SPATIAL AND NON-SPATIAL BINDING IN ALZHEIMER'S DISEASE

by

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Abstract

Early diagnosis of Alzheimer's disease is important because current treatments only provide symptom relief or slow the disease and therefore rely on early diagnosis to be effective. Neuropsychological tests are important in early diagnosis because there is currently no reliable diagnostic test using biomarkers. Previous research has suggested that binding processes in memory might be particularly vulnerable in the early stages of the disease, and therefore useful in diagnosis. The thesis critically reviews this research, and highlights a number of methodological problems and gaps. The thesis then describes a study designed to address some of these issues. Groups of people with Alzheimer's disease, age-matched healthy controls, and younger people (n=26 in each group) completed six binding tests, along with a battery of other measures. The results suggested that binding tests do provide a promising method for early diagnosis, but that they vary in their effectiveness. The Face-Name and the Paired Associates Learning tests performed best. More research is needed to establish the characteristics of binding tasks that are most vulnerable to the early disease processes. The results provided no evidence to support the claim made in previous literature that spatial binding may be more vulnerable than non-spatial binding.

To my beautiful boys,

Ben & Nico

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List of abbreviations

ACE-III	Addenbrooke's Cognitive Examination -III
AD	Alzheimer' disease
ADAS-cog	The Alzheimer's disease Assessment Scale- Cognitive Subscale
aMCI	Amnestic mild cognitive impairment
AmNART	American National Adult Reading Test
ANOVA	Analysis of variance
ANCOVA	Analyses of covariance
APOE 4	Apolipoprotein E allele 4
BNT	Boston Naming Test
BVMT-R	Brief Visuospatial Memory Test Revised
CANTAB	Cambridge Neuropsychological Test Automated Battery
CERAD	Consortium to Establish a Registry for Alzheimer's disease
CES-D	Centre for Epidemiologic Studies Depression
CINALH	Cumulative Index to Nursing and Allied Health Literature
CLEAR	Clearinghouse for Labor Evaluation and Research
CPAL	Continuous Paired Associate Learning
CRN	Cued Recall names
CRO	Cued recall occupations
CRN30	Cued Recall Names (30-minute delay)
CRO30	Cued Recall Names (30-minute delay)
CRT	Choice Reaction Time
CVLT-II	The California Verbal Learning Test II
DLB	Lewy Body Dementia
DMS	Delayed Matched to Sample
EMQ	Everyday Memory Questionnaire
EWCST	Emory Short form of the Wisconsin Card Sorting Test
fAD	Familial Alzheimer's disease
FAS	Letter Fluency
FCSRT	Free and Cued Selective Reminding Test
FNAME	Face-name Associative Memory Exam
FN-N	Total Face-Name score
FN-O	Total Face-Occupation score
FSIQ	Full Scale Intelligence Quotient
FTD	Frontotemporal dementia
FvFTD	Frontal variant Frontotemporal Dementia
GDA	Graded Difficulty Arithmetic Test
GDS	Global Deterioration Scale
GNT	Graded Naming Test
GMI	General Memory Index from the Weschler Memory Scale
HVLT	Hopkins Verbal Learning Test
IALD	Instrumental Daily Living Activity
IRAS	Integrated Research Application System
IRN	Initial recall names
IRO	Initial Recall Occupations

JDR	Join Dementia Research
KAT	Kitchen Arrangement Test
LLT	Location Learning Test
MAS	Memory Assessment Service
M-ACE	Addenbrooke's Cognitive Examination validated for use in Malayalam-speaking population
MCI	Mild cognitive Impairment
MCN	Multiple Choice Names
MCO	Multiple Choice Occupation
MMSE	Mini Mental Status Examination
MOT	Motor Screening Test
MRI	Magnetic Resonance Imaging
MTS	Matching to Sample
NA	Not Applicable
NART	National Adult Reading Test
NART-R	National Adult Reading Test Revised
NIHR	National Institute for Health Research
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
OLTT	Object Location Touchscreen Test
PAL	Paired Associates Learning
PET	Positron Emission Tomography
PD	Dementia associated with Parkinson's disease
PIS	Participant Information Sheet
PRM	Pattern Recognition Memory
QD	Questionable Dementia
RPS	Research Participant Scheme
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RMT	Recognition Memory Test
RVIP	Rapid Visual Information Processing
SD	Standard deviation
SDem	Semantic Dementia
SPSS	Statistical Package for the Social Sciences
SRM	Spatial Recognition Memory
SRMT	Short-Recognition Memory Test
SRT	Selective Reminding Test
STM	Short-term Memory
SWM	Spatial Working Memory
TMT-A	Trail Making Test-A
TMT-B	Trail Making Test-B
TOL	Tower of London
VasD	Vascular Dementia
VIQ	Verbal Intelligence Quotient
VFDT	Visual Form Discrimination Test
VOSP	Visual Object and Space Perception Battery
VPA	Verbal Paired Associates
WAIS	Wechsler Adult Intelligence Scale
WAIS-R	Weschler Adult Intelligence Scale Revised
WAIS-III	Weschler Adult Intelligence Scale 3rd edition

WCST	Wisconsin Card Sorting Test
WLDR	Word List Delayed Recall Test
WMS	Wechsler Memory Scale
WMS-III	Wechsler Memory Scale - third edition
WMS-IV	Wechsler Memory Scale - fourth edition
WMS-R	Wechsler Memory

CHAPTER 1

THESIS OVERVIEW

1. Introduction

Alzheimer's disease (AD) is characterized by gradual cognitive deterioration, starting with episodic memory impairment (McKhann et al., 2011). Given that binding can be considered as a key feature of episodic memory (Bastin et al, 2014), a deeper understanding of how binding is affected in AD and which kind of memory binding is more vulnerable in the disease is crucial.

Binding can be characterized by the capacity to create associations between items (Baddeley, 2000) allowing the brain to integrate these multiple features of the object, such as colour, shape and location, into unified representations (Wheeler & Treisman, 2002).

However, research on this topic is limited, with few studies directly compare different types of binding in AD population or on those with higher risk to develop dementia, such as people with Mild Cognitive Impairment (MCI).

2. Aims

This study aims to directly compare spatial and non-spatial binding tasks in people with AD, healthy older adults and healthy younger adults. The purpose was to see whether there is a preferential decline in spatial compared to non-spatial binding in AD. For that, all participants will perform a set of spatial and non-spatial binding tasks to identify which type of binding (if any) is more susceptible to normal and pathological ageing processes.

3. Overview of present thesis

The overall central idea of the studies carried out for the present thesis is to investigate the type of binding that is more affected by AD, specifically whether spatial component of binding plays an important role in this process. Because findings are scarce and

not consistent, so far there have not been any robust evidence of which type of binding is more vulnerable to AD or which binding task is more appropriate to identify this susceptibility.

Additionally, the present thesis also explored differences in binding pattern in AD and the main differences in binding performance between healthy (younger and older adults) and pathological ageing (AD patients). This thesis reports the results from two experiments, providing comparative analyses on spatial and non-spatial binding tasks in three different groups: healthy younger adults, healthy older adults and AD patients.

4. Summary of content of thesis

Chapter 2

Chapter 2 outlines some of the key concepts and relevant evidence about AD and normal ageing:

- The neuroanatomic and biological markers of AD
- Current and potential new treatments of AD
- Who is at high risk of developing AD
- The meaning of binding, different types of binding and evidence about its neuroanatomic basis
- A brief review of the impairment of binding in normal ageing.

Chapter 3

Chapter 3 describes a systematic review of the literature about the performance of AD and those at risk of developing AD on binding tasks. The questions address by the review are:

- Is there a good evidence that binding tests are sensitive and specific in relation to early-stage AD and those at high risk?
- Is there good evidence that poorer performance on these tests is due to the binding process?
- Is there a good evidence that certain kinds of binding testes are more sensitive than others? And specifically, is there a good evidence that spatial binding tests are more sensitive than non-spatial ones?

Overall, the conclusions from this review are that there is a reasonable evidence that some binding tests are more sensitive and specific (not in relation to other types of dementia) in relation to the earlier stages of AD and those at high risk; that the evidence that poorer performance is due to the binding processes is weaker; and that there is little evidence about whether spatial binding is more vulnerable to AD, or that any other type of binding is more vulnerable (there were in fact, very few studies that compared different kinds of binding tests).

Chapter 4

Chapter 4 is an empirical study that explores differences in performance in healthy younger and older adults and between healthy older adults and AD on three spatial binding testes and three non-spatial binding tests. Participants also completed a range of other neuropsychological tests in an attempt to control for other cognitive processes that may have

contributed to performance on binding testes. Therefore, the study expected to contribute to the evidence that is it binding process that is vulnerable to AD, rather than some other aspect of task performance. Comparing the three spatial and three non-spatial tasks was intended to address the question of whether spatial binding is preferential impaired to AD; comparing this number of tests also allowed some consideration of whether there are other kinds of binding that may be particularly vulnerable to AD. Comparing healthy younger and healthy older adults and people with AD on the same tests also allowed a comparison between how normal ageing and AD might affect performance.

Chapter 5

Chapter 5 provides a summary of the study and its contribution for the research field. Limitations of the studies and implications for future research on the search for more effective neuropsychological diagnostic tests for the early stages of AD are also discussed.

CHAPTER 2

ALZHEIMER'S DISEASE AND MEMORY BINDING

1. Alzheimer's disease

In recent years, due to the ageing global population and rise in life expectancy, an increasing number of people are receiving the diagnosis of dementia (Connel, Janevic, & Gallant, 2001). In the UK it is estimated that there are 850,000 people with dementia, with a likelihood of further increase to over 1 million by 2025 and over 2 million by 2051 (Alzheimer's Society, 2017). Beyond the enormous impact of this diagnosis for patients and their families, there is a significant economic effect due to increasing health care costs (Caramelli & Barbosa, 2002; Risacher et al., 2013; Van Dam et al., 2013). The incidence of dementia is a major problem for public health within ageing populations (Montano, Andreoni, & Ramos, 2013), with costs in the UK at around £26 billion a year (Alzheimer's Society, 2017). Additionally, there are many implications when identifying those at risk of developing dementia, such as social, financial planning and appropriate disease management (Sperling et al., 2011). Thus, extensive research is essential not only for the patients, but also for their families and the 'wider community' (Levey, Lah, Goldstein, Steenland & Bliwise, 2006).

Alzheimer's disease is considered the most frequent cause of dementia, accounting for more than 80% of all dementia diagnosis (Crous-Bou et al., 2017). Ninety-five percent of the cases affects people over 65 years of age known as late-onset AD. Early onset dementia includes patients who experience onset before 65 years and correspond to approximately 5% of cases. Early-onset are mostly cases of familial AD, with an important genetic component (Kuzmickiene & Kaubrys, 2016). It is a neurodegenerative disorder that affects memory, language, visuospatial skills, executive functions and abstraction (Bottino, Laks & Blay, 2006), which are associated with decline in daily activity performance (Weller & Budson, 2018). One of the earliest manifestations of AD is impairment of episodic memory (Jahn, 2013). This type of memory involves the conscious remembrance of one's own previous

experiences in life (Gold & Budson, 2008), which involves the ability to bind individual elements of an event together. Binding can be considered as a hallmark of episodic memory and essential to keep track of simple daily activities (Della Sala et al., 2018).

Many patients who exhibit memory difficulties and perform poorly on memory tests but do not fulfil diagnosis criteria for AD, can be considered as having a mild cognitive impairment (MCI) (Petersen, 1999). MCI is a group at increased risk of developing AD and been referred to as a transition phase between normal functioning and AD (Petersen, 1999). The conversion rate has been reported to be between 6 to 25 % annually (Petersen, 2001). MCI is defined by memory impairment, despite the preservation of other cognitive functions and everyday activities, and absence of dementia (Petersen 2001).

There is no cure for AD. Medication currently available focuses on the symptomatic improvement of cognitive functioning. New developments focus on preventing or slowing some aspect of the disease process. These treatments are most likely to be effective if they are delivered before, or at the very beginning of, the disease process in order to delay or slow the decline (Sperling et al., 2011; Montano et al., 2013; Levey et al., 2006; Rodda et al., 2013).

The early detection and diagnosis of AD is therefore critical for the success of these treatments, and there is now considerable interest in how AD can be detected in the pre-clinical stage or at least as early as possible in the clinical stage (Schmid et al., 2013). There is reason to be optimistic about this because it is estimated that pathological changes of AD start between 10 and 15 years before its clinical diagnosis (Pike et al., 2011; Price et al., 2009). However, there are no clear biomarkers that can be used for the early diagnosis of AD, and certainly none that is currently available in standard clinical practice (Blennow &

Zetterberg, 2018). Because of this, there is interest in whether neuropsychological tests can be developed for the early diagnosis of AD.

1.1. Neuropathology and biomarkers of Alzheimer's disease

Alzheimer's disease can be diagnosed definitively after death, with the amyloid plaques and neurofibrillary tangles as the main neuropathological lesions associated with the disease. Plaques are extracellular accumulation of amyloid protein between neurones and are associated with neuronal loss (DeTure & Dickon, 2019). They are considered as the earliest manifestation of the disease and there is evidence of amyloid deposition up to 20 years before the onset of the dementia (Batemen et al., 2012) with the main deposition in the medial temporal lobe (Thal et al., 2006). The neurofibrillary tangles are composed of tau protein, which is also associated with neuronal death. They begin to appear in the cell body and dendrites of neurons of the hippocampus and associative cortex, basal nucleus of Meynert, raphe nuclei, substantia nigra and locus coeruleus (DeTure & Dickon, 2019). The sites where the neurofibrillary pathology first begin is also consistent with earliest cognitive impairment associated with AD (Braak & Braak, 1991). Taken together, plaques and tangles are associated with cognitive decline in AD (DeTure & Dickon, 2019).

Definite diagnosis of AD requires the presence of these two neuropathological changes in association with clinical manifestation during life. However, the final diagnosis can only be achieved with evaluation of the brain tissue at autopsy. Biomarkers associated with clinical criteria can support diagnosis in living patients (Weller & Budson, 2018). PET scans can evaluate the amyloid-B peptides deposition into plaques, reaching diagnostic accuracy of 86% of sensitivity and 100% of specificity. The technique has been validated in normal elderly using PET scans that showed that performance on the face-name associative task is correlated with amyloid deposit in cortical areas of the brain related with memory,

such as frontal cortex, posterior precuneus, posterior cingulate and lateral parietal lobe (Rentz et al., 2011). No association between worse performance and amyloid deposition was found with other less challenging associative tasks (e.g. face-occupation and verbal associative memory task, such as Selective Reminding Test) (Rentz et al., 2011). However, PET scans are expensive and mostly only available for clinical trials rather than in routine clinical practice (Weller & Budson, 2018).

A less expensive option has focused on biomarkers of AD in the cerebro-spinal fluid (CSF). Since it was shown that the amyloid is secreted to the CSF, the CSF amyloid has been considered a valuable biomarker for AD. Additionally, this amyloid brain accumulation detected on CSF showed a high concordance with amyloid detected on PET scan. Tau proteins in CSF can be another earlier biomarker for AD, reflecting the intensity of neurodegeneration (Blennow & Zetterberg, 2018). It has been reported that both amyloid and tau CSF can achieve a high diagnostic sensitivity of 95%, predicting AD in the prodomal stage of the disease and also distinguishing AD from MCI and other forms of dementia, such as Lewy and frontoparietal dementia (Hansson et al., 2006). Despite the CSF method being cheaper than a PET scan, things like availability and risks (radiation exposure vs. lumbar puncture) must be considered (Blennow & Zetterberg, 2018).

Blood biomarkers would be a preferable choice as it has more accessible fluid than CSF, however blood biomarker for AD is difficult to be developed. For example, only a fraction of brain proteins enters the blood stream, differently from the CSF that is in continuous exchange with the brain extracellular fluid. However, in the near future blood tests may be very valuable for screening for AD (Blennow & Zetterberg, 2018).

In the earlier stages of AD, plaques and tangles tend to accumulate in certain areas of the brain rather than others. The main area affected in the early stages is the medial temporal

cortex, and specifically the hippocampus and the entorhinal cortex (Adachi et al., 2003; Barnes et al., 2007; Wang et al., 2006). In AD, senile plaques, neurofibrillary tangles and abnormal dendritic growth are more evident in the hippocampus and adjacent structures (Van Hoesen & Damasio, 1987). According to Serrano-Pozo, Frosch, Masliah & Hyman (2011) the neurofibrillary degeneration starts in both entorhinal and hippocampus cortex and then they spread to other areas of the brain, such as associative isocortex, primary sensory, motor areas and visual areas.

Pennanen et al. (2004) suggested that AD pathology starts in the entorhinal cortex before spreading to the hippocampus. In their study, volumetric loss in the entorhinal cortex discriminated more effectively between MCI participants and controls than hippocampal volume loss. However, hippocampal volumetric loss more effectively discriminated between AD and MCI participants.

This pattern of the disease process (i.e. beginning in the entorhinal cortex and hippocampus before spreading to other areas) corresponds to the pattern of cognitive impairments typically seen in AD in which an impairment of episodic memory is usually the first manifestation (Jahn, 2013). The entorhinal cortex plays a critical role in connecting the hippocampus with other cortical areas and the hippocampus plays a critical role in episodic memory (Kitamura et al., 2015). Lesion studies, and more recently neuroimaging data, have supported the view that the medial temporal lobe is strongly related to episodic memory functioning (Gold & Budson, 2008; Schmid et al., 2013), and specifically with binding processes (Meulenbroek et al., 2010; Piekema et al., 2006).

1.2. New treatments for Alzheimer's disease

Currently, there is no cure for dementia and available treatments are symptomatic and more likely to be administered when the disease has already manifested. Although there is

evidence that current medications can ease symptoms and improve the quality of life for both patients and caregivers, they do not change the course of the AD or prevent cognitive decline (Weller & Budson, 2018).

There are four drugs available for AD in UK (Alzheimer's Society, 2018). Three of these are acetylcholinesterase inhibitors and are used for people at any stage of the disease, whereas one is a dopamine antagonist and glutamate antagonist that is recommended for moderate-to severe stages.

Acetylcholinesterase inhibitors were the first drugs available for AD and are the most frequently prescribed medication for the disease (Gold & Budson, 2008). This class of drug includes donepezil, galantamine and rivastigmine. AD is associated with lower levels of a neurotransmitter called acetylcholine and all the medications mentioned above prevent the enzyme acetylcholinesterase from breaking down the acetylcholine. This leads to a higher concentration of this neurotransmitter in the brain, which is assumed to improve the communication between nerve cells and, thereby, global cognitive functioning (Alzheimer's Society, 2018; Gold & Budson, 2008).

The other available drug is memantine, which is both a dopamine agonist and a glutamate antagonist. Glutamate is another neurotransmitter associated with AD that causes damage to the nerve cells when its concentration is too high in the brain. The medication works partly by blocking glutamate neural receptors that are overactive in these raised levels of glutamate (Alzheimer's Society, 2018; Gold & Budson, 2008).

Besides the improvement of memory and concentration, acetylcholinesterase inhibitors are reported to help anxiety, motivation and to help patients to maintain their daily activities, whereas memantine has also been reported to help with delusions, aggression and agitation in AD patients (Alzheimer's Society, 2018). In the later stages, a combination of

both acetylcholinesterase inhibitor and memantine may be useful, as the two classes of medications work in different ways in the brain (Alzheimer's Society, 2018). However, the effects of these drugs are limited. Symptoms will continue to worsen gradually over the following months, even if the patients are still taking the medication. Also, responses to the drugs vary and cannot always be determined clinically. For example, even when patients with AD are thought not to have responded to acetylcholinesterase inhibitor, they might display a decline in function when the medication is discontinued (Holmes et al., 2004).

Research into future treatments of AD has been targeting the etiologic pathologies: neurofibrillary tangles and senile plaques (Cummings, Lee, Ritter & Zhong, 2018; Godyn et al., 2016; Weller & Budson, 2018). The tau protein or beta-amyloids are being targeted by means of vaccines, antibodies and agents acting on the enzyme precursors of the proteins. For example, one approach is to try to remove the plaques through an injection of an antibody that targets abnormal amyloid and facilitates its removal from the brain. Another approach to decrease plaques is to inhibit the enzymes that produce the amyloid peptide from its precursor, amyloid precursor protein (APP). Currently, multiple drugs are under development (Weller & Budson, 2018). Because earlier intervention with these newer medications seems more advantageous and effective than later intervention (van Dyck, 2017), most of the trials have been investigating people with a genetic vulnerability to AD (e.g. homozygous APOE4 allele, presenilin-1 E280 A mutation and people with family or parental history of AD) (Cummings et al., 2018). However, there is a high failure rate in clinical trials of these new approaches due to lack of therapeutic effect or adverse side effects (Godyn et al., 2016). Despite all the research into new medications, no new drug has yet been approved for use in the UK for AD since 2002 (Alzheimer's Society, 2018).

It is important to note that drug treatment is only one aspect and other alternative approaches should be included in the care and support of people with AD and their families.

1.3. People at higher risk of developing Alzheimer's disease

1.3.1. Mild Cognitive Impairment (MCI)

Brent (2019) outlines the three stages of AD as follows:

1. The pre-clinical stage: In this stage, there are biological changes associated with the earliest signs of the disease (e.g. amyloid plaques and tau tangles) but the person has no symptoms. It has been suggested that such biological changes can occur up to 20 years before the appearance of any symptoms.

2. Mild Cognitive Impairment (MCI): In this stage, the person has both the biological changes associated with the disease and has started to develop symptoms. These symptoms involve cognitive decline, but they are not severe enough to significantly affect performance of the activities of daily living

3. Dementia of the Alzheimer's type: At this final stage, the person has the biological changes and their cognitive symptoms are severe enough that performance of the activities of daily living is significantly affected (i.e. the person is classed as having 'dementia').

It should be noted that, although all people with AD will pass through the MCI stage, not everyone with MCI has AD (i.e. not all will go on to develop dementia of the Alzheimer type). This is because the concept of MCI is applied more widely to anyone who experiences cognitive difficulties in old age that are (1) more severe than would occur with normal ageing but not severe enough to affect the performance of the activities of daily living (2) not attributable to some other definite cause (e.g. a traumatic brain injury). Some diagnosed with MCI will go on to develop other types of dementia and some will not progress to the dementia stage at all.

The concept of MCI was introduced for the first time in 1991 to "fill the gap between cognitive changes associated with normal ageing and those associated with dementia" (Alescio-Lautier et al., 2007, p.1949). Research into MCI has attracted a lot of interest in the field of neurodegenerative disorders because it is estimated that the pathological changes of AD start between 10 and 15 years before its clinical diagnosis (Pike et al., 2011; Price et al., 2009) and it is suggested that at least some cases of MCI might be an intermediate stage between normal ageing and AD. Given the value of providing treatments for AD as early as possible (Sperling et al., 2011; Montano et al., 2012; Levey et al., 2006), identifying and treating those with MCI who are at particular risk of developing AD may be an important way forward.

The exact connection between MCI and AD is unclear. Some individuals may never progress to AD or another type of dementia (Levey et al., 2006; Petersen et al., 1999). Different studies have provided different estimates of the risk of someone with MCI going on to develop AD. According to Petersen et al. (2001) the conversion rate could reach between 15 to 25% over two years, whereas another study found that individuals with MCI have the risk of developing AD at the rate of 10% to 12% per year in contrast to the 1%-2% of the normal population (Petersen et al., 2004). Differences in sampling and use of different neuropsychological tests might contribute to these different rates of conversions.

Another factor in this variation is the diagnosis of MCI. In general terms, MCI is characterised by cognitive decline without any notably interference in daily life activities (Petersen, 2004). Among the various diagnostic criteria suggested for MCI, the most widely adopted is the original Mayo criteria that includes memory complaint corroborated by an informant, objective memory impairment relative to age, general cognition preserved relative

to age, and activities of daily living intact (Petersen, 2004). However, MCI is a heterogeneous condition, with diverse clinical presentation and aetiology. The subtypes of MCI are amnestic-MCI (aMCI) and non-amnestic-MCI (naMCI). Moreover, the subtypes can be subclassified into single or multiple-domain categories (Petersen, 2003). Several studies suggest that different subtypes of MCI are preferably linked to different rates of conversion to dementia. Although the small sample should be noted, the longitudinal study by Saunders and Summers (2011) found that the MCI group had a conversion rate to AD of 7.69% across the 20 months duration of the study. The lack of a clear typology and associated specific diagnostic criteria is an issue that needs further research (Saunders & Summers, 2010; Saunders & Summers, 2011; Petersen, 2004; Petersen, 2005). A better way of classifying MCI may enable better classification of those at most risk of going on to develop AD.

Recent research efforts have focussed on investigating the cognitive profile of MCI. Binding impairments have been highlighted as an issue. These have been reported in a range of tasks, such as object and location (Skolimska et al., 2011; Cooper & Odegard, 2011; Heo et al., 2010) and face-name (Amariglio et al., 2012; Naveh-Benjamin, Guez & Reedy, 2004; Troyer, D'Souza, Vandermorris & Murphy, 2011). Moreover, at least in some cases of MCI the earliest brain changes are related to the medial temporal lobe, such as hippocampus and entorhinal volume loss (Masdeu, Zubieta &Arbizu, 2005), which are brain areas also associated with binding memory (Meulenbroek et al., 2010; Piekema et al., 2006) and AD (Barnes et al., 2007; Wang et al., 2006). Therefore, these findings suggested that the investigation of binding in preclinical AD might be a promising approach, since it may help to identify those at a higher risk of developing AD.

The challenge within this field is to improve our ability to identify those individuals with MCI that are at higher risk of developing AD. This would improve our ability to then identify the specific cognitive impairments that start in the very beginning of the disease

process. Binding impairment has promise as an early impairment, but better classification and diagnosis of MCI would confirm whether this is the case.

1.3.2. Apolipoprotein E allele 4 (APOE4)

Genetically, AD is heterogeneous, since polymorphisms in multiple genes interact with non-genetic factors (Tanzi & Bertram, 2001). However, studies have found an association between the ε4 alleles of the apolipoprotein E (APOE) gene and higher risk of late-onset AD (Caselli et al., 2009; Wolk & Dickerson, 2010; Gold & Budson, 2008), with an estimative heritability between 58% and 79% (Gatz et al., 2006). This has consistently been found in the literature across many ethnic groups (Tanzi & Bertram, 2001).

APOE is located in chromosome 19 and plays a crucial role in neuronal metabolism (Bu, 2009). It has three major alleles: Ɛ2, Ɛ3 and Ɛ4, with a mean frequency in the general population of approximatively 8%, 78% and 14%, respectively (Utermann, Langenbeck, Beisiegel, & Weber, 1980). The combined alleles produce six genotypes: Ɛ2/2, Ɛ2/3, Ɛ2/4, Ɛ3/3, Ɛ3/4 and Ɛ4/4. The possession of at least one Ɛ4 allele increases the risk of developing AD, and therefore the genotype Ɛ4/4 increases the chance of developing AD by eight times, in comparison to having Ɛ2/3 or Ɛ 3/3 genotypes (Corder et al., 1993). In contrast, the possession of an Ɛ2 allele seems to confer a protective effect and it is linked with lower risk of cognitive decline in normal aging (Han & Bondi, 2008).

Due to the complexity of AD, the role of genes in cognitive decline is unclear, and it is difficult to understand how genes and the environment interact in the aetiology and pathogenesis of the disease (Tanzi & Bertram, 2001). In terms of the pathological hallmarks of AD, such as amyloid plaque deposition and neurofibrillary tangles, many studies have provided evidence of an association with APOE4 (Bu, 2009; Kim, Basak & Holtzman, 2009). One study, for example has illustrated that there are increased amyloid b-peptide deposits in

the cortex of homozygous APOE4 AD patients (Schmechel et al., 1993). More recent findings also show that the allele 4 is associated with impaired brain function, such as a reduced cerebral blood flow in older Ɛ4 carriers (Filippini et al., 2011) and smaller hippocampal volume (Pievani et al., 2011).

Greenwood et al. (2005) investigated the association of APOE4 with visuospatial attention and spatial working memory in a middle age healthy sample. These studies showed impairment in the disengagement of spatial attention and slower performance in target discrimination following invalid cues in APOE4 carriers compared to non-carriers. These findings were corroborated by Caselli et al. (2009) in a longitudinal study that revealed worse performance in visuospatial function in APOE4 carriers, but only in individuals who have the two Ɛ4 alleles (homozygotes). This group showed poorer accuracy in retaining the location of the target in spatial working memory over a delay, particularly with high memory load (3 target locations). Their results also suggested that APOE4 might influence the relation between cognitive systems, such as tasks requiring integration of attention and working memory in that homozygotes were slower and less accurate than the other groups. Furthermore, shape-colour binding impairment has been associated with APOE in a study with MCI (Parra et al., 2016). The findings reported that patients with MCI and at least one e4 allele (APOE+4) were worse on the binding task than MCI non carriers, even when the severity of the disease was controlled.

Being a carrier of APOE4 may influence the symptoms of AD. Wolk and Dickerson (2010) compared APOE4 carriers and non-carriers with a diagnosis of mild AD and found that Ɛ4 carriers were extensively impaired on episodic memory measures, whereas non-carriers showed greater impairment in sustained attention, executive function, and lexical access and also in working memory tasks. APOE 4 carriers exhibited stronger medial temporal lobe atrophy, whereas non-carriers displayed more frontoparietal atrophy (Wolk &

Dickerson, 2010). However, given the uncertainties surrounding the diagnosis of AD, it is unclear whether all the participants were correctly diagnosed.

Other studies have reported a hyperactivation in younger age APOE4 carriers in regions like medial temporal lobe, which suggests that this could be related to a compensatory mechanism (Han & Bondi, 2008; Wishart et al., 2006). This hyperactivation and the recruit of additional regions to execute a task may be used to maintain the same level of performance in young carriers (Han & Bondi, 2008). This increased activation observed in young Ɛ4 carriers seems to reduce with age (Filippini et al., 2011), maybe because "…cognitive symptoms could emerge when this additional activation can no longer be supported after a critical threshold of brain pathology is reached" (Wishart et al., 2006, p. 1606). It is therefore suggested that the APOE genotype might modulate brain function even before any clinical or cognitive symptoms are detected (Filippini et al., 2011).

Nevertheless, the exact relationship between APOE4 and AD is still unclear and further evidence is required. In particular there is a need for longitudinal studies to identify the role of this gene in the pathogenesis of AD. According to Lind et al. (2006), genetic information itself is not sufficient to determine the development of the disease. Genetic information may need to be combined with neuroimaging and neuropsychology assessment to improve the diagnosis of prodromal and early AD.

2. Binding

At a general level, binding can be understood as the capacity to learn and remember the relationship between items, integrating multiple elements (Baddeley, 2000). In cognitive science, binding is a phenomenon that allows the brain to integrate features of the object, such as colour, shape, name and location, creating unified representations (Wheeler & Treisman, 2002). Thus, to recall objects accurately, it is necessary to bind these various

features of the objects (e.g. colour, size, shape, orientation) in memory, more than simply retaining information about the objects in isolation (Brockmole & Logie, 2013).

This ability to bind information is a key feature of episodic memory (Mayes, Montaldi, & Migo, 2007), and is crucial to daily activity (Pertzov et al., 2012; Postma, Kessels, & Van Asselen, 2008; Hampstead et al., 2008) and intelligent behaviour in the real world (Hollingworth & Rasmussen, 2010). Ordinary actions such as remembering friends' names and where one has parked the car are practical examples of how binding is required to successfully function. (Sapkota, Linde & Pardhan, 2018). In addition to that, misplacing household objects like keys (Hampstead et al., 2008) or forgetting someone's name (Kessels & De Haan, 2003) are frequent complaints of elderly people and people with memory problems that reflect a failure of binding.

Authors have described binding (or associative memory, as it is often called) in many ways and have categorized it into different kinds, such as being short-term or long-term, or having spatial component or even how the features relate to each other. To facilitate the understanding of binding for this thesis, some distinctions between different types of binding are described below. However, it is important to clarify that these distinctions are just a guide to understand binding and do not cover all the complexities and diversities encountered in the literature.

Table 2.1. Types of binding and their neurological correlates

Types of binding	Description	Evidence of neurological correlates
Long-term vs. short-term memory binding	LTM: integrative memory that links aspects of complex and meaningful experiences. Also knows as associative learning (e.g. PAL task) STM: a context-free memory, occurs when conjunctions of features within objects	LTM: seems to be rely on hippocampus function STM: seems to rely on region along the visual ventral stream

	representation are retained temporary in memory (e.g. shape-colour task)	
Within domain vs. between domain	Within-domain: associations formed between the same or similar types of information (e.g. word-word) Between-domain: involves different classes of items (e.g. object - location and face and name)	With-domain: processed by the primary sensory areas in the neocortex, with the information converging on to the perirhinal areas of the medial temporal lobe Between-domain: processed in the associative areas of the neocortex before converging on the hippocampus
Relational vs. conjunctive	Relational: involves relation between separate items (e.g. faces and names or object-location) Conjunctive: involves binding of features of the same object (e.g. remembering the colour of different shapes)	Relational: processed via dorsal route, that projects forward from the primary visual cortex towards the parietal lobe. Conjunctive: processed via ventral route of the brain that projects forward the primary ventral cortex towards the temporal lobe.
Spatial vs non-spatial	Spatial: involves memory for spatial information (e.g. position of objects in the environment) Non-spatial binding involves binding with no reference to spatial locations (e.g. faces and names, shape-colours, word pairs)	Spatial binding: right hippocampus and right parietal cortex Non-spatial: hippocampus and other areas, dependent on item type.

