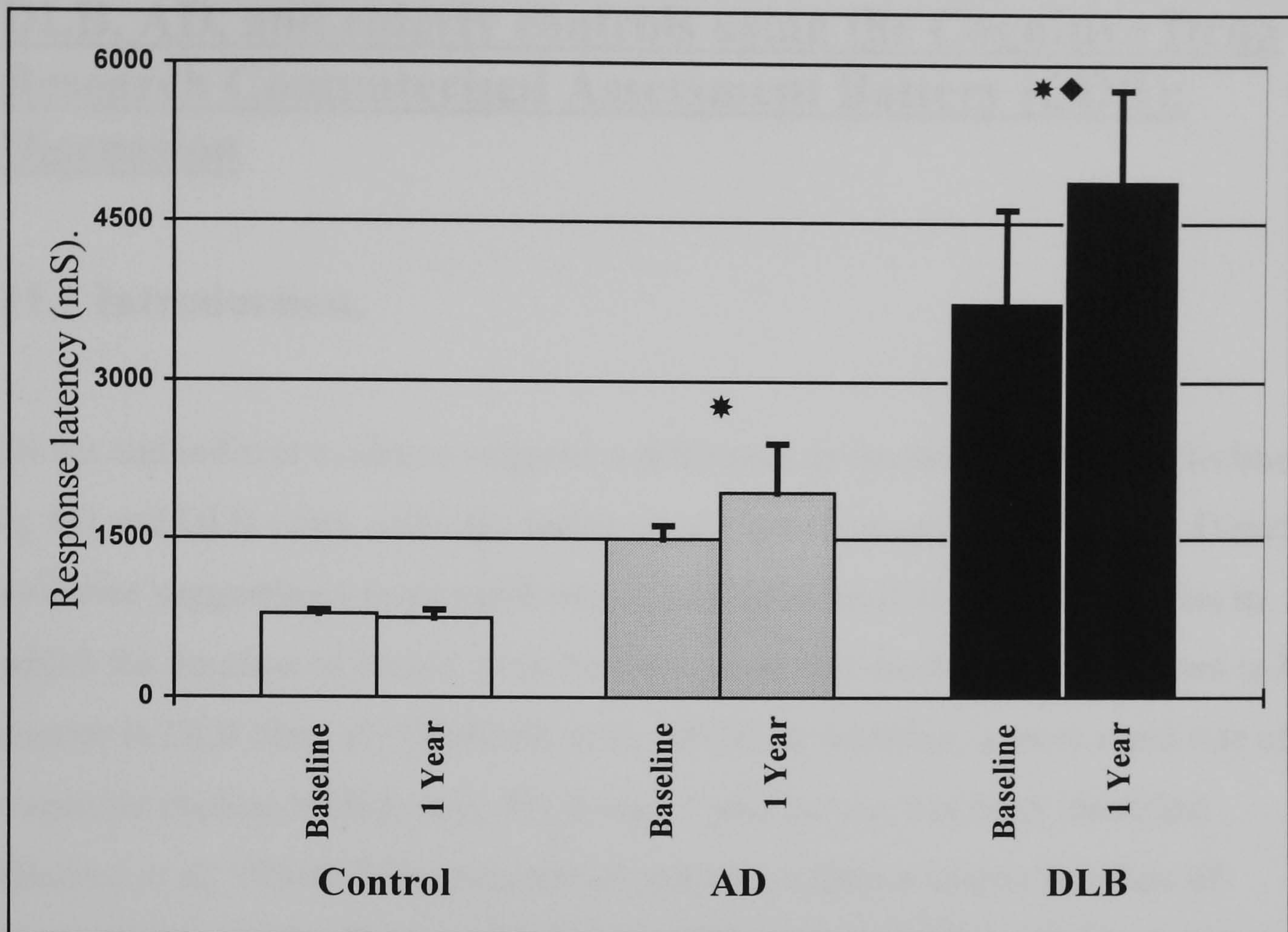
* significant difference ($p < 0.05$) compared to controls; ♦ significant difference ($p < 0.05$) compared to other dementia group

Analysis of sensitivity indices for the memory scanning task indicated a main effect of group ($F_{(2,39)}=27.1, p < 0.001$). The DLB group performed worse than both the AD and control groups, who performed equivalently. There were no differences between baseline and 1 year follow-up visits. The interaction term (diagnostic group x visit) was not significant.

Table 10.30: Memory scanning: summary of ANOVA for response latencies.

Source of variance	ANOVA summary	Newman-Keuls analysis ($p < 0.05$)
Diagnostic group	$F_{(2,39)}=57.0, p < 0.001$	Control < AD < DLB
Visit	$F_{(1,39)}=3.6, p=0.064$	-
Diagnostic group x Visit	N.S.	-

Figure 10.16: Memory scanning: mean response latencies (mS) (\pm SEM) for control (n=18), AD (n=18) and DLB (n=6) groups at baseline and 1 year follow-up.



* significant difference ($p < 0.05$) compared to controls; ◆ significant difference ($p < 0.05$) between dementia groups

Comparison of response latencies for the memory scanning task indicated a main effect of group ($F_{(2,39)}=57.0, p < 0.001$). Response latencies were in the order: control < AD < DLB. Comparison of response latencies at baseline and 1 year follow-up indicated a trend towards longer response latencies at 1 year follow-up ($F_{(1,39)}=3.6, p=0.064$). However further pair-wise comparisons revealed the difference was not significant. Analysis of response latencies for the group x visit interaction indicated no significant interaction.

Chapter 11:

A comparative study of cognitive decline over one year in DLB, AD, and elderly controls using the Cognitive Drug Research Computerised Assessment Battery (CDR): Discussion

11.1 Introduction.

Direct and indirect evidence suggests a difference in the rate of cognitive decline in AD and DLB cases, although further investigation is certainly required. Direct evidence suggesting a more rapid rate of decline in DLB comes from studies in which the duration of illness (time between onset and death) has been shown to be shorter in DLB than AD (McKeith et al, 1992b). In addition, a more rapid rate of cognitive decline in DLB than AD, over a 1 year period, has been identified (Ballard et al, 1996b). However, not all studies confirm a shorter duration of illness in DLB than AD (e.g. Förstl et al, 1993) and, in addition, there is some evidence that administration of neuroleptic medication may have contributed to shorter duration of illness (McKeith et al, 1992b).

Indirect evidence of a more rapid rate of cognitive decline in DLB has been inferred from a number of studies investigating clinical predictors of cognitive decline in AD. Alzheimer's disease patients with extrapyramidal symptoms and hallucinations have been shown to have a shorter duration of illness and faster rate of cognitive decline than AD cases without these symptoms (Mortimer et al, 1992; Chui et al, 1994; Miller et al, 1991). Many of the AD patients with extrapyramidal symptoms and hallucinations are likely to have been misdiagnosed DLB cases who were included in these studies (Chui et al, 1994).

11.2 The comparative decline in cognitive function over one year in AD and DLB.

The current body of work aimed to compare rate of cognitive decline in AD and DLB using procedures sensitive to decline and with proven test-retest reliability (Simpson et al, 1991). On the basis of the findings described above, it was predicted that the rate of cognitive decline in DLB would be greater than in AD.

This study did not, however, aim to report the cross-sectional comparison of groups, as this has already been described with a larger cohort in Chapters 6, 7, and 8. Notwithstanding, the smaller control and dementia groups showed profiles of cognitive impairment similar to those reported for the larger cohort previously described in Chapter 7.