2.1. Pre-attentive binding

Some researchers have suggested that binding is automatic and not dependent on attentional processes. On the basis of evidence that visual and spatial working memory are not completely dissociable, some have argued that binding of visual and spatial components in visual short-term memory is likely to be automatic (Olson & Marshuetz, 2005; Vergauwe, Barrouillet & Camos, 2009). Mandler, Seegmiller and Day (1977) likewise argued that spatial locations are automatically encoded with the items when they are learned.

However, the automaticity of binding is a controversial issue and others have suggested at least some types of binding do require attentional processing (Treisman & Zhang, 2006). To support the idea that binding is not completely automatic, Naveh-Benjamin et al. (2004) investigated face-name associations in younger and older adults under different attention conditions. They demonstrated that attention disruption affected associative memory in the older group. This is inconsistent with the claim of automatic binding both because attention disrupted performance, and because automatic processes are thought to be relatively unaffected by ageing. Other studies have similarly found that age appears to have an impact on binding (Pertzov et al., 2012; Postma et al., 2008). Possibly the degree of attention required by binding depends on the type of binding involved.

2.2. Long-term versus short-term binding

Binding operates in both short-term memory (STM) and long-term memory (LTM) (Della Sala, Parra, Fabi, Luzzi & Abrahams, 2012). STM binding occurs when conjunctions of features within object representations are retained temporarily in memory (Mayes et al., 2007). STM binding can be assessed when a study array is replaced on the next trial with a different one, leaving no trace of residual memory (Parra et al., 2009). On other hand, LTM binding, also sometimes referred to as associative learning, is an integrative memory that links aspects of complex and meaningful experiences (Parra et al., 2015). It has been suggested that STM binding is a context-free memory, whereas LTM binding involves integrating the bound information with the wider context in which it was presented (Parra et al., 2015).

Studies have claimed that LTM binding is impaired in the early stages of AD (Swainson et al., 2001; Gallo, Sullivan, Daffner, Schacter & Budson, 2004). LTM binding impairments also occur in healthy older adults (Naveh-Benjamin et al., 2004), including

objects and locations (Heo et al., 2010; Pezdek, 1983), faces and names (Amariglio et al., 2012; Naveh-Benjamin et al., 2004; Troyer et al., 2011) or pairs of words (Badham & Maylor, 2011; Naveh-Benjamin & Kilb, 2014; Troyer et al., 2011). More recently, it has been suggested that AD also impairs STM binding (Parra et al, 2010a), however the effect of normal ageing on STM binding is less well known.

In a study with early-onset familial AD and carriers of E280A single presenilin-1 mutation (Parra et al., 2015), both STM and LTM binding seemed to be impaired. In a STM binding task, participants were required to detect changes across two consecutive screens displaying arrays of shapes, colours or shapes-colours binding. The LTM binding was assessed using the PAL test from CANTAB. Impairment in these two forms of memory was much higher when compared with performance on non-associative memory tasks. Both PAL and STM shape-colour binding showed high sensitivity and specificity in terms of identifying early-onset familial AD, but only the STM proved to be more sensitive at detecting asymptomatic carriers. Participants with familial AD performed poorly in both tasks, whereas asymptomatic carriers differed from controls only in STM binding task.

It has been suggested that STM and LTM binding are supported by different brain systems (Parra et al., 2009). Studies have showed the role of the hippocampus in associative learning (Mayes et al., 2007) and that performance on the PAL (i.e. the LTM task) seems to rely on hippocampus and is strongly associated with its dysfunction (Mayes et al., 2007; Lowndes et al., 2008). Parra et al. (2015) suggested that the STM task that they used (i.e. the shape-colour task) does not require the hippocampus, but instead relies on regions along the visual ventral stream. This reliance on different brain areas may explain the different pattern of sensitivity and specificity shown by these two memory binding functions. For example, the suggestion that STM (at least as measured by the shape-colour task) may be unimpaired in healthy ageing in contrast to the findings of impaired LTM may reflect the fact that normal

ageing is associated with some degree of atrophy in the hippocampus (Grady, McIntosh & Craik, 2003).

2.3. Within domain versus between domain binding

Binding can involve within domain features or between domain features. Associations that are formed between the same or similar types of information, for example (word-word or object pairs) are known as 'within-domain' binding (Troyer et al., 2011) or 'intra-item' (Badham & Maylor, 2011). 'Between-domain', 'across feature' and 'inter-item' are all labels used for the type of binding that involve information drawn from different sources that can differ either by sensory modality (e.g. visual and audio) or spatial temporal context (e.g. face-voice, scene-sound or object-location) (Troyer et al., 2011).

According to the study by Troyer et al. (2011) normal ageing differentially affects these two categories of binding. In the study, age differences were greater on face-name than word pairs. One explanation for that is that each task makes a different demand on the hippocampus. Different brain regions seem to support inter-item (e.g. pattern-location binding such as PAL task) and intra-item binding (e.g. shape-colour binding task) (Piekema et al., 2006). It has been suggested that primary sensory areas in the neocortex process inter-item binding, such as word-word associations, with the information then converging on the perirhinal areas of the medial temporal lobe to produce a unified representation. On the other hand, intra-item bindings, such as object-location, appear to be processed in the associative areas of the neocortex before converging on the hippocampus (Mayes et al., 2007). In support of this, Vargha-Khadem et al. (1997), in a study with bilateral hippocampal pathology, reported that neuroimaging revealed that hippocampal lesions were associated with impaired between-domain binding, such as voice-face and object-location. In contrast, no significant impairment was found on within-domain associations. These findings suggest that episodic

memory, which is supported by the hippocampus and which is vulnerable to normal ageing, may be particularly required for between-domain associations.

In contrast, Bastin and Van der Linden (2006) found no significant differences between within-domain binding tasks, such as face-face, and between-domain tasks, such as face-location, in healthy older adults. According to Troyer et al. (2011), differences in methodologies might explain these contradictories results; in particular, they claimed that Bastin and Van der Linden did not compare tasks with the same level of difficulty.

2.4. Relational versus conjunctive binding

Closely related to the distinction between within and between domain binding is the distinction between relational and conjunctive binding. Relational binding involves the binding of separate items (e.g. faces and names) whereas conjunctive binding involves the binding of features of objects that are part of the same object (e.g. remembering the colour of different shapes) (Della Sala et al., 2012).

Like between-domain binding, relational binding has been linked to the hippocampus network (Piekema et al., 2006). It is suggested that the hippocampus is affected by normal ageing (Grady et al., 2003) and by AD (Barnes et al., 2007); and also that relational binding declines with ageing (Naveh-Benjamin et al., 2004), AD and other types of dementia (Clague et al., 2005; Taylor, Saint-Cyr & Lang, 1990). Unlike associative memory, conjunctive binding appears to be age insensitive (Brown et al., 2017; Isella et al., 2015) and not dependent on the integrity of the hippocampus (Della Sala et al., 2012).

2.5. Spatial versus non-spatial binding

Another way to understand binding is to divide it into spatial and non-spatial binding. Spatial binding involves memory for spatial information which can relate to the position of objects in the environment (e.g. learning a route through an unfamiliar building or remembering the position of objects) (Hanaki et al., 2011). On the other hand, non-spatial binding involves the stimuli/responses that do not contain any references to spatial locations (e.g. learning someone's name).

Remembering where things are is a complex mechanism that requires object processing, spatial-location processing and object-location binding (Postma et al., 2008). It is essential for daily life functioning and seems to be affected by age (Pezdek, 1983; Postma et al., 2008; Brockmole & Logie, 2013), amnestic MCI (Hampstead et al., 2011) and AD (Fowler et al., 2002; Kessels et al., 2010; Lee et al., 2003). Forgetting where things are is a common everyday complaint in normal ageing and is prominent in MCI and the early stages of AD (Kessels et al., 2010).

Several studies have shown substantial impairments in AD in memory for object location and spatial memory generally. For example, Adelstein, Kesner and Stressberg (1992) found that both mild and moderate AD patients demonstrated a significant deficit in spatial recognition memory compared with healthy controls. They suggested that AD impairment had a similar pattern of deficit of individuals who had damage to the parietal cortex and hippocampus, both areas strongly linked with episodic memory. Bucks and Willison (1988) found significant deficits of spatial location in AD patients using the Location Learning Test (LLT). They also suggested that the right hippocampus and right parietal cortex are brain areas related to both spatial location memory and AD. In a more recent study using the same task (Kessels et al., 2000), MCI, AD and healthy controls were

assessed. It was reported that AD group had a worse performance than MCI on LLT and both clinical groups had a worse performance than healthy controls.

In a comparative study between AD and Parkinson's disease (medicated and non-medicated groups), the AD group showed significant impairment in visual recognition memory for patterns and spatial location memory (Sahakian et al., 1988). A study by Brandt et al. (2005) that investigated spatial location in AD, Parkinson's disease and Huntington disease, found that AD had a worse performance in both individual feature and binding compared with the other two groups. In addition, Swainson et al. (2000) showed that AD could be distinguished from questionable dementia and those diagnosed with major depression with 98% of accuracy using an object-location task. Finally, visuo-spatial deficits have been reported to be associated with the severity of the dementia and considered a good predictor of its progression (Sahgal et al., 1992).

Because AD appears to be associated with particular difficulties with spatial memory and learning (in terms of both subjective complaints and neuropsychological testing), it has been suggested that spatial binding may be particularly vulnerable to AD compared to non-spatial binding (Hanaki et al., 2011). However, the evidence to support this idea is not particularly strong. There are few direct comparisons of spatial and non-spatial memory tests, and so it is difficult to be certain that people with AD show a particular impairment on spatial memory tasks. In terms of subjective complaints, complaints relating to non-spatial binding (e.g. forgetting people's names) are also common in MCI and the early stages of AD. Hanaki et al. (2011) also suggest that spatial memory is supported by the hippocampus and the parietal lobes (Meulenbroek et al., 2010), that these are affected in the early stages of AD and so spatial memory may be particularly vulnerable to AD. However, non-spatial binding is also supported by the hippocampus, and the evidence suggests that the hippocampus is affected by AD before the damage caused by the disease appears in other lobes of the brain

(Serrano-Pozzo et al., 2011). One aim of the current thesis was to provide a clearer test of this claim that spatial binding may be particularly affected by AD.

3. Ageing and binding

An increasing number of studies have investigated whether binding ability deteriorates in normal ageing. Inconsistent results have been found, with some studies reporting no age-related binding impairment (Isella et al., 2015; Parra et al., 2009 Meulenbroek et al., 2010, Pertzov et al., 2015, Brockmole et al., 2008, Read et al., 2016) and others showing an impact of ageing (Pezdek, 1983, Skolimowska et al., 2011, Cooper & Odegard, 2011, Hanaki et al., 2011; Badham & Maylor, 2011; Amariglio et al., 2012; Naveh-Benjamin et al., 2004; Naveh-Benjamin & Kilb, 2014; Troyer et al., 2011). Inconsistent results have occurred even when the same task has been used. Interestingly, in a study that investigated two types of binding, different results were found depending on the type of task (Brockmole & Logie, 2013).

According to some studies, binding skills appear to be vulnerable to the ageing process. In comparison to younger counterparts, samples of healthy older people have performed significantly worse across a range of binding tasks. For example, older adults performed worse than younger adults in a verbal-spatial binding task (Meier et al., 2014), word pairs binding studies (Badham & Maylor, 2011; Naveh-Benjamin & Kilb, 2014; Troyer et al., 2011) and in a face-name association task (Amariglio et al., 2012; Naveh-Benjamin et al., 2004; Troyer et al., 2011).

Binding tasks involve a range of cognitive processes other than just the binding itself. So, it is not always clear from these studies whether the impairment in performance is specific to the binding process. More convincing evidence is provided by studies that have shown impairment in the binding aspect of the task but preserved performance in other

aspects of the task. For example, Mitchell et al. (2000) found that older adults had deficits in object-location binding in a task using coloured line drawings presented in different locations. However, there were no deficits in the recognition of the individual features used in the task, suggesting that memory for single features is relatively less affected. Similar findings were reported by Cooper and Odegard (2011). Skolimowska et al. (2011) used the Paired Associates Learning (PAL) from the CANTAB to assess object-location binding, and also assessed spatial navigation using real–life settings. The results showed that younger participants outperformed older adults in object-location associations, but there was a lack of any age effect on navigation skills, showing preservation of this type of spatial memory in advanced age up to approximately 70 years old. Naveh-Benjamin et al. (2004) investigated face-name learning. Younger adults outperformed older adults in all categories of the test (face recognition, name recognition and face-name association), but, crucially, there was a significantly bigger discrepancy between the groups on face-name association. To confirm this, the authors also compared young and older adults who presented comparable scores on item memory. The impairment on associative memory in older adults was still present, supporting the argument that the impairment in associative learning in the older participants was not due simply to their poorer memory for components.

Contrary to the findings above that reported age-related difference, Meulenbroek et al. (2010) and Pertzov et al. (2015) found no evidence of age-dependent impairment in object-location binding between healthy young and older adults. In Meulenbroek et al's (2010) experiment, a 3x3 grid of nine object-location associations were used, either in a rich encoding environment (all objects visible at same time) or a poor encoding environment (isolated objects becoming visible sequentially). Both young and older groups performed better with the rich encoding environment, but only the young group used the environmental cues, such as neighbouring items, to reconstruct the grid. Although older adults were not able

to benefit from the environment support, they still performed similarly compared to their younger counterparts. Pertzov et al. (2015) used a novel short-term memory (STM) object-location binding task with no grid involving a touchscreen. Although it was found that precision for object identity and location declined with age, the ability to bind both sets of information was unimpaired. Older people did show worse performance on trials with more items (three compared with one item) to be remembered. However, the increased localization error in the older participants appeared to be related to failures to remember the identity of the items in memory rather than a true binding deficit.

Preservation of shape-colour binding in normal ageing was reported by Brown et al (2017). In this study, no age-dependent binding deficit appeared under a range of different experimental conditions, such as different encoding times (900 or 1500ms), presentation format (simultaneous, sequential) and interference. A study by Parra et al. (2009) similarly found no ageing effect in shape-colour binding even when memory demands were increased by using four objects instead of three or a presentation time of one second instead of two seconds. These results indicate that even with a more cognitively demanding task and the manipulation of time intervals or number of items, binding ability is still relatively preserved. In conformation with these results, other studies reported a similar lack of age-related effect in shape-colour binding (Brockmole et al., 2008; Parra et al., 2010; Isella et al., 2015). However, a recent web-based study including a sample of more than 55,000 reported a weak, but significant age-related impairment in binding shape-colour, in addition to a strong decline in the precision of single-feature memory (Brockmole & Logie, 2013). The inconsistency may be due to the increase in statistical power arising from the use of a very large sample.

A study described by Troyer et al. (2011) highlighted that differences in associative memory in normal ageing may depend on whether the combinations are between–domain (such as face-name) or within-domain (word-word associations). Comparing two different

recognition tasks with same level of difficulty, the study found that greater age-related differences between young and older participants occurred in associative recognition rather than item recognition in both types of binding tasks. However, associative memory was significantly more impaired on the face-name than on the word-word task.

Binding may also depend on the familiarity and unfamiliarity of the items. Badham and Maylor (2011) found that younger adults outperformed older adults in both memory for individual words and memory for their pairing, with a greater impairment shown on memory pairing. However, in a condition using non-words, the older adults performed equally badly on both the individual words and the memory pairing. They suggested that the explanation lies in the fact that the individual words have been seen by the participants many times before (pre-existing in memory), whereas the non-words and the associations between words were a novel experience. They suggested that older adults benefit more from pre-existing knowledge and struggle more when learning new and unfamiliar material.

Despite all of the research done on this issue, there remains a lot of uncertainty about how binding ability is impaired by normal ageing and which type of binding is more vulnerable. Mixed findings are likely to be due to differences in method. For example, interval durations could produce divergent results. It may be that studies with longer delays between presentation of the items and the retrieval test are more likely to show age-dependent binding deficits. The familiarity of items, or the ease with which the material can be verbalised, might also affect the results. According to Pertzov et al. (2015) younger adults are more inclined to use verbal strategies to help remember object-location information. However, when objects and their verbal coding are not easily linked, younger subjects may not use verbal strategies and have to rely on visual memory similarly to older people. Whether the binding is spatial or non-spatial may also be relevant. Few studies have directly compared spatial and non-spatial binding performance, and so it is unclear if normal ageing

affects all binding performance equally or it preferentially affects spatial over non-spatial binding (or vice versa). Generally, there is a need for research to systematically vary these different characteristics of binding (spatial vs. non-spatial, relational vs. conjunctive, short-term vs. long-term etc.) to see whether the impact of ageing is affected by this.

4. The neural correlates of binding

As already discussed, the hippocampus plays a key role in certain kinds of binding. Information from the primary sensory areas of the cortex and the associative areas appears to be relayed to the hippocampus which maintains the integrated representation of the stimuli and makes it available for retrieval. Various studies have provided evidence of its involvement. For example, in a study by Olson, Page, Moore, Chatterjee and Verfaellie (2006), people with medial temporal lobe lesions completed a task using pictures of animals and objects and nine locations. Isolated features were remembered at normal levels, but binding was impaired significantly after an eight seconds delay. Analysis showed that the amount of damage to the hippocampus was closely associated with deficits in binding. In a study using fMRI, Postma et al. (2008) found increased activation in the right hippocampus during the encoding phase of a spatial binding task (Corsi Blocks). Adelstein et al. (1992) also showed that the right hippocampus and right parietal cortex are important areas associated with the processing of spatial location and coding. Additionally, patients who had right temporal lobectomy showed specific deficits on the recall of spatial locations (Smith & Milner, 1981). Other studies have also suggested that poor binding performance is strongly associated with dysfunction of the hippocampus (Lowndes et al., 2008; Mayes et al., 2007; Piekema, Kessels, Rijpkema & Fernandez, 2009; Piekema et al., 2006).

There are, however, some forms of binding in which the hippocampus may play less of a role. It has been suggested that it is less involved in short term memory (vs. LTM)

binding (Parra et al., 2009 and 2015); within-domain (vs. between-domain) binding (Mayes et al., 2007); and conjunctive (vs. relational) binding (Della Sala et al., 2012). Within-domain binding is likely to be represented by activity in closely adjacent and interacting neocortical neurons, and represented as one unit. Between-domain binding, on the other hand, may not be perceived or represented as one item, and may be represented by patterned activity in relatively distant and weakly connected neocortical neurons. It is suggested that the primary sensory areas in the neocortex process within-domain binding (such as word-word) and conjunctive binding (aspects of the same item, such as shape and colour), with the information then converging on the perirhinal areas of the medial temporal lobe to produce a unified representation. On the other hand, between-domain bindings, such as object-location, appear to be processed in the associative areas of the neocortex before converging on the hippocampus (Mayes et al., 2007). In support of this, Vargha-Khadem et al. (1997), in a study with bilateral hippocampal pathology, reported that neuroimaging revealed that hippocampal lesions were associated with impaired between-domain binding, such as voice-face and object-location. In contrast, no significant impairment was found on within-domain associations.

Even within particular types of binding, such as conjunctive binding, different stimuli may be supported by different areas of the brain (Rao et al., 1997). For example, whereas colour, form or shape are more likely to be processed via the so-called ventral route, other features like spatial location, motion and location are processed via the so-called dorsal route (Goodale & Milner, 1992).

It has also been suggested that pre-frontal areas may play a role in binding. For example, Meulenbroek et al. (2010) found activation in pre-frontal areas such as the dorsolateral pre-frontal cortex during retrieval of object-location associations. Other studies involving a range of binding tasks have also suggested a role for prefrontal areas (e.g.

Chalfonte et al.,1996; Lekeu et al., 2002). The involvement of the prefrontal cortex in binding may be related to its role in the planning and execution of encoding and retrieval strategies (Buckner & Wheeler, 2001). It is possible, then, that it only has a role in certain types of binding (e.g. between-domain) and not in others (e.g. pre-attentive, conjunctive).

CHAPTER 3

LITERATURE REVIEW

1. Aim

The aim was to provide a systematic review of research literature that has investigated the performance of people with AD or people at risk of developing AD on binding tasks. The broader aim is to establish whether binding tasks are promising methods for the early detection and diagnosis of AD.

2. Search strategy

A systematic search of the literature was conducted using the following databases: MEDLINE, PsycINFO, Web of Science and CINAHL. The time frame used was from 1974 to 2019, considering the date of the original working memory model proposed by Baddeley and Hitch in 1974. The link between binding and working memory gained even more attention after the addition of the episodic buffer in the model in 2000, which was a component strongly associated with the ability to bind information across domains into integrated units (Baddeley, 2000). However, the search for papers was dated from the original model to gather any other relevant study. Additionally, initial searches did not identify any relevant articles published prior to this date.

The computer-based search was primarily conducted using the key terms “dementia”, “binding” and “types of binding” in the title, keywords, or abstracts (Table 3.1). The full list of search terms was as follows: a first search was conducted using the terms (dementia or Mild Cognitive Impairment or MCI or Alzheimer’s disease or AD = block 1) and (memory binding or associative memory or associative learning = block 2). Studies that involved those at high risk of developing AD (e.g. MCI, genetic high risk) were also included in the review. The terms enclosed in parentheses were combined with the logical operator *or* to identify any study which contained at least one of these terms (i.e. at least one term from block 1, and at least one term from block 2). The logical operator *and* was then added to combine the terms

of block 1 and block 2, resulting in papers containing at least one term of block 1 and one term of block 2. A second search was conducted using the terms from the Block 3. Using the logical operator *and,* the search from block 3 was combined with the first search combination between block 1 and 2. A wider range of terms was captured by the truncation of some words using '*' or '$' (e.g. 'shape colo*' captured colour, colours and also American spelling color). For example: object location OR face name OR shape colo* AND memory binding OR associative memor* OR associative learning.

Table 3.1: Search terms

BLOCK I	**BLOCK II**	**BLOCK III**
Dementia	**Binding**	**Types of binding**
Dementia	Memory binding	Object location binding
Alzheimer's disease	Associative memory	Object location memory
AD	Associative learning	Spatial binding
Mild Cognitive Impairment		Spatial associative memory
MCI		Spatial associative learning
		Face name memory
		Face name association
		Face name associative memory
		Face name associative learning
		Face name binding
		Shape colour memory
		Shape colour binding
		Shape colour associative memory
		Shape colour associative learning
		Word pairs
		Word-word
		Verbal associative learning
		Verbal associative memory

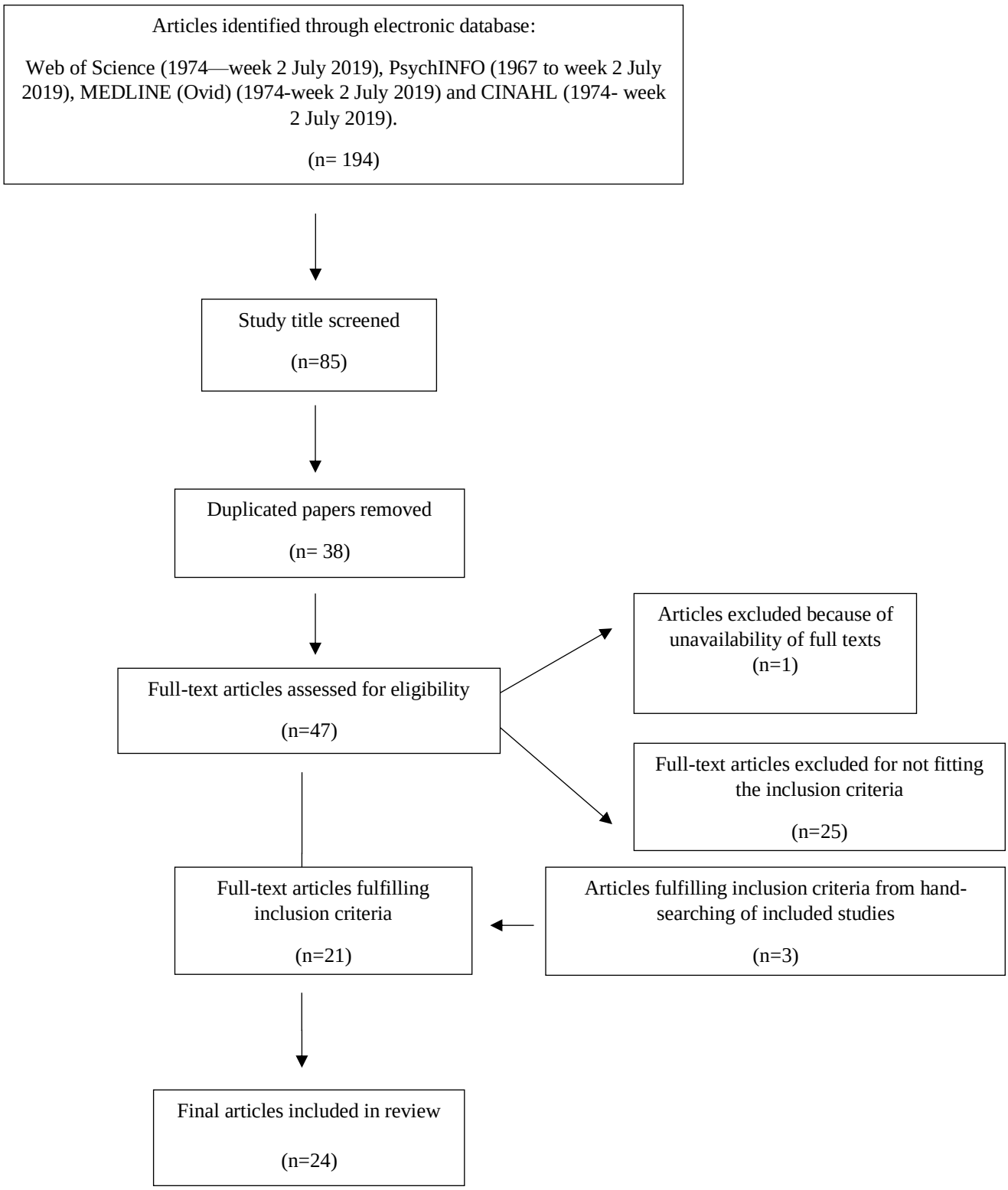
3. Search results: selected papers

The search combination among terms from block 1, 2 and 3 resulted in 194 matches. Based on the relevant study titles and the inclusion/exclusion criteria (Table 3.2), 85 papers were selected. After duplicated papers were removed, a total of 47 papers remained. One paper was excluded because the full text was not available. For all the 46 selected papers the full text was checked to ensure they met the inclusion/ exclusion criteria. Twenty-five papers were irrelevant or inappropriate for the study and were filtered out. Three additional papers were found through hand-searching of the reference lists of selected papers and were included. The total number of papers was thus 24. Figure 3.1 shows the details of the paper selection procedure. A summary of the main characteristics and findings of the selected papers is presented in Table 3.3 and 3.4.

Table 3.2.: Inclusion and exclusion criteria

Inclusion criteria	***Exclusion criteria***
• Papers reporting the results from empirical studies that collect and analyse data from performance on binding tasks. • Included participants with diagnosis of AD, or MCI or otherwise at risk for AD.	• Papers not available in English, Portuguese or Spanish language • Research conducted on non-humans or other clinical groups, such as stroke, head injury, schizophrenia and brain lesions patients. • Studies including unspecified dementia or other types of dementia, unless there was a comparison between AD and this group on the binding tasks.

Figure 3.1: Flow chart depicting search strategy



4. Methods

4.1. Description and quality of the studies

Information about study design, sample characteristics, e.g. sample size, mean age and gender, binding task and other cognitive measures and main outcomes was extracted from all 24 papers. These details were arranged in two different tables. The first table (Table 3.3) contains information about studies that investigated binding in MCI population or any other at-risk condition. The second table (Table 3.4) provides information about studies that investigated binding performance in an AD sample. The main findings extracted from all selected papers are also reported.

In order to access the quality of the papers selected, an evaluation of each study quality was conducted and based on the quality assessment criteria provided by Clearinghouse for Labor Evaluation and Research (CLEAR, 2014). This quality framework comprises the domains of study design, data quality, data collection, study sample, analysis methods and findings and conclusions (Appendix 3a). CLEAR guidelines are presented in the form of a checklist and, for each criterion, the studies are assessed in terms of whether the issues were appropriately addressed in the study using Yes (Y), No (N) or Mixed (M) reviews. Table 3.5 summarises the outcome of the evaluation, including brief note about the key strengths and limitations of each study.

The CLEAR framework only points out confounding factors as a weakness of the framework but did not include any reference on how to control them. Because of confounding variables are particularly challenging to the interpretation of findings in this area, a specific set of criteria relating to the control of confounding variables was supplemented. The same criteria as CLEAR (Yes, No and Mixed) was used to review the papers (See Table 3.5). The added criteria referred to how well matched the samples were on

variables associated with cognitive abilities – specifically, demographic variables, estimated/pre-morbid IQ and emotional status (e.g. depression); and how well the study dealt with floor and ceiling effects (which is often an issue when comparing groups of differing ability on the same test). For example, papers that reported that the groups in their study were matched on all demographic variables showed that this issue was appropriately addressed in the study (Y). If some of the variables were matched or (if non-matched) they were included as covariates in the analyses, the papers received a mixed review (M) whereas a negative review (N) was given when the samples did not match on any of the demographic variables or did nothing to address the problem in the analysis. The same pattern of rating was used for ceiling/ floor effects. Studies that reported how they controlled for ceiling/floor effects or reported no ceiling/floor effects, received a better rating (Y). Studies that reported some ceiling /floor effects but these were entered into the analysis as covariates or otherwise dealt with (e.g. variable with ceiling/floor effect was not entered into analysis at all) received a mixed review (M), whereas studies that did not report on whether or not they checked for ceiling/floor effects or did nothing to address the problem in the analysis received a worse review (N).

One major source of confounding is that performance on binding tasks depends on general memory, attention and other cognitive processes and not just on specific binding processes. Poor performance on a binding task does not necessarily mean that the binding process itself is impaired. All of the papers included scores on non-binding neuropsychological tests. Information about performance on these tests is included in Tables 3.3 and 3.4. Some of the binding tasks involved scores related to performance on the non-binding aspects of the task (e.g. memory for individual items). These can provide some control over other non-binding cognitive processes that contribute to binding performance, and the tables highlight where the paper has compared performance with the binding aspect

of the task with performance on these other aspects ('within task control'). The tables also record whether the groups were matched on variables associated with cognitive abilities such as demographic variables, estimated/pre-morbid IQ and emotional status (e.g. depression). These variables may be associated with both binding processes and other cognitive processes that are related to binding performance. Matching on these variables is important because differences between groups in binding performance could be due to these variables rather than to the presence of the underlying disease processes of AD. Tables 3.3 and 3.4 report whether groups were matched on these variables and, if not, whether they were entered as covariates in the analysis of binding performance.

4. Results

Tables 3.3 and 3.4 summarise the method and results of each individual study. Table 3.5 is then presented, showing the findings of the quality evaluation. A summary of the quality evaluation is provided (5.1) and then the method and results are summarised across the studies and critically evaluated (5.2 and 5.3).

Table 3.3: Overview of binding studies and outcomes: Binding and people at risk of developing Alzheimer's disease.

Binding and people at risk of developing AD					
Spatial binding studies					
First author, year	**Study design**	**Sample**	**Binding test and type of stimuli bound**	**Other neuropsychological measures**	**Main outcomes**
Hampstead, 2018	Comparison with healthy older and healthy young groups Correlation of	MCI (N= 47; Age=72; Gender not given) Healthy older (N=31; Age=70; Gender not given)	Object Location Touchscreen Test (OLTT) (Object and location)	RBANS TMT-A TMT-B EWCST	-Sample matched on age, education and estimated/pre-morbid IQ. Information about gender not given -Significant differences on binding task between younger and older adults

	performance with biological markers of AD	Healthy young (N=36 Age=24; Gender not given)			-Significant differences on binding task between older adults and MCI -Significant differences between older adults and MCI on RBANS and EWCST -Significant associations between binding task performance and volumetric analysis of medial temporal lobe structures, particularly the entorhinal cortex, known to be affected early on in Alzheimer's. -RBANS scores were not significantly associated with volumetric analysis of these areas.
Harel, 2011	Comparison with healthy older group	aMCI (N=30; Age=68; 22M and 8F) Healthy older (N=30; Age=66; 22M and 8F)	Continuous Paired Associate Learning Task (CPAL) from CANTAB (Visual pattern and location)	CERAD WMS-R BNT TMT-A TMT-B PAL MMSE	-Sample matched on age, gender, education, estimated/pre-morbid IQ, depression and anxiety. -Significant differences on binding task between older adults and aMCI - Significant differences on CERAD, WMS-R, TMT-B, MMSE -Performance of both groups declined as memory load of the binding task increased, but the decline was greater for the aMCI group -APOE4 carriers (MCI: n=3 and healthy control: n=2) analysed separately. No significant findings were reported.
Sapkota, 2017	Comparison with healthy older group	MCI (N=10; Age=67; Gender not given) Healthy older (N=10; Age=64;Gender –not given)	Object - location task Name-location task	ACE-III	-Samples matched on age and educational level only. Information about gender not given -MCI significantly lower scores on object-location and name-location, but not on objects and locations (within task control) -Significantly worse on memory domain of ACE-III
Non-spatial binding studies					
Irish, 2011		aMCI	Face-name task	RBANS	

	Comparison with healthy older Following people over time to see how many of them converted to dementia.	(N=16; Age=71.8; 10M and 6F) Healthy older (N=18; Age=76.0; 4M and 4F)		Range of non-binding spatial memory tasks EMQ	-Sample matched on years of education only, not on age or gender -Significant differences between MCI and healthy controls on face-name task. -Significant differences on RBANS, EMQ and some but not all measures of spatial memory -Delayed recall of names on the face-name task emerged as the best predictor of conversion to AD in the sample.
Papp, 2014	Comparison with healthy older group	MCI (N=18; Age=70.48; 35.40%M) Healthy older adults (N=65; Age=73.82; 24%M)	FNAME-12 (Face and name pairs and face and occupation pairs)	MMSE FCSRT Verbal fluency: 3 categories Verbal fluency: F-A-S VIQ TMT-A TMT-B VFDT	-Sample matched on age and educational level, but not on gender. -Significant differences between groups on face-name and face-occupation binding. -Significant differences on MMSE, FCSRT, Verbal fluency – 3 categories
Rentz, 2011	Correlation of performance with biological markers of AD	Healthy older adults (N=45; Age=71.72; 42%M and 58%F)	FNAME-16 (Face and name pairs and face and occupation pairs)	SRT Digit Span Trails A and B BNT Category Generation Visual Form Discrimination Test Covariates: Age AmNART IQ	-Significant relationship between all aspects of face-name task and amyloid deposition in frontal region, but only marginally significant (p=.05) for area comprised of precuneus, posterior cingulate and lateral parietal. -No significant relationship between amyloid deposition and any other neuropsychological test, including face-occupation task. -No significant relationship between APOE carrier status and either degree of amyloid deposition or any of the neuropsychological tests (including face-name).
Spatial and non-spatial studies					
Collie, 2002	Comparison with healthy older adults	Older people with cognitive decline (N=16; Age=69.20;	PAL from CANTAB (pattern-location task)	CERAD - MMSE -Verbal fluency -Naming -Constructional praxis	-Samples matched on age, gender, education level and estimated/pre-morbid IQ.

		6M and 10F) Healthy controls (N=16; Age=69.0; 7m and 9F)	Face-name task Pattern-word task (abstract patterns paired with common words) Task designed to be sensitive to hippocampus function (no details provided other than it involved familiar and non-spatial stimuli)	-WLDR CANTAB -SWM -TOL	-Significant differences between groups on pattern-location task (PAL) but not on Face-name or Pattern-word. - Significant differences on WLDR, but no other CERAD or CANTAB task -Significant difference on some measures from the 'hippocampus' task but not others.
Pike, 2012	Comparison between aMCI and healthy older adults	aMCI (N=70; Age=76.53; 35.7%M) Healthy older adults (N=101;71.49; 27.7%M)	La Trobe Face-name La Trobe Number plate (Object and location) VPA (Verbal Paired Associates)	MMSE CVLT-II	-Sample matched on gender only, not on age, education or estimated/premorbid IQ. But age and education entered as covariates -Significant differences between aMCI and healthy controls on all three binding tasks - Also significant difference on CVLT-II - Effect sizes (eta-squared) reported for difference between group performance, but significance of difference between them not analysed. Face-name=.34; number plate=.40; VPA=.35; CVLT= .57
Troyer, 2008	Comparison between aMCI and healthy older adults	aMCI (N=29; Age=75.1; 55%F Healthy older adults (N=30; Age=75.2; 57%F)	Brief Visual Spatial Memory Test-Revised (BVMT-R) (Object and location) Digit Symbol recall (WAIS-III) (digit and symbol binding)	MMSE HVLT-R Vocabulary Digit span TMT-B	-Sample matched on age, education level and gender -Significant differences between healthy controls and aMCI on both binding tasks. -Significant differences remained on both tasks even when using a binding score corrected for item recall (within task control) -Significant group-x-recall type (item vs. binding) interaction effect on both tasks indicating significantly greater difference between

					groups on binding recall compared to item recall -Sensitivity and specificity were 76 and 90% for digit-symbol and 86 and 97% for object-location to distinguish aMCI from healthy controls. -Significant differences on MMSE and HLVT-R, no differences on Vocabulary, Digit Span or TMT-B

Note: ACE-III=Addenbrooke's Cognitive Examination III; AD=Alzheimer's disease; aMCI = amnestic Mild Cognitive Impairment; AmNART= American National Adult Reading Test; APOE 4= Apolipoprotein E allele 4; BNT= Boston Naming Test ; BVMT-R= Brief Visuospatial Memory Test Revised; CANTAB= Cambridge Neuropsychological Test Automated Battery; CERAD= Consortium to Establish a Registry for Alzheimer's disease; CPAL= Continuous Paired Associate Learning; CVLT-II = The California Verbal Learning Test II; EMQ = Everyday Memory Questionnaire; EWCST= Emory Short form of the Wisconsin Card Sorting Test; FCSRT= Free and Cued Selective Reminding Test; FNAME-12= Face-Name Associative Memory Exam-12; HVLT, Hopkins Verbal Learning test; IQ = Intelligence Quotient; MCI = Mild Cognitive Impairment; MMSE= Mini Mental Status Examination; OLTT = Object Location Touchscreen Test; PAL= Paired Associate Learning; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SRT = Selective Reminding Test; SWM= Spatial Working Memory; TMT-A, Trail Making Test-A; TMT-B= Trail Making Test-B; TOL = Tower of London; VIQ= Verbal Intelligence Quotient; VFDT= Visual Form Discrimination Test; VPA=Verbal Paired Associate; WAIS-III= Wechsler Adult Intelligence Scale - 3rd edition; WLDR= Word List Delayed Recall Test; WMS= Wechsler Memory Scale; WMS-R= Wechsler memory Scale

Table 3.4. Overview of binding studies and outcomes: Binding and Alzheimer's disease

Binding and AD					
Spatial binding studies					
First author, year	**Study design**	**Sample**	**Binding test and type of stimuli bound**	**Other neuropsychological measures**	**Main outcomes**
Clague, 2005	Comparison with MCI, fvFTD, SD and healthy older adults	AD (N=22; Age=67.6; Gender not given) MCI (N=23; Age=67; Gender not given) fvFTD (N=11; Age=61.3; Gender not given) SDem (N=13; Age=64.9; Gender not given) Healthy older	Face-place task (Faces of famous people and location)	MMSE Digit Span Logical memory (WMS-R) Complex Figure of Rey RMT (words) RMT (faces) Category fluency Naming test WCST VOSP	-Samples matched on years of education and age, but no information about gender. - Significant differences between groups on binding aspect of task, with AD group showing worst performance: Healthy Older = fvFTD>MCI=SDem>AD -AD worse than controls on naming and item recognition aspects of performance, but not significantly worse than all other dementia groups (within task control). -Wide range of significant differences between all dementia groups and healthy older adults on non-binding tests. No

		(N=23; Age=63.3; Gender not given)			analysis reported of differences between dementia groups on non-binding tests, apart from significant differences on MMSE.
Dudas, 2005	Comparison with MCI and healthy older group	AD (N=22; Age= 67.6; 11M and 11F) MCI (N=24; Age= 68.2; 15M and 19F) Healthy Older (N=29; Age=63.8; 12M and 17F)	Face-Place task (Faces of famous people and location)	VOSP Letter fluency Digit span Logical memory Rey figure RMT Naming Test Graded Pyramids and Palm Trees (pictures)	-Sample matched on age and educational level. -Healthy Older significantly better than MCI and AD on all three components of task (naming, recognition and face-place binding) (within task control) - No significant difference between AD and MCI group except on binding component (AD worse) (within task control) -Wide range of differences between groups on other neuropsychological tests except letter fluency and some subtests of VOSP
Fowler, 2002	Longitudinal study to determine the best predictor of AD	AD (N=16; Age=65; 8M and 8F) Healthy Controls (N=19, Age= 58; 5M and 14F) QD (N=21; Age= 58; 8M and 8F) 9 of these went on to develop AD over the 2-year period	Paired Associate Learning (PAL) from CANTAB (Visual pattern and location)	DMS from CANTAB GMI Letter and category fluency WMS-R WAIS-R MMSE RAVLT Maze learning	-Samples were matched on age, gender, years of education, occupational level and estimated/ premorbid IQ -At 6 months, all of those who went on to develop AD had shown significant deterioration on the PAL, but not all had shown significant deterioration on other tests. Unclear if this represented a statistically significant difference.
Kessels, 2010	Comparison with MCI and healthy older group	AD (N=30; Age= 75.4; 10M and 20F) MCI (N=30; Age=73.6; 17M and 13F) Healthy older (N=40; Age= 75.2; 26M and 14F).	Location Learning Test (LLT) (Object and location – includes measure of memory for location regardless of object, and object-location binding)	RAVLT MMSE	-Samples matched on age, educational level and estimated/pre-morbid IQ, but Healthy Older not matched on gender. Gender entered as covariate -Significant differences between MCI and healthy controls, and between AD and MCI, on both location memory and binding.

					- Binding was better discriminator than location memory between AD and MCI, but no analysis of whether difference was statistically significant (within task control). -MCI significantly worse than controls on MMSE and RAVLT, but AD significantly worse than MCI only on MMSE
Lee, 2003	Comparison with frontotemporal dementia, semantic dementia and healthy older group	AD (N=10; Age=62.50; Gender not given) SDem (N=11; Age=61.64; Gender not given) fvFTD (N=11; Age=62.50; Gender not given) Healthy older (N=18; Age=60.23; Gender not given)	Paired Associate Learning (PAL) from CANTAB (Visual pattern and location)	Category fluency Naming test Recognition memory MTS from CANTAB	-Sample matched on age and level of education, no information about gender - AD significantly worse on PAL than fvFTD, SDem and control groups - No significant differences between AD and other dementia groups on MMSE or MTS - Significant differences between controls and dementia groups (including AD group) on other tasks
Liang, 2016	Comparison between familial AD and healthy controls. Correlation with hippocampal volume loss	Asymptomatic fAD mutation carriers (N=12; Age=37.2; 25%M) Healthy controls (N=50; Age= 36.9; 50%M) Symptomatic fAD mutation carriers (N=8; Age=47.4; 63%M) Healthy controls (N=12; Age=46.8; 46%M)	What was where? (Object and location) (separate scores for object memory, location memory and object-location binding)	Digit span Spatial Span RTM for faces and words WMS FAS Stroop TMT Category fluency GNT GDA VOSP Digit symbol Rey Figure (copy) WAIS	-Asymptomatic carriers and their healthy controls matched on age, gender, estimated IQ, MMSE, anxiety, but not on depression or education. -No significant differences between asymptomatic and healthy controls on neuropsychological tests except WASI IQ -Symptomatic carriers and their healthy controls matched on age, gender, education, depression and anxiety, but not on estimated/pre-morbid IQ. -Significant differences between symptomatic and healthy controls on most of the other neuropsychological tests -Significant differences between symptomatic and

					healthy controls on object identity, localization and object-location binding. -Significant differences between asymptomatic and healthy controls on object-location binding, despite intact memory for single items (within task control) -Significant correlation between hippocampal volume and object-location binding in symptomatic and asymptomatic carriers, but not with object or location memory (within task control).
Swainson, 2001	Comparison AD and healthy controls, and depression Follow-up of QD over two years with neuropsychological tests to predict their clinical outcome.	AD (N=26; Age= 68.6; Gender not given) QD (N=43; Age=65.0; Gender not given) Major Depression (N=37; 60.8; Gender not given) Healthy controls (N=39; Age= 64.6; Gender not given)	Paired Associate Learning (PAL) from CANTAB (Visual pattern and location)	Extensive battery: ADAS-cog MMSE Semantic naming Category fluency WMS Logical memory CRT RVIP Stroop Letter fluency Warrington SRMT (faces and words) Recognition tests (patterns, spatial and doors) Various tests from CANTAB Also: GDS	-Samples are stated to match on age and estimated/pre-morbid IQ, plus the three non-depressed groups on depression. But no statistical analysis reported and information about gender not given. -Significant differences between AD and depressed/controls/QD subjects on PAL; depressed and controls not different on PAL -Significant differences between AD and others on wide range of other tests - PAL error score showed least overlap (7%) between AD and controls/depressed out of all tests, and only predictor of AD vs. not-AD in a stepwise logistic regression involving all task measures - In QD group, correlation between test performance at start and degree of subsequent cognitive decline was highest for PAL error score, but some of the other tests also showed significant correlation and no statistical analysis of whether PAL error score was significantly better than other predictors.

Non-spatial binding studies					
Della Sala, 2012	Comparison with other types of dementia and with healthy older	AD (N=15; Age=72.93; Gender not given) FTD (N=17; Age=69.12; Gender not given) PD (N=14; Age=70.00; Gender not given) VasD (N=14; Age=73.36; Gender not given) DLB (N=10; Age=72.90; Gender not given) Older adults (N=20; Age=69.35; Gender not given)	STM object-colour task (separate scores for object, colour and object-colour binding)	TMT Prose Memory Digit Span Verbal fluency Raven's Progressive Matrices VOSP	-Samples matched on age and education. Dementia samples matched MMSE, VIQ, GDS and IADL. Information about gender not given. - All dementia groups showed significantly worse performance on most of the other tests compared to controls -Only the AD group was significantly worse than controls on the binding score. -AD group also significantly worse on some of the non-binding tasks than other dementia groups - On object and colour scores (non-binding), there were no differences between dementia groups (within-task control) - In classification analysis using a cut-off score, binding score and Prose Memory led to equal numbers of non-AD participants showing impairment, but binding score had significantly fewer false negatives for AD (i.e. fewer who had AD scored above the cut-off)
Nanda, 2019	Comparison with MCI and healthy older adults Correlation with brain volume loss	AD (N= 19; Age= 68.05; 10M and 9F) MCI (N= 22; Age= 69.91; 15M and 7F) Healthy Controls (N=20; Age=65.05; 8M and 12F)	Face-name test	M-ACE RAVLT WMS WCST Semantic battery TMT-A and B Warrington face recognition test VOSP	-Sample matched on age, gender and years of education with exception that MCI and controls not matched on age. -Significant differences between MCI and healthy controls on face-name binding task. -Significant differences between AD and MCI on face-name binding task -AD worse than controls on all other tests, and MCI worse that controls on most other tests

					-Face-name performance correlated significantly with volume reductions in right and left cuneus in AD, but not in MCI
Lowndes, 2008	Comparison with healthy elderly	AD (N= 22; Age= 79.6; Gender not given) Healthy elderly (N=50; Age=78.5; Gender not given)	Word pairs with varying degrees of imageability	Digit span Vocabulary (WAIS-III) HVLT-R	-Samples matched on age, estimated IQ and depression. Information about gender not given. -Significant differences between AD and healthy elderly on word pairs performance. Classification accuracy using logistic regression above 95%. -AD also significantly worse on Vocabulary, HVLT-R -Controls benefitted significantly more than AD from concrete vs. abstract manipulation
Parra, 2010a	Comparison with major depression and healthy older adults.	AD (N=14; Age=76.29; 7M and 7F) Major Depression (N=14; Age=72.71; 4M and 10F) Healthy older adults (N=14; Age=70.71; 7M and 7F)	Shape-colour binding	MMSE VIQ ACE-III Word list (recall) Word list (recognition) FAS Verbal fluency (animals) TMT-A TMT-B Rey Complex figure	-Sample matched on age, gender, years of education and verbal IQ -Significant differences between AD and patients with major depression on short-term memory binding for shape and colour -No significant differences between controls and depression group on shape-colour binding. -Performance for shape only and colour only was equivalent across groups (within-task control). Significant differences between AD and depressed group on ACE-III, Word list, FAS, Verbal fluency, TMT-A and B and Rey Figure
Parra, 2010b	Comparison between familial AD and asymptomatic carriers and healthy controls.	fAD (N=22; Age=45.2; Gender not given) Asymptomatic carriers	Shape-colour binding	MMSE TMT-A Verbal fluency (animals) FAS The Complex Figure of Rey VPA (WMS) WCST	-Sample matched on years of education. Information about gender not given. -No significant differences among familial AD, asymptomatic carriers and controls on the shape only and colour only

		(N=30; 35.6; Gender not given) Healthy controls non carriers (N=30; Age=40.9; Gender not given)		.	conditions (within-task control). -AD significant worse than healthy controls (but not than asymptomatic) in shape-colour binding. -Asymptomatic carriers performed significantly more poorly than controls on shape-colour binding - Significant differences on all neuropsychological tests between symptomatic fAD carriers and both control and asymptomatic carriers. -Healthy controls and asymptomatic carriers did not differ on any of the neuropsychological tests.
Parra, 2011	Comparison with familial AD and healthy controls	1st study AD (N=14; Age=76.29; Gender not given) Healhy older adults (N=14; Age=70.71; Gender not given) 2nd study fAD (N=22; Age=45.18; Gender not given) Asymptomatic (N= 25; Age=37.24; Gender not given) Healthy controls (N=29; Age= 39.55; Gender not given)	Colour-colour binding	MMSE TMT-A Verbal fluency (animals) The Complex figure of Rey VPA from WMS (2nd study only)	1st study: -Sample matched on age and years of education. Information about gender not given. -Significant differences between AD and healthy controls on colour-colour binding. -Significant differences on MMSE, TMT-A, Rey Figure and verbal fluency (animals) 2nd study: -Sample matched on years of education only. Information about gender not given. -Significant differences between asymptomatic carriers and healthy controls in the colour-colour binding condition. No significant differences between symptomatic and asymptomatic carriers. -Significant differences between symptomatic carriers and healthy/asymptomatic carriers on all neuropsychological tests (except Rey figure between fAD and asymptomatic). Asymptomatic and healthy controls did not

					differ in any of the measures.
Van Geldorp, 2015	Comparison with MCI, young adults, older adults and middle age adults	1st study Older adults (N=25; Age=72.84; 8M and 17F) Middle-age adults (N=18; Age=52.22; 14M and 4F) Younger adults (N=26; Age=29.58; 14M and 12F) 2nd study AD (N=27: Age=76.57; 15M and 12F) MCI (N=19; Age=74.37; 10M and 9F) Older adults (N= 25; Age=72.84; 8M and 17F)	Face-house Binding task	1st study NART 2nd study Digit span forward and backwards MMSE TMT-A TMT-B RAVLT	1st study -Sample did not match on age, gender, level of education or NART IQ -Significant differences between older adults and both middle age and young adults on binding task -No significant differences between young and middle age on face-place task. 2nd study: -Sample matched on age and gender. MCI and AD groups matched on educational level -Significant differences between MCI and controls and AD and controls on face-house binding task. -No significant differences between MCI and AD on binding task -Significant differences on digit span backwards and TMT-B across groups, but no differences on Digit span forward or MMSE (MCI and controls), TMT-A (MCI and controls) or RAVLT (AD and MCI).
Spatial and non-spatial studies					
Hanaki, 2011	Comparison with older adults and younger adults	Probable AD (N=25, Age=77.7; 4M and 21F) Healthy elderly (N=22; Age=75.7; 3M and 19F) Healthy younger (N=25; Age=20.8; 5M and 20F)	Object-colour-location binding Coloured photographs of living things and inanimate objects surrounded with a red or blue square placed on the right or left side of a	Digit span Spatial span ADAS-cog word recall MMSE	-AD and older matched on gender, age and education. Younger had more years of education. -Significant differences between young and older adults on both item-location and item-colour binding, but equivalent on item recognition (within task control). -AD showed significantly worse performance than older controls on item recognition and item-location, but equivalent on

			black background Task gave 3 scores – item recognition, item-colour binding and item-location binding		item-colour binding (within task control). -Healthy older adults had better performance for item-location than item-colour, but item-location and item-colour performance equivalent for AD group - AD worse than healthy older on all other tests except digit span (forwards) - Healthy older worse than young on Digit Span and ADAS

Note: ACE-III=Addenbrooke's Cognitive Examination III; AD=Alzheimer's disease; ADAS-cog= The Alzheimer's disease Assessment Scale- Cognitive Subscale; CANTAB= CANTAB, Cambridge Neuropsychological Test Automated Battery; CRT= Choice Reaction Time; DLB= Lewy Body Dementia; DMS= Delayed Matched to Sample; fAD= familial Alzheimer's disease; FAS= Letter Fluency; FTD= Frontotemporal dementia; FvFTD= frontal variant Frontotemporal Dementia; GDA= Graded Difficulty Arithmetic test; GDS: Global Deterioration Scale; GNT = Graded Naming Test; GMI =General Memory Index from the Weschler Memory Scale; HVLT-R= Hopkins Verbal Learning test; IQ = Intelligence Quotient; IALD= Instrumental Daily Living Activity; LLT, Location Learning Test; M-ACE, Addenbrooke's Cognitive Examination validated for use in Malayalam-speaking population; MMSE= Mini Mental Status Examination; MTS= Matching to Sample; NART= National Adult Reading Test; PAL= Paired Associates Learning; PD= dementia associated with Parkinson's disease QD= Questionable dementia; RAVLT= Rey Auditory Verbal Learning Test; RMT= Recognition Memory Test; RVIP= Rapid Visual Information Processing; SDem= Semantic dementia; SRMT= Short- Recognition Memory Test; STM=Short-term memory; TMT= Trail Making Test; VasD = Vascular Dementia; VIQ= Verbal Intelligence Quotient; VPA=Verbal Paired Associates; VOSP= Visual Object and Space Perception Battery; WAIS-R= Weschler Adult Intelligence Scale Revised; WAIS-III= Weschler Adult Intelligence Scale 3rd edition; WCST= Wisconsin Card Sorting Test; WMS= Weschler Memory Scale; WMS-R= Weschler Memory Scale-Revised.

Table 3.5. Quality assessment of the selected papers based on CLEAR

	1.Study Design				2.Data quality				3.Data Collection			4.Study Sample					5.Analysis Methods				6.Findings and Conclusions		Sample match	Floor and ceiling effects	NOTES
	1.1	1.2	1.3	1.4	2.1	2.2	2.3	2.4	3.1	3.2	3.3	4.1	4.2	4.3	4.4	4.5	5.1	5.2	5.3	5.4	6.1	6.2			
Clague, 2005	M	Y	Y	Y	Y	M	Y	Y	Y	Y	Y	Y	M	N	N	M	Y	Y	Y	M	Y	Y	M	M	Sample size per group was very small and groups were not age and education matched.
Collie, 2002	Y	N	M	N	M	N	Y	Y	Y	M	Y	Y	M	Y	N	M	Y	Y	Y	M	M	M	Y	N	Lack of details about sample and study design. Limitation of the study not explicitly discussed.
Della Sala, 2012	M	Y	Y	Y	Y	M	Y	Y	Y	Y	Y	Y	M	Y	N	M	Y	Y	Y	M	Y	Y	M	Y	Small sample size per group.
Dudas, 2005	M	Y	Y	Y	Y	M	Y	Y	Y	M	Y	Y	Y	Y	N	Y	Y	Y	Y	M	Y	Y	M	M	Limitations of the study not clearly discussed. Ceiling effects reported.
Fowler, 2002	M	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	M	N	N	M	Y	Y	Y	M	Y	Y	Y	N	Small sample sizes. Inclusion and exclusion criteria not reported. Floor and ceiling effects.
Hampstead , 2018	Y	Y	Y	Y	Y	M	Y	Y	Y	Y	Y	Y	M	M	M	Y	Y	Y	Y	M	Y	Y	M	N	Adequate size. Binding task well characterized, reporting psychometric properties.
Hanaki, 2011	Y	Y	Y	Y	Y	N	Y	Y	Y	M	Y	Y	M	M	N	Y	Y	Y	Y	M	Y	Y	M	N	Ceiling effects reported.
Harel, 2011	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	M	M	Y	Y	Y	M	Y	Y	Y	N	Extensive neuropsychological battery.
Irish, 2011	M	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	M	N	Y	Y	Y	Y	M	Y	Y	N	M	Small sample size per group. Poor matching. Ceiling effects.
Kessels, 2010	M	N	M	Y	M	NA	Y	Y	Y	M	Y	Y	N	M	M	N	Y	Y	Y	M	M	Y	M	N	Sample characteristics, recruitment and inclusion/exclusion criteria not well described. Limitations about the study not discussed.

Lee, 2003	Y	Y	Y	Y	M	NA	Y	Y	Y	M	Y	Y	M	N	N	Y	Y	Y	Y	M	Y	Y	M	N	Small sample size. Limitations of the study not explicitly discussed.
Liang, 2016	Y	Y	Y	Y	Y	M	Y	Y	Y	Y	Y	Y	Y	M	N	Y	Y	Y	Y	M	Y	Y	M	N	Small and unequal sample size across groups.
Lowndes, 2008	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	M	Y	N	Y	Y	Y	Y	M	Y	Y	M	N	Limitations of the study not explicitly discussed
Nanda, 2019	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	M	Y	Y	M	N	Small sample size
Papp, 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	M	N	Y	Y	Y	Y	M	Y	Y	M	N	Study design well described
Parra, 2010a	M	Y	Y	N	Y	M	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Small sample size. Extensive cognitive assessment. Floor and ceiling effects dealt with by using different versions of task for different groups.
Parra, 2010b	Y	Y	Y	M	Y	M	Y	M	M	Y	Y	Y	M	Y	N	Y	Y	Y	Y	Y	Y	Y	M	Y	Small sample size per group and recruitment strategy and inclusion/ exclusion criteria not well described. Floor and ceiling effects dealt with by using different versions of task for different groups.
Parra, 2011	Y	Y	Y	N	Y	M	Y	Y	Y	Y	Y	Y	M	Y	N	Y	Y	Y	Y	M	Y	Y	M	Y	Small sample size per group. Floor and ceiling effects dealt with by using different versions of task for different groups.
Pike, 2012	M	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	M	Y	Y	M	Y	Large sample size
Rentz, 2011	M	Y	Y	Y	Y	Y	Y	Y	Y	M	Y	Y	M	M	M	Y	Y	Y	Y	M	Y	Y	NA	N	Procedures of data collection not well described
Sapkota, 2017	M	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	M	Y	Y	M	N	Small sample size and samples poorly described. Very few other neuropsychological tests used.
Swainson, 2001	M	Y	N	N	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	M	Y	Y	Y	Y	M	Y	Y	M	N	Study design not well described, with no clear discussion about inclusion and exclusion criteria.
Troyer, 2008	Y	Y	Y	N	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	M	M	Y	Y	Y	Y	Y	Y	M	N	Limitations about the study were not discussed and sampling strategy not well defined. Ceiling effects.

Van Geldorp, 2015	Y	Y	Y	Y	Y	M	Y	Y	Y	M	Y	Y	M	M	N	M	Y	Y	Y	M	Y	Y	N	N	Differences between controls and AD and MCI might have been underestimated due to floor effect.

Note: MCI, mild cognitive impairment; AD, Alzheimer's disease; MRI, Magnetic Resonance Imaging; FNAME, Face-Name Associative Memory Exam; PET, Positron Emission Tomography. NA, not applicable.

5.1. Quality of studies reviewed

One study (Pike et al., 2012) did not receive any negative ratings (N) and their findings can be interpreted with more confidence but even these three papers did not receive a positive rating (Y) for all the checklist criteria. Six papers (Della Sala et al., 2012; Dudas et al., 2005; Hampstead et al., Harel et al., 2011; 2018; Parra et al., 2010b; Rentz et al., 2011) met most of the methodological quality criteria with only one negative rating, and their findings can also be interpreted with more confidence.

Seventeen studies got a mixture of positive, mixed and negative ratings, with more than one negative rating (Clague et al., 2005; Collie et al., 2002; Fowler et al., 2002; Hanaki et al., 2011; Irish et al., 2011; Kessels et al., 2010; Lee et al., 2003; Liang et al., 2016; Lowndes et al., 2008; Nanda et al., 2019; Papp et al., 2014; Parra et al., 2010a; Parra et al., 2011; Sapkota et al., 2017; Swainson et al., 2001; Troyer et al., 2008; Van Geldorp et al., 2015). This is an indication that their methodology was less rigorous and suggests the need for a more cautious interpretation of their findings. Although overall there were significant limitations highlighted by the quality assessment, it was judged that no paper was sufficiently poor that it required exclusion.

5.2. Summary and critique of study methodology

Studies used a wide range of binding tasks. Ten reported on spatial binding tasks, 10 on non-spatial and four on a combination of both. Tasks differed in other ways, such as whether retrieval was immediate or delayed, and the degree of memory load imposed. Many different kinds of stimuli were used, from faces to shapes to locations. Stimuli also differed in other ways too, such as familiarity, imageability, whether they involved ‘relational’ or ‘conjunctive’ binding, and whether they could be encoded verbally.

Several kinds of design were used. For studies involving participants at risk of AD, all 9 involved a comparison of mean performance with a healthy older control group, 10 a comparison with those diagnosed with AD, one a comparison with a healthy younger group, one a comparison with other types of dementia and one a comparison with a group who had depression. Three were longitudinal studies which evaluated the effectiveness of the binding task in predicting which participants at risk of dementia went on to develop AD. Two reported correlations between binding performance and biological markers of AD, such as brain volume loss. Two used some kind of within-task control to evaluate whether there were specific deficits on binding in comparison to other aspects of task performance such as memory for individual items.

A similar range of designs was evident in studies involving participants diagnosed with AD. All 15 studies reported a comparison with a healthy older or age-matched control group; 10 a comparison with groups at risk of AD; three a comparison with other forms of dementia; two studies a comparison with a group with depression; and two a comparison with a healthy younger group. Two studies reported correlations between binding performance and brain volume loss, and eight reported some kind of within-task control in which binding performance was compared with memory for other aspects of the task.

All studies reported whether groups were matched on variables associated with cognitive abilities such as age. However, there was wide variation in what was reported. The variables reported most often were age and years of education. Fewer reported whether groups were matched on estimated/pre-morbid IQ or emotional status (specifically, depression). Several papers also failed to report on the gender composition of their samples. In some studies, it was reported that groups were not matched on the listed variables. In some, but not all, cases the variables were then entered as covariates in the analysis.

All studies also involved participants completing a range of other standardised neuropsychological tests. In some cases, very extensive batteries of tests were used, but in other cases a relatively small number were used (e.g. Sapkota et al., 2017). The rationale for the choice of tests and, in several cases, the rationale for including any tests, was not always made clear.

Most studies reported using the NINCDS-ADRDA criteria (McKhann et al., 1984) for diagnosing AD. Samples at risk of AD included those with some genetic or biological marker of AD, or those showing some degree of cognitive decline. Although published criteria were used in most studies to classify those showing some degree of cognitive decline, in some cases (e.g. Collie et al., 2002) no clear classification criteria were provided.

Six studies involving those at risk of AD involved more than one binding task and thereby allowed a comparison between binding tasks, but only one study involving AD (Hanaki et al., 2011) involved more than one. The study of Hanaki et al. (2011) involved both spatial and non-spatial tasks, as did three of those focused on people at risk of AD. Two of the other studies involved different kinds of non-spatial binding (the face-name and face-occupation parts of the FNAME test), and one involved two kinds of spatial binding (Sapkota et al., 2017).

A number of issues about the methodology of the studies were highlighted by the quality evaluation:

- Inadequate sample size was an issue in many of the studies. Most of the studies were rated as having an inadequate sample size (Table 3.6). This resulted in reduced statistical power, thereby increasing the probability of Type II errors.
- Floor and ceiling effects are often an issue when comparing groups of different ability on the same test. They can impact on the suitability of the data for parametric statistical analysis,

and on the size of the difference between groups. Few of the studies explicitly considered the issue. To avoid possible ceiling and floor effects, Parra et al. (2010a and 2010b) used different versions of the binding task. For example, the AD group started off with two items and the depression group with three items. This solution may bring other difficulties. Differences between groups may be underestimated if they are not learning the same amount of material.

- Matching on demographic, pre-morbid intelligence and emotional status was variable across studies. Some studies matched on only a few relevant variables. Depression was often not included, although some of the studies found that depression appeared to have no impact on binding (Lee, Kim & Moon, 2019). The gender composition of the samples was sometimes not even reported on, even though gender may be associated with cognitive performance (Voyer, Postma, Brake & McGinley, 2007). Occupational history was not included as a matching variable in any of the studies, even though again there is evidence of its association with cognitive performance (Jorm et al., 1998).
- Some of the studies failed to provide full descriptions of their method that would allow the study to be replicated. For example, many studies failed to provide enough information about recruitment or the procedures for data collection. Eleven studies provided little or no information about inclusion/exclusion criteria for recruitment.