The CDR test battery was sensitive to decline at one year follow-up on a number of indices of performance: simple reaction time; choice reaction time (but not accuracy); digit vigilance accuracy; and response latencies for delayed word, picture and face recognition tasks. A significant improvement between baseline and follow-up assessments on the spatial working memory task was found for both dementia groups, although both dementia groups were impaired compared to controls at baseline and follow-up.

Analysis of interaction terms revealed disproportionate changes in group performance between visits. The DLB group declined more than the AD and control groups in terms of accuracy on the number vigilance task, and showed a significantly greater increase in response latency for the delayed face recognition task. Both dementia groups declined compared to controls on response latencies for the delayed picture recognition task.

These data demonstrate that the CDR battery was sensitive to changes (both decline and improvement) in performance between baseline and 1 year follow-up. Overall, both AD and DLB dementia groups showed decline over the 1 year period between assessments, although the decline was restricted to certain aspects

of cognitive function. Furthermore, these findings support more rapid cognitive decline in DLB than in AD. In particular, the ability to sustain attention (measured by the digit vigilance task) declined faster in the DLB group. These data are novel as previous studies comparing cognitive decline in AD and DLB groups have failed to adequately assess attentional function and in particular vigilance.

Findings from the secondary memory tasks highlight the need to assess speed as well as accuracy when examining mnemonic function. Although performance on these tasks as measured by the ability to discriminate novel and previously seen exemplars failed to discriminate between visits, the response latencies increased between visits for both AD and DLB groups compared to controls on the delayed picture recognition task. Furthermore, DLB cases showed disproportionate slowing of response latencies in the delayed face recognition task. These data suggest changes in response strategy in these secondary visual recognition memory tasks between baseline and one year follow-up visits, such that speed of responding is reduced to improve accuracy of responding.

The finding that spatial working memory sensitivity indices actually improved between baseline and follow-up in both dementia groups without a concomitant increase in response latencies is somewhat surprising. As, by definition, dementia is progressive and degenerative, it is unlikely that the improved performance in the dementia groups on the spatial working memory task was due to underlying neurochemical or neuropathological changes associated with dementia progression. It is, however, conceivable that improved performance may have been due to a practice effect between visits. Nonetheless, the long delay (1 year) between assessments and the poor mnemonic function associated with both of the dementia groups would argue against this interpretation.

The observed improvement in spatial working memory performance may be attributable to alterations in strategy which attempt to compensate for the marked problems completing such tasks in dementia groups. The change in response strategy did not, however, involve a speed-accuracy trade-off as response latencies were similar for all groups at baseline and follow-up assessments. Nonetheless,

previous studies have reported differences in measures of spatial working memory strategy in dementia groups which are not associated with changes in responsivity (Sahgal et al, 1995).

11.3 Methodological considerations

A number of methodological considerations are salient to this, and other studies measuring decline in dementia groups.

The comparisons detailed in this study may have been subject to a degree of sampling bias. Firstly, only patients who were still alive; cognitively not too impaired; and not adversely behaviourally disturbed, were included for detailed follow-up assessment. Thus, individuals excluded from follow-up assessment may well include cases with rapid cognitive deterioration. In consequence, data from the current study may underestimate the degree of cognitive decline in the total cohort investigated in the original cross-sectional study.

Secondly, not all of the participants who attempted follow-up assessment were able to complete a full assessment. For example, only half (n=5) of the DLB group were able to complete the spatial working memory task at follow-up assessment. Individuals who were unable to complete the task were thus excluded from this task. Exclusion of patients unable to complete this task would therefore distort the sample towards individuals with less deteriorated spatial working memory

The influence of sampling factors on the observed profiles of cognitive decline cannot be disregarded, and suggest these data must be applied to a clinical population with some caution. Notwithstanding, the data described are for repeated measures comparisons and suggest qualitatively distinct profiles of cognitive decline in DLB and AD within the cohort able to complete follow-up assessments.

11.4 Summary.

The investigation of cognitive decline in dementia is, to some extent, limited by the progressive nature of cognitive impairment in dementia. Sampling biases associated with a cognitively deteriorating population somewhat restrict the extrapolation of findings to more general dementia populations. These methodological limitations are, nonetheless, common to all studies comparing rates of cognitive decline in dementia

Notwithstanding, these data have further demonstrated distinct profiles of cognitive decline over one year in DLB and AD in the cohort of patients able to complete both baseline and follow-up assessments. This study supports and extends previous findings suggesting a more rapid rate of decline in DLB than AD. The more rapid decline in cognitive abilities the DLB group is not apparent in all aspects of cognition. Specific aspects of cognitive performance, most notably sustained attention, appear to decline more rapidly in DLB than AD.

Chapter 12:

General Discussion

12.1 Introduction

- The body of work described in this study includes the largest prospective comparative study to date of cognition in DLB with a well characterised and investigated clinical cohort. This study has successfully replicated previous work suggesting poor visuospatial function and relatively preserved recognition memory in DLB. Furthermore, fundamental aspects of attentional function have been assessed for the first time and were shown to differ between DLB and AD.
- Concurrent rigorous clinical evaluation has facilitated the comparison of DLB groups with distinct clinical symptoms. The cognitive impairment described in DLB cases with persistent visual hallucinations is distinguishable from the cognitive impairment described in both AD and DLB cases without persistent visual hallucinations. Much of the neuropsychological distinction described (see Section 7.3) between AD and DLB groups appears to be associated with the occurrence of persistent visual hallucinations in the DLB group.
- In addition, a comparative longitudinal study of cognitive decline in DLB and AD over a 12 month period is reported. While these data confirm previous work suggesting a more rapid rate of decline in DLB, the use of a broad range of sensitive tests has identified this to be restricted to specific areas of cognition. Sustained attention, and speed of making recognition memory decisions appear particularly susceptible to decline in DLB and this confirms the central role of attentional dysfunction.

12.2 General methodological considerations

12.2.1 Patient diagnosis and recruitment.

When comparing neuropsychological profiles in different types of dementia, it is preferable that cohorts studied are representative of the clinical population from which they are drawn. Systematic misdiagnosis of dementia patients can lead to spurious conclusions from neuropsychological and other investigations comparing different types of dementia.

12.2.1.1 The clinical diagnosis of dementia with Lewy bodies and Alzheimer's disease.

Until relatively recently, DLB cases have generally been ascribed a diagnosis of AD or, less often VaD (McKeith et al, 1994b). The recent publication of consensus clinical criteria for the clinical diagnosis of DLB (McKeith et al, 1996a) and their ongoing neuropathological validation should further improve the sensitivity and specificity of operationalised criteria for the clinical diagnosis of DLB.

All patients in the studies reported in this thesis were recruited from the Medical Research Council Prospective Study of Memory Disorders. The primary aim of this study is to validate clinical diagnostic criteria for DLB. As neuropathological investigations remain the gold standard for subtype diagnosis, autopsy evaluation has a pivotal role in the MRC study. Publication of this thesis could not, however, await autopsy confirmation of clinical diagnoses of cases included, although eventual autopsy findings are intended to be employed for analysis at a later date. Nonetheless, data from the first forty-six cases from the MRC study to have received autopsy validation are available (Ballard et al, 1997b), which includes only one of the cases included in this thesis. Consensus clinical diagnoses made by three senior psychogeriatricians were compared with neuropathological diagnoses (McKeith et al, 1996a) to provide measures of specificity (% of clinically identified cases pathologically confirmed) and sensitivity (% of pathological

identified cases which met clinical criteria). The procedures for clinical and neuropathological diagnosis are standardised and the subsequent findings are intended to be indicative of the specificity and sensitivity of diagnoses made by this research group.