Although some studies used binding tasks from standardised or previously published tests, 15 studies used tasks specifically developed for the study or by the research group that authored the study. This raises issues about reliability and validity. Some of the papers refer to previous studies for more details about the task. Only three studies described some psychometric properties of the task and managed to discuss, at least partly, issues such as reliability and

validity (Pike et al., 2012; Rentz et al., 2011; Papp et al., 2014). Some papers failed to provide any information about this issue (Sapkota et al., 2017; Collie et al. 2002; Hanaki et al., 2011).

5.3 Summary and critique of study findings

In terms of comparisons with healthy age-matched/older controls on the binding task, all studies showed that the AD group or the group at risk of AD performed significantly worse – with the exception of the studies by Collie et al. (2002) and Rentz et al. (2011). In Collie et al. (2002), the group of 'older people with cognitive decline' showed significantly worse performance on the PAL task (pattern-location) but they were not significantly worse on a face-name or a pattern-word task. The small sample size in this study (16 in each group) should be noted. The failure to find a difference on two of the tasks could be due to inadequate statistical power. In Rentz et al. (2011) APOE ε4 carriers did not score significantly worse than other healthy controls on a face-name task, but there were only eight carriers and again inadequate statistical power may provide the explanation.

In terms of comparisons with other groups, Hampstead et al. (2018), van Geldorp et al. (2015) and Hanaki et al. (2011) included a healthy younger group. In all three studies the younger group outperformed the healthy older group on the binding task, and the healthy older group outperformed the MCI/AD group. However, none of the studies compared the size of the impact of normal ageing on binding performance with the size of the impact of MCI/AD. Swainson et al. (2001) and Parra et al. (2010a) both reported that a group diagnosed with depression performed as well as controls on a binding task that an AD group performed significantly worse on. Only three studies compared an AD group with participants with other kinds of dementia. In Clague et al. (2005), the AD group was significantly worse than other dementia groups on the binding task, but not on naming or item recognition components of the

task. Similarly, in Lee et al. (2003) binding performance in the AD group was significantly worse than any other dementia group. In Della Sala et al. (2012) out of all the dementia groups, only the AD group was significantly worse than the controls on the binding task. However, there was no direct comparison of the performance of the dementia groups. These three studies were statistically underpowered, with relatively few participants in each dementia group.

Significant correlations of binding performance with biological markers of AD were reported in two studies involving AD and three studies involving MCI. In AD participants, Liang et al. (2016) reported a significant correlation with hippocampus volume loss in AD and Nanda et al. (2019) with cuneus volume loss. For MCI participants, Hampstead et al. (2018) reported significant correlation with volume loss in the entorhinal cortex, and Rentz et al. (2011) reported significant correlation with amyloid deposits in the frontal region, although the correlation with deposits in the parietal region was only marginally significant ($p=.05$). Although Nanda et al. (2019) reported a correlation with cuneus volume loss for AD participants, the correlation for MCI participants was not significant. With the exception of Nanda et al. (2019), these studies also reported on whether biological markers were associated with non-binding performance. Liang et al. (2016) found that the correlation with hippocampus volume loss only applied to the binding aspect of their task, and not to memory for the individual objects or locations. Hampstead et al. (2018) reported that volume loss was not associated with performance on the RBANS, and Rentz et al. (2011) that amyloid deposits were not associated with performance on an extensive battery of non-binding tests.

Three longitudinal studies compared the effectiveness of a binding task with other tasks in predicting which participants eventually were diagnosed with AD. Irish et al. (2011) used a series of separate regression analyses and reported that two scores from the binding task provided the highest odds ratio, compared to two scores from the RBANS. However, there was

no analysis of whether these differences in odds ratio were statistically significant. Fowler et al. (2002) reported that, at 6 months, all of those who subsequently went on to develop AD had shown significant deterioration on the binding task, but not all had shown significant deterioration on other neuropsychological tests. Again, however, it was not reported whether this represented a statistically significant difference. In Swainson et al. (2001) for a group with possible dementia, the correlation between test performance at the start of the study and the degree of subsequent cognitive decline was highest for a binding task score, but some of the other tests from an extensive battery also showed significant correlation and there was no statistical analysis of whether the binding score was significantly better than other predictors.

Seven of the studies involving those at risk of AD and nine of those involving people with AD reported a comparison between the binding score and memory for the individual characteristics. All but one study (Troyer et al., 2008) simply reported whether the groups were significantly different on the binding score and whether they were significantly different on the individual memory score. With the exception of Hanaki et al., (2011), the groups differed significantly on the binding score, but not on memory for individual characteristics. In the Hanaki et al. study the AD group was significantly worse than controls on individual item recognition and an object-location binding task, but equivalent on an object-colour binding task. However simply reporting that groups differed significantly on one score but not another does not give an indication of whether there was a statistically significant difference between the binding score and the individual score in their ability to discriminate between groups: a significant difference and a non-significant difference may be very close in size. Troyer et al. (2008) involved a comparison between those with MCI and healthy controls. They used ANOVA and reported a significant group-x-recall type (individual item vs. binding) interaction

effect on both binding tasks, indicating a significantly greater difference between groups on binding recall compared to the difference on individual item recall.

All of the studies included some other standardised neuropsychological tests. There were group differences between the controls and the AD/at risk groups on many of these tests, as well as the binding task. In fact, in every study there was at least one non-binding task on which there was significantly worse performance. In the case of the studies comparing AD and other dementia groups, there were at least some non-binding tests on which the AD group performed significantly worse than another dementia group (Lee et al., 2003; Della Sala et al., 2012) or there was no analysis of the differences (Clague et al., 2005). In most studies, these differences were not commented upon and there was no further analysis involving scores on these non-binding tasks. This is a serious omission. To provide evidence that it is the binding process itself that is vulnerable to AD, it is necessary to control other cognitive processes represented in these other tests. To provide evidence that binding tasks have the best potential for discriminating AD from age-matched or other dementia groups, it is necessary to show that they do this more effectively than other tests. Only four studies tried to compare binding with non-binding tasks in terms of their ability to discriminate AD from other groups. Two of these involved correlating test performance with biological markers of AD. Hampstead et al. (2018) reported that the binding task performance was correlated with volumetric loss in the entorhinal cortex, but that performance on the RBANS was not; and Rentz et al. (2011) reported than amyloid deposition was correlated with binding task performance but not with any other test scores in a battery. Again, finding that one test is correlated but another is not does mean that there is a significant difference in the size of the two correlations. Neither study performed a direct comparison of the two correlations. Swainson et al. (2001) reported the percentage overlap between AD and controls/depressed groups on the binding task and other tests. When all test

scores were entered into a stepwise logistic regression predicting AD vs. not-AD, the binding task score was the only one that remained in the analysis and it misclassified only one from each group. It also showed the least overlap (7%) between AD and not-AD out of all tests. Della Sala et al. (2012) compared the effectiveness of a binding task and Prose Memory in correctly classifying AD and non-AD cases of dementia using cut-off scores for both. The binding score and Prose Memory led to equal numbers of non-AD participants showing impairment, but binding score had significantly fewer false negatives for AD (i.e. fewer who had AD scored above the cut-off).

Some of the studies involved more than one binding task. In the only one of these involving AD (Hanaki et al., 2011), participants with AD were worse than healthy older controls on item-location binding, but there was no difference on item-surrounding colour binding. However, there was no analysis of whether the effect sizes of the two variables were significantly different (i.e. whether they were significantly worse on item-location binding compared to item-colour binding). In Sapkota et al. (2017), the MCI group performed significantly worse than the control group on a name-location and an object-location; and in Papp et al. (2014) they performed significantly worse on a face-name and a face-occupation task. However, in neither study was there an analysis of whether the difference between groups was greater for one task than the other, and both studies were statistically underpowered. In the remaining studies, there was a difference between binding tasks, but there was no analysis of whether this difference was statistically significant. Rentz et al. (2011) reported that there was a significant correlation between amyloid deposition and face-name binding, but not with face-occupation binding. Collie et al. (2002) reported group differences on pattern-location, but not face-name or pattern-word. Pike et al. (2012) reported effect sizes for the different tasks, with face-name showing the largest effect size, followed by object-location and then word-word.

Again, though, there was no analysis of whether one effect size was significantly larger than another. Finally, Troyer et al. (2008) reported the sensitivity and specificity figures (in terms of discriminating between an MCI group and controls) for an object-location and a digit-symbol task. Although the figures were better for object-location, there was no analysis of whether this was a statistically significant difference.

6. Discussion

The aim was to provide a systematic review of research literature that has investigated the performance of people with AD or people at risk of developing AD on binding tasks. The broader aim is to establish whether binding tasks are promising methods for the early detection and diagnosis of AD. There are several questions to ask of the evidence in relation to this broader aim. The first is whether there is evidence that binding processes are affected by the disease process in the earlier stages of AD. Obviously, a neuropsychological test is going to be useful for the early diagnosis of AD only if it assesses a process that is directly affected by the early stages of the disease. Second, we can ask whether there is evidence of impaired binding processes in those at risk of AD who have not yet developed it. If binding is to be useful as a diagnostic test for early AD, then binding impairments should also be evident in those at risk of developing AD but who have not yet met the diagnostic criteria for AD. Third, we need to ask whether binding deterioration is specific to AD, rather than to other kinds of dementia. A useful neuropsychological test needs to be able to pick out those with AD from other cases of dementia, rather than just from healthy older people. Fourth, we need to ask whether binding tests are better than other tests at picking out those with AD. There are other non-binding tests currently used in the diagnosis of AD that show some reasonable sensitivity to it. We need evidence that we should use binding tests rather than these other tests. Fifth, we need to ask whether there are any particular kinds of binding that are more sensitive than others to early AD. As discussed in

Chapter 2, claims have been made about spatial binding being particularly sensitive. Is there evidence from the studies of binding that this is the case? As noted earlier, binding tasks also differ in many other ways. Is there evidence of these other differences being important in considering what binding tests may be most effective in diagnosis? Sixth, it is useful to consider the impact of AD on binding relative to the impact of normal ageing on binding. As discussed in Chapter 2, normal ageing does appear to have an impact on binding. The advantage of comparing the impact of AD and normal ageing is that tests that show an accelerated rate of decline in AD may be better options than ones for which the rate of decline is similar – because they are likely to show greater specificity and sensitivity. Such comparisons are also useful from a theory perspective, contributing to a better understanding of how binding processes may deteriorate with normal ageing and AD. The following sections consider how well these questions are answered by the literature reviewed in this chapter.

6.1. Are binding processes impaired by the early stages of Alzheimer's disease?

People in the earlier stages of AD clearly do poorly on binding tasks. In terms of comparisons with healthy age-matched/older controls on the binding task, all the studies showed that the AD group performed significantly worse. However, doing poorly on a binding task does not necessarily mean that the underlying binding processes are impaired. Performance on these tasks relies on other cognitive and executive processes, such as memory and attention. Poorer performance could be due to impairment on these other non-binding processes rather than on binding. All of the studies included other non-binding neuropsychological tests and in all of them the AD group was worse than controls on at least one of these tests. This highlights that AD groups differ in cognitive terms from controls in many other ways. Scores on these other

tests could have been used to control for these other cognitive and executive processes, but few of the studies did this, and they simply reported that the AD group performed worse than healthy controls. The problem is made worse by the fact that many of the studies also failed to match particularly well on other variables that are associated with cognitive performance (i.e. demographics, pre-morbid IQ and emotional status). This could have resulted in the groups not being matched on the non-binding processes that contribute to binding performance, or on 'pre-morbid' binding ability.

More convincing evidence of impairment in binding processes is provided by the nine AD studies that reported a comparison between the binding score and memory for individual items in the binding task. With the exception of Hanaki et al. (2011), the groups differed significantly on the binding score, but not on memory for individual characteristics. In the Hanaki et al. study (2011) the AD group was significantly worse than controls on individual item recognition and an object-location binding task, but equivalent on an object-colour binding task. However simply reporting that groups differed significantly on one score but not another does not give an indication of whether there was a statistically significant difference between the binding score and the individual score in their ability to discriminate between groups: A significant difference and a non-significant difference may be very close in size. Also, it is not clear whether memory for individual items provides adequate control over all of the non-binding processes that may be contributing to task performance. Many of the studies had participants complete extensive test batteries that would have provided a broader measure of non-binding processes that could contribute to test performance, but none of them used scores from the tests as covariates in the analysis.

Another type of design used by the studies was to correlate performance on the binding task with some known biological marker of AD. Only two studies involving AD participants

reported data of this kind. Nanda et al. (2019) reported that face-name binding was correlated significantly with volume reductions in right and left cuneus in AD. However, a correlation in itself is not particularly compelling evidence. More persuasive is the study by Liang et al. (2016) in which there was a significant correlation between hippocampus volume and object-location binding, but not with object or location memory.

Overall, many of the studies do not provide particularly persuasive evidence that binding processes are impaired in AD because they simply report on whether people with AD do worse than controls on a binding task. There are studies that use a better design approaches, but these are more limited in number and not without criticism. Nevertheless, there is probably enough evidence to suggest that binding tasks do merit further investigation as tests for the detection of early AD.

6.2 Are binding processes impaired in those at risk of Alzheimer's disease?

The studies that addressed this issue are subject to the same concerns as the literature about those with AD. Many simply reported that those at risk performed worse on binding tasks than controls. There was one study that reported a lack of impairment on some binding tasks. In Collie et al. (2002) the group of 'older people with cognitive decline' showed significantly worse performance on pattern-location binding but they were not significantly worse on a face-name or a pattern-word task. The small sample size in this study (16 in each group) should be noted, which could explain the lack of significant effect.

There were studies that reported a comparison between performance on binding and memory for individual items in the binding task. These all reported that memory for binding was impaired but memory for individual items was not. However, Troyer et al. (2008) went beyond this and reported a significant group (MCI vs. controls) -x-recall type (individual item vs.

binding) interaction effect in an ANOVA, indicating a significantly greater difference between groups on binding recall compared to the difference on individual item recall.

There were also studies involving those at risk that correlated performance on the binding task with some known biological marker of AD. In Rentz et al. (2011) APOE ε4 carriers did not score significantly worse than other healthy controls on a face-name task, but there were only 8 carriers and inadequate statistical power may explain the lack of effect. Although Nanda et al. (2019) reported a correlation with cuneus volume loss for AD participants, the correlation for MCI participants was not significant. However, there was a problem again with small group sizes in this study. Significant correlations were reported by Hampstead et al. (2018) and Rentz et al. (2011). Rentz et al. (2011) reported significant correlation with amyloid deposits in the frontal region, which were not associated with performance on an extensive battery of non-binding tests. Hampstead et al. (2018) reported significant correlation with volume loss in the entorhinal cortex, which was not associated with performance on the RBANS.

Studies involving those at risk of AD face the problem that not all of those at risk will actually have AD or go on to develop AD. This would have the effect of reducing the chances of finding significant effects when comparing at-risk groups with controls. However, a more convincing type of study design involves a longitudinal study to see whether performance on binding tests accurately predicts who will go on to develop AD. Three studies used this design. Irish et al. (2011) reported that the binding task provided a better odds ratio than two measures from the RBANS, and Fowler et al. (2002) reported that, at six months, all of those who subsequently went on to develop AD had shown significant deterioration on the binding task, but not all had shown significant deterioration on other neuropsychological tests. However, in neither study was there an analysis of whether the binding test was a significantly better predictor than other tests. In Swainson et al. (2001), the correlation between test performance at

the start of the study and the degree of subsequent cognitive decline was highest for a binding task score, but some of the other tests from an extensive battery also showed significant correlation and there was no statistical analysis of whether the binding score was significantly better than other predictors.

In summary, as for the studies involving people with AD, many of the studies involving those at risk do not provide clear evidence of impairment in binding processes because they simply report that people at risk do worse than controls. However, there are studies that used a better approach, particularly a longitudinal design. Again, there is evidence to suggest that binding tasks do deserve further investigation as tests to detect early AD.

6.3. Is the binding impairment specific to Alzheimer's disease relative to other dementias?

The review found only three studies that compared the binding performance of AD and other types of dementia. In all three cases (Clague et al., 2005; Lee et al., 2003; Della Sala et al., 2012) there was some evidence that binding performance was worse in the AD than in the other dementia groups. However, it should be noted that these three studies had small sample sizes in each dementia group. Clearly this is an area where more evidence is needed.

6.4. Are binding tests better than other neuropsychological tests at picking out those with Alzheimer's disease?

Despite the fact that all of the studies included some other standardised neuropsychological tests and that in every study there was at least one non-binding task on which there was significantly worse performance by the AD compared to healthy controls (or other dementia groups), only four studies compared binding with non-binding tasks in terms of their

ability to discriminate AD from other groups. Two of these involved correlating test performance with biological markers of AD. Hampstead et al. (2018) reported that the binding task performance was correlated with volumetric loss in the entorhinal cortex, but that performance on the RBANS was not; and Rentz et al. (2011) reported than amyloid deposition was correlated with binding task performance but not with any other test scores in a battery. However, neither study performed a direct comparison of the two correlations. Swainson et al. (2001) reported that the binding task score was the only one required in a stepwise logistic regression model predicting AD vs. not-AD, and that it had the smallest percentage overlap between the AD and controls/depressed. Della Sala et al. (2012) reported that a binding score and Prose Memory led to equal numbers of not-AD participants showing impairment, but the binding score had significantly fewer false negatives for AD (i.e. fewer who had AD scored above the cut-off).

Clearly more investigation is needed that compares the effectiveness of binding tasks to other neuropsychological tests in diagnosing AD.

6.5. Are some kinds of binding more sensitive than others to early Alzheimer's disease?

Six studies involving people at risk, and only one involving an AD group, used more than one binding task or a binding task that combined two different types of binding. None of these studies analysed whether one task showed a larger difference than another between the AD/at-risk group and the control group. The studies only provided a descriptive account. Even from this descriptive account, no consistent pattern emerges. The studies provide no consistent evidence that spatial binding is more impaired than non-spatial binding. In favour of spatial binding being more impaired, Collie et al. (2002) reported a significant group difference on

pattern-location binding, but not on face-name or pattern-word; Troyer et al. (2008) reported higher sensitivity and specificity for object-location vs. digit symbol; and Hanaki et al. (2011) (the only study involving AD participants) reported a significant group difference on item-location but not on item-colour surround. However, against the idea that spatial binding is preferentially impaired, Pike et al. (2012) reported that face-name binding had a larger effect size than object-location binding. Three studies compared only spatial or only non-spatial. Sapkota et al. (2017) reported significant group differences on both name-location and object-location binding, as did Papp et al. (2014) for the face-name and face-occupation scores of the FNAME test. For the same test, Rentz et al. (2011) reported that amyloid deposition was significantly correlated with face-name, but not with face-occupation.

More research comparing different kinds of binding is required. This should address other ways that binding tasks can differ (e.g. relational vs. conjunctive binding, familiarity of the stimuli) as well as the spatial vs. non-spatial difference. The research should also complete statistical analysis of the difference between binding tests, rather than relying on just a descriptive account of the pattern of results.

6.6. How does the impact of normal ageing on binding compare with the impact of Alzheimer's disease?

Only three studies included a healthy younger group (Hampstead et al., 2018; Van Geldorp et al., 2015; Hanaki et al., 2011) and none of them provided a statistical comparison of the impact of normal aging and the impact of AD on binding.

Again, this is an issue that is worth investigating. A test that shows an accelerated rate of decline in AD is more likely to show greater specificity and sensitivity than a test where normal

ageing and AD have similar impacts. This information is also useful in developing theoretical accounts of how binding processes deteriorate with normal ageing and AD.

6.7. Limitations of the reviewed studies

Most of the studies used small non-random sample sizes, which increases the risk of unreliable statistical findings and Type 2 errors (i.e. failing to detect a real difference between groups) and reduces the generalizability of the findings. The variation of tasks, designs, outcome measures and different terminologies that was used to refer to binding resulted in difficulties in making direct comparison between studies and drawing general conclusions across them. The majority of the papers received moderate ratings on the CLEAR framework and a number of limitations were noted, such as the failure to address floor and ceiling effects adequately.

This review also highlighted the lack of research investigating spatial and non-spatial binding in clinical groups with only a few studies investigating both types of binding in AD (Hanaki et al., 2011) and in MCI or people with cognitive decline (Pike et al., 2012; Troyer et al., 2008; Collie et al., 2002). The lack of studies comparing spatial and non-spatial binding performance makes it difficult to draw any firm conclusion about a preferential decline in one particular type of binding in AD or MCI. More generally, there was a failure to compare different kinds of binding and this makes it difficult to draw any conclusions about whether some kinds are more vulnerable to AD than others.

CHAPTER 4

SPATIAL AND NON-SPATIAL BINDING IN YOUNGER ADULTS, OLDER ADULTS AND PEOPLE WITH ALZHEIMER'S DISEASE

1. Introduction

The conclusions from the literature review were:

- People with Alzheimer's disease (AD) and at high risk of developing AD do significantly more poorly than healthy older adults on a range of binding tests.

- However, it is not clear whether this is due to the binding aspects of these tests. There are few studies that have controlled adequately for differences in other cognitive processes that may contribute to performance on these tests. Many of the studies controlled for gender, education and pre-morbid functioning, but dementia can also impact on general memory and attentional processes that contribute to performance on these tests. To address this issue, the study described in this chapter measured a range of general memory, attention and other cognitive processes, and controlled for them in the statistical analysis to determine if the difference between samples of healthy older people and people with AD on binding tasks was due to the binding process itself. Some of the binding tests used in this study also allowed us to derive a binding score that took account of differences in the ability to remember individual items. These scores were also used to address the question of whether the difference between healthy older people and those with AD on binding tasks is due to the binding process itself.

- Although some have claimed that spatial binding is particularly vulnerable to AD, there is little evidence of this from the neuropsychological studies that were reviewed. Very few papers have compared spatial and non-spatial binding tests. Although Collie et al. (2002), Pike et al. (2012), Troyer et al. (2008) and Hanaki et al. (2011) did compare them, there were other methodological problems with these studies. Also, binding tasks vary in many ways, not just in terms of whether they involve spatial or non-spatial binding. Even if we find that people with AD are more impaired on a test involving spatial binding, it is not clear, just

from this comparison alone, that spatial binding is particularly impaired in AD. The difference in performance could be due to these other differences between the tasks. To address this problem in the current study, we compared three spatial and three non-spatial binding tasks. If there is a particular problem with spatial binding, one would expect that a comparison between the overall mean of the three spatial tasks and the three non-spatial tasks would be sensitive to this.

- Leaving aside the spatial vs. non-spatial issue, it is a problem that very few papers have compared different kinds of binding task. If the overall aim is to identify tests that are effective in the early detection of AD, comparisons between binding tests on sensitivity and specificity, in relation to healthy people of a similar age, are important to identify which ones are best. The current study compared the six binding tests in terms of their sensitivity and specificity.

- The sensitivity and specificity of binding tests also needs to be compared to the sensitivity and specificity of other tests that might be vulnerable to AD. These comparisons are needed to establish the claim that binding is particularly vulnerable to AD and that therefore binding tests are the best option in terms of finding neuropsychological tests that can be effective in diagnosis. Although many of the papers reviewed did include other tests that might be affected by AD, very few of them actually compared the binding tests with these other tests in terms of their specificity and sensitivity. To address this, the current study did compare the six binding tests with the other measures of memory and attention used in the study in terms of their sensitivity and specificity.

- There are also few papers that have compared the impact of normal ageing on binding with the impact of AD – i.e. papers that have obtained data about the performance of healthy

young participants, healthy old participants and people with AD, and then compared the rate of decline in normal ageing with the rate of decline in AD. The advantage of such comparisons is that tests that show an accelerated rate of decline in AD may be better options than ones for which the rate of decline is similar – because they are likely to show greater specificity and sensitivity. Such comparisons are also useful from a theory perspective, contributing to a better understanding of how binding processes may deteriorate with normal ageing and AD. To address this issue, the present study also included a group of healthy younger participants.

1.1. Hypotheses

a. Participants with AD will show significantly poorer performance on binding tests than older healthy participants, and this will be the case even when differences in other aspects of memory, attention and other cognitive processes that contribute to task performance are controlled for.
b. Relative to healthy older participants, participants with AD will show greater impairment on spatial binding tasks compared to non-spatial ones.
c. The six binding tests will show greater sensitivity and specificity in relation to discriminating between AD participants and the healthy older participants than the other tests of memory and attention used in the study.

1.2. Exploratory aims of the study

a. To compare the six binding tests in terms of their ability to discriminate between AD participants and the healthy older participants.
b. For spatial vs. non-spatial tasks and for each of the six binding tasks individually, to compare the rate of decline in normal ageing (measured by comparing the

performance of healthy older and younger adults) with the rate of decline in AD (measures by comparing the performance of healthy older adults and people with AD).

2. Methodology

2.1. Ethical issues / approval

Ethical approval was granted by the University of Birmingham School of Psychology Human Research Ethics Committee on November 2016 (approval number ERN_16-1174 see Appendix 4a), covering all healthy participants.

Another application was made on February 2017 to cover the clinical participants. In September 2017, ethical was approved by Birmingham and Solihull Mental Health National Health Service (NHS) Foundation Trust and the project commenced (approval number: IRAS 217888 see Appendix 4b). Several difficulties were encountered during the recruitment process, which resulted in very few potential participants being identified. To increase the sample size, it was necessary to identify an alternative source of participants, and therefore further ethical approval was obtained (Appendix 4c). It was possible to gain access to another pool of participants through a voluntary dementia research website: Join Dementia Research (JDR) (joindementiaresearch.nihr.ac.uk). Sixty-five percent of the AD participants were recruited via this method.

All procedures and contact details were described on the Participant Information Sheet (PIS) on Appendix 4d. Written informed consent was obtained from all participants. If there were any concerns about the wellbeing of the participant, then the intention was to gain their consent to discuss any concerns with the researcher supervisor to identify appropriate support pathways.

Information and contact details were provided for all participants in case they needed to discuss any issues or to make a complaint.

2.2. Participants

Three groups of participants were recruited: one of healthy young adults, one of healthy old adults, and one of people diagnosed with Alzheimer's disease or probable Alzheimer's disease. The target for the sample size was 26 per group. A range of statistical tests were used. The one requiring the largest sample to meet power requirements was an analysis of covariance with one within-participant factor (spatial vs. non-spatial binding), one between-participant factor (one group vs another group) and a set of covariates (to be decided based on the results of the study). A power analysis for sample size requirements using analysis of covariance with these parameters was conducted using G*Power (Faul, Erdfelder, Lang & Buchner, 2007). With alpha set at .05 and power at .80, a sample of 52 (i.e. 26 in each group) is required to detect a large effect size (f=.40) in relation to the main effects and interaction effect. The intention was therefore to recruit a sample of at least 26 participants in each group.

2.2.1. Inclusion criteria

All potential participants who met the following inclusion criteria were eligible to take part in the study:

a. Should have the capacity to give informed consent
b. Should be a fluent English speaker able to follow the instructions given in the testing sessions
c. Sight and hearing are sufficient for compliance with the testing
d. Normal-corrected or normal vision

For the healthy groups the inclusion criteria also included:

a. Aged between 18 to 25 years old (for young group) or above 60 (for old group).
b. Should not have any memory complaint or meet criteria for dementia or mild cognitive impairment.

For the AD group participants should:

a. Have a diagnosis of Alzheimer's disease or probable Alzheimer's disease provided by a NHS Memory Clinic or medical practitioner.
b. Be in the earlier stages of the disease. For those recruited from the NHS Memory Clinic, they were required to have scored at least 88 on their most recent Addenbrooke's Cognitive Examination (ACE-III), as suggested as a cut-off for mild dementia in Bruno & Vignaga (2019). Participants recruited from JDR did not always have an ACE-III score information in their profile, but information about scores on other cognitive tests was available and these were used to ensure that the participant was not in the more advanced stages. Also, a capacity to consent was required and assessed (see below). This would also ensure that participants were in the earlier stages of the disease.

2.2.2. Exclusion criteria

The exclusion criteria for all groups consisted of:

a. Prior or current diagnosis of a severe mental illness
b. History of any psychiatric disorder or neurological condition, such as stroke
c. Use of any medication that could affect cognition or mood.
d. Cannot read or write
e. Does not have fluency in the English language.

2.3. Recruitment and procedures

2.3.1. Young Adult Participants

All young participants were recruited via Research Participant Scheme (RPS) at the University of Birmingham in exchange for credits. The RPS is a recruitment website for the School of Psychology at the University of Birmingham that advertise research studies. Students from University of Birmingham were giving credits for participating, and they are required to accumulate a certain amount of credit for taking part in research studies over the course of each term. A full description of the study with a PIS (Appendix 4d) was available on the RPS and students who met the inclusion criteria could voluntarily sign in to take part in the study in exchange of 1.5 credits. All young participants were students from University of Birmingham, and all were tested using university facilities. All completed the battery of tests in one session.

2.3.2. Older Adults Participants

The older participants were paid volunteers at the University of Birmingham and all were contacted via a university research database. A staff member from the university (not one of the researchers) was responsible for calling participants who met the inclusion criteria to check if they were interested in taking part of the study. A copy of the PIS (Appendix 4d) was given to the individuals who expressed an interest in taking part. An information session was offered to explain the study and to give the participants the chance to ask questions before they consent to take part, but no participants wanted to book an information session. A testing session was then arranged for those confirming their interest. The participants could choose the most convenient place for testing (at the university or their own homes). However, all participants from the healthy older group chose to be tested within university facilities and were paid £15 per one hour and half of testing. Older participants were also offered the opportunity to spread participation over two sessions if they felt tired, but all completed within one session.

2.3.3. Alzheimer's disease participants

The AD participants were locally recruited through a Memory Assessment Service (MAS) at Birmingham and Solihull Mental Health NHS Foundation Trust or across the West Midlands area via the JDR.

At the MAS, participants were sampled purposively. The local collaborator identified potential participants using the set of inclusion and exclusion criteria. The local collaborator accessed medical records, such as ACE-III scores, to ascertain whether or not the participant met the criteria required for the study. The researcher did not access these records**.**

Individuals meeting these criteria were approached via letter or face-to-face by the local collaborator. A letter inviting them to participate in the study (Appendix 4e) was given or send by post. For those expressing interest, the local collaborator obtained their written consent to pass their contact details to the researcher, through the "Expression of interest" document (Appendix 4f). Potential participants were not approached by the researcher before this occurred. An information session with these participants was arranged to explain the study and answer any questions the participant may have. At this session, participants were given a copy of the PIS (Appendix 4d) and 'Participant Consent Form' (Appendix 4g) to keep.

Participants were given at least 24 hours to make their decision about participation. After 24 hours, the researcher phoned to ask whether they want to participate. It was made clear to participants that whatever decision they took would not influence any services or support they may have access to. If participants decided to taking part on the study, a testing session was arranged for the most convenient time and place for them. In the first testing session, all participants signed a consent form (Appendix 4g) before the testing commenced.

Due to difficulties in recruiting participants from MAS, an alternative database had to be identified. Join Dementia Research (JDR) (joindementiaresearch.nihr.ac.uk) is a UK-based research website developed by the National Institute for Health Research (NIHR), the Alzheimer's Society and Alzheimer's Research UK in 2014. This service enables people with AD and other types of dementia to participate in dementia research nationwide. The study was registered on the website and became available for the potential volunteers. A full description of the study with a leaflet (Appendix 4h) and a PIS (Appendix 4d) was available for all volunteers registered in the website. A list of 127 volunteers across West Midlands was produced based on the inclusion and exclusion criteria of the study. Potential participants had their profile reviewed by the researcher to ascertain eligibility for taking part in the study. The volunteer's information that was available for the researcher were: diagnosis, date of diagnosis, medication in use, cognitive test scores, brief medical history, possible disabilities and contact details. The volunteers could choose to be contacted directly or to indicate a representative to be contacted on their behalf, such as spouse or another relative. Most of the volunteers were located outside of Birmingham, but priority was given to those who lived closest to the University of Birmingham to reduce travel times.

The researcher contacted the volunteers or their representatives via post or phone or email, depending on the preference listed on their profile. For those who expressed interest in taking part, a copy of the PIS (Appendix 4d) was sending by post or email and within 24 hours the researcher called them to confirm their participation and arrange the first session. A total of 17 out of 26 participants were recruited via JDR.

Regardless of how the participant was recruited, participants were given a choice of time and testing venue (e.g. University of Birmingham or their own homes) to minimise any inconvenience. They were reimbursed for any travel expenses that may have been incurred

because of participation in the study (up to £5 for the participant plus £5 for carer if required). However, all participants with AD chose to be tested at their own homes.

To test the capacity of the participants to provide consent in the AD group, the researcher asked the participants two questions to ensure that they understood what their participation would involve. The questions were: - If you take part in this study, what do you need to do? - About how long will the tests take to complete? Their responses were recorded on the Participant Consent Form (Appendix 4g).