Specificity values indicate how likely clinically identified cases are to have the assigned diagnosis at post mortem. Sensitivity values indicate the number of cases with pathological features who also meet clinical criteria. High specificity and sensitivity rates are the most desirable if a cohort under investigation is to be maximally representative of a population.

Twenty two of 24 clinically identified probable DLB cases also met pathological criteria (92% specificity), whilst three pathologically confirmed probable DLB cases failed to meet clinical criteria (88% specificity). One DLB case was misdiagnosed as VaD and two DLB cases were misdiagnosed as AD cases. All DLB cases fell into the probable diagnostic category, hence data is not available for criteria for the diagnosis of possible DLB.

Eight out of ten clinically identified probable AD cases were pathologically confirmed (80% specificity), and 14 out of 15 pathologically identified probable AD cases met clinical criteria (93% sensitivity). One probable AD case was misdiagnosed as DLB, and one probable AD case also had significant vascular pathology and met criteria for the diagnosis of VaD. Clinically identified possible AD was pathologically confirmed in 6 out of 9 cases (67% specificity).

The index of primary importance for this thesis is specificity, as it is essential that groups are made up of the diagnostic categories. Low diagnostic specificity would mean numerous misdiagnoses would be included in each diagnostic group. The specificity ratios for probable DLB (92%), probable AD (80%) and possible AD (67%) suggest the majority of cases in these diagnostic categories were correctly diagnosed.

If these data are applied to the main comparative study which used the CDR procedures, it can be estimated that 18 out of 20 probable DLB cases will actually show pathology supporting the clinical diagnosis. Furthermore 18 out of the 22 clinically diagnosed probable AD cases and 16 out of the 24 clinically diagnosed possible AD cases will show corresponding pathology.

Sensitivity provides an indication of how many patients who meet neuropathological criteria also meet clinical criteria and as such, provides a idea of how representative a clinically identified group is of the total neuropathologically diagnosed population. The relatively high sensitivity in both probable DLB (88%) and AD (93%) suggest the majority of probable AD and DLB cases would be identified by application of these clinical criteria. These values are comparable with those found in AD using NINCDS-ARDRA criteria (e.g. Kukull et al, 1990).

Although the misclassification of cases might well have occurred, these data suggest the problem to be of equivalent magnitude to other studies prospectively comparing AD and DLB. Data from the MRC prospective study can, therefore be confidently extrapolated to the neuropathologically defined AD and DLB diagnostic categories.

12.2.1.2 Selectivity of assessment tools - are the neuropsychological findings genuinely representative of the population from which cases were drawn?

A further level of selection of dementia patients occurs when participants are requested to complete neuropsychological assessment, since increasingly severe cognitive impairment impacts on the ability of some patients to complete neuropsychological testing. Even with appropriately designed testing procedures and skilled experimenters, it is inevitable that the cognitive impairment associated with severe and end stage dementia precludes some dementia patients from understanding the most simplified testing procedures. Furthermore, in patients able to complete assessment, 'floor' effects may reduce the power of neuropsychological tests to discriminate experimental groups. The selectivity of CANTAB and CDR assessment procedures are outlined in this section and

discussed in terms of their application in a demented population. As all controls approached were able to complete full neuropsychological assessment, they will not be considered further in this section.

The decision whether to approach a referred patient for neuropsychological assessment was based on a number of factors. Previous recent neuropsychological test performance was a major consideration which was discussed with senior psychogeriatricians and an experienced psychiatric nursing sister. Suitability for detailed neuropsychological assessment was initially discussed in terms of chronic factors unlikely to be resolved such as: severity of dementia; marked behavioural disturbance; impaired sensory capabilities; and physical disability (e.g. severe arthritis) preventing the necessary responses (see Appendix V).

In addition, a number of patients, who were not excluded from neuropsychological assessment, did not partake in neuropsychological assessment for reasons not necessarily related to their ability to complete neuropsychological assessment. These included: objections or refusals to partake in cognitive assessment, withdrawal from main MRC study, research overload, and death.

If a patient was considered appropriate for neuropsychological assessment, acute problems which might affect compliance and performance were considered. These might include: a recent move into residential nursing care, a recent change in medication, infection or other acute physical illness. Assessments were subsequently attempted only upon resolution of acute difficulties ensuring care was taken to minimise inappropriate testing.

Patients deemed as 'borderline' were generally approached and tested when the approach was thought not likely to negatively affect them. The experimenter made over 40 visits to attempt testing with 'borderline' cases to find 30 patients unable to usefully complete neuropsychological assessment. It is likely, therefore, that all referred patients capable of completing neuropsychological testing were included.

All patients were able to at least attempt the CAMCOG schedule. However, differences in exclusion rates associated with the different computerised batteries used in the cross-sectional studies were evident.

CANTAB: A total of 137 patients were consecutively referred for the CANTAB study from the MRC study. Fourteen (10%) were appropriate for CANTAB assessment and 123 (90%) were excluded, the most common reason being severity of dementia (80 cases). For all dementia cases consecutively referred from the MRC study, 58% were too demented to comprehend and complete CANTAB assessment.

The relatively high (90%) exclusion rate of consecutively referred cases from the CANTAB study reflects, in part, the procedural complexity, duration, and nature of the tests. Many of the tests which comprise the CANTAB battery are based on experimental procedures which generally have numerous complex trials (e.g. 40 trials in simultaneous and delayed matching to sample task) to maximise task sensitivity. In addition, stimuli in many of the CANTAB battery tests (e.g. pattern recognition, and matching to sample procedures) are complex and small requiring good visual acuity to complete the tasks which is reflected in the number (10) of cases excluded from neuropsychological testing due to sensory difficulties. Nonetheless, all participants who completed the CANTAB study were required to read a line of size twelve font prior to testing to confirm adequate visual abilities.

Although the CANTAB battery is a sophisticated and sensitive battery of neuropsychological tests, the complexity of these may restrict the applicability of the system to relatively mildly demented populations. The data reported using the CANTAB battery are therefore representative of cognitive changes only in the early stages of dementia in AD and DLB.

CDR: A total of 104 patients were referred for the CDR cross-sectional study, of whom 34 patients (33%) were unable to complete CDR assessment and 70 patients (67%) were capable of completing CDR assessment. The major reason for non-inclusion in the study was severity of dementia: of the 104 cases consecutively referred from the MRC study, 11% (11 cases) were too severely demented to complete CDR assessment. Four patients were unable to partake in assessment as physical disabilities (3 severe arthritis, 1 severe parkinsonian tremor) prevented the use of the response box. In addition, 'floor' effects were observed on the spatial working memory task, which may have reduced the ability of this task to discriminate dementia groups.