Due to the length of the assessment it was possible that the participants with AD could get fatigued. To minimise distress and tiredness, several measures were taken to manage this:

a. Participants were given the option of completing the testing across two sessions (involving approximately 45 minutes of actual testing each) on different days.
b. There was a 10 minute break half way through each session.
c. Participants were also offered breaks in between tests.
d. If a participant became noticeably tired during the testing, they were given the option of rescheduling the session or withdrawing from the study.

2.4. Measures

All participants, regardless of which group they were assigned to, completed the same computer and pen-and-paper tests. The material consisted of the following: demographic questionnaire, a measure of depression, a measure of reading ability, binding tasks and control tasks that access memory and attention. The order of the administration of the tasks was random across participants.

2.4.1. Demographic Questionnaire

The Demographic Questionnaire (Appendix 4h) asked about gender, age, hand preference, ethnicity, further education and English as a first language. The participants were also asked whether there was any history of Alzheimer's disease or any other dementia in their family.

The demographic variables were used to describe the sample and identify differences between groups that could impact on their performances and interfere in the results. Significant differences on these variables, such as gender, education, language and dementia history were taking into consideration in the analysis by seeing whether they were associated with test performance. If they were, they could be included as covariates.

The questionnaire was completed in less than two minutes by the participant.

2.4.2. Centre for Epidemiologic Studies Depression Scale (CES-D)

The CES-D is a self-reported depression scale, originally developed to measure depressive symptoms in general population (Appendix 4i) (Vilagut, Forero, barbaglia & Alonso, 2016). CES-D has been used largely in research and many studies, as a measure of depressive symptoms among older persons (Wilson, Mendes de Leon, Bennett, Bienias & Evans, 2004) and individuals with AD (Gatz, Tyas, John & Montgomery, 2005). Depressive symptoms can impair cognitive performance (Lee, Kim & Moon, 2019) and so the measure was used in case it needed to be included as a covariate.

The tool consists of 20 items; participants are asked to answer each item considering how they felt in the previous week, responding to statements using the response options of 'rarely or none of the time', 'some or a little of the time', 'occasionally or a moderate amount of time' and 'most or all of the time'. The scale includes 16 indicators of depression, such as 'I felt lonely' and

four items covering positive affect, such as ‘I enjoyed life’. The scale takes approximately 5 minutes to be completed.

The scale scores each item from 0 to 3 points, and the total score ranges from 0 to 60, with a higher score indicates higher depressive symptoms. The four items that ask about positive affect are reverse-scored. The standard cut-off score for indicating depression symptomatology in the general population is 16 (Gatz et al., 2005). Therefore, a score of 16 was determined as the cut-off point in the present study. The variable was treated as a categorical variable, with the value of either depressed (above 16) or not depressed (16 or below).

2.4.3. National Adult Reading Test Revised (NART-R)

The NART-R comprises 50 written words printed in two columns which were given to participants to read (Appendix 4j). The test is of graded difficulty and all words are in British English with irregular spellings, violating grapheme to phoneme rules (e.g. ache, thyme, topiary). NART-R tests the participant’s reading vocabulary rather than ability to translate graphemes to phonemes using rules and, therefore is sensitive to education (Nelson & Willison, 1991). Scores are converted to an estimated intelligence quotient (IQ).

The NART was first developed for estimating general intelligence in English-speaking adults (Nelson, 1982) and is widely used in clinical and research settings, including published studies on dementia (Petterson, Graham & Hodges, 1994; Taylor, 2000; Cockburn, Millar &Milne, 2000). The aim of including the NART-R was to provide a potential control in the analysis for differences in general cognitive abilities that might explain differences in binding performance between groups.

Although the NART-R has been used in published research on dementia to provide an estimate of pre-morbid intelligence, there is evidence that reading ability can be affected by AD

even in the earlier stages (Petterson et al., 1994), and so the NART-R may underestimate ability. During the study, it was clear that some of the participants with AD did struggle with the NART-R. To overcome this problem, an estimated IQ score based on demographic variables was used for the AD group instead of the NART-R score. According to Crawford et al. (2001), demographic variables, such as social class code, years of education and age, can also be used for estimation of the same Wechsler Adult Intelligence Scales (WAIS) IQ predicted by the NART-R. The social class coding in UK has 5 categories: 1= professional, 2= intermediate, 3= skilled, 4= semi-skilled, 5= unskilled. Retired, unemployed people and housewives were coded by their previous occupations. Those who never worked were coded as class 5. The demographic data were entered into Crawford and Allan's (1997) equation as follows:

Predicted FSIQ = 87.14 – (5.21 x class) + (1.78 x years of education) + (0.18 x age).

It should also be noted that, for six of the Young group, English was not their first language. It was likely that the NART-R also underestimated their ability. However, the demographic estimate was considered inappropriate for this group because of their age and still being in full-time education. The NART-R is therefore likely to underestimate the ability of the Young group. For one of the Old group also English was not their first language, but their NART-R estimate was higher than their demographic-estimate and may be more accurate.

2.4.4. Control tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB)

Performance on the binding tasks might be affected by other general memory, executive functions and attentional processes, as well as binding processes. This raises the possibility that any impairment in performance on the binding tasks could be due to impairments in these general processes, rather than in binding. To address this problem, some tests of general

memory, executive processes and attention were included so that covariance analysis can investigate whether any decline in binding performance can be explained by the decline in these general processes rather than by impairments in binding abilities.

The CANTAB is a computer-based test battery which assesses many cognitive domains, such as memory, attention, executive function, decision making and social cognition. CANTAB uses a touch-tone screen and press-pad with two buttons. The Motor Screening Test (MOT) is a training procedure and was used to familiarise the participants with the CANTAB user interface. It was given at the beginning of the test session and introduced them to the computer and touch screen. It was also used to ascertain that the participant can follow simple instructions. Scores from this were not used in the analyses.

Some tests on the CANTAB have several different versions (e.g. 'clinical', 'high functioning' and 'shortened'). In selecting the version for each CANTAB test in this study, the aim was to avoid ceiling and floor effects, since all three groups completed the same version of the task, but also to avoid high administration time.

The following tests were used from the CANTAB battery:

2.4.4.1. Spatial Working Memory (SWM)

This task assesses executive function and manipulation of visuospatial information in working memory (CANTAB Test Administration Guide, 2014). Based on evidence that spatial working memory is impaired in AD patients with moderate dementia (Guariglia, 2007), SWM task seemed to be an appropriate measure to be included in the study.

In this task, participants are presented with coloured squares on the screen (Figure 4.1). The participants, by process of elimination, should find one blue token in each of a number of boxes. They use the tokens to fill up an empty column on the right side of the screen.

The participant must touch each box in turn until they find a box with a blue token inside. The participant must place the blue token that has been found in the empty column by touching the right side of the screen. Then, a new search begins for the next blue token. The new token may be in any of the boxes in which a blue token has not appeared. The search is repeated until a blue token has been found in every box on the current screen. An error is considered when participant touched any box in which a blue token has already been found. The order in which the boxes are searched is decided by the participant.

The number of squares increases gradually from three until there is a total of eight boxes on the screen. Changes in colour and positions of the squares from trial to trial prevent a learning effect. A shortened version was selected for this task. The shortened mode is an abbreviated version of the clinical mode with same level of difficulty, but with a shorter administration time. It has a practice phase of four three-box sets, and then six assessed trials, two each of four, six and eight boxes.

The outcome measure used in the analyses was Total Errors, which evaluates the number of times the participant touches any box in which a blue token has already been found. The scores start from zero with unlimited number of errors, where lower scores indicate better performance.

Display: A blue token is shown in one of the coloured boxes

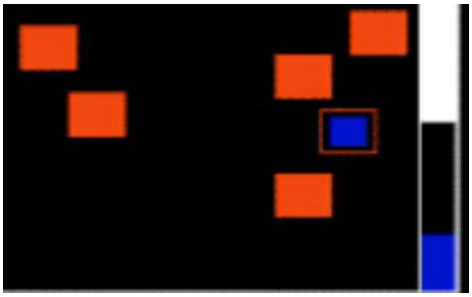


Figure 4.1.: The SWM task screen (6 boxes)

2.4.4.2. Spatial Recognition Memory (SRM)

The SRM task assesses visuo-spatial recognition memory and is claimed to be primarily sensitive to dysfunction in the frontal lobe, and relatively insensitive to temporal lobe damage (CANTAB Test Administration Guide, 2014). Worse performance on SRM has been associated with some biomarkers of AD, such as cerebrospinal fluid levels (Nathan et al., 2005).

The task consists of a choice between two locations, characterising a discrimination paradigm. In the presentation phase, a white square is presented on the screen in five different locations in sequence (Figure 4.2). In the recognition phase, the white square appears again in the same five locations as in the presentation phase, again in sequence and in the reverse order. On each time of the appearance of the white square, an identical distractor square is shown in a location on the screen not used in the presentation phase. The participant must ignore the distractor and touch the square that is in the location that appeared before. The clinical version was selected for this task. The task is repeated four times, each time with five new locations. Feedback about whether the response is correct or not is given each time the participant selected a square.

The SRM Number Correct was the outcome selected for the study, measuring the number of correct responses (out of a possible 20). Higher scores indicate better performance.

Display : A white square is shown on the screen in various locations

Figure 4.2: The SRM presentation phase (left figure) and recognition phase (right figure).

2.4.4.3. Pattern Recognition Memory (PRM)

The PRM is a test of visual recognition memory and it is claimed to be sensitive to dysfunction in medial temporal areas of the brain which are thought to be affected in prodromal Alzheimer's disease and mild cognitive impairment (www.cambridgecognition.com).

The presentation phase consists in a series of 12 visual patterns presented in the centre of the computer screen, one by one (Figure 4.3). The patterns cannot easily be verbally labelled. The participants are asked to look carefully at the patterns. No description or recall of the order of patterns presentation is requested. In the recognition phase, the participants are asked to choose between a pattern they have already seen and a novel pattern. Feedback about the correctness of the response is provided. In the recognition phase, the test patterns are presented in the reverse order to the original order of presentation. The clinical version was used in which two trials of different patterns are presented.

The Number Correct was the outcome for this task, corresponding to the number of correct responses in both trials (out of a maximum of 24). Higher scores indicate better performances.

Display: Series of visual patterns, one at a time, is presented in the centre of the screen.

Figure 4.3.: The PRM task screen showing the presentation phase (left figure) and the recognition phase (right figure).

2.4.4.4. Choice Reaction Time (CRT)

The CRT is a reaction time test, presenting two possible stimuli with two possible responses (CANTAB Test Administration Guide, 2014). This task was selected as a control for the processes of attention that are involved in the binding tasks and that may be impaired in mild AD (Kuzmickiene & Kaubrys, 2016).

For this task, the 'no-assessed-feedback' version was selected instead of the usual clinical mode. In this version feedback is given only in the practice stage, not in the assessed phase, as in the clinical version. It is also shorter than the clinical version.

The task involves the use of a press pad placed in front of the participants. They were asked to sit with the forefingers of both hands gently resting on the press pad buttons, ready to press. An arrow-shaped stimulus was displayed on either the left or the right side of the screen (Figure 4.4.). The participants are asked to press the left hand button on the press pad if the stimulus was displayed on the left hand side of the screen, and the right hand button if the stimulus was displayed on the right hand side. The task has a practice stage of 24 trials and one assessment stage of 50 trials. Automated feedback is provided throughout the practice stage (too soon, too late and wrong). The CRT Total Correct was the outcome selected, corresponding to the number of correct responses (maximum of 50). Higher is better.

Display: An arrow-shaped stimulus is displayed on either the left or the right side of the screen.

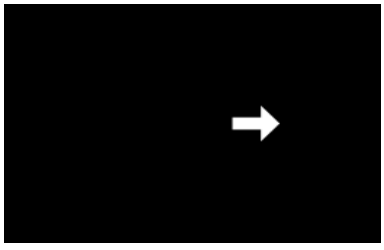


Figure 4.4.: The CRT task screen (right side)

2.4.5. Binding tasks

Six binding tasks were used, three spatial and three non-spatial. Tasks were selected on the basis of evidence that the particular binding ability involved appears to be impaired in AD. Another criteria for selection was how frequent the task appeared in the literature. Based on the results of the literature review, the most frequent types of binding encountered in studies involving AD and people at higher risk were face-name associations, shape-colour binding, word pairs and object-location binding. Based on that, two standardised tests and one experimental task were selected for each category (spatial and non-spatial).

2.4.5.1. Spatial Binding tasks

2.4.5.1.1. The Kitchen Arrangement Test (KAT)

The KAT assesses object-location binding (Abreu et al., 2014). It is characterized by its ecological and user-friendly features in the form of the everyday activity of food shopping. Sequences of three, four and five visual stimuli, that represent real-world objects, are displayed on the computer screen with a background image of a kitchen cupboard with 16 doors (Figures 4.5 and 4.6). All visual stimuli are nameable and semantically associated with the kitchen. There are in total 40 stimuli and 16 locations.

The demonstration trial presents two object-location sequences. The first object appears in the centre of the computer screen for 2000ms. One of the 16 doors open, the object slides into the opened door and the door closes. The same thing happens with the second object. After being shown which cupboards the both objects go in, the objects are shown again with two other distractors in the middle of the screen. The background image shows all doors opened. Then, the participant is asked to place the objects that he had seen before in their correct locations by

dragging them to the correct cupboards using the mouse. The participants were provided with feedback only on the demonstration trial. Once all correct objects are placed in the correct doors on the demonstration trial, the assessed phase starts.

In the assessment trials, the presentation phase consists of three trials of three objects, three trials of four and three trials of five objects. Each trial follows the same procedure described above, except that no feedback is given. The object-location sequences do not repeat. Objects can appear more than once, but never in the same trial.

In the retrieval phase, for each trial, all previous items from the presentation phase and the same number of distractors are shown in the middle of the screen. For example, in the trial where three object-location sequences are shown, in the retrieval phase, six objects (three targets and three distractors) are presented in the centre of the screen. The participants have to identify the to-be-remembered items and their locations.

Three scores are generated on this task. The number of correct objects, number of correct locations and the number of correct object-location bindings. In each condition, scores range from 0 to 36. A higher score indicates better performance.

Display: Objects were put into different cupboards in the kitchen. Subjects were asked to remember which cupboard each object is put into.

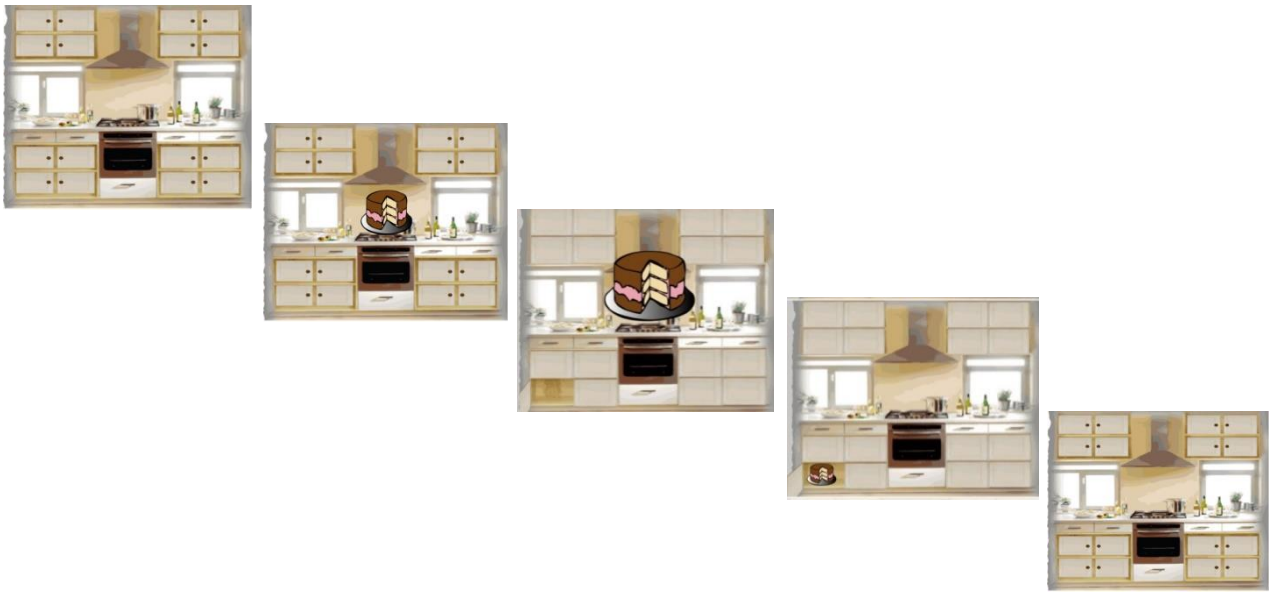


Figure 4.5: The KAT task showing stages of one object on learning phase.

Figure 4.6.: The KAT task recognition phase (3 objects).

2.4.5.1.2. Design

The Memory Design from the Wechsler Memory Scale - 4th edition (WMS-IV) (Wechsler, 2009) assesses spatial memory for unfamiliar visual material. This task involves shape-location binding. The WMS manual reports its use with a sample of people with AD.

The examiner shows the participant a grid with designs on a page for 10 seconds, which is then removed from view. A set of cards with the target designs alongside an equal number of distractors is shown and the participant is then requested to select the right designs and place the cards in a grid in the same place as previously shown. There is one trial of four designs, two trials of six and one trial of eight designs.

There are no demonstration or practice trials and no feedback is given for this task. This task gives scores for the number of correct designs, correct locations and correct bindings (correct design placed on a right location in the grid) for each trial. The score ranges from 0 to 24 each, with higher scores indicating better performance. Only the immediate recall part of the task was given. Delayed recall was not administered.

The Design I Record form, set of cards and grid have not been reproduced due to copyright issues.

3.5.5.1.2. Paired Associates Learning (PAL)

PAL is a test of visual memory and new learning from the CANTAB, which is claimed to be sensitive to changes in medial temporal lobe functioning (CANTAB Test Administration Guide, 2014). PAL task assesses the ability to remember patterns and their locations and it has been extensively used in dementia research, including research on AD (Kuzmickiene & Kaubrys, 2015).

In the presentation phase, boxes are displayed on the screen and opened in a randomised order (Figure 4.7). One or more of them contain a pattern. The patterns shown in the boxes are then displayed in the middle of the screen, one at a time, and the participant is asked to touch the box where the pattern was originally located. In the clinical version used in this study, the task has eight stages in total, including two stages of one pattern in six boxes, two stages of two

patterns in six boxes, three stages of three patterns in six boxes, one stage of six patterns in six boxes and one stage of eight patterns located in eight boxes. The participant has to correctly remember the pattern and their correspondent location to proceed to the next trial. Each stage has maximum of 10 attempts. If the participant fails after 10 trials at any stage, the task is ended automatically.

The PAL Memory score was selected on the grounds that it was the best measure of binding. This score represents the number of patterns corrected located after the first trial only, summed across the stages completed. The scores ranged from 0 to 26, with 26 meaning all the patterns were corrected located for all stages first time. Therefore, higher is better.

Display : Boxes were displayed on the screen and they were opened in a random order. There was a pattern in one or more boxes. Subjects were asked to remember which box the pattern was and to touch the box where they saw pattern appear.

Figure 4.7: PAL learning phase showing a pattern in an open box (right figure)

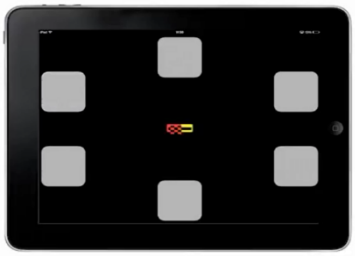


Figure 4.8.: PAL recognition phase showing a pattern in the middle. Participants were asked to touch the box where the pattern was.

2.4.5.2. Non-Spatial Binding tasks

2.4.5.2.1. Verbal Paired Associates (VPA)

The VPA from the WMS-IV (Wechsler, 2009) assesses word-word binding. Associations between words in VPA has been reported to be impaired in older individuals (Silver, Goodman & Bilker, 2012), and to be sensitive to pre-clinical AD (Pike et al., 2013).

The task involves 14 word pairs that are read aloud to the participants. After the examiner has read the whole list of word pairs, the first word of each pair is read, and the participant is asked to provide the corresponding word. There are four trials of the same list of word pairs read in different order. Only the Immediate Recall was used, not the Delayed Recall.

The participant scores 0 for any incorrect response or when they answered correctly beyond the time limit (two seconds). For each correct word-pair within two seconds, the participant receives one point. A total of 14 points for each trial can be obtained. The sum of the scores of each recall gives the Total Score, which could be up to 56 points. The VPA items and record form have not been included due to copyright issues.

2.4.5.2.2. Face-Name Associative Memory Exam (FNAME)

FNAME assesses associative memory using pictures of unfamiliar faces paired with common first names and occupations (Rentz et al., 2011). Considering that forgetting names can be a common early sign of AD (Tak & Hong, 2014), FNAME has been suggested as a promising tool for assessing people with MCI and AD (Papp et al., 2014).

The original task required participants to learn 16 novel face-name and face-occupation pairs (FNAME-16) (Rentz et al., 2011; Amariglio et al., 2012). However, this proved to be very demanding (Amarilgio et al., 2012) and too challenging even for healthy older adults, due to the length and attention demands (Papp et al., 2014). A shorter version was created (FNAME-12),

and consisted of fewer stimuli, more learning trials and a delayed recognition trial (Papp et al., 2014). For the present study, the modified version seemed to be a more suitable to be applied on clinically normal older adults and people with AD diagnosis.

FNAME-12 includes a learning phase, initial recall, cued recall, delayed cued recall, facial recognition, and multiple- choice recognition of face-name and face-occupation shown on PowerPoint slides, with one face per page (Figure 4.9). Each stimulus is displayed for eight seconds and all photos are coloured against a grey background. In the learning phase, the participants are shown a face with the name and occupation printed beneath it. They are asked to read out loud the name and occupation. After the presentation of all 12 items, the participants are shown each face and asked to recall their name and occupation. The initial learning phase is then repeated in a different order, keeping the same pairings. The number correct from both trials produces a total score of initial recall names (IRN) and initial recall occupations (IRO).

After that, there is a short delay when a distracter task, with 12 pictures of well-known famous faces is administered. Participants are asked to provide the name and occupations of each famous face. After the distracter task, participants are shown the 12 faces from the initial learning phase again and asked to provide their names and occupations, resulting in scores for cued recall names (CRN) and cued recall occupation (CRO).

After a 30-minute delay, a facial recognition task is administered in which participants are asked to identify the target face from a set of three faces matched for age, race and gender. Participants are then shown the correct faces again, one by one, and asked to provide the names and occupations of each face (CRN30, CRO30). Finally, participants are shown the correct faces again, along with a choice of three names and three occupations, and they are required to choose

the correct name (MCN) and occupation (MCO). All the answers were registered in a record sheet (Appendix 4k).

Several scores are generated on this task. The FN-N score is the total of IRN, CRN and CRN30, and the FN-O score is the total of IRO, CRO and CRO30. The total score is the sum of FN-N and FN-O. In the present study, the total FN-N score was used instead of the total. The reason for this is the FN-N score, but not the FN-O score, has been found to be related to amyloid deposition in the brain (Rentz et al., 2011), and face-name associations have been suggested to be a particularly demanding task for people with AD (Amariglio et al., 2012). A higher score indicates higher levels of performance.

Display: Slides of face-name and face-occupation pairings to be remembered, showing different phases of the task.

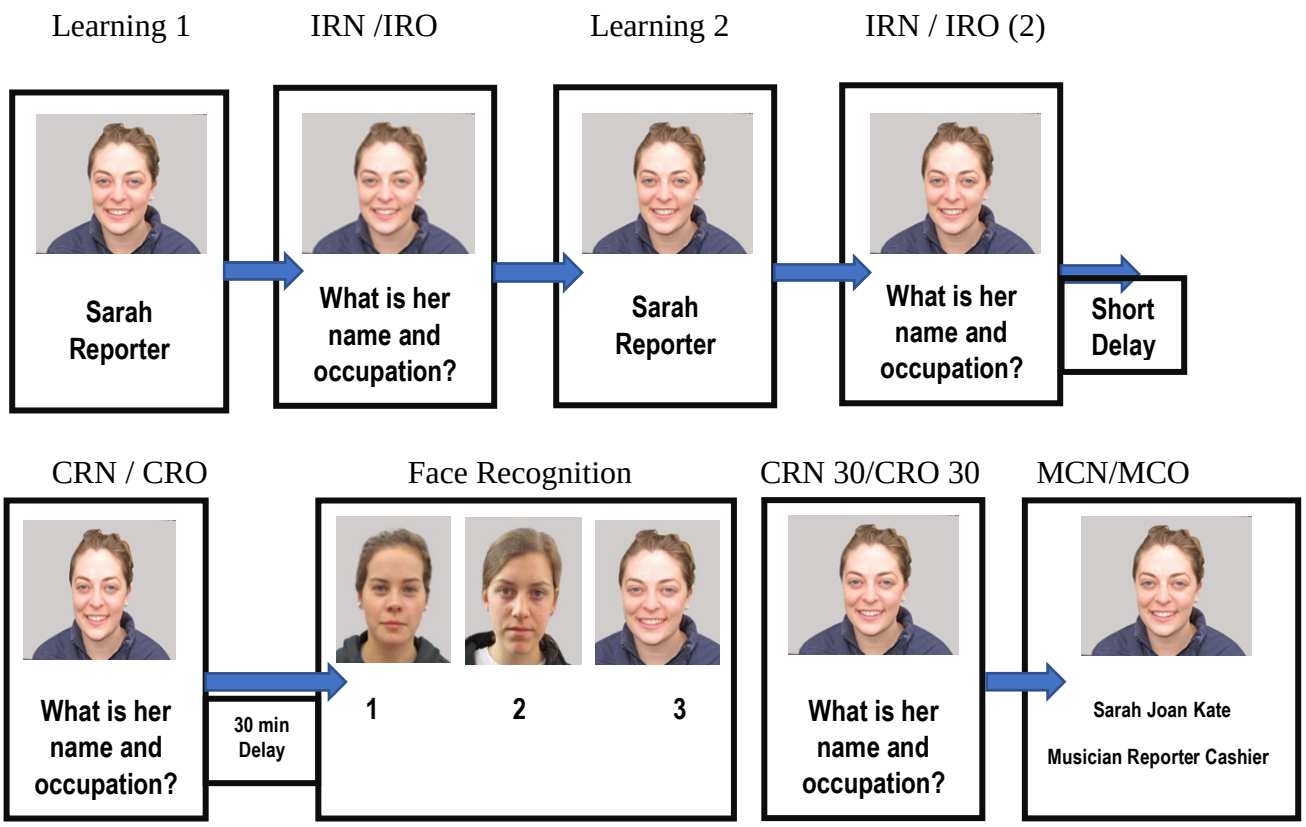


Figure 4.9.:The Face-Name task showing all the phases of the test.

2.4.5.2.3. Shape-Colour Task

There are several versions of this task. The one used in this study was based on the study by Parra, Abrahams, Logie & Della Sala (2010a) and was provided by Parra for the purposes of this study. The task assesses shape-colour bindings. It has been suggested that performance on this task is impaired in familial AD (Parra et al., 2015) and AD patients, but not in non-AD dementias (Della Sala, Parra, Fabi, Luzzi & Abrahams, 2012) or normal aging (Parra, Abrahams, Logie & Della Sala, 2009).

The task comprises three phases: perception, shape-only and shape-colour binding. The stimuli include eight types of shapes (six-sided random polygons) and eight colours (perception phase and shape-colour binding phase) or black shapes (shapes only phase) (Figures 4.10, 4.11 and 4.12). The task was run on E-prime 2.0 using a personal laptop computer. The perception condition is always the first phase to appear to the participant; however the program automatically randomizes the order of the shape-only and shape-colour phases for each administration, thereby eliminating any potential order effects. The task is first introduced using a paper version of the task that allows the participant to go over the instructions and ensure clear understanding before the task starts on the computer.

For all phases (perception, shape-only and shape-colour binding) shapes changed location randomly during trials, not allowing the location to be used as a memory cue. Thus, participants were instructed that shapes could move position and their orientation could change, but that was not important for the task. Participants were also prompted to answer as quickly as possible.

The perception phase involves showing simultaneously two arrays of coloured shapes, located on the upper and the lower half of the computer screen (Figure 4.10). The task is to say

whether the coloured shapes on the upper half are the same or different from the coloured shapes on the lower half of the screen. There are in total 10 trials. The perception phase was used to reinforce the understanding of the task and scores from it were not used in the analysis.

In the shape-only phase, there was a fixation cross for 500ms, followed by a study display which was presented for 2000ms (Figure 4.11). Two black shapes were presented for 2000ms. After that, new shapes replaced the old shapes and the participant had to say whether they were the same or different. If all the black shapes were the same the participant should say 'SAME'. If any the shapes were different to the shapes in the first slide, the participant should say 'DIFFERENT'. There were 32 trials, with 16 trials being 'the same' and 16 trials being 'the different'. For each correct response they scored one point. Scores range from 0 to 32, with higher indicating better performance.

In the shape-colour binding phase, there was a fixation cross for 500ms, followed by a display of two coloured shapes for 2000ms (Figure 4.12). After that, two new coloured shapes replaced the old ones and the participant had to answer if they were the same or different from the first ones. If all coloured shapes were the same, the participant should say 'SAME', and if any of the coloured shape was different, they should say 'DIFFERENT'. There were 32 trials, with 16 trials were 'the same' and 16 were 'the different'. For each correct response they scored one point, which could reach 32 points. Higher is better.

For all phases, the examiner entered the participants responses using the left click for 'DIFFERENT' and the right click for 'SAME' of the computer mouse. The shape-colour binding score was used in the analyses.

Display: The task consisted of three phases: perception, shapes only and shape-colour binding

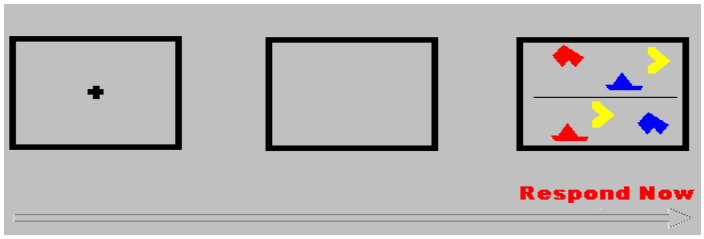


Figure 4.10: The Shape-Colour task: Perception phase showing the trial sequence on the computer

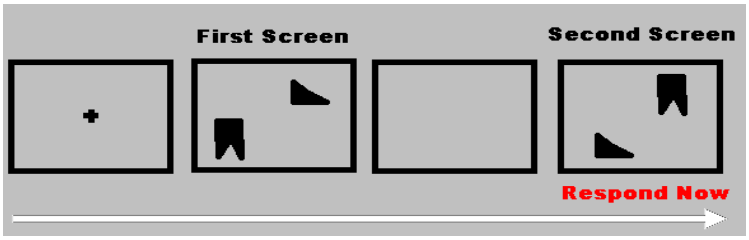


Figure 4.11: The Shape-Colour task: Shapes only phase showing the trial sequence on the computer (example of ‘SAME’).

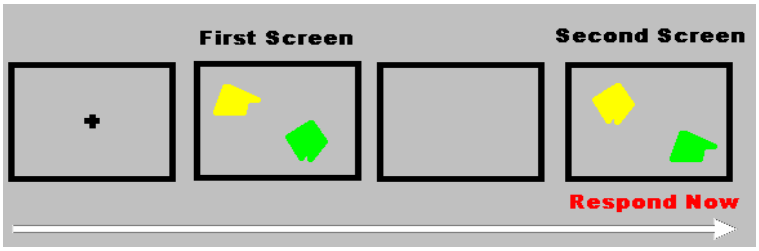


Figure 4.12: The Shape-Colour task: Shape-colour binding phase showing the trial sequence on the computer (example of ‘DIFFERENT’).

3. Statistical analysis and overview of the results

3.1. Data preparation and checking

All participants provided a full set of data. Each continuous variable was checked for any outliers or abnormal distribution. Outliers were classed as scores of ± 3.29 standard deviations from the mean ($p<.001$, two-tailed test) (Tabachnick & Fidell, 2013). This was calculated within each of the three groups (younger adults, older adults and AD) not across all three groups (i.e. the mean and standard deviation of the AD group's scores was used to determine outliers for the AD group etc.). On the control variables (Estimated IQ, CRT, SRM, PRM and SW), there were no outliers in any of the groups apart from several in each group on the CRT. This was because of ceiling effects on the variable that were particularly severe in the Young and Old group. This variable was therefore not included in any further analysis. On the six binding tasks, one participant in the AD was classed as an outlier on both the Design and VPA tasks, scoring very highly on these. He also scored higher than all the other AD participants on the KAT and the Face-Name task, although not enough to be classified as an outlier. The scores of this participant were adjusted to one unit higher than the next highest scorer on the Design and VPA tasks (Tabachnik & Fidell, 2013). The analyses were also run with this participant excluded to check whether his inclusion changed the overall pattern of the results (which it did not).

As another way of controlling the impact of non-binding cognitive processes on task performance, percentage scores were calculated for three of the binding tasks (KAT, Face-Name and Design). There were several outliers for the percentage score on the Face-Name task in the Young group, but there were severe ceiling effects for this group on this variable and so it was not used in any further analysis.