The CDR battery used was specifically designed (Simpson et al, 1991) for use with a demented population and this is reflected in the high (70%) inclusion rate of consecutively referred cases. A number of specific modifications are included:

1. The experimenter was also able to briefly pause testing without the loss of data if participants became fatigued and / or became distracted.
2. Negative feedback on performance can highlight cognitive deficits to dementia patients and hence reduce participant compliance, and such feedback has been kept to a minimum. In addition to the removal of ongoing performance feedback, tasks requiring recall testing were avoided, as the participant is too clearly aware of the poor quality of performance.
3. The size of words and digits were increased to minimise the impact of visual deficits on cognitive test performance.
4. The number of trials for each task was reduced compared to the CDR battery used in healthy volunteer populations.

The findings from the CDR study appear to be representative of mild to moderate dementia patients, however, severely demented patients were unable to complete the battery.

In summary, high sensitivity and particularly specificity rates for the differential diagnosis of dementia in the cohort from which the participants in this study were recruited, imply that the DLB and AD groups include patients who at autopsy are likely to receive confirmation of their clinical diagnosis. The inclusion of misclassified dementia patients is inevitable although this would be likely to add 'noise' to group comparisons rather than creating or magnifying group differences. The cohort of patients assessed using the CANTAB battery of tests appears representative of relatively mildly demented population. The CDR battery, which is specifically adapted for use with a dementia population, is representative of a broader range of dementia patients. Neither system was capable of assessing severely demented cases, however, when patients become severely demented differential diagnosis has usually been made and the administration and interpretation of psychometric assessments becomes severely restricted (Lezak, 1983).

12.2.2 Retrospective validity of matching methodology.

Matching procedures were employed to minimise the effect of any systematic sampling differences between groups. All groups were matched for measures of activities of daily living and global severity of cognitive impairment using the CAMCOG schedule. Groups were not consistently matched for age, although as previously discussed (see Chapter 8) this is highly unlikely to account for the observed differences between groups.

12.2.2.1 Matching for severity of global cognitive impairment using the CAMCOG schedule

Although the CAMCOG schedule provides a relatively comprehensive assessment of cognitive impairment in dementia (Roth et al, 1986), the attentional subsection of the CAMCOG schedule failed to discriminate between AD and DLB despite the marked differences in attention described in both CANTAB and CDR studies. The failure of CAMCOG to discriminate AD and DLB groups probably reflects the cognitive processes purported to be assessed by questions in the ‘attentional’ subsection which all involve numeric calculations (counting backwards from 20, subtracting 7 from 100 five times, adding 10p and 5p, and taking 15p from £1). These questions undoubtedly involve attentional resources, however, they are all primarily tests of numeric working memory which has been shown to be equivalently impaired in AD and DLB (see Section 7.3.3.2). This highlights the problems associated with the assessment of attentional function, and in particular vigilance, using traditional psychometric tests.

The identification of a particularly severe reduction in the attentional abilities of DLB patients confirms the earlier assertion (see Section 1.5) that mnemonically based tools for measuring the severity of global impairment in dementia may underestimate the degree of overall cognitive impairment in DLB patients.

Nonetheless, the CAMCOG provided further evidence of a discrimination between neuropsychological profiles in AD and DLB. A double dissociation was observed between more impaired recall and recognition memory in AD than DLB, and a better performance of AD patients on the visuo-spatial praxis section. These parallel the findings of the computerised assessment procedures and confirm the value of the CAMCOG schedule in profiling most aspects of cognitive performance in dementia. In addition, these findings replicate a recent study comparing cognitive impairment in LBD and AD using the CAMCOG schedule (Walker et al, 1997).

12.2.2.2 Matching for estimated pre-morbid intellectual ability using the NART.

Matching groups for pre-morbid IQ using the NART schedule aims to prevent spurious group distinctions due to differences in pre-morbid intellectual capabilities. The NART has been frequently employed to match dementia and control groups (for review see O'Carroll, 1995b), however, there is increasing evidence that NART performance is not impervious to the effects of dementia (Fromm et al, 1991; O'Carroll et al, 1995). These authors have reported significant correlations between severity of dementia in AD (as measured by MMSE scores) and estimated pre-morbid IQ (as measured by NART performance). The ability to pronounce irregular words appears to remain intact only in the mild stages of dementia. (Fromm et al, 1991, Patterson et al, 1994).

Comparison of pre-morbid intellectual ability between dementia groups and controls from the cross-sectional studies reported in this thesis support these findings. For example, in the CANTAB study, which included predominantly mildly demented patients, no differences were described between dementia groups and the control group for estimated pre-morbid intellectual ability. In the study using CDR assessment procedures, a broader range of mild to moderately demented patients were included and although both dementia groups were matched for NART performance, the control group performed significantly better than both dementia groups and at a similar level to that described for all groups in the CANTAB study. The introduction of the more severely demented patients in the CDR study may have resulted in the lowered estimated pre-morbid IQ in the dementia groups. Notwithstanding the evidence suggesting dementia patients retain the ability to pronounce irregular words only in the mild stages of dementia, the primary comparison in this study was between AD and DLB dementia groups and NART performance of these groups was similar.

12.3 A neurochemical model of the cognitive deficits in DLB

12.3.1 Introduction

This section will examine the relationship between neuropsychological deficits, neurochemical dysfunction, and neuropathological damage in DLB. A composite model relating known neurochemical, neuropathological, and neuropsychological features of DLB and AD with lesion and drug studies in both animals and humans will be proposed.

12.3.2 Neurochemical pathology and cognitive impairment in DLB.

12.3.2.1 Introduction

Absolute levels of cholinergic activity are more severely reduced in DLB than AD (Dickson et al, 1987; Perry, E. et al, 1990b; 1994). Archicortical cholinergic depletion has been shown to be more severe in AD than DLB (Perry, E. et al, 1994) which contrasts with the more severe cholinergic depletion in many neocortical areas in DLB (Perry, E. et al, 1990b, Langlais et al, 1993). Cholinergic receptors remain relatively preserved in DLB compared to AD, this is true for both muscarinic M₁ (Perry, E. et al, 1990b) and nicotinic receptors (Perry, E. et al, 1995a). The reduced neocortical cholinergic activity in DLB does not appear to be due to loss of receptor sites, but may be due to pathological processes which contribute to the degeneration of cholinergic neurones in the nucleus basalis of Meynert, a rich supplier of acetylcholine innervation to the neocortex (Perry, E. et al, 1994).

Furthermore, acetylcholine depletion appears to be particularly severe in DLB patients with visual hallucinations. An 80% reduction of neocortical ChAT has been reported in hallucinating cases compared to a 50% reduction in non-hallucinating cases (Perry, E. et al, 1994). The cholinergic depletion in non-hallucinating cases was similar to the reduction seen in AD cases from the same series of patients. The presence of hallucinations may also be related to findings

suggesting the ratio of serotonergic hyperactivity (although absolute levels are reduced) and relative cholinergic hypoactivity are associated with visual hallucinations (Perry, E. et al, 1993a) which is consistent with the psychopharmacological effects of drugs acting on these systems.

Reductions in subcortical dopaminergic activities differentiate AD and DLB particularly in the neostriatum (caudate nucleus) where dopamine depletion (which reflects neuronal depletion in the substantia nigra) may be as much as 60% (Perry, E. et al, 1990a, Langlais et al, 1993). Neocortical monoamine activities do not, however, discriminate DLB, AD and controls (Langlais et al, 1993).

A proposed relationship between cholinergic depletion and neuropsychological dysfunction can be based on findings from studies of cholinergic function and separate studies (including findings reported in this thesis) of cognitive function in AD and DLB, as well as studies comparing of AD with DLB groups with different levels of cholinergic dysfunction (DLB+VH and DLB-VH).