Normality of distribution of all the six binding variables was assessed within groups, not across groups. The criterion for abnormal was a statistic on the Shapiro-Wilk test that was

significant at p<.001. On the binding tasks, the Young group showed moderate negative skewing on the Face-Name total, and the AD group showed moderate positive skewing on Design. The Young group also showed moderate negative skew on the PRM. These variables were not transformed to bring them closer to the normal distribution because of the need for scores to be compared across groups. Analyses involving these variables should be treated with some caution, although the statistical methods used are reasonably robust to moderate departures from the normal distribution (Tabachnik & Fidell, 2013). Two variables showed severe negative skewing due to ceiling effects and were therefore excluded from subsequent analysis: all three groups showed severe negative skewing on the CRT and the Young group showed this for the Face-Name percentage score.

Further inspection of the distributions on the variables showed that on the Shape-Colour binding score, 15 of the Young group and seven of the Old group obtained the maximum score or one below, and the variance on the variable was low for these two groups. In consequence, when the scores were converted to standard scores for comparing across tests (see below) the AD group showed large standard score differences for quite small differences in raw scores. Also there was limited opportunity for the Young group to outscore the Old group, and so the difference between the Old and Young group on this variable may have underestimated true differences in ability.

Homogeneity of variances between groups for t-tests and between-group ANOVAs was assessed with the Levene's test. A statistically significant result of this test, at $p < .05$, indicates violation of the assumption of equality of variances. When this was the case, the degrees of freedom were adjusted as indicated within SPSS.

Sphericity was assessed for repeated measures ANOVAs and ANCOVAs with the Mauchly's Test of Sphericity using SPSS. A statistically significant result of this test, at $p \leq .05$, indicates violation of the assumption of sphericity. When this was the case, the degrees of freedom were adjusted according to the Greenhouse-Geisser method and the outcome following this adjustment is reported.

To allow comparison of performance across tests, all test scores used in the analysis were converted to standard scores using the Old group as the reference. That is, the mean and standard deviation of the Old group on a variable were used to calculate the standard scores for all three groups: (Score of participant – mean of Old group on that variable) / standard deviation of Old group on that variable. As a result, the standard scores of the Old group had a mean of zero and a standard deviation of 1.

3.2. Analysis strategy

The analysis strategy for addressing the various aims and hypotheses is summarised in Table 4.1. More detail is provided in the Results section as each aim or hypothesis is dealt with. Because of the number of tests involved, the alpha level was set at .01.

Table 4.1. Hypothesis, aims and analysis strategy

Hypotheses	**Analysis strategy**
1. Participants with AD will show significantly poorer performance on binding tests than older healthy participants, and this will be the case even when differences in other aspects of memory, attention and other cognitive processes that contribute to task performance are controlled for.	• For each binding task, one-way ANOVA with group (Old vs. AD) as the factor • To control for other cognitive differences, analysis repeated but including the control variables as covariates • For Face-Name, Design and KAT, initial analysis repeated using percentage scores (another way of controlling other cognitive variables contributing to task performance)

2. Relative to healthy older participants, participants with AD will show greater impairment on spatial binding tasks compared to non-spatial ones.	• For each participant, the mean of the 3 spatial and the mean of the 3 non-spatial binding scores were calculated • A mixed repeated measures ANOVA, with test (spatial vs. non-spatial) as the repeated measure and group (Old vs. AD) as the between-groups factor • This analysis was repeated, but with control variables included as covariates
3. The six binding tests will show greater sensitivity and specificity in relation to discriminating between AD participants and the healthy older participants than the other tests of memory and attention used in the study.	• A series of paired-sample t-tests was used, comparing the standard score of each binding test with the standard score of each CANTAB control test (SRM, PRM and SWM) • Descriptive statistics are provided about the percentage overlap between the Old and AD group on each binding task and each control task
Exploratory aims	**Analysis strategy**
4. To compare the six binding tests in terms of their ability to discriminate between AD participants and the healthy older participants	• A series of paired-sample t-tests was used, comparing the standard score of each binding test with the standard score of every other binding test • Descriptive statistics are provided about the percentage overlap between the Old and AD group on each binding task
5. For spatial vs. non-spatial tasks and for each of the six binding tests individually, to compare the rate of decline in normal ageing (measured by comparing the performance of healthy older and younger adults) with the rate of decline in AD (measured by comparing the performance of healthy older adults and people with AD)	• A repeat of the analyses for Hypothesis 1, but comparing Old vs. Young participants • Standard scores for AD and Young group treated as absolute scores (i.e. no negative signs) to provide an index of the distance from the mean of the Old group. • A series of independent sample t-tests using these absolute standard scores, comparing the Young and Old scores on the mean of the spatial tasks, the mean of the non-spatial tasks, and each binding task individually

Note: AD= Alzheimer's disease; CANTAB= Cambridge Neuropsychological Test Automated Battery; KAT=The Kitchen Arrangement Test; PRM=Pattern Recognition Memory; SRM=Spatial Recognition Memory; SWM=Spatial Working Memory.

4. Results

4.1. Demographic variables

Demographic differences between groups were investigated using ANOVA (for age) and chi-squared tests (for other variables). Table 4.2 shows a summary of demographic variables per

group (Young, Old and AD), as well as overall and pairwise statistical comparisons on each variable. The Old and AD groups were reasonably well matched on age, gender, handedness, ethnicity, education and having English as a first language. Unsurprisingly, there were more in the AD group with a family history of Alzheimer's disease, but this was not significant. The Young group was less well matched to the Old and AD groups. There were significantly more women, more with higher education and greater ethnic diversity. Compared to the AD group, again fewer had a family history of dementia.

Some demographic factors have been shown in the literature to have an association with binding task performance, such as gender or level of education (Voyer, Postma, Brake & McGinley, 2007) and so there was a concern that the unequal distribution of demographic variables across groups observed in Table 4.2 may have biased the analyses. To investigate this, one-way ANOVAs to compare performance on the binding tasks of the different demographic groups within each of the three main groups (i.e. Young, Old and AD). Some groups were too small to be meaningfully analysed (e.g. there was only one person in the Old group who was not a native English speaker). With alpha set at .01, there were no significant differences between demographic groups on any of the binding scores used in the analysis with the exception that, in the Old group, those with no further education did significantly worse that those with further education on the Face-Name Total ($p<.001$) (see Appendix 4l). Given this general lack of an association of demographic factors with performance, none was entered as a covariate in the analysis in order to avoid weakening its statistical power.

Table 4.2. Demographic information of all participants per group and group comparisons

Demographic variables	Younger Adults	Older Adults	AD	STATISTIC (main effects and pairwise comparisons)
Sample size	N= 26	N=26	N=26	
Age	Mean= 19.04 SD= 0.77 Range= 18-20	Mean= 73.35 SD= 5.28 Range= 65-82	Mean=70.42 SD= 8.80 Range= 60-85	F (2,75) = 687.31, p< .001; PW: Y-O = p<.001; Y-AD: p<.001; O-AD = p=.24
Gender	Men= 2 (8%) Women= 24 (92%)	Men= 11 (42%) Women= 15 (58%)	Men= 12 (46%) Women= 14 (54%)	$X^2(2) = 10.71$, p = .005. PW: Y had significantly fewer men than both O and AD
Handedness	Right-handed= 21 (81%) Left-handed= 4 (15%) Both= 1 (4%)	Right-handed=22 (85%) Left–handed=4 (15%)	Right-handed= 24 (92%) Left–handed= 1 (4%) Both= 1 (4%)	$X^2(4) = 4.09$, p = .394. PW: none significant.
Ethnicity	White/Caucasian=18 (69%) Black/African/Caribbean=2(8%) Asian=3(11.5%) Other=3(11.5%)	White/Caucasian=26 (100%)	White/Caucasian= 25 (96%) Other= 1 (4%)	$X^2(8) = 19.65$, p = .012. PW: White/Caucasian: Y showed significantly more diversity than O and AD.
Further Education	Yes= 26 (100%)	Yes= 21 (81%) No= 5 (19%)	Yes= 18 (69%) No= 8 (31%)	$X^2(2) = 9.05$, p = .011. PW: Y significantly more educated than AD
English Native-speaker	Yes= 20 (77%) No= 6 (23%)	Yes=25(96%) No= 1 (4%)	Yes=25(96%) No= 1 (4%)	$X^2(2) = 6.96$, p = .031. PW: none significant.
History of dementia or Alzheimer's disease in the family	Yes= 4 (15%) No= 22 (85%)	Yes= 6 (23%) No= 20 (77%)	Yes= 13 (50%) No= 13 (50%)	$X^2(2) = 7.58$, p = .023. PW: Y had significantly less history than AD.

Note: SD= standard deviation; Y = Young, O = Older, AD= Alzheimer's disease; PW = pairwise comparisons

4.2 Control variables

Table 4.3 shows a summary of control variables per group (Young, Old and AD), as well as group and pairwise comparisons for each variable. The Old and AD groups were matched on estimated IQ, but there were significantly more of the AD group classed as depressed. As expected, the AD group was significantly worse on all of the control tests from the CANTAB (the CRT was excluded from analysis because of severe ceiling effects). The Young group obtained significantly lower estimated IQ than both other groups, but this is probably a reflection of the fact that some of the Young group were not native English speakers and the NART-R may have underestimated their IQ. The Young group was similar to the Old group in terms of the

number classed as depressed. On the CANTAB tests, they outperformed the Old group on the SWM, but there were no significant differences on the SRM or PRM.

Scores on these control variables were correlated with the binding test scores to decide which ones needed to be included as covariates. This was done within rather than across groups to avoid confounding (e.g. if depression were correlated with binding performance across all participants, this could be simply because more participants in the AD group were classed as depressed, rather than because depression affected binding performance). Results are shown in Appendix 4m. The three CANTAB tests included in the analysis (PRM, SWM and SRM) and estimated FSIQ all showed some significant correlations with binding, and therefore these variables were included as covariates in the ANCOVAs. Depression was not correlated with any of the binding variables and therefore was not included as a covariate.

Table 4.3. Descriptive statistics: control tasks and group comparisons

Control Tests	Groups	Depressed	Not depressed	Possible score Min/Max	Lowest obtained score	Highest obtained score	STATISTICS (main effects and pairwise comparisons)
CES-D_16	Young	Yes= 22 (84.6%)	No= 4 (15.4%)	0/60	2	22	$X^2(2) = 10.16$, p = .006; PW*: Yes / No: Y-AD and O-AD.
	Older	Yes= 23 (88.5%)	No= 3 (11.5%)		0	34	
	AD	Yes= 14 (53.8%)	No= 12 (46.2%)		1	39	
	Groups	**Mean**	**SD**	78/126	92	110	F (2, 75) = 20.64, p<.001; PW: Y-O: p<.001, Y-AD: p<.001, O-AD: p= .475
Predicted FSIQ	Young	101.19	5.30				
	Older	114.96	9.65		84	126	
	AD	111.77	8.65		91.83	121.75	
CANTAB CRT	Young	49.96	0.20	0/50	49	50	Not performed due to severe ceiling effects
	Older	49.92	0.39		48	50	
	AD	44.65	9.87		11	50	
CANTAB SRM	Young	16.77	1.82	0/20	13	19	F (2, 75) = 28.89, p<.001; PW: Y-O: p= .096, Y-AD: p< .001, O-AD: p<.001.
	Older	15.26	2.46		9	19	
	AD	11.69	3.00		6	18	
CANTAB PRM	Young	22.35	2.13	0/24	16	24	F (2, 75) = 54.97, p <.001; PW: Y-O: p= .15, Y-AD: p< .001, O-AD: p<. 001.
	Older	20.81	2.23		16	24	
	AD	14.69	3.64		8	24	
CANTAB SWM errors	Young	6.88	6.31	From 0	0	24	F (2, 75) = 41.91, p< .001; PW: Y-O: p < .001, Y-AD; p < .001, O-AD: p <.001
	Older	19.08	10.49		2	47	
	AD	32.46	12.44		16	60	

Note: SD= Standard deviation; AD= Alzheimer's disease; CES-D =Centre for Epidemiologic Studies Depression Scale; CRT= Choice Reaction Time; SRM=Spatial Recognition Memory; PRM=Pattern Recognition Memory; SWM= Spatial Working Memory; PW = pairwise comparisons;

Post-hoc pairwise comparisons with Bonferroni correction were then carried out. Predicted FSIQ: NART-R used to estimate for Old and Young group, demographic equation for AD group.

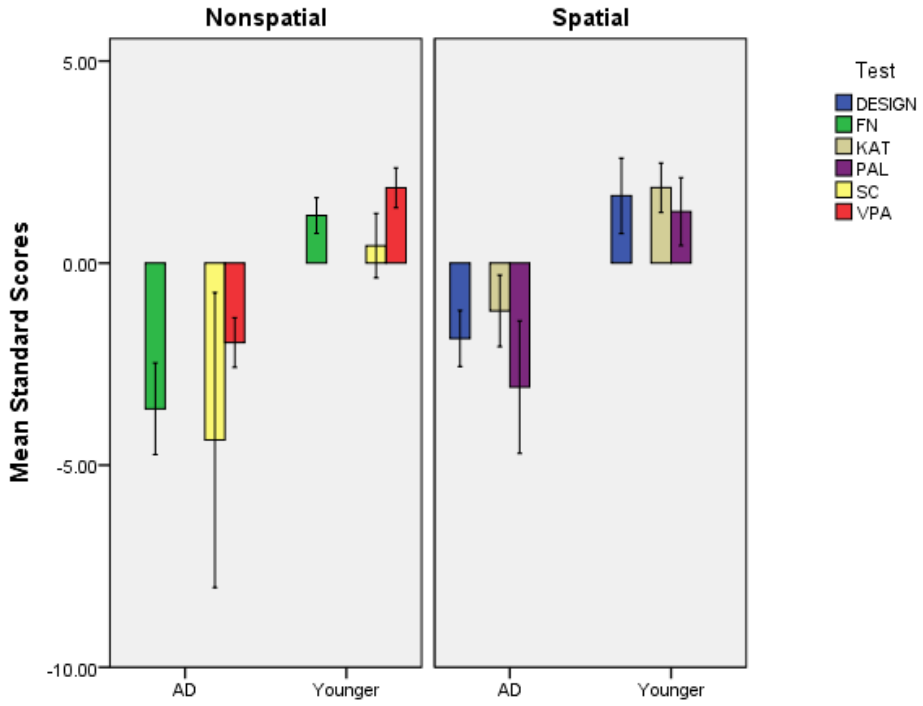
4.3 Binding scores

Table 4.4 shows information regarding the means, standard deviations and raw scores of all spatial (KAT, Design and PAL) and non-spatial (VPA, Face-Name and Shape-Colour) binding tasks per group. The table also shows the results of a one-way ANOVA comparing the three groups on each of the binding tests. Comparisons between the Old and Young groups and between the Old and AD groups on each of the tests is reported later (Table 4.5 for AD vs. Old, and Table 4.9 for Old vs. Young). As noted earlier, raw scores were converted to standard scores using the Old group as the reference point (so the Old group have a mean of zero). Figure 4.13 shows the mean of the standard scores for each group on each binding task.

Table 4.4. Descriptive statistics: spatial and non-spatial binding tasks

Binding type	Binding task	Groups	Mean	SD	Possible score Min/Max	Lowest obtained score	Highest obtained score	F-value	p-value
Spatial	**KAT**	Young	28.07	4.12	0/36	21	36	85.18	p<.001
		Older	15.5	6.74		6	27		
		AD	7.53	5.97		0	22		
	Design	Young	17.23	3.76	0/24	11	23	103.71	p<.001
		Older	10.5	4.03		4	19		
		AD	3.30	3.79		0	16		
	PAL	Young	23.07	2.74	0/26	17	26	88.25	p<.001
		Older	18.92	3.26		13	23		
		AD	8.92	5.35		0	19		
Non-spatial	**VPA**	Young	49.30	4.22	0/56	39	56	176.36	p<.001
		Older	33.34	8.56		18	49		
		AD	17.19	7.53		7	46		
	Face-Name	Young	38.31	7.08	0/48	22	46	103.48	p<.001
		Older	29.19	9.33		13	47		
		AD	7.92	6.79		9	26		
	Shape-Colour	Young	30.38	1.49	0/36	27	32	36.94	p<.001
		Older	29.57	1.87		26	32		
		AD	21.34	6.85		11	32		

Note: SD = Standard deviation; AD = Alzheimer's disease; KAT=The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates.



Note: AD = Alzheimer's disease; KAT = The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates

Figure 4.13. Mean standardised scores by task and group. Standardised mean scores of the older group corresponds to the zero or reference. The x-axis displays the groups and the y-axis displays the means. Error bars represent one standard deviation.

4.3.1. Normative data

In order to provide further description of the samples, age-related scaled scores (mean=10, standard deviation=3) were calculated using the normative data provided by the WMS manual for the Design and VPA tests. There is an Older Adult Battery for the WMS for adults above the age of 65. However, it does not include the Design test and has an easier version of the VPA test. For the present study, the Design and VPA tests from the standard battery were used. The manual only provides normative data for the standard version of the battery up to the

age of 69. Some of the participants in the Older and AD groups were older than this. The age-related scaled scores for these participants had to be calculated using the 65-69 normative age group, and so the means reported here may be underestimate. For other participants, their actual age was used to select the appropriate normative age group and obtain the age-related scaled score.

Table 4.4.1. shows the means, standard deviations and ranges for each group. One of the participants in the AD group was an outlier on both tasks, and so these values were also calculated with this participant removed from the sample. As can be seen from the table, the Young and Old group were above average in both tests, and the AD well below. The WMS manual also provides data from a sample of 50 participants (mean age = 72.8) diagnosed with MCI for the Design and VPA tests. Some of them completed the Older Adult battery and some the standard battery. Data from a sample of 48 participants (mean age= 78.5) diagnosed 'with "probable dementia of the Alzheimer's type- mild severity" are also provided for the VPA test only. The AD group in the current study scored between the MCI and mild severity dementia samples on the VPA test and somewhat worse on Design than the MCI sample, indicating that the present study was generally in the milder range of the disease: Design Means- current sample= 4.44; MCI sample = 7.6.; VPA means-current sample=6.48; MCI sample= 8.9, mild AD sample= 5.2.

Table 4.4.1. Age-related scores for the three groups on the WMS tasks.

Group	Binding task	Mean	Standard deviation	Range
Young	Design	13.38	2.28	9-17
	Verbal Paired Associates	13.38	2.21	10-19
Old	Design	13.15	2.44	8-18
	Verbal Paired Associates	11.35	2.30	7-16
AD (N=26)	Design	4.88	3.63	1-16
	Verbal Paired Associates	6.81	2.30	4-15
AD (N=25; outlier removed)	Design	4.44	2.89	1-11
	Verbal Paired Associates	6.48	1.61	4-10

4.3.2. Hypothesis 1: Alzheimer's disease group will perform worse than Old group on binding tasks

The first hypothesis is that participants with AD will show significantly poorer performance on binding tests than older healthy participants, and this will be the case even when differences in other aspects of memory, attention and other cognitive processes that contribute to task performance are controlled for. The literature review provided evidence that people with AD do poorly on binding tests, but there is little evidence about whether this poor performance is due to differences in the binding process, or differences in other cognitive processes that contribute to performance on the task. To test this hypothesis, for each binding task a one-way ANOVA was carried out, with group (Old vs. AD) as the factor. This analysis was then repeated but entering the covariates (estimated IQ, PRM, SWM and SRM) as well.

Table 4.5 shows the results of the ANOVAs for each binding task with and without the covariates. Without the covariates, the AD group scores were significantly lower than the Old group on all of the tasks. However, when the covariates were entered, there were significant differences between the groups only on PAL, VPA and Face-Name (alpha = .01).

Table 4.5. Binding tasks with and without covariates: Old versus Alzheimer's disease

Binding type	Binding task	Without covariates		With covariates	
		F	p-value	F	p-value
Spatial	KAT	18.13	<.001	0.54	.467
	Design	46.69	<.001	5.69	.021
	PAL	66.21	<.001	9.69	.003
Non-spatial	VPA	72.90	<.001	17.76	<.001
	Shape-Colour	34.83	<.001	5.44	.024
	Face-Name	147.59	<.001	52.92	<.001

Note: KAT=The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates.

As another check on whether the differences in performance were due to binding rather other cognitive processes, a further analysis used percentage scores derived from three of the tests (Face-Name, Design and KAT). The other tasks did not provide data that could be used in the required way. For KAT and Design, the total binding score was divided by the total number of objects remembered and multiplied by 100. This provided a score that represented the percentage of objects correctly recognised that were also put in the correct place. Expressing the correct memory of where the object went as a percentage of the number of objects correctly remembered provided some degree of control over other cognitive processes that contributed to correctly remembering the object. To calculate the percentage in the Face-Name task, the delayed cued name recall (CRN30) and delayed cued occupation recall (CRO30) were used. In CRN30 and CRO30, participants provided the names and occupations of each face shown, after

the 30 minutes delay. The following calculation was carried out: ((CRN30 + CRO30) / number of items where face and name were recognised on the multiple-choice task + number of items where face and occupation were recognised on the multiple-choice task)) x 100. It was intended that this would provide some control over the other cognitive processes that contributed to correctly remembering the face, name and occupation individually. For each percentage score, a one-way ANOVA was carried out, with group (Old vs.AD) as the factor. There was a significant difference on all three tasks: KAT; $F = 11.85$; $p=.001$; Design; $F = 40.74$; $p<.001$; Face-Name; $F = 65.65$; $p<.001$.

4.3.3. Hypothesis 2: Spatial vs. non-spatial binding

The second hypothesis was that, relative to healthy older participants, participants with AD will show greater impairment on spatial binding tasks compared to non-spatial ones. To test this hypothesis, the mean of the three spatial and the mean of the three non-spatial scores were calculated. A mixed repeated measures ANOVA was then carried out, with test (spatial vs. non-spatial) as the repeated measure and group (Old vs. AD) as the between-groups factor. This analysis was then repeated with the covariates included (estimated IQ, PRM, SWM and SRM). Because of the psychometric difficulties with the Shape-Colour task, these analyses were also repeated using a mean for the non-spatial based on VPA and Face-Name only.

The mean standard scores for each task and the overall mean for the spatial and non-spatial tasks are shown in Table 4.6. Contrary to the hypothesis, the mean standard score for AD group on the non-spatial tests showed a greater impairment relative to the Old group than the mean on the spatial tests. In the initial ANOVA, there was a significant interaction effect suggesting that there was significantly greater impairment on the non-spatial tasks ($F=26.67$; $p<.001$). The interaction effect remained significant when the covariates were entered into the analysis ($F=14.50$; $p<.001$). The same pattern of results was observed when the mean excluding

Shape-Colour was used. The interaction effect was significant both with (F=15.08; p<.001) and without the covariates (F=8.67; p=.005).

Table 4.6. Binding scores analyses: Old and Alzheimer's disease

Binding type	Binding task	N	Mean	SD
Spatial	KAT	26	-1.18	0.89
	Design	26	-1.81	0.85
	PAL	26	-3.07	1.64
	Overall Mean		**-2.02**	**1.00**
Non-spatial	VPA	26	-1.97	0.62
	Shape-Colour	26	-4.38	3.65
	Face-Name	26	-3.61	1.14
	Overall Mean		**-3.32**	**1.34**
	Overall Mean excluding shape-colour		**-2.79**	**0.75**

Mean for Older group was zero for all tasks. Note: SD= Standard deviation; KAT = The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates

4.3.4. Hypothesis 3: Binding tasks discriminate between Alzheimer's disease and Old groups better than control measures

The third hypothesis was that the six binding tests will show greater sensitivity and specificity in relation to discriminating between AD participants and the healthy older participants than the other tests of memory and attention used in the study. Sensitivity and specificity are typically calculated with reference to a specific cut-off score on a test. The sensitivity of the test refers to the percentage of people with AD who score below this cut-off; and specificity refers to the percentage of people who do not have AD who score above the cut-off. However, for the purposes of simplifying the analysis, a different approach was taken here. A test is likely to have high sensitivity and specificity if the distribution of scores of a sample with AD is clearly separated from (i.e. little or no overlap with) the distribution of scores of the comparison sample. To examine this, a series of paired-sample t-tests was used, comparing the standard scores obtained by the AD group on each binding test with the standard scores of each

CANTAB control test (SRM, PRM and SWW). The mean standard score gives a measure of the degree of separation between the distributions of the Old group and the AD group. If the mean standard score on a binding test is significantly lower than the mean on a control test, then the degree of separation from the distribution of the Old group scores is greater, and the test is likely to have greater sensitivity and specificity than the control test (at least in reference to healthy older people). A second descriptive method used to compare the distributions of the binding tests and the control tests was to calculate the percentage overlap between the Old and AD group on each task. The lowest-scoring participant from the Old group and the highest-scoring participant from the AD group on each task were identified. The percentage of the combined AD and Old sample who scored between these two points (inclusive) was then calculated. A higher percentage indicates more of an overlap between the two distributions, and therefore poorer specificity.

The mean standard scores of the AD group on the binding tasks are shown in Table 4.7. The results of the t-tests in which each binding task is compared with each control variable are shown in Appendix 4n. Only the Face-Name total was significantly lower than all three of the control tests (alpha = .01); PAL and Shape-Colour were significantly lower than the SRM and SWM, but not the PRM; and VPA was significantly lower only than the SWM. The KAT and Design were not significantly lower than any of the control tasks and were, in fact, significantly higher than the PRM.

Table 4.7. The mean standard scores of the AD group on the binding tasks and percentage overlap

Type of tasks	Tasks	N	Mean	SD	Percentage overlap including outlier	Percentage overlap excluding outlier
Binding tasks	KAT	26	-1.18	0.89	90%	91%
	Design	26	-1.81	0.85	60%	48%
	PAL	26	-3.07	1.64	35%	33%
	VPA	26	-1.97	0.62	65%	31%
	Shape-Colour	26	-4.38	3.65	65%	65%
	Face-Name	26	-3.61	1.14	33%	17%
Control tasks	SRM	26	-1.45	1.22	89%	75%
	PRM	26	-2.63	1.56	73%	73%
	SWM	26	-1.28	1.19	77%	76%

Note: KAT=The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates.

Table 4.7 also shows the percentage overlap of the Old and AD groups on each test. Two figures are shown, one that includes the participant in the AD group who was the highest scorer on most of the tests and an outlier on Design and VPA. The raw scores of participants were used in calculating the overlap – i.e. the outlier scores on Design and VPA were not adjusted. Generally, with the exception of the KAT, the binding tests did show less overlap than the control tests, and the Face-Name showed the least overlap.

4.3.5. Exploratory aim 1: Which binding tasks better discriminate between the Old and Alzheimer's disease groups?

This aim was explored through a series of paired-sample t-tests in which the standard score of each binding test was compared with the standard score of every other binding test. The rationale is the same as that used in testing Hypothesis 3: If a binding task has a significantly higher negative standard score than another, then it is likely to be a more sensitive and specific

diagnostic test. The means for each test is shown in Table 4.7 and the results of the t-tests are shown in Appendix 4o. Face-Name, PAL and Shape-Colour had the highest means (i.e. showing the greatest difference from the Old reference group) and did not differ significantly from one another. They were significantly higher than VPA and Design, which did not differ significantly, but both were significantly higher than KAT. This can be summarised as follows:

Face-Name = PAL= Shape-Colour > VPA = Design > KAT

This analysis suggests that Face-Name, PAL and Shape-Colour offer more promise as diagnostic tests. Preference for Face-Name and PAL is supported by the information about the percentage overlap between the Old and AD groups on each test (Table 4.9) in which these two tests showed the least overlap. Shape-Colour did less well in terms of the percentage overlap.

4.3.6. Exploratory aim 2: Does Alzheimer's disease lead to accelerated decline on binding tasks relative to normal ageing?

The aim was to compare the rate of decline in normal ageing (measured by comparing the performance of healthy older and younger adults) with the rate of decline in AD (measured by comparing the performance of healthy older adults and people with AD). This was done for each of the six binding tests individually, and for the means of the spatial and non-spatial binding tests. Initially, the analysis for Hypothesis 1 was repeated, but the Young and Old groups were compared rather than the Old and AD groups. This was to establish whether normal ageing affected performance on all of the binding tasks. The Shape-Colour task was excluded from this analysis because of the ceiling effects both groups showed on the task.

Table 4.8. Binding scores analyses: Young and Old

Binding type	Binding task	N	Mean	SD
Spatial	KAT	26	1.87	0.61
	Design	26	1.67	0.93
	PAL	26	1.27	0.84
	Overall Mean		**1.60**	**0.62**
Non-spatial	VPA	26	1.86	0.49
	Shape-colour	26	0.43	0.80
	Face-name	26	1.18	0.44
	Overall Mean		**1.52**	**0.38**

Means for older group are zero on all tests. Note: SD= Standard deviation; KAT = The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates.

Table 4.9. Binding scores with and without the covariates: Old versus Young

Binding type	Binding task	Without covariates		With covariates	
		F	p-value	F	p-value
Spatial	**KAT**	65.81	<.001	20.49	<.001
	Design	36.69	<.001	16.81	<.001
	PAL	27.72	<.001	10.70	.002
Non-spatial	**VPA**	72.59	<.001	36.54	<.001
	Face-Name	30.19	<.001	16.00	<.001

Note: KAT=The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates.

Table 4.8 shows the mean standard scores for the Young group on each binding task, and Table 4.9 shows the results of the one-way ANOVA (Old vs. Young as the factor) with and without the covariates (estimated IQ, SRM, PRM and SWM). All tests showed significant differences between groups, suggesting that, across a range of tasks, binding performance and the binding process (indicated by the results with the covariates taken into account) decline with normal ageing.

To explore whether the rate of decline on binding tasks accelerates with Alzheimer's disease (i.e. whether there is a larger difference between Old and AD than there is between Young and Old), the valence of the standard scores for each participant in the AD group was

reversed (i.e. a negative value was changed to a positive value, and any positive values to a negative value) in order to allow a comparison between the Young and AD group in terms of their difference from the older group. (If the valences remained the same, the Young group would obviously show a larger difference because the means of the AD group are all negative values.) When the valence of each score is altered, these negative means become positive means but the numerical value of the mean remains the same (e.g. a mean of -.3.07 for PAL becomes +3.07). A series of independent sample t-tests using these adjusted standard scores was then used to compare the Young and AD group on each test, except the Shape-Colour test which showed severe ceiling effects in the Young group as well as a large variance in the AD group. The results are shown in Table 4.10. The PAL and Face-Name tests showed a significantly greater rate of decline in the AD group, and the KAT showed a significantly lower rate of decline in this group.

Table 4.10.: Rate of decline on binding tasks: Young versus Alzheimer's disease

Binding type	Binding task	Mean Young	Adjusted Mean AD	t-value	p-value
Spatial binding	**KAT**	1.87	1.18	3.24	.002
	Design	1.67	1.81	0.58	.566
	PAL	1.27	3.07	4.96	<.001
Non-spatial binding	**VPA**	1.86	1.97	.67	.507
	Face-Name	1.18	3.61	10.16	<.001
Mean Spatial		1.60	2.02	1.82	.077
Mean non-spatial		1.52	2.79	7.87	<.001

Note: KAT=The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates.

Table 4.10 also shows the means of the spatial and non-spatial tests (excluding the Shape-Colour test). The rate of decline in the non-spatial tests was significantly greater, but there was no significant difference on the spatial tests. Using a paired-samples t-test, the means for the spatial and non-spatial tests were compared for the Young group. The difference was not significant (t=0.62; p=.540).

In summary, table 4.11 shows how each binding task matches some of the hypothesis and exploratory aims.

Table 4.11. Binding tasks and hypothesis and exploratory aims

Hypothesis and exploratory aims	Binding tasks					
	Spatial binding			Non-spatial binding		
	KAT	Design	PAL	VPA	Shape-Colour	Face-Name
Hypothesis 1: Evidence that binding process contributes significantly to task performance	N	N	Y	Y	N	Y
Hypothesis 3: Better discriminator of Old and AD group than control cognitive tests	N	N	Y	Y	__	Y
Exploratory aim 1: Better discriminator of Old and AD groups than other binding tests (ranked from 1 (best) to 3 (worst)).	3	2	1	2	1	1
Exploratory aim 2: Evidence of greater decline in AD compared to impact of normal ageing	N	N	Y	N	N	Y

Note: AD: Alzheimer's disease; KAT=The Kitchen Arrangement Test; PAL= Paired Associate Learning; VPA= Verbal Paired Associates; Y: yes; N: no.

5. Discussion

Hypothesis 1: Participants with Alzheimer's disease will show significantly poorer performance on binding tests than older healthy participants, and this will be the case even when differences in other aspects of memory, attention and other cognitive processes that contribute to task performance are controlled for.