The correlation of cholinergic and cognitive impairment in AD, DLB-VH and DLB+VH groups is based on the assumption that cholinergic depletion at post mortem reflects the cholinergic dysfunction at the time patients completed cognitive assessments. This assumption is based on a number of findings. Firstly, the presence of visual hallucinations are a more prominent feature at all stages in DLB than AD (e.g. McKeith et al, 1992c; 1996a). Secondly, pharmacological agents which compromise cholinergic function such as scopolamine and atropine induce hallucinations (Perry, E. et al, 1996). Thirdly, the type of visual hallucinations reported in DLB are mainly of circumscribed visual images of familiar objects, faces or animals (Ballard et al, 1996a) and are consistent with the ability of acetylcholine receptor antagonists to induce similar types of visual hallucinations (Perry, E. et al, 1995b). In contrast, serotonergic enhancing agents such as LSD produce altered sensory perception including a degree of 'cross writing' or synaesthesia - hearing colours for example, and an often disturbing sense of depersonalisation (Perry, E. et al, 1995b). Thus, the neurochemical basis of the increased incidence of visual hallucinations in living DLB patients appears

to be related to the concomitant cholinergic depletion rather than the apparent serotonergic hyperactivity. On this basis, it is assumed that the level of cholinergic depletion reflects that seen at post mortem, such that there is similar cholinergic depletion in the AD and DLB-VH groups, however cholinergic depletion is greatest in the DLB+VH group.

12.3.2.2 Cholinergic depletion and cognitive impairment in DLB and Alzheimer's disease.

If the level of cholinergic depletion is pivotal to the cognitive deficits seen in DLB then, profiles of cognitive impairment should reflect the level of cholinergic depletion in DLB+VH, DLB-VH and AD groups. The demonstration that DLB-VH and AD groups have similar reductions (~50%) in cholinergic activity coupled with DLB+VH patients from the same series showing a greater cholinergic deficit (~80% reduction) could imply that profiles of cognitive impairment in the DLB-VH and AD groups would be similar. Furthermore, the profile of cognitive impairment in the DLB+VH group would be distinct from both DLB-VH and AD groups in a manner which would account for the neuropsychological distinctions identified between pooled AD and DLB groups.

The findings reported in the comparison of DLB+VH, DLB-VH and AD groups reported in this thesis (see Section 7.4) support this prediction. The DLB-VH and AD groups performed similarly on all tests in the CDR battery apart from the choice reaction time test. Choice reaction times reported for the DLB-VH group were increased compared to the AD group, but were equivalent to those described for the DLB+VH group.

Performance of the DLB+VH group was, however, quite distinct from both DLB-VH and AD groups. The DLB+VH group showed more impaired performance than both AD and DLB-VH groups on the simple reaction time task, and the sustained attention task, which mirrors the distinctions between DLB and AD groups. In addition, the DLB+VH group performed at chance levels on the spatial working memory task which further analysis indicated was worse than both AD

and DLB-VH group. The DLB-VH and AD groups performed equivalently on the spatial working memory task. This finding is not necessarily at odds with findings from comparison of pooled AD and DLB groups, where it has been argued that floor effects contributed to the failure to discriminate pooled AD and DLB groups on the spatial working memory task. It is conceivable that subtle changes in variance of each groups performance, which may be particularly relevant where floor effects are demonstrated, lead to the discrimination between AD and DLB+VH as well as between DLB-VH and DLB+VH on the spatial working memory task.

All of the secondary memory tasks failed to discriminate DLB+VH, DLB-VH and AD groups, in contrast to the previously reported less impaired delayed word recognition in the DLB group (see Section 7.3.2). The failure of the delayed word recognition task to dissociate between DLB+VH, DLB-VH and AD groups may reflect the reduced statistical power associated with splitting the DLB group. Nonetheless, response latencies in all secondary memory tasks were greater in the DLB+VH group than in both AD and DLB-VH groups who responded following similar latencies.

These neuropsychological data provide support for the proposal that level of cholinergic depletion is pivotal in the genesis of the cognitive deficits associated with DLB. It has been demonstrated that comparison of DLB and AD groups reveal a pattern of cognitive impairment that is associated with the level of cholinergic depletion in the DLB group. The cholinergic model proposed cannot, however, account for all of the observed differences in cognitive function (choice and cognitive reaction times and response latencies in the secondary memory tasks) between DLB groups with and without visual hallucinations. Explanations are proposed for these differences in the subsequent paragraphs.

12.3.2.3 Neostriatal dopamine depletion and choice reaction times in DLB and Alzheimer's disease.

Increased choice reaction times were found in the DLB group compared to AD, independent of the presence of visual hallucinations and associated degree of cholinergic depletion. This implies that differences in neurochemical pathology not associated with cholinergic depletion might account for these differences in choice reaction times. The other major distinction in neurotransmitter function between AD and DLB groups is the degree of dopamine depletion in subcortical structures and in particular the neostriatum (Perry, E. et al, 1993b; Langlais et al, 1993). However, no differences in dopamine depletion have been described between hallucinating and non-hallucinating DLB groups.

A possible neurochemical substrate for the observed longer choice reaction times is the dopaminergic depletion seen in DLB. Support for this is derived from studies showing a selective increase in choice but not simple reaction times when dopaminergic antagonists (Haloperidol) are administered to healthy young controls, and the selective decrease in choice but not simple reaction times when pro-dopaminergic agents are administered to healthy young controls (Wesnes et al, in preparation).

A similar dopaminergic based explanation has also been proposed for the increased cognitive reaction time seen in DLB compared to AD and control groups (see Section 8.2.1.2). Evidence from a large study comparing the cognitive impairment profile of AD patients with scopolamine induced impairment demonstrated that a selective increase in simple reaction times accounted for all of the increase in choice reaction times in both groups (Wesnes, 1996; Wesnes et al, 1996). Thus cognitive reaction time is not affected at any stage of AD or following various doses of scopolamine administration. These findings strongly suggest that increased cognitive reaction time in DLB patients is not related to muscarinic dysfunction.

On the basis of this finding, dopamine dysfunction was previously proposed as the neurochemical substrate of the increased cognitive reaction time observed in the DLB compared to AD and control groups (see Section 8.2.1.2). It is therefore logical to predict similarly increased cognitive reaction times would be observed in both DLB+VH and DLB-VH groups. However, this pattern of results was not apparent, although means were clearly (see Section 7.4.3) in the right direction. Reduced statistical power associated with the smaller DLB+VH and DLB-VH groups, as well as the large variability of recorded cognitive reaction times, may account for the failure to discriminate between DLB+VH, DLB-VH, and AD groups. Although the mean cognitive reaction time for the DLB-VH group (699 milli-seconds) was slightly longer than reported for the pooled DLB group (519 milli-seconds), comparison with the same AD and control groups failed to identify the increased cognitive reaction time described for the pooled DLB group. The relationship between cognitive reaction time and dopamine requires further investigation in a larger cohort of DLB+VH, DLB-VH, and AD cases.

12.3.2.4 The putative impact of a reduced ability to sustain attentional resources on task performance.

Response latencies for all secondary memory tasks were significantly longer in the DLB+VH than the AD and DLB-VH groups, although there were no between group differences for sensitivity indices. These data suggest a specific slowing of decision making in the delayed secondary memory tasks which was not apparent in the earlier immediate word recognition task. These findings are difficult to explain in terms of the neurochemical model proposed as other comparisons did not describe differences in response latencies on delayed secondary recognition memory tasks between dementia groups. Nor do the increased response latencies generalise to all secondary recognition memory tasks as they were not apparent in the earlier word recognition task.

A possible explanation for the observed increase in response latencies in the DLB+VH group is a susceptibility to fatigue effects in the DLB+VH group. This supposition would be consistent with task ordering, as the increased secondary

recognition memory response latencies were observed only on the final three tests. Furthermore, a particularly reduced capability of the DLB+VH group to sustain attentional resources has been demonstrated (see Section 7.3.1).

12.3.2.5 Summary.

In summary, relative cholinergic depletion has been proposed as the basis of the majority of the neuropsychological distinctions between pooled DLB and AD groups. Comparison of DLB groups with different levels of cholinergic depletion suggest this assumption to be valid. A number of findings appeared to weaken this model, however, these have been explored and explained in terms of differential dopamine depletion, reduced statistical power associated with division of the DLB group, and fatigue effects.

12.3.3 Evidence suggesting differential involvement of nucleus basalis of Meynert-cortical and septo-hippocampal cholinergic projections in AD and DLB

As recently as 1983, antibodies to ChAT were developed enabling for the first time the accurate description of the organisation of cholinergic innervation in the brain. Even more recently, the immunotoxin ¹⁹²IgG-Saporin has been developed which has been employed in a growing number of studies investigating basal forebrain cholinergic lesions. IgG-Saporin is a powerful and, importantly, selective lesioning tool which has led to the functional discrimination of nucleus basalis of Meynert and septo-hippocampal cholinergic pathways in the basal forebrain (Wiley et al, 1991). The septo-hippocampal projection is associated primarily with mnemonic function (e.g. Steckler et al, 1995) whilst cortical projections from the nucleus basalis of Meynert are thought to contribute to visual attentional function, but not to mnemonic function per se (e.g. Everitt et al, 1997).

It is possible that DLB is associated with particularly disrupted nucleus basalis of Meynert projections, whilst AD is associated with relatively severe septo-hippocampal disruption. The basis of this distinction is based on neurochemical,

neuropathological, and most importantly neuropsychological studies of DLB and AD.

All tests in the CDR battery employed in this study have been shown to have a linear dose-dependant relationship between performance and the administration of increasing doses of scopolamine (Wesnes, 1994). Scopolamine is an indiscriminate muscarinic antagonist and therefore affects all cholinergic synapses. The results described in this study (see Chapter 7), and others, suggest relative mnemonic preservation in DLB compared to AD, and relative attentional preservation in AD compared to DLB. The finding that DLB cases, which show a greater neocortical depletion of cholinergic function, have relatively preserved mnemonic processing suggests the septo-hippocampal projection may not be as disrupted as in AD, whilst the relatively poor attentional function suggests the nucleus basalis of Meynert-cortical projection (which has been recently shown to be important in visual attentional function; Everitt et al, 1997) may be more severely disrupted in DLB than AD.

This assertion is consistent with known neurochemical and neuropathological alterations observed in AD and DLB. Archicortical (including hippocampal) cholinergic depletion has been shown to be more severe in AD than DLB (Perry, E. et al, 1994), and conversely cholinergic function is more disrupted in neocortical areas in DLB than AD (Perry, E. et al, 1990a; 1990b; 1993a). These findings are consistent with the pathological burden in the hippocampus (Dickson et al, 1991) and cell loss in the nucleus basalis of Meynert (Perry, E. et al, 1990b).

Preliminary neurochemical, neuropathological, and neuropsychological findings appear consistent in suggesting the differential involvement of nucleus basalis of Meynert and septo-hippocampal cholinergic projections in the genesis of cognitive impairment in AD and DLB. Nonetheless, studies describing differences in neocortical and cortical cholinergic function in DLB and AD (Perry, E. et al, 1990a; 1994) involved small cohorts of highly selected patients and await replication. Furthermore, the relationship between pathological burden and functional disruption is not clear, indeed, synaptic loss might be a better indicator

of functional disruption than pathological burden per se (Terry et al, 1994). Further investigations might explore this area by comparing nucleus basalis of Meynert and medial septum neuropathology and neurochemistry in DLB and AD groups. The relative involvement of septo-hippocampal and nucleus basalis of Meynert-neocortical projections may help account for the observed pattern of neuropsychological deficits in AD and DLB.

12.4 Future directions.

The proposal that cholinergic deficits underlie many of the neuropsychological deficits observed in DLB patients, combined with the relative preservation of cholinergic receptor populations, suggests these patients may respond to cholinomimetic therapy. Indeed, some investigations have already suggested this may be the case (e.g. Eagger et al, 1996). Trials of putative pharmacological treatments for DLB must include adequate assessment of attentional abilities and, in particular, the ability to sustain attentional resources. Solely mnemonically based cognitive assessments may underestimate potential improvements in cognition in the DLB group to cholinergic enhancement.

The distinction between DLB+VH and DLB-VH outlined in this theses requires further investigation. It is conceivable that the profile of cognitive deficits identified in DLB+VH cases might be symptom rather than disease specific. This question might be addressed by the comparative neuropsychological and neurochemical investigation of hallucinating and non-hallucinating AD cases. Unfortunately, such a comparison was not possible in this study due to the small number of AD cases with visual hallucinations included in the cohort.

In addition, several areas of cognitive function remain relatively under-investigated. Visuospatial abilities have been shown to differentiate DLB and AD cases (e.g. Gnanalingham et al, 1997) and data from the current study suggest a particularly severe impairment of spatial working memory in hallucinating DLB cases. Work is currently underway in Newcastle to develop a battery of tasks which assess aspects of spatial working memory, visual working

memory and spatial planning. The Newcastle frontal assessment battery (NewFAB) has been developed specifically for use with a demented population using similar adaptations to those previously described for the dementia version of the CDR battery. In addition, complex motor response patterns are not required (as in Hansen et al, 1990; Gnanalingham et al, 1997; Walker et al, 1997), which will facilitate the dissociation of visuospatial deficits from problems making complex motor responses.

12.5 Summary and Conclusions: Neuropsychology and the nosological status of DLB.

That neuropsychological impairment is a central feature of DLB is not disputed. Of interest is whether the type of cognitive decline observed in DLB has a characteristic profile and course which distinguish it from other forms of dementia, and in particular AD. Much of the early controversy surrounding the nosological and neuropsychological status of DLB arose through the use of disparate selection criteria and small cohorts. The body of work presented in this thesis has attempted to address these shortcomings. This is the first neuropsychological study to employ the recently described consensus criteria for the clinical diagnosis of DLB (McKeith et al, 1996a) in a large prospectively investigated cohort.

Findings from this thesis suggest that DLB patients share with AD patients a global impairment of cognitive function compared to elderly controls. There is considerable overlap between the neuropsychological deficits observed in DLB and AD. This is not, however, surprising as the brains of both AD and DLB patients show diffuse neurodegenerative changes and similar findings have been previously reported by a number of groups (Gnanalingham et al, 1997; Walker et al, 1997; Sahgal, 1996; Hansen 1990).