The findings of the present study were in line with reports in the literature, showing that people with AD exhibit impaired performance compared with healthy older people on a variety of binding tasks, such as pairs of unrelated words (Gallo et al., 2004), shape-colour (Parra et al., 2010a) and object-location (Swainson et al., 2001). Performance of the AD group was significantly worse than a demographically-matched group of healthy older people on all six binding tasks that were used. However, the literature review suggested that there is little evidence about whether this poor performance is due to differences in the binding process, or differences in other cognitive processes that contribute to performance on binding tasks. This is important to establish in deciding whether binding tasks are worth investigation as diagnostic tests for the early stages of AD.

The results of attempts to control for these other cognitive processes were mixed. When percentage scores were used for three tests (Face-Name, Design and KAT), the AD group continued to show significant impairment in performance. However, when the covariates were

entered into the analysis of the binding scores, a significant impairment was only evident on PAL, VPA and Face-Name and not on the other three tests. Overall, the study provides some evidence that binding processes can be impaired by AD, but suggests that, at least on some binding tasks, other impairments may be a more important influence on task performance. As measures of the binding process itself, these tasks (KAT, Design and Shape-Colour) may be less useful.

Hypothesis 2: Relative to healthy older participants, participants with Alzheimer's disease will show greater impairment on spatial binding tasks compared to non-spatial ones.

It has often been suggested in previous literature that the patterns of impairment in AD, such as entorhinal and hippocampal damage, are strongly associated with the particular deficits in spatial memory (Wood & Chan, 2015). Generally, people with AD do poorly on tests of spatial memory in general (not just spatial binding) (e.g. Adelstein et al., 1992; Sahakian et al., 1988). Subjective complaints of memory difficulties in AD often include spatially-related ones, such as getting lost (Hanaki et al., 2011). On the basis of this, it has been suggested that spatial binding may be particularly vulnerable to AD compared to non-spatial binding (Hanaki et al., 2011). However, the literature review suggested that there is little evidence from neuropsychological studies to support the claim. The present study failed to support it. Contrary to the hypothesis, the non-spatial binding tasks showed significantly greater impairment, even when the covariates were entered into the analysis. This does not necessarily mean that the non-spatial binding process is particularly impaired by AD. It was evident that the binding tasks used in this study differed in other dimensions, not just in terms of whether they involved spatial or non-spatial binding. It could be that performance on the non-spatial binding tasks was more

impaired because they differed from the spatial tasks on these other dimensions. For example, the KAT task involves a relatively limited number of kitchen items and a relatively limited number of cupboards that the items can be placed in, but the Face-name task involves a much larger pool of possible faces, names and occupations. Perhaps the reason why the AD group found the latter more difficult is this difference in the pool of potential stimuli, rather than whether the bindings are spatial or non-spatial.

Although the results do not necessarily mean that non-spatial binding is more impaired by AD, they do suggest that the spatial / non-spatial dimension may be less important in determining the performance of people with AD than has been suggested by previous authors. If it is the critical dimension, one would not have expected the AD group to show the greatest impairment on the non-spatial tasks.

Hypothesis 3: The binding tasks will show greater sensitivity and specificity in discriminating between Alzheimer's disease participants and the healthy older participants than the other tests of memory and attention used in the study.

If binding is a process that is particularly vulnerable to the early stages of AD, then one would expect binding performance to show greater impairment than tests of other memory and attention processes, and a satisfactory test of binding should show a distribution of scores that shows a greater degree of separation from the distribution of healthy older people than tests of these other memory and attention processes (in which case they should show greater sensitivity and specificity). The results of the test of this hypothesis were again mixed, depending on which binding task was being considered. Only the Face-Name total showed a significantly greater impairment than all three of the control tests (alpha = .01); the KAT and Design did not show significantly greater impairment than any of the control tasks and, in fact, showed

significantly less impairment than the PRM. In terms of the percentage overlap between the distribution of the Old and the AD scores, again Face-Name performed best and the KAT worst.

Exploratory aim 1: To compare the six binding tests in terms of their ability to discriminate between Alzheimer's disease participants and the healthy older participants

Tests that show a larger difference between the AD group and the Old group in terms of their mean and in terms of the percentage overlap between the two samples are likely to be more useful as diagnostic tests because they are likely to have greater specificity and sensitivity. The mean of each binding test was compared with every other binding test mean to see whether they were at a significantly greater distance from the mean of the Old group on that test. The outcome was summarised as follows:

Face-Name = PAL= Shape-Colour > VPA = Design > KAT

This suggests that Face-Name, PAL and Shape-Colour offer more promise as diagnostic tests. Preference for Face-Name and PAL was also supported by the information about the percentage overlap between the Old and AD groups on each test: These two tests showed the least overlap.

Exploratory aim 2: Does Alzheimer's disease lead to accelerated decline on binding tasks relative to normal ageing?

Consistent with previous literature (Old & Naveh-Benjamin, 2008; Kessels & De Haan, 2003; Heo et al., 2010; Sapkota, Linde & Pardhan, 2018), the Old group performed significantly worse than the Young group across a wide range of binding tasks in this study. Performance remained significantly worse even when the influence of other cognitive contributors to task

performance was controlled (i.e. the covariates were entered into the analysis). This suggests that normal ageing has a substantial impact on binding processes.

Because binding is affected by normal ageing, it is useful to compare the impact of AD and normal ageing on binding in terms of their size. If a binding task shows a greater impact from AD, this task has more potential as a diagnostic indicator because it is likely to show greater specificity and sensitivity in terms of discriminating people with AD from healthy older people. Such comparisons are also useful from a theory perspective, contributing to a better understanding of how binding processes may deteriorate with normal ageing and AD.

Results were again mixed across the binding tests. Face-Name and PAL showed a significantly greater impact from AD than from normal ageing, but the KAT showed significantly less of an impact. In terms of spatial and non-spatial binding, the Old group showed equal losses on the mean of the spatial and non-spatial tasks, whereas the AD group showed a significantly larger impact on the non-spatial tasks. Hanaki et al. (2011) similarly found an equal impairment for a spatial and non-spatial task in normal ageing. Taken together, these findings might suggest that normal ageing affects spatial and non-spatial binding equally, but AD has more of an impact on non-spatial binding. However, as we noted when discussing Hypothesis 2, other dimensions may explain the difference between tasks rather than the spatial one.

5.1. Which binding tests show greater potential as diagnostic tests?

Overall the results suggest that binding tests do have promise as diagnostic tests. People with AD performed significantly worse than a matched sample of healthy older adults, and the analysis suggested that AD affects the binding process. However, some tests offered more promise than others in terms of their usefulness as diagnostic tests. Table 4.10 summarises how

well each test performed on the criteria used in the study. Face-Name and PAL were clearly the best performers, and KAT and Design the worst. Additionally, it should be noted that Shape-Colour showed some unsatisfactory psychometric properties. Ceiling effects in the Old group (and the consequent small variance) meant that the AD group showed large standard score differences for quite small differences in raw scores.

Why did the Face-Name and PAL tests outperform the others? What distinguishes them? One involves spatial and the other non-spatial binding, and, as suggested earlier, this may not be the most important dimension to consider. At least two other dimensions varied across the different tasks. One was the familiarity of the stimuli. For example, the KAT used familiar kitchen items, whereas Design used unfamiliar shapes. Another was the number of potential items that had to be drawn from when binding the stimuli. For example, in terms of location on the KAT, there were only 16 doors to choose from; but in terms of name for the Face-Name test, the number of personal names that the participant is familiar with is very large. Perhaps the KAT did not do well as a potential diagnostic test because of its use of familiar stimuli and the limited choice (16 doors and a relatively limited number of items related to the kitchen). By contrast, the Face-Name may have performed well because of its use of unfamiliar stimuli (the faces) and the very large choice of alternative names. There are very likely other dimensions that need to be considered. For example, PAL and Design appear to be similar tasks – both involve binding unfamiliar stimuli to a limited number of locations. One difference is that, in Design, the item-location stimuli are all shown at the same time and then the participant is presented with the items and distracters and asked to put the correct items in the correct location. In PAL the items are shown one at a time before the first item is displayed in the centre and the participant has to remember which location it was in. Perhaps having to keep the binding information available for longer is what enabled PAL to perform better than Design on the

criteria shown in Table 4.10. Another issue is some tasks may involve conjunctive binding (as opposed to relational binding) (see Chapter 2). In the Shape-Colour test, conjunctive binding may have been involved, which seems to be less dependable on the hippocampus (Baddeley, Allen & Vargha-Khadem, 2010; Mayes, Montaldi & Migo, 2007) and therefore may be less likely to show deterioration in AD. All of these suggestions about differences between binding tasks clearly need to be researched further.

These considerations highlight the problems in researching the issue of whether spatial or non-spatial binding is preferentially affected by normal ageing or by AD. Tasks differ in respect of the non-binding abilities they involve and, even considering binding abilities alone, tasks may involve different abilities other than just whether the binding is spatial or non-spatial (i.e. conjunctive vs. relational, short-term vs. long term) and make different demands on these other abilities. Consequently, it may be difficult to devise two tasks that differ only in respect of whether the binding is spatial or non-spatial.

5.2. Limitations of the study

Although this study provides new insights into binding abilities in ageing and AD, there are number of limitations. Firstly, in the case of the Old and Young group, the two groups were not matched on key demographic variables. Previous research has reported that gender, for example, has an impact on binding performance, with females outperforming males on associative memory, such as on object-location memory (Voyer et al., 2007). Although no association was found in the current study between demographic variables and binding performance (apart from a history of further education and Face-Name total in the Old group), and therefore demographic variables were not entered as covariates, the group sizes used to explore these associations were small and unbalanced.

Recruitment of the AD group proved challenging, and another source of participants had to be used. Participants from the first source were all diagnosed as having Alzheimer's or probable Alzheimer's by a specialist dementia assessment service, and an ACE-III score was available to assess how severe their cognitive difficulties were. The source of the diagnosis in participants from the JDR was not clear, and may have been less accurate. Information about their current level of general cognitive functioning was also more variable. Diagnosis of AD is a particular problem because there are no biological tests in regular current use for its diagnosis. Diagnosis is often a diagnosis by default: The person has dementia and there is no evidence that it is caused by other forms of the disease.

Difficulties with recruitment of the AD group also gave rise to another limitation. The aim was to recruit those within the early stages of the dementia stage of AD – i.e. when the person was showing mild/moderate cognitive difficulties that were affecting their ability to carry out activities of daily living. For those recruited from the NHS Memory Clinic, they were required to have scored at least 88 on their most recent Addenbrooke's Cognitive Examination (ACE-III), as suggested as a cut-off for mild dementia in Bruno and Vignaga (2019). However, the time since their most recent ACE-III varied, and some could have experienced significant deterioration in the intervening period. The same criterion was applied to those recruited from the JDR service, but not all the profiles contained ACE-III scores and it was necessary to rely on less accurate estimations of the severity of their dementia based on scores from other cognitive tests and, again, the interval between participation and the date of those tests varied. It should be noted that capacity to consent was assessed for all participants, and they were all judged capable of giving informed consent. However, these concerns about the accuracy of claiming that the participants were all in the stage of mild dementia do mean that one should be cautious about generalizing the findings of the present study. One would expect that, as the disease develops

and the cognitive impairment worsens, there would be an increase in the ability of binding tests and, indeed, any other test of memory to discriminate between those who have AD and healthy older people. So the possible inclusion of people in the present sample of people who had progressed beyond the 'mild' stage of dementia may have exaggerated the ability of the binding tests to discriminate during the mild stage.

Finding tasks that could assess the abilities of the whole range of participants was a challenge. There were some skewed distributions, due to the Young group scoring very highly or the AD group scoring very low. One participant in the AD group scored consistently highly on the tests and was an outlier on some of them. This again affected the distribution of scores. There were particular problems created by severe ceiling effects on the Shape-Colour task. For the subtests from the WMS-IV, the Adult battery was used instead of the Older Adult battery. This was because the Design test is not available on the Older Adult battery.

Finally, the tasks differed not only in terms of whether they involved spatial or non-spatial binding, but also in terms of the extent to which they involved other cognitive abilities such as executive function, attention and working memory. Binding tasks involve a range of cognitive processes (other than just the binding itself) that could affect performance on binding tasks. For example, Postma et al. (2008) provide a detailed model of the specific cognitive processes involved in an object-location binding task. The person will engage in:

- Processes related to the object: This includes generic object recognition, involving the access of representations about the physical and semantic properties of the object. The person must also store information about its occurrence, which may be in working memory, short-term store or long-term store depending on the parameters of the experimental task.

- Spatial-location processing: Postma et al. distinguish two methods of spatial-location processing. One provides a fine-grained code offering more precision about the location of the object in relation to oneself; the other provides a coarser more global categorization of the space around (e.g. the object is in the top right hand corner). The latter may mirror something provided in the external world (e.g. the grid provided in some spatial neuropsychological tasks) or be imposed on the external world by the participant. A further aspect of spatial processing is categorising an object by reference to where it is in relation to other objects.

- Binding of the object and the location

As well as these more task-specific processes, other more generic processes are involved, such as paying proper attention to the task. Executive processes may also be involved to a greater or lesser extent, depending on the participant. For example, some participants may develop a strategy to assist them in remembering where objects are, such as trying to remember where objects in a grid by naming them in order starting at the top left.

Measures of general cognitive abilities were taken and entered as covariates in the analyses. However, these would not have provided full control over all of the differences in general cognitive abilities that may have contributed to binding task performance. As is clear from the complexity of the model offered by Postma et al., it would be impossible to control for every type of cognitive process that may be involved in a range of binding tasks.

CHAPTER 5

GENERAL DISCUSSION

1.Introduction

As current treatments for AD and many of the newer potential treatments aim to stop progress of the disease rather than cure it, the identification of AD as soon as possible is crucial for the effectiveness of the available treatments. There are no tests currently available in routine clinical practice for biological markers of AD. So there has been much interest in identifying neuropsychological tests that may be sensitive to cognitive impairments in the early stages of the disease and in those at risk of developing AD. More recently, tests of binding / associative learning have attracted some interest as potential indicators of the early stages of AD. This interest is consistent with some of the neuroanatomical evidence about AD that suggests that areas involved in binding may be particularly affected by the disease, specifically the hippocampus. Additionally, it has been suggested that spatial binding may be particularly affected because of the role that spatial deficits appear to play in the beginning stages of AD.

The focus of this thesis has been on binding in AD, and specifically on whether, and which, neuropsychological tests of binding may be effective in diagnosing early AD. In this chapter, a summary of the main chapters is presented with a focus on the key findings, followed by some considerations about future research and implications for clinical practice.

2. Overview of the findings

2.1. Chapter 3: Literature review

A systematic review was conducted to investigate the performance of people with AD and those at high risk of developing AD on binding tests. The broader aim was to establish

whether binding tests may be a promising way forward in developing better methods for the early detection and diagnosis of AD. The main conclusions from the review were as follows:

- People with AD and those at higher risk to develop AD do perform significantly poorer than healthy older adults on a range of binding tests.
- However, it was not entirely clear that it is impairment in the binding process that explains poor performance on these tests. Most of the studies failed to provide adequate control over other cognitive processes that may have affected binding performance. In many studies, the only control was matching the samples on demographic variables. More effective control was provided by studies in which performance on the binding aspect of the task was compared with memory for the individual items. Even in these studies, however, there were issues – such as not providing a statistical comparison of the difference on memory for individual items with the difference on binding. Despite many of the studies including extensive batteries of neuropsychological tests, scores on these tests were not entered as covariates in the analysis of binding scores.
- Most of the studies that included other non-binding tests also failed to explore the issue of whether binding tests are better than non-binding tests at identifying those with AD. Only four studies addressed this issue. Although all four reported that the binding test was more effective in some way, in most cases the conclusion was based on a description of findings rather than a statistical analysis.
- Only three papers were found that addressed the issue of whether binding impairment is specific to AD compared to other dementias. Although all three provided evidence that people with other types of dementia do not show binding

impairments to the same degree, there were issues about the low sample sizes in these studies.

- Although some have claimed that spatial binding is particularly vulnerable to AD, there was little evidence of this from the studies that were reviewed. Only one paper directly compared spatial and non-spatial binding tests in AD (Hanaki et al., 2011), and another three compared them in those at risk of developing AD. No consistent pattern of results emerged. Three studies reported that spatial was affected more than non-spatial, but the fourth reported that non-spatial was more affected.
- More generally, very few papers compared different kinds of binding task. If the overall aim is to identify tests that are more effective in the early detection of AD, direct comparisons of the diagnostic effectiveness of binding tests are needed.
- There were also few studies that have compared the impact of normal ageing on binding with the impact of AD. A test that shows an accelerated rate of decline with AD may be more promising as a diagnostic test.

2.2. Chapter 4: Spatial and non-spatial binding in younger adults, older adults and people with Alzheimer's disease.

The empirical study aimed to overcome some of the limitations encountered in the review. The performance of an AD group, a healthy old group and a healthy young group was compared on a range of binding tasks. To control for the impact of other non-binding cognitive processes on binding performance, scores on other cognitive tests were included as covariates in the statistical analysis. Some of the tests also provided another method of control involving the use of a percentage score that took account of differences between groups in the memory for

individual items. The study compared three spatial and three non-spatial binding tasks, in order to provide a more effective test of the claim that spatial binding is more vulnerable to AD. The effectiveness of each individual test in discriminating between the AD and healthy older group was also examined, as was their effectiveness in comparison to the non-binding tests that were used. Finally, the study included a young healthy group to allow a comparison of the effects of normal ageing and of AD on binding performance.

The main results from the study were as follows:

- Performance on all six binding tasks was significantly worse in the AD group compared to the healthy older group. For the three tasks in which percentage scores could be used to control for memory of individual items (Face-Name, Design and KAT), performance continued to be significantly worse. However, when scores on non-binding tasks were entered as covariates, significantly worse performance was evident only on the PAL, VPA and Face-Name and not on the other three tests (KAT, Design and Shape-Colour). Overall, the study provides some evidence that binding processes can be impaired by AD, but suggests that, at least on some binding tasks, other impairments may be a more important influence on task performance. As measures of the binding process itself, these tasks may be less useful and therefore less useful for diagnostic purposes.
- There was no evidence that spatial binding is more vulnerable to AD than non-spatial binding. Indeed, the AD group performed significantly worse on the non-spatial tasks compared with spatial ones, even when the covariates were included in the analyses. We should not conclude from this that non-spatial binding is more vulnerable to AD since it was clear that the tasks differed in many other ways related to binding, and not just whether they measured spatial or non-spatial binding

- As expected, normal ageing also had an impact on binding performance. The healthy older group performed worse on all the binding tasks than the healthy younger group, even when the covariates were included in the analysis. Comparisons of the effect of normal ageing with the effect of AD were mixed. Face-Name and PAL showed a significantly greater impact from AD than from normal ageing, but the KAT showed significantly less of an impact. The healthy old group showed an equal impairment on spatial and non-spatial binding tasks, whereas the pattern of AD impairment showed a preference for non-spatial binding.
- The ability of the individual binding tests to discriminate those with AD from healthy older controls was compared with the ability of the control neuropsychological tests from the CANTAB. Again, there were differences in how well the binding tests performed. When comparing standard scores, only the Face-Name total was significantly lower than all three of the control tests. In contrast, the KAT and Design totals were not significantly lower than any of the control tasks and were, in fact, significantly higher than the PRM. In terms of the degree of overlap between the distribution of scores between the healthy older and AD groups, the Face-Name test showed the least overlap and the KAT showed the most overlap, showing more overlap even than the control tests.
- The ability of each binding test to discriminate the AD group from the healthy old group was also compared with the ability of every other binding test, with the following outcome: Face-Name = PAL = Shape-Colour > VPA = Design > KAT.
- These different analyses suggested that the Face-Name test and PAL may be the most promising tests for diagnosing early AD, whereas the KAT and Design showed less promise.

3. Directions for future research

This area of research still needs further exploration to develop a better understanding and offer support for the initial findings. In order to build a more robust evidence base about binding in AD, some recommendations for future research are suggested.

3.1 What aspects of binding are particularly vulnerable to Alzheimer's disease?

It is clear that binding tasks differ not only in the class of item being bound (object-location, face-name etc.) but also along various other dimensions, such as the familiarity of the items and the involvement of spatial vs. non-spatial information. It seems likely that at least some of these dimensions may influence the extent to which AD impairs task performance. The present study provided little evidence to support the idea that the spatiality of the information is relevant. However, the relevance of other dimensions needs to be explored. Future research needs to manipulate these dimensions in a systematic way, and to compare the impact on performance of those with AD. Knowing which dimensions are more affected by AD will provide the basis for selecting and designing more effective diagnostic tests.

Potential dimensions that could be explored include:

- Pre-attentional vs. attentional binding – i.e. the degree to which the binding depends on attentional processes

- Within- vs. between-domain binding – i.e. whether the binding involves different classes of item (e.g. object and place) or the same class (e.g. word pairs).
- Relational vs. conjunctive binding – i.e. whether the binding involves separate items (e.g. faces and names) or the binding of features of the same object (e.g. remembering the colour of different shapes)
- Familiar vs. unfamiliar items – i.e. whether the binding involves items that the person is familiar with (such as the kitchen items in the KAT) or is unfamiliar with (such as the faces in the Face-Name test).
- Meaningful vs. arbitrary – i.e. whether the items can be related readily to the person's previous experience even if they are unfamiliar (such as the faces in the Face-Name test) or are arbitrary and difficult to verbalise or relate to (e.g. the arbitrary shapes in the PAL test)
- The number of potential responses that can be given – for example, on the Face-Name test, the number of possible names that a participant is familiar with is very probably far greater than the number of possible occupations
- Memory load - i.e. how much binding information has to be stored during the task
- Length of time in memory – i.e. how long the information has to be stored before it is retrieved. This includes the issue of whether only a temporary binding is required (i.e. short-term memory) or associative learning requiring a relatively enduring representation is required (i.e. long-term memory).

Some of these dimensions may help explain the difference in diagnostic effectiveness between the different tests used in the present study. For example, in the Shape-Colour test, conjunctive binding may have been involved. It has been suggested that this is less dependent on the hippocampus (Baddeley, Allen & Vargha-Khadem, 2010; Mayes, Montaldi & Migo, 2007). Given that the hippocampus is the main region that appears to be affected in the early stages of

AD, this might explain why the Shape-Colour test performed less well than some of the other tests. The KAT task also did relatively poorly. This uses familiar items; the number of potential responses is restricted in terms of both the number of kitchen items that could have been used and the number of locations that were used. By contrast, the Face-Name may have performed well because of its use of unfamiliar stimuli (the faces) and the very large choice of alternative names. It is worth noting that the Face-Name score from the Face-Name test performs better in identifying AD than the Face-Occupation score from the same test (e.g. Rentz et al., 2011). One possible explanation of this is that the pool of names with which the participants are familiar with is much larger than the pool of occupations. Another possibility is that the Face-Occupation score is less effective because occupations can be more easily associated with previously stored semantic knowledge (Rentz et al., 2011). The potential importance of memory load and time in memory is suggested by a comparison between the PAL and Design tasks. These tasks appear to be similar – both involve binding unfamiliar and meaningless stimuli to a limited number of locations. One difference is that, in Design, the item-location stimuli are all shown at the same time and then the participant is presented with the items and distracters and asked to put the correct items in the correct location. In PAL the items are shown one at a time before the first item is displayed in the centre and the participant has to remember which location it was in. Perhaps having to keep the binding information available for longer is what enabled PAL to perform better than Design.

From a neuroscience perspective there are also reasons to expect that some of these dimensions will impact on binding performance in AD. Specifically, there may be some forms of binding in which the hippocampus may play less of a role, and therefore one would expect them to be less vulnerable to AD. It has been suggested that the hippocampus is less involved in short term memory (vs. LTM) binding (Parra et al., 2009 and 2015); within-domain (vs.

between-domain) binding (Mayes et al., 2007); and conjunctive (vs. relational) binding (Della Sala et al., 2012). Within-domain binding is likely to be represented by activity in closely adjacent and interacting neocortical neurons, and represented as one unit. Between-domain binding, on the other hand, may not be perceived or represented as one item, and may be represented by patterned activity in relatively distant and weakly connected neocortical neurons. It is suggested that the primary sensory areas in the neocortex process within-domain binding (such as word-word) and conjunctive binding (aspects of the same item, such as shape and colour), with the information then converging on the perirhinal areas of the medial temporal lobe to produce a unified representation (Mayes et al., 2007). On the other hand, between-domain bindings, such as object-location, appear to be processed in the associative areas of the neocortex before converging on the hippocampus (Mayes et al., 2007). In support of this, Vargha-Khadem et al. (1997), in a study with bilateral hippocampal pathology, reported that neuroimaging revealed that hippocampal lesions were associated with impaired between-domain binding, such as voice-face and object-location. In contrast, no significant impairment was found on within-domain associations.

There is evidence, though, to suggest that the picture may be more complicated. Some studies have reported that AD participants do not benefit from familiarity when tested for pairs of words (Gallo et al., 2004; Lowndes et al., 2008). In Gallo et al.'s (2004) study, patients with AD and healthy controls were asked to distinguish between same pairs (studied) and new pairs of words that contained either rearranged studied words or non-studied words. The findings showed that performance was affected by familiarity only in the case of the healthy controls and the AD group did not benefit from this manipulation, suggesting that familiarity does not contribute to a better performance in mild AD. Instead, the AD group showed increased false alarms when rearranging pairs of words. Similarly, Lowndes et al. (2008) found that only a healthy older

control group benefitted from the use of familiar concrete words, whereas the AD group performed equally poorly on unfamiliar concrete and abstract unfamiliar stimuli.

3.2. Neuroimaging

Another direction for future research would be greater use of neuroimaging to support the data from neuropsychological tests about binding. Only four of the papers in the systematic review reported neuroimaging data (Hampstead et al., 2018; Liang et al., 2016; Nanda et al., 2019; Rentz et al., 2011). These data can support conclusions about the impact of AD on binding. For example, in the study by Liang et al. (2016) there was a significant correlation between hippocampal volume and object-location binding in symptomatic and asymptomatic carriers of the fAD mutation, but not with object or location memory. This gives greater confidence in the conclusion that AD is associated with binding impairments compared to a study which just reported on the difference in neuropsychological test performance between those with the fAD mutation and controls.

3.3. Binding in those at risk of Alzheimer's disease

Given the value of detecting AD as early as possible in order to ensure that treatments are as effective as possible, it is important to study binding in the pre-dementia stages of dementia – that is, at the pre-clinical stage (when there are biological changes but no symptoms) and at the MCI stage (when there are symptoms of cognitive decline but this is not sufficient to have any major impact on activities of daily living) (Brent, 2019). The most effective diagnostic neuropsychological tests will be those that can detect impairments in these early stages and so the diagnostic effectiveness of binding tests needs to be evaluated at these stages. In terms of the pre-clinical stage, the person may have no subjective experience of abnormal cognitive decline (i.e. no symptoms of cognitive decline) but the biological changes may already be having a more

subtle impact on cognitive abilities (i.e. there are signs of cognitive decline). A study to evaluate the effectiveness of binding tests at this stage would need to identify a sample who have begun to develop the biological changes associated with the disease but who have no symptoms of cognitive decline. Given the expense and risk associated with current biomarker tests for AD, such a study would present considerable practical challenges. One option to address these challenges would be draw the sample from those at relatively high risk of developing AD (e.g. because of a family history). The study would also need to be longitudinal to evaluate whether all participants did go on to develop dementia, since those showing biological markers who did not develop dementia may confound the accuracy of the results. In terms of the MCI stage, a study is required that compares the diagnostic accuracy of binding tests in terms of discriminating those with and without MCI. Again, because not all those with MCI will go on to develop dementia of the Alzheimer type, it would be important that such a study was longitudinal so that diagnostic accuracy could be evaluated using only those participants who eventually did develop dementia of the Alzheimer type.

3.4. Discriminating Alzheimer's disease from other dementias

Another major issue that future research needs to address is how good binding tests are in discriminating AD from other forms of dementia. To be a good diagnostic test for early AD, the test needs to have good sensitivity and specificity when comparing AD and other forms of dementia. Future research should look at the better performing tests in the present study, such as Face-Name and PAL, to see how well they perform in discriminating AD from other kinds of dementia.

3.5. Other issues

If the aim is to identify or develop the most effective diagnostic tests for early AD, the effectiveness of binding tests must be compared with the effectiveness of non-binding tests. Only four of the papers in the systematic review did this, even though many of the papers included an extensive battery of other tests. Binding tests must also be compared with one another in order to determine which are more effective. In the systematic review, only four of the papers involving at-risk participants compared different binding tasks, and there was only one paper involving participants with AD.

4. Clinical implications

Current approaches to neuropsychological testing in the diagnosis of AD typically involve, at the minimum, the administration of some global screening measure such as the Mini Mental State Examination or the ACE-III. A cut-off score is used as an indicator of whether AD is likely. These global measures perform poorly in the diagnosis of AD, particularly in the MCI or early stages of dementia of the Alzheimer type when accurate diagnosis is required. They lack specificity and sensitivity, and are poor to predict which people with MCI will go on to develop dementia of the Alzheimer type (Arevalo-Rodriguez et al., 2015)

Where there is access to more specialist assessment services, a battery of traditional neuropsychological tests may be used covering a range of different cognitive functions (e.g. Chapman et al., 2010). The NINCDS-ADRDA criteria for the diagnosis (McKhann et al., 1984), which are widely used in research and clinical contexts, suggest a diagnosis of AD requires impairment (below the 5th percentile of an age-defined general population) in at least two

cognitive domains from the following: memory, language, perception, attention, praxis, visuospatial orientation, problem-solving, and 'daily functioning'. This approach leads to greater accuracy in diagnosis (Chapman et al., 2010; Chapman et al., 2011; Ewers et al., 2012; Gainotti et al., 2014). More recently, a battery of tests selected from the CANTAB range of tests has been recommended for use in the diagnosis of AD in MCI and the early stages of dementia of the Alzheimer type (Cambridge Cognition, 2019), based on research about which of the tests are more sensitive and specific to AD (Blackwell et al., 2004; Chamberlain et al., 2011; Swainson et al., 2001). However, a battery of tests is relatively expensive in terms of scarce expert time. It can also be challenging and tiring for participants who may disengage from the assessment process because of this. It is also the case that, for both batteries that are composed of very traditional tests (such as the Trail Making Test) and more recent batteries such as the CANTAB, the tests were not developed specifically for the diagnosis of AD and are not based on recent theories and evidence in neuroscience about where the disease starts to develop in the brain and what the function of those areas is (Wood et al., 2016).

Rather than the shotgun approach of non-specific test batteries, a better approach to diagnosing AD in the pre-dementia and early dementia stages of the disease may be the use of a smaller number of tests specifically designed to evaluate processes associated with the areas of the brain where the disease process begins (i.e. the entorhinal cortex and hippocampus). For example, on the basis of evidence implicating the hippocampus in the development of allocentric spatial maps representing objects around us and where we are in relation to those objects, Wood et al. (2016) compared the diagnostic accuracy of some traditional tests used in the diagnosis of AD with a virtual reality test (the Four Mountains Test) designed to evaluation the ability to develop an allocentric spatial map. In a longitudinal study, performance on this test proved more effective in predicting which of a sample of participants with MCI went on to develop dementia

of the Alzheimer type than the Rey Auditory Verbal Learning Test and the Trail Making Test. It was also a more effective than a measure of hippocampal volume, and equivalent in accuracy to the levels of tau/beta-amyloid proteins in the cerebrospinal fluid.

As discussed in Chapter 2, the entorhinal cortex and hippocampus have also been implicated in the binding process. Using a relatively small number of these tests may be a better option than a traditional battery approach. Of the four control tests from the CANTAB used in the study reported in Chapter 4, two of these are in the battery recommended for the diagnosis of pre-dementia AD (Cambridge Cognition, 2019) – specifically, Spatial Working Memory and Pattern Recognition Memory. As reported in Chapter 4 and Appendix 4n, the difference between the AD and Older group was significantly larger on the Face-Name test than on either of these CANTAB tests, and the same was true for the Paired Associate Learning and Shape-Colour tests in relation to the Spatial Working Memory test. All three binding tasks also showed less overlap in the distributions between the two groups than Spatial Working Memory and Pattern Recognition Memory, with the Face-Name test performing particularly well in this respect (Table 4.7).

It should be noted that the emphasis in this thesis has been on the diagnostic usefulness of tests. However, neuropsychological tests have value for other reasons. They can be useful in helping a person develop awareness of their difficulties, in planning rehabilitation and in monitoring the effectiveness of intervention. A test that is useful for diagnosis may not be useful for these rehabilitative purposes, and vice versa. For example, although the KAT did relatively poorly in diagnostic terms, it may be more useful than some of the other tests in a rehabilitation context. Its use of familiar items and a task of obvious everyday relevance may make it more useful in helping people understand their difficulties and in planning rehabilitation. These

features may also make it more engaging for people to complete. Engagement and maximum effort may be reduced in tasks where the person cannot see their relevance.

5. Conclusions

The current thesis added to existing knowledge about binding impairments in AD in a number of ways. First, it added to the current weak evidence that poor performance on binding tasks is due to impairment in the actual binding process rather than in other cognitive processes contributing to task performance. This is an important point to establish because it would be unhelpful to continue to explore the value of binding tests in the early diagnosis of AD without first establishing that it is the binding process itself that is vulnerable to the disease. Second, the study cast doubt on the claim that spatial binding is more vulnerable to AD than non-spatial binding. Finally, through comparing six different binding tests, the study provided evidence about which existing tests are likely to be more effective in diagnosing early AD, highlighting that the Face-Name test and the PAL were the best performers.