Marked differences in the profile and course of cognitive impairment in DLB have been described in comprehensively matched DLB and AD groups in this body of work. The impact of attentional dysfunction and in particular the ability to sustain

attention has not previously been addressed in AD and DLB, but appears to be a strong discriminator of these two dementing disorders. The impact of fundamental attentional deficits cannot be considered in isolation and are likely to affect many aspects of cognitive performance. These attentional impairments may represent the first quantified demonstration of the so called 'fluctuations' and 'idiopathic clouding of consciousness' seen in these patients. Previous failures to identify the marked attentional deficits in DLB are likely to reflect the non-attentional nature of the 'attentional' tasks employed by many previous researchers.

In addition, the course of change in DLB appears to be distinct from that seen in AD. This body of work has described decline in the cognitive function in AD and DLB groups over a 1 year period. Of particular interest is the increased rate of decline of attentional function observed in DLB compared to AD patients. This finding supports previous studies which have identified a more rapid rate of decline in DLB, and suggests that decrement in the ability to sustain attentional resources may underlie the faster rate of decline. Furthermore, the central role of attentional dysfunction in the profile of cognitive impairment and decline associated with DLB has been reaffirmed.

The reported comparison of hallucinating and non-hallucinating DLB cases adds further intricacies to the nosological debate. Hallucinating DLB (DLB+VH) cases show a markedly different profile of cognitive impairment to both non-hallucinating DLB (DLB-VH) and AD groups. The non-hallucinating DLB group were only distinguished from the AD group on one measure of performance: choice reaction time. Thus the profile of cognitive impairment in non-hallucinating DLB cases could not readily be described as distinct from that seen in AD. This raises the possibility that non-hallucinating DLB cases may form a distinct subgroup of DLB patients, and are similar to AD cases on the basis of neuropsychological findings.

Hallucinations are not, however, a necessary prerequisite for the diagnosis of DLB, indeed neuropathological studies have often described cortical Lewy bodies in non-hallucinating DLB cases at autopsy. Furthermore, to receive a clinical

diagnosis of DLB, non-hallucinating DLB cases must have shown both spontaneous motor features of parkinsonism and fluctuations. These features would distinguish them from AD cases as parkinsonism and fluctuations are also associated with the presence of Lewy body pathology at autopsy.

Although non-hallucinating DLB cases are not markedly distinct in terms of neuropsychological impairment from AD cases, clinical and neuropathological features support their continued distinction from AD. The possibility of a subgroup of hallucinating DLB cases with distinct neurochemical and neuropsychological features awaits the necessary neuropathological investigation anticipated in this group at autopsy.

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Appendix I:

The Nottingham criteria for the clinical diagnosis of LBD (Byrne et al, 1991).

1. Probable LBD

Either

- (i) gradual onset of DSM-III-R dementia with prominent attentional deficits or early unexplained apparent confusional states
- (ii) classical Parkinson's disease with subsequent dementia as above
- (iii) simultaneous onset of both dementia (as described) and parkinsonism with three or more of tremor, rigidity, postural change, bradykinesia and gait abnormality

2. Possible DLB

Either dementia (as described) with acute onset and rapid progression \hat{u} plateaux, frequently associated with psychiatric symptoms *or* dementia (as described) with subsequent parkinsonism with one or two of tremor, rigidity, postural change, bradykinesia and gait abnormality

Appendix II:

Newcastle criteria for the clinical diagnosis of senile dementia of the Lewy body type (SDLT) (McKeith et al (1992c)).

1. Fluctuating cognitive impairment affecting both memory and higher cortical functions (e.g. language, visuospatial ability, praxis or reasoning skills). The fluctuation is marked with the occurrence of both episodic confusion and lucid intervals and is evident either on repeated tests of cognitive function or by variable performance on daily living skills.
2. At least one of the following:
 - (a) visual and / or auditory hallucinations which are usually accompanied by secondary paranoid delusions
 - (b) mild spontaneous extrapyramidal features or neuroleptic sensitivity syndrome (i.e. exaggerated adverse responses to standard doses of neuroleptics)
 - (c) repeated unexplained falls and / or transient clouding or loss of consciousness.
3. Despite the fluctuating pattern the clinical features persist for weeks or months (unlike delirium) and progress, often rapidly, to severe dementia

Appendix III:

Consensus guidelines for the clinical diagnosis of dementia with Lewy bodies (DLB) (McKeith et al, 1996a)

1. The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not occur in the early stages. Deficits on tests of attention and of frontal-cortical skills and visuo-spatial ability may be especially prominent.
2. **Two** of the following core features are **essential** for a diagnosis of *probable* DLB, **one** is **essential** for *possible* DLB.
 - a) Fluctuating cognition with pronounced variations in attention and alertness.
 - b) Recurrent visual hallucinations which are typically well formed and detailed.
 - c) Spontaneous motor features of Parkinsonism.
3. Features **supportive** of the diagnosis are
 - a) Repeated falls
 - b) Syncope
 - c) Transient losses of consciousness
 - d) Systematised delusions
 - e) Neuroleptic sensitivity
 - f) Hallucinations in other modalities
4. A diagnosis of DLB is **less likely** in the presence of
 - a) Stroke disease evident in focal neurological signs or on brain imaging.
 - b) Evidence on physical examination and investigation of any physical illness, or other brain disorder, sufficient to account for the clinical picture.

Appendix IV:

Summary of Neuropsychological Test Procedures and Main Cognitive Functions Measured.

Blessed Information Memory and Concentration Test (IMC, Blessed 1968)

The IMC was first published in 1968 as part of the Blessed dementia rating scale. The IMC is one of the only scales which has been correlated with neuropathological parameters of severity in AD. The IMC consists of three subsections (information, memory and concentration), although each section does not receive an equal weighting. The Blessed IMC is particularly sensitive to mnemonic dysfunction. The information section (total 13 points) of the IMC examines how well the subject is orientated in time and place. The memory section (total 14 points) is further divided into three sections, the first assesses personal memories (5 points), the second assesses non-personal memories (4 points) and the third assesses five minute recall of a name and address (5 points). The concentration subsection (6 points) of the IMC requires the subject to recite the months of the year backwards, and to count from 1-20 forwards and backwards.

Boston Naming Test (Kaplan et al, 1978)

The full version of this test consists of 85 large pen and ink drawings of items which range in familiarity. When a subject is unable to correctly name a drawing, the examiner provides a stimulus clue, and if the subject is still unable to correctly name the object a phonetic clue is offered. This test was initially developed to investigate naming deficits, but is also sensitive to perceptual fragmentation as is often seen following right-sided frontal lobe damage.

Buschke-Fuld Selective Reminding Test (Buschke et al, 1974)

This test aims to differentiate between disorders of retention, storage, and retrieval by using selective reminding. In selective reminding the subject attempts to recall as many words as possible in any order from a list of words just presented to them. Subsequent to each trial, the examiner repeats all of the words the patient omitted in that trial. reminding and recall continues until the patient has correctly recited the whole list.

Cambridge Cognitive Function Examination (CAMCOG, Roth et al , 1986)

The CAMCOG is part of a standardised psychiatric assessment schedule CAMDEX and is designed specifically for use in an elderly population with a diagnosis of dementia. CAMCOG assesses a broader range of cognitive functions than other standardised schedules. Sixty items yield eight subsection scores and a total score of 107. The subsections of the CAMCOG include orientation, language, memory, attention, visuospatial praxis, calculation, perception, and abstract thinking. In comparison with the Mattis Dementia Rating Scale (DRS), CAMCOG is more sensitive to language or visuospatial dysfunction, but contains less very easy items and subsequently prove less sensitive in more advanced dementia cases.

Copy-a-Cross Test (Goodglass & Kaplan, 1972)

The Copy-a-Cross test requires subjects to copy a line drawing of a Greek cross, and the drawings are scored on an ordinal scale of 1 (good) to 5 (poor), and is an indicator of visuospatial/ constructional abilities. This provides an index of visuo-graphic abilities, and is sensitive to visual inattention as well as preservation of spatial relationships.

Letter and Category Fluency (Benton et al, 1968)

In the Letter Fluency Test, participants are required to generate as many words as possible (excluding proper names and different forms of the same word) beginning with the letters “F”, “A”, and “S”. In the Category Fluency test, participants are required to generate as many different kinds of animals, fruits, or vegetables as possible. Participants are allowed one minute for each letter or category. The tests measure the speed and ease of verbal production of material. The category sub-test requires a more intact level of semantic functioning than the letters for normal scores to be obtained.

Mattis Dementia Rating Scale (DRS; Mattis et al, 1976)

The DRS assesses a fairly broad range of cognitive functions, and contains sufficient less demanding items to be valid and reliable in more severely demented cases. The first four sections - attention (37 points), initiation/perseveration (37 points), construction (6 points) and conceptualisation (39 points) - contain screening tests which if passed mean the rest of the section need not be administered. The final memory section (25 points) is administered to all subjects. The total score possible score for the DRS is 144 points. The DRS provides comprehensive assessment of broad cognitive functions, but little assessment localised functions such as language.

Mini-Mental State Examination (MMSE; Folstein et al, 1975)

The MMSE is the most widely applied and studied screening test for dementia, and is widely applied in clinical practice and research alike. The MMSE is very vulnerable to the effects of age, education, and socio-economic status. The MMSE may be subdivided into 6 sections - orientation (10 points), registration (3 points), attention (5 points), recall (3 points), language (8 points) and copying (1 point). The MMSE is of practical value in detecting dementia and measuring the progress

of the disease, but is of limited use in measuring focal cognitive deficits or progression in severely demented patients.

Visual Reproduction Test (Russell, 1975)

The Russell adaptation of the Visual Reproduction Test provides an index of memory for geometric forms by asking participants to reproduce a complex geometric figure. In the three trials which contain increasingly complex figures, participants are firstly required to reproduce the figure immediately following a 10 second presentation period. Participants are subsequently required to simply copy the figures with the stimulus present. This aims to assess and eliminate any visuo-perceptual / praxis dysfunction which would contaminate the memory performance. The reproductions are assessed for the number of components present from the original stimulus drawings and presented as a percentage of the total score in the copy condition.

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

Arithmetic Sub-test (WAIS-R)

The arithmetic sub-test assesses an individual's ability to perform a range of calculations. The sub-test contains 14 items, but items 1 and 2 are omitted unless the subject fails items 2 and 4, testing is continued until the subject fails four consecutive items or completes all fourteen. The items have time limits ranging from 15s to 120s for the final question ("Four men can finish a job in eight hours, how many men would it take to complete the job in half an hour?"). For the final four questions, bonus points are awarded for rapid responses. Difficulties in immediate memory, concentration, or conceptual manipulation and tracking can prevent even mathematically skilled individuals from performing well on this test.

Block Design Sub-test (WAIS-R)

The block design sub-test is a construction test in which the subject is presented with either four or nine (depending on the item) red and white blocks. The task is to replicate two block constructions made by the examiner, and to replicate a further seven designs printed in smaller scale. The order of presentation differs from the order of difficulty. The four-block designs have a time limit of 1 minute and the nine block designs have a time limit of 2 minutes. In addition, bonus points may be earned for the rapid completion of items 3-9. Block design is generally recognised as a valuable measure of visuospatial functioning, although it is sensitive to dyspraxia.

Digit Span Sub-test (WAIS-R)

The Digit Span sub-test comprises two different tests, namely the digits forwards and digits backwards, both tests assess auditory attentional function and working memory. The tests consist of seven pairs of random number sequences that the examiner reads aloud at the rate of one per second, the participant is required to repeat the numbers back to the examiner in either the forward or the reverse order to which they were read out. The tests continue until the subject fails a pair of sequences, or is able to complete the longest sequence of eight letters in either direction. Combining the two scores is commonplace and useful in participants up to middle age. Older subjects, however, tend to show a decrement in digit backwards, whilst digit forwards remains relatively stable. The discrimination between digits forward and backwards is thought to be due to different loads being placed on working memory.

Similarities Sub-test (WAIS-R)

The similarities sub-test is a test of verbal concept formation. The test requires the subject to explain what a pair of words have in common. Word pairs range in difficulty from easy (“banana-orange”) to difficult (“praise-punishment”). The test

begins with the first item and is discontinued after four successive failures or when the subject completes the task. Scores are on a two point scale with one point awarded for a specific concrete likeness, and two points awarded for an abstract generalisation. The similarities sub-test is fairly independent of mnemonic ability, and especially in old subjects becomes the best test of verbal ability in the WAIS-R. The similarities sub-test is relatively independent of educational, socio-economic, and other background experiences.

Vocabulary Sub-test (WAIS-R)

The vocabulary sub-test consists of 35 words arranged in order of difficulty. The examiner reads the question “What does _____ mean?”. Administration usually starts with the fourth word on the list (the first three are assessed only if the response to the fourth word is unsatisfactory) and continues until the subject fails five words consecutively or the list is exhausted. The subject gains one or two points for each acceptable definition depending on the accuracy, precision and aptness of their response. The final score reflects the participants ability to recall vocabulary and the effectiveness of their speaking vocabulary. Vocabulary has been identified as the single best measure of both verbal and general mental ability, and is sensitive to the patient’s socio-economic and cultural origins, but relatively insensitive to schooling.

Appendix V:

Selectivity of computerised assessment procedures for cross-sectional comparative studies of AD and DLB

Patients were consecutive referrals from the MRC Prospective Study of memory disorders based in Newcastle upon Tyne. Referrals to the MRC were made by collaborating psychogeriatricians and neurologists in the Tyne & Wear district.

Summary of reasons for patient exclusion from the CANTAB cross-sectional study.

<u>Reason for non-inclusion in the study</u>	<u>Number of patients excluded</u>
Died prior to assessment	5
Too demented to complete assessment	80
Refused approach	4
Dysphasia	2
Sensory difficulties (e.g. poor eyesight)	10
Unable to contact patient	4
Physical illness	7
Inappropriate due to research overload	4
Withdrawn from MRC study	3
Objections to cognitive testing	4
Total number of patients referred	137
Total patients referred who were excluded	123 (90%)
Total number of assessments completed	14 (10%)

Summary of reasons for patient exclusion from the CDR cross-sectional study

<u>Reason for non-inclusion in the study</u>	<u>Number of patients excluded</u>
Died prior to assessment	4
Too demented to complete assessment	12
Refused approach	1
Dysphasia	1
Sensory difficulties (e.g. poor eyesight)	2
Unable to contact patient	4
Physical illness	4
Inappropriate due to research overload	1
Withdrawn from MRC study	2
Objections to cognitive testing	3
Total number of patients referred	104
Total patients referred who were excluded	34 (33%)
Total number of assessments completed	70 (67%)