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APPENDICES

Appendix 3a

Checklist for Assessing Technical Quality for Quantitative Descriptive Studies provided by Clearinghouse for Labor Evaluation and Research (CLEAR)

1. Study Design	
Criterion 1.1: Is the study design clear and appropriate for addressing the research questions?	
	- Demonstrates how the overall research strategy was designed to meet the study's aims (for example, what the study will do) - Discusses the rationale for the study design (for example, why the study does it this way) - Presents a convincing argument for different features of the design (for example, reasons for different components or stages of research; selection of any groups for examination and description of any comparisons [for example, across groups or over time]; and the rationale for particular methods or data sources, multiple methods, or time frames)
Criterion 1.2: Are the program(s) or conditions applying to the group(s) of interest clearly described in sufficient detail to understand and replicate?	
Criterion 1.3: Are key features of the design—including time, place, and context (such as labor market conditions)—clearly described? This includes the sampling design, if applicable.	
Criterion 1.4: Does the study explain limitations of the design and draw appropriate implications for interpreting findings?	
2. Data Quality	
Criterion 2.1: Are data sources clearly identified and appropriate for addressing the research questions?	
	- Documents data sources and variables used to address specific research questions - Discusses any strengths and weaknesses of the data sources
Criterion 2.2: Do key variables have face validity and does the study discuss their reliability and validity?	
Criterion 2.3: Are issues of data completeness, consistency, and accuracy, as well as steps researchers took to resolve these issues, addressed clearly, in sufficient detail, and appropriately?	
	- These issues could include, as relevant, response rates, potential reasons for nonresponse, attrition, movement in and out of the sample, and missing or inconsistent data.
Criterion 2.4: Is the description of constructed variables clear and do constructed variables make sense given the outcome of interest for the research question?	

3. Data Collection
Criterion 3.1: Are the data collection methods, sources, and instruments clearly described and appropriate for the research questions?
- If the study uses administrative data or surveys conducted by federal agencies, some or all of the data collection criteria might not apply (for example, the American Community Survey). Studies using these types of data should discuss or refer to the publicly available materials about the data's reliability and unbiasedness as well as the basic data collection methods. - Discusses creation of the analytic sample, including details on sampling methods if appropriate
Criterion 3.2: Does data collection reflect sound and systematic methods to produce reliable data?
- Discusses who collected the data and procedures used - Describes quality assurance procedures in data collection and verification - Discusses how data collection settings or methods might have influenced the data collected - Discusses instrumentation for surveys, if appropriate
Criterion 3.2: Does data collection reflect methods that produce unbiased results?
- Presents evidence of independence and objectivity of the research team - Documents consent procedures and information and incentives provided to respondents, if applicable
4. Study Sample
Criterion 4.1: Does the study examine a population relevant to the research questions?
Criterion 4.2: Is the sampling design clearly defined and defensible?
- Indicates whether sample is purposive or representative - Discusses sample identification and recruitment procedures, if relevant - If a sample of respondents cannot be drawn to represent a relevant universe, it is acknowledged and explained - Approach to selection reflects the purpose of the study and use/interpretation of the findings - Discusses what can be generalized to a wider population from which the sample is drawn or the site selection is made and limitations on drawing wider inferences - Discusses methods for drawing samples from extant data sources or identifying and sampling respondents for data collection
Criterion 4.3: Are inclusion and/or exclusion restrictions clear and defensible?
Criterion 4.4: Is the analytic sample appropriate and described clearly and in adequate detail?
- Gives the rationale for the sufficiency of the sample size for answering the research question(s) of interest
Criterion 4.5: Does the study discuss limitations of the sample and/or sampling procedure?

5. Analysis Methods	
Criterion 5.1: Are the analysis methods clearly described, appropriate for the research questions, sufficiently rigorous, and correctly executed?	
	- Describes and gives rationale for methods of analysis, including use of specific analysis methods, models, and procedures for hypothesis testing - The description of the analysis methods should be sufficiently detailed to understand how the analysis was conducted and how the empirical findings are to be interpreted - The reviewer should have some confidence that the findings could be replicated based on the description of the methods
Criterion 5.2: Does the report clearly explain and justify key analysis decisions?	
Criterion 5.3: Are appropriate statistical procedures used?	
	- These procedures could include methods to account for stratification, methods to account for clustering, and sample weights.
Criterion 5.4: Are limitations of the analytic methods discussed, especially those that could lead to bias?	
	- These limitations could include treatment of missing data, confounding factors, omitted variables, endogeneity, and statistical power. - Discusses how limitations of the analytic methods could affect interpretation of the findings - Discusses sensitivity tests conducted and their results
6. Findings and Conclusions	
Criterion 6.1: Are findings fully supported by the data and analysis?	
	- Are findings presented accurately and objectively without introducing a point of view? - Findings make sense as a whole and are coherent; seemingly odd or inconsistent findings are acknowledged and addressed appropriately. - Findings are placed in an appropriate context given limitations in design, data sources, and analytic methods of the study.
Criterion 6.2: Are conclusions supported by the findings?	
	- Conclusions are based on a reasonable interpretation of the findings. - Conclusions do not appear to reflect biases on the part of the researchers or authors. - Conclusions are placed in appropriate context with respect to the theory proposed and/or conclusions based on previous literature.

Appendix 4a

Ethical Approval – University of Birmingham

SC

Susan Cottam (Research Support Group) [redacted] Juliana Jezler (PhD Psychology Lab FT); 21/11/2016

Application for Ethical Review ERN_16-1174

Dear Ms Jezler and Dr Riley

Re: "Spatial and non-spatial binding in ageing and Alzheimer's disease"
Application for Ethical Review ERN_16-1174

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly bought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at [redacted]

Kind regards

Susan Cottam
Research Ethics Officer
Research Support Group
[redacted]
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT
Tel: [redacted]
Email: [redacted]
Web: https://intranet.birmingham.ac.uk/finance/accounting/research-support-group/Research-Ethics

Appendix 4b

Ethical Approval – Birmingham and Solihull Mental Health National Health Service Foundation Trust

NHS
Health Research Authority

Mrs Juliana Jezler
School of Psychology, University of Birmingham
Edgbaston
Birmingham
B15 2TT

Email:

07 September 2017

Dear Juliana

Letter of HRA Approval

Study title:	**Spatial and non-spatial binding in ageing and Alzheimer's disease**
IRAS project ID:	**217888**
Protocol number:	**RG_17-077**
REC reference:	**17/WM/0305**
Sponsor	**Organization not set**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

Appendix 4c

Ethical Amendment

Juliana Jezler (PhD Psychology Lab FT)
Wed 15/08/2018, 20:02
[redacted]

Reply all

Dear Donna

Find below the email regarding the second amendment. You can check the dates of the email I have sent previously to you (email to HRA with the non-substantial form regarding data collection extension)

Kindest regards
Juliana
...

From: [redacted]
Sent: 04 April 2018 11:07
To: Juliana Jezler; [redacted]
Cc: [redacted]
Subject: ?spam? IRAS 217888. Amendment categorisation and implementation information

Amendment Categorisation and Implementation Information

Dear Mrs Jezler,

IRAS Project ID: 217888
Short Study Title: Spatial and non-spatial binding in ageing and Alzheimer's disease
Date complete amendment submission received: 19 March 2018
Amendment Type: Non-substantial
Outcome of HRA Assessment
This email also constitutes HRA Approval for the amendment, and you should not expect anything further from the HRA.

Implementation date in NHS organisations in England
35 days from date amendment information together with this email, is supplied to participating organisations (providing conditions are met)

For NHS/HSC R&D Office information
Amendment Category
A

UNIVERSITY OF BIRMINGHAM

Birmingham and Solihull NHS
Mental Health NHS Foundation Trust

Appendix 4d

Participant Information Sheet (PIS)

Title of project: Spatial and non-spatial binding in ageing and Alzheimer's disease

The study is being sponsored by the University of Birmingham and is being undertaken as part of a PhD qualification.

Introduction to the research and invitation to take part:

Thank you for taking the time to read this information sheet. It is important that you understand why the research is being done and what it will involve before you decide whether or not to take part. Please read the following information carefully, and please discuss this with others if you wish. You can contact the Patient Advisory Liaison Service (PALS) for an advice on taking part in research. Details about contacting PALS are given at the end of this leaflet. Feel free to ask us if there is anything that is not clear or if you would like more information.

What is an information sheet?

The information sheet explains to you clearly and openly all the steps and procedures of the study. The information is to help you to decide whether or not you would like to take part in the research.

What is this research study about?

The aim of the study is to investigate which types of memory are more likely to be affected by Alzheimer's disease. We are testing the idea that Alzheimer's disease may have a particularly damaging effect on memory for where things are located.

Do I have to take part?

No. Participation is entirely voluntary. The person who gave you this leaflet will ask you if you are interested in finding out more about the study. If you are not interested, tell this to the person who gave you the leaflet. If you are interested, the person will ask you for permission to give your contact details to the researcher so that she can contact you.

If you give your permission to be contacted, on the day following your receipt of this leaflet, the researcher (Juliana Jezler) will contact you to ask you if you want to take part. If you do not want to take part, tell the researcher this when she contacts you. The researcher will not ask for a reason or try to persuade you to take part.

You may also withdraw from the study at any time while you are taking part. If you decide to withdraw, any data collected from you, including personal details, will immediately be destroyed.

What happens if I decide to take part?

If you decide to take part, an appointment will be arranged at a time convenient for you. Appointments will take place at the University of Birmingham or in your own home – whichever

is most convenient for you. If you have to pay for transport to the appointment, we will reimburse you for this (up to a maximum of £5). If you need someone to travel with you, we will also reimburse the person travelling with you (again, up to a maximum of £5).

In your appointment, a researcher will go through this information sheet with you again. You will have the opportunity to ask any questions you may have. If you decide to continue with the study, you will be asked to sign a consent form.

After you have signed the consent form, you will be asked some general questions about yourself (such as your age and ethnicity). You will then complete a number of tasks of memory, attention and other mental abilities with total duration of 90 minutes. You will have the option of completing the testing across one or two sessions. There will be a break of 10-15 minutes half way through the testing, and you can also ask for a break at any time during the testing. If you become noticeably tired during the testing, you will be given the option of rescheduling the session or withdrawing from the study.

What are the possible benefits of taking part?

Although there no direct benefits to you from participating in this study, we hope the information we learn will benefit people being diagnosed with Alzheimer's disease in the future.

Are there any risks?

Due to the length of the assessment you may get fatigued. In order to minimise distress and tiredness, you will have the option to split the testing into two sessions. You will be allowed to take as many breaks between tests as you need to avoid fatigue and tiredness.

The researcher cannot discuss with you your performance on the tests. If you get upset or worried about how poorly you think you have done on the tests, you should arrange to see [redacted] at the Memory Assessment Service (MAS) at Hob Moor Road, Small Heath, Birmingham B10 9JH.

Will my taking part in the study be kept confidential?

Yes. All the information about your participation in this study will be treated with strict confidence. Any personal information collected about you, such as your address and contact details, will be kept in a locked cabinet in a locked room and only the researchers, Dr. Gerard Riley and Juliana Jezler, and University of Birmingham sponsor representatives and regulatory authorities will have access to it. All other information will be stored in an anonymous form on password-protected computers.

What will happen to the results of this study?

Results from your participation will be analysed together with results from all the other participants in this study and will be submitted for publication in a scientific journal and for presentation at a scientific conference. You will not be identified in any publication because only the results of the whole group will be described. You will be asked if you wish to receive a summary of the research findings once the study has been completed.

What will happen to the information I provide?

- The paper 'expression of interest form' on which you provide your contact details will be kept for 10 years in a locked cabinet at the University and then securely shredded after that.

- The paper 'consent form' and the paper records of your performance on the tests will be kept separately in a locked cabinet at the University and then securely shredded after 10 years according to University policy.

- Electronic records of your data (which will not contain any identifying personal details such as your name) will be kept on password-protected computers for 10 years, according to University policy, and then deleted.

Your name and contact details will not be written on the questionnaires and tests. Instead, a unique code will be used to identify them.

Your scores on the tests will be kept on a computer file on a password-protected computer system. This file will not contain your name or any other information that would allow you to be identified.

The only people allowed to access the data will be the two researchers and regulatory authorities and Sponsor representatives to monitor the research.

What if I want to complain?

If you are unhappy about the way this research is being conducted, then please contact Patient Advisory Liaison Service (PALS) (contact details are given at the end of this leaflet). You may also contact the head of the research governance department at the University of Birmingham: Sean Jennings, Research Governance and Ethics Manager, Research Support Team, Room , Aston Webb Building, University of Birmingham, Edgbaston, Birmingham, B15 2SQ, e-mail: ; phone:

I want to know more before I decide to take part. What should I do?

Please contact one of the two researchers with any questions you may have. You can contact either Juliana Jezler (e-mail - ; phone - ; address –School of Psychology, University of Birmingham, Edgbaston, Birmingham, B15 2TT) or Gerard Riley (e-mail – ; phone – ; same address).

Further advice and support

For further advice about research participation or to register any concern about the way the research is being conducted, you may contact the local Patient Advisory Liaison Service at:

Address: PALS service, Birmingham and Solihull Mental Health NHS Foundation Trust,

Trust Headquarters, Unit 1, B1, 50 Summer Hill Road, Birmingham B1 3RB

Telephone: Text: Fax:

Email: Website: http://www.bsmhft.nhs.uk/service-user-and-carer/customer-relations/pals/

Appendix 4e

Invitation Letter

Have you recently been diagnosed with Alzheimer's disease?

Would you be interested in taking part in some research being sponsored by the University of Birmingham to help us understand the effects that Alzheimer's Disease has on the brain and mental abilities?

The research is investigating different kinds of memory tasks to see which ones are more likely to be affected by normal ageing and by Alzheimer's Disease. We are testing the idea that Alzheimer's Disease may have a particularly damaging effect on memory for where things are located.

If you take part, you will complete a range of different tests of your mental abilities, including memory, some of which will be presented on a computer screen. Many are fun to complete, and all are stimulating!

Testing should take around 90 minutes altogether. To prevent participants from getting mentally tired, testing can take place over two sessions on different days. There will be a break of 10 minutes half way through each session. You can also have as many breaks as you need between tests.

You would complete the tasks at the University of Birmingham, at the centre where you were given this letter, or in your own home – whichever suits you best. If you came to the University, we would pay your travel expenses, up to a maximum of £5.00 (or a maximum of £10.00 if you need someone to come with you).

Please note that you can only take part in this study if:

- You are aged 60 or over
- You have been diagnosed with Alzheimer's Disease and are in the early stages of the disease.
- English is your first language, or you are fluent in spoken English.
- You have adequate vision for reading. If you need glasses to read, you can still take part.
- You do not currently have any other major health problems relating to your brain function (e.g. stroke) or to your mental health.

If you want to contact the researchers, you can do so by phoning Juliana Jezler on [redacted] or by emailing her at: [redacted]. Alternatively, you can write requesting further information to: Juliana Jezler, School of Psychology, The University of Birmingham, Edgbaston, Birmingham, B15 2TT

Appendix 4f

Expression of Interest Form

Project title: Spatial and non-spatial binding in ageing and Alzheimer's disease.

Researcher: Juliana Jezler, University of Birmingham; e-mail – [redacted]

Please write your initials in the box

I have been approached by [redacted] about this research project. I agree ☐ that she can pass on my contact details to the Chief Investigator (Juliana Jezler) as listed below.

I understand that the Chief Investigator will contact me about arranging a meeting where she will explain more about the research. ☐

_____	_____	_____
Name of Participant	Date	Signature
[redacted] or other member of staff of MAS Memory Assessment Service)	Date	Signature

I would prefer to be contacted by e-mail ☐ telephone ☐ letter ☐

Please provide your preferred contact details here: …….....

FOR COMPLETION FOLLOWING INFORMATION MEETING WITH THE CHIEF INVESTIGATOR

I understand that the Chief Investigator will contact me the day after our meeting, using the contact details I have provided, to ask whether I want to take part.

_____	_____	_____
Name of Participant	Date	Signature
Juliana Jezler	Date	Signature

Appendix 4g

Participant Consent Form

Spatial and non-spatial binding in ageing and Alzheimer's disease.

Participant Identification Number:

Juliana Jezler, PhD Student, University of Birmingham (Researcher)

Please write your initials in each box

1. I confirm that I have read and understood the Participant Information sheet, (v1.0, 06/07/2017) for the above study. ☐
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
3. I confirm that I understand that my participation is **voluntary** and I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that my data will be stored at the University of Birmingham. I understand that no identifiable information will be shared with any other organisation. ☐
5. I understand that relevant sections of data collected during the study may be looked at by appropriate individuals authorised by the University of Birmingham to monitor the conduct of the research. ☐
6. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
7. I agree that my GP can be informed of my participation in the study. ☐
8. I agree to take part in the above study ☐

_____	_____	_____
Name of Participant	Date	Signature

_____	_____	_____
Name of researcher	Date	Signature

If you would like to receive a summary of the findings from the research then please provide your postal or e-mail address below.
You do not have to give these details if you don't wish to.
Please note it may take up to 12 months
before feedback is available and any feedback provided will be about the overall results and not specific to your individual questionnaires.
Address (for receiving summary of findings):_____

Please contact Dr. Gerard Riley or Juliana Jezler if you have any questions
E-mail: [redacted] (Mrs. Juliana Jezler); [redacted] (Dr. Gerard Riley)

Assessment of capacity to consent

If you take part in this study, what will you be asked to do?

.....
.....

About how long will the tests take to complete?

……
……...

Appendix 4h

Demographic Questionnaire

Please state your age: ……

1. Please state your gender:

☐ **Male** ☐ **Female** ☐ **Transgendered** ☐ **rather not say**

2. Please state your ethnicity:

☐ **White/Caucasian** ☐ **Hispanic/Latino** ☐ **Black/African/ Caribbean** ☐ **Asian**

☐ **Rather not say** ☐ **Other, please specify.....**

3. Please state which hand you write with:

☐ **Left hand** ☐ **Right hand** ☐ **No preference (both hands)**

4. What is the highest level of education that you have completed?

☐ **No formal education** ☐ **School** ☐ **Technical college, polytechnic or equivalent** ☐ **University**

5. Do you have any close family relation (living or dead) who has been diagnosed with Alzheimer's disease or any other dementia?

☐ **No** ☐ **Yes**

6. What is your occupation? If you do no longer work, what was your main job when you were working?

- ☐ **Manager, director, senior official**
- ☐ **Professional occupation**
- ☐ **Skilled technical occupation**
- ☐ **Administrative and secretarial occupation**
- ☐ **Skilled trade occupation**
- ☐ **Caring, leisure or other service occupation**
- ☐ **Sales and customer service occupation**
- ☐ **Plant or machine operative**
- ☐ **Manual labour**
- ☐ **Other [Please specify: .....]**

Appendix 4i

Centre for Epidemiologic Studies Depression Scale (CES-D)

Instructions for question: Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

During the past week:	**Rarely or none of the time (less than 1 day)**	**Some or little of the time (1-2 days)**	**Occasionally or a moderate amount of time (3-4 days)**	**Most or all of the time (5-7 days)**
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with help from my family or friends.				
4. I felt that I was just as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep is restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people dislike me.				
20. I could not get "going".				

Appendix 4j

National Adult Reading Test (NART)

National Adult Reading Test (NART)
Word Card

CHORD	SUPERFLUOUS
ACHE	SIMILE
DEPOT	BANAL
AISLE	QUADRUPED
BOUQUET	CELLIST
PSALM	FACADE
CAPON	ZEALOT
DENY	DRACHM
NAUSEA	AEON
DEBT	PLACEBO
COURTEOUS	ABSTEMIOUS
RAREFY	DETENTE
EQUIVOCAL	IDYLL
NAIVE	PUERPERAL
CATACOMB	AVER
GAOLED	GAUCHE
THYME	TOPIARY
HEIR	LEVIATHAN
RADIX	BEATIFY
ASSIGNATE	PRELATE
HIATUS	SIDEREAL
SUBTLE	DEMESNE
PROCREATE	SYNCOPE
GIST	LABILE
GOUGE	CAMPANILE

Appendix 4k

FACE NAME ASSOCIATIVE MEMORY EXAM Version A (FNAME-12A)

Participant ID:_____ Data___/___/_____

Materials: Powerpoint FNAME-12A, stopwatch

Read instructions on screen to subject: **Read out loud and try to remember the name and occupation that goes with each face.** Exhibit each slide for 8 seconds. After going through all 12 slides, say, **What was the name and occupation of each face?** Click through each face and record responses below. Allow approximately 15 seconds for a response.

Learning Trial 1

Name	Correct	Occupation	Correct
Sarah		Reporter	
Ralph		Janitor	
Diane		Teacher	
Andrew		Pilot	
Nancy		Doctor	
Fred		Fireman	
Kim		Secretary	
Henry		Waiter	
Joan		Musician	
Bill		Mechanic	
Elizabeth		Therapist	
George		Architect	
Initial Name Retrieval (INR1)	/12	Initial Occupation Retrieval (IOR1)	/12

You will now see the same faces, but in a different order. Read out loud and try to remember the name and occupation that goes with each face. Exhibit each slide for 8 seconds. After going through all 12 slides, say, **What was the name and occupation of each face?** Click through each face and record responses below.

Learning Trial 2

Name	Correct	Occupation	Correct
Elizabeth		Therapist	
Bill		Mechanic	
Nancy		Doctor	
Ralph		Janitor	
Sarah		Reporter	
Henry		Waiter	
Joan		Musician	
Andrew		Pilot	
Kim		Secretary	
George		Architect	
Diane		Teacher	
Fred		Fireman	
Initial Name Retrieval (INR2)	/12	**Initial Occupation Retrieval (IOR2)**	/12

SHORT DELAY (during which you administer Famous Faces & Logos)

What is the name and occupation of this famous person? Allow a maximum of 20 seconds for a response. Mark correct even if the subject produces only the first or last name.

Famous Faces

Name	Correct	Occupation	Correct
John Lennon		Musician/Beatle	
Oprah Winfrey		Talk Show Host	
Gerald Ford		President	
Jackie Kennedy Onassis		First Lady	
Sidney Poitier		Actor/ Movie Star	
Audrey Hepburn		Actress/ Movie Star	
Walter Cronkite		Newscaster/journalist	
Mother Theresa		Nun/ humanitarian	
Bill Cosby		Comedian/ Actor	
Barbara Walters		TV Newswoman	
Nelson Mandela		President	
Lucille Ball		Actress/ Comedian	

Famous Face Naming	/12	Famous Occupation Naming	/12

A few minutes ago I showed you some faces. What was the name and occupation of each face? Click through each face and record responses below. Do not provide feedback.

Cued Name and Occupation Recall

Name	Correct	Occupation	Correct
Sarah		Reporter	
Ralph		Janitor	
Diane		Teacher	
Andrew		Pilot	
Nancy		Doctor	
Fred		Fireman	
Kim		Secretary	
Henry		Waiter	
Joan		Musician	
Bill		Mechanic	
Elizabeth		Therapist	
George		Architect	

Cued Name Retrieval (CRN)	/12	**Cued Occupation Retrieval (CRO)**	/24

Try to remember these names and occupations. I will ask you to recall them again later.

LONG DELAY (30 minutes)

Read aloud: **Which of these three people do you recognize from before?** Record the response in the "Facial Recognition Column" but correct them if they indicate the wrong person. Ask for the name (CRN30) and occupation (CRO30) of the correct person and record below. Do not let them know if they are correct or not. Regardless of their response, proceed to multiple choice.

Delayed Cued Recall of Names and Occupations

Names	Occupation	Facial Recognition	Cued Name Retrieval (CRN)	Cued Occupation Retrieval (CRO)	Multiple Choice Names (MCN)			Multiple Choice Occupations (MCO)		
Elizabeth	Therapist	**1** 2 3			Nancy	**Elizabeth**	Amanda	Doctor	Conductor	**Therapist**
Bill	Mechanic	1 **2** 3			Ralph	Bob	**Bill**	Pastor	**Mechanic**	Janitor
Nancy	Doctor	1 **2** 3			Sarah	**Nancy**	Pam	**Doctor**	Therapist	Gardener
Ralph	Janitor	**1** 2 3			**Ralph**	Fred	Bruce	Fireman	**Janitor**	Chemist
Sarah	Reporter	1 2 **3**			**Sarah**	Joan	Kate	Musician	**Reporter**	Cashier
Henry	Waiter	1 2 **3**			**Henry**	Al	Bill	Grocer	Architect	**Waiter**
Joan	Musician	1 **2** 3			Diane	Ellen	**Joan**	**Musician**	Teacher	Designer
Andrew	Pilot	**1** 2 3			Daniel	Henry	**Andrew**	**Pilot**	Detective	Mechanic
Kim	Secretary	1 **2** 3			**Kim**	Elizabeth	Kathleen	Salesperson	**Secretary**	Reporter
George	Architect	1 2 **3**			Andrew	Eugene	**George**	Waiter	Actor	**Architect**
Diane	Teacher	1 2 **3**			Anna	**Diane**	Kim	Secretary	Lawyer	**Teacher**
Fred	Fireman	**1** 2 3			Martin	**Fred**	George	**Fireman**	Athlete	Pilot
			CRN 30	CRO 30			MCN			MCO
		/12	**/12**	**/12**			**/12**			**/12**

FN-N = INR + CRN + CRN30 = _____
FN-O = IOR + CRO + CRO30 = _____
Total FNAME Score = FN-N + FN-O = _____

Appendix 4l

Tests of relationship between binding variables and demographic variables

			Spatial			Non-spatial		
Demographic variable	**Groups**	**N**	**KAT**	**Design**	**PAL**	**VPA**	**Shape-Colour**	**Face-Name**
Gender	**Old**	15F 11M	t(24)=1.82, p=.08, Fm=17.47(6.22), Mm=12.82(6.77)	t(24)=1.04, p=.31, Fm=11.20(4.30), Mm=9.55(3.62)	t(16.71)=.94, p=.36, Fm=19.47 (2.70), Mm=18.18 (3.92)	t(24)=2.61, p=0.02, Fm=36.73(8.23), Mm=28.73(6.93)	t(17.82)=-.39, p=.70, Fm=29.47(2.42), Mm=29.73(.79)	t(22.87)=1.04, p=.31, Fm=71.73(14.94), Mm=66.91(8.51)
	AD	14F 12M	t(24)=-.49, p=.63, Fm=7.00(6.63), Mm=8.17(5.32)	t(15.52)=-1.43, p=.17, Fm=2.21(1.76), Mm=3.83(3.56)	t(24)=-.58, p=.57, Fm=8.36(5.24), Mm=9.58(5.63)	t(24)=-.22, p=.83, Fm=16.29(5.34), Mm=16.75(5.41)	t(24)=-1.33, p=.20, Fm=19.71(6.50), Mm=23.25(7.05)	t(24)=-1.54, p=.14, Fm=20.21(12.50), Mm=28.67(15.55)
Further education	**Old**	21 Yes 5 No	t(23.99)=.62, p=.54, Ym=15.71(7.48), Nm=14.60(1.67)	t(24)=.92, p=.37, Ym=10.86(4.14), Nm=9.00(3.54)	t(24)=1.17, p=.25, Ym=19.29(3.29), Nm=17.40(2.97)	t(24)=-.76, p=.45, Ym=32.71(9.23), Nm=36.00(4.74)	t(24)=1.03, p=.31, Ym=29.76(1.67), Nm=28.80(2.68)	t(21.25)=4.87, p<.001, Ym=72.67(12.18), Nm=57.20(3.90)
	AD	18 Yes 8 No	t(24)=1.17, p=.25, Ym=8.44(6.60), Nm=5.50(3.90)	t(24)=.25, p=.80, Ym=3.06(2.98), Nm=2.75(2.55)	t(24)=.26, p=.79, Ym=9.11(5.30), Nm=8.50(5.81)	t(24)<0.001, p=1, Ym=16.50(5.88), Nm=16.50(3.89)	t(24)=1.11, p=.28, Ym=22.33(7.21), Nm=19.13(5.79)	t(24)=1.86, p=.08, Ym=27.44(15.29), Nm=16.63(8.72)
Native English Speaker	**Young**	20 Yes 6 No	t(24)=.84, p=.41, Ym=28.45(4.33), Nm=26.83(3.37)	t(24)=1.72, p=.10, Ym=17.90(3.46), Nm=15.00(4.20)	t(24)=.93, p=.36, Ym=23.35(2.89), Nm=22.17(2.14)	t(24)=.53, p=.60, Ym=49.55(4.27), Nm=48.50(4.32)	t(24)=.40, p=.69, Ym=30.45(1.47), Nm=30.17(1.72)	t(24)=.37, p=.72, Ym=84.80(5.73), Nm=83.83(5.42)
History of AD	**Young**	4 Yes 22 No	t(24)=-.04, p=.97, Ym=28.00(4.97), Nm=28.09(4.09)	t(24)=-.85, p=.40, Ym=15.75(3.86), Nm=17.50(3.78)	t(24)=-1.23, p=.22, Ym=21.50(3.32), Nm=23.36(2.61)	t(24)=1.71, p=.10, Ym=52.50(1.91), Nm=48.73(4.29)	t(24)=.16, p=.87, Ym=30.50(1.91), Nm=30.36(1.47)	t(24)=-1.01, p=.32, Ym=82.00(8.76), Nm=85.05(4.94)
	Old	7 Yes 19 No	t(24)=.95, p=.35, Ym=17.57(3.74), Nm=14.74(7.50)	t(24)=.38, p=.71, Ym=11.00(4.93), Nm=10.32(3.79)	t(24)=.21, p=.84, Ym=19.14(2.97), Nm=18.84(3.44)	t(24)=1.57, p=.13, Ym=37.57(6.24), Nm=31.79(8.92)	t(24)=.45, p=.65, Ym=29.86(2.04), Nm=29.47(1.87)	t(24)=-.27, p=.79, Ym=68.57(13.87), Nm=70.11(12.54)
	AD	13 Yes 13 No	t(24)=1.12, p=.27, Ym=8.85(683), Nm=6.23(4.90)	t(24)=1.66, p=.11, Ym=3.85(2.97), Nm=2.08(2.43)	t(24)=1.34, p=.19, Ym=10.31(5.84), Nm=7.54(4.63)	t(24)=1.49, p=.15, Ym=18.00(5.97), Nm=15.00(4.16)	t(24)=.82, p=.42, Ym=22.46(7.11), Nm=20.23(6.69)	t(24)=.28, p=.78, Ym=24.92(13.40), Nm=23.31(15.76)

Note: Gender (for Young), Handedness, Ethnicity, Native English speaker (for Old and ad) and Further education (for Young) were not included in the table because the number of observations in some levels of the variables was too small to allow analysis. Independent t tests were used for the analyses; AD = Alzheimer's disease; F = female; M= Male; KAT = Kitchen Arrangement Test; PAL: Paired Associates Learning; VPA= Verbal Paired Associates; Ym = mean of yes, Nm = mean of no, Rm/Lm= mean of Right/of Left, Wm/Om= mean of White/Other, Fm= mean of females, Mm = mean of males, Bm = mean of below, Am = mean of above.

Appendix 4m

The relationship between binding variables and control variables

Control variables	Groups	N or Mean	Spatial			Non-Spatial		
			KAT	Design	PAL	VPA	Shape-Colour	Face-Name
Predicted IQ	**Young**	Mean= 101.19	r =.06 p= .79	r= .53 p <.01	r=.25 p=.23	r=.05 p=.80	r= .29 p=.15	r=.07 p=.72
	Old	Mean=114.96	r=.18, p=.37	r=.20, p=.32	r=.21, p=.30	r=.34, p=.09	r=-.01, p=.96	r=.19, p=.35
	AD	Mean=111.77	r=.17, p=.40	r=.06, p=.76	r=-.08, p=.70	r=.04, p=.84	r=.25, p=.22	r=.35, p=.08
CES-D_16	**Young**	n=below cut off of 16: 22, at or above: 4	t(24)=-.61, p=.55, Bm=27.86(4.18), Am=29.25(4.19)	t(24)=1.97, p=.06, Bm=17.82(3.38), Am=14.00(4.69)	t(24)=1.27, p=.22, Bm=23.36(2.61), Am=21.50(3.32)	t(24)=-1.14, p=.27, Bm=48.91(4.10), Am=51.50(4.80)	t(24)=-.16, p=.87, Bm=30.36(1.36), Am=30.50(2.38)	t(3.26)=.25, p=.82, Bm=84.77(4.76), Am=83.50(9.88)
	Old	n=below cut off of 16: 23, at or above: 3	t(24)=-.49, p=.63, Bm=15.26(7.11), Am=17.33(2.52)	t(13.98)=3.86, p=.002, Bm=10.96(4.06), Am=7.00(1.00)	t(5.31)=.59, p=.58, Bm=19.00(3.44), Am=18.33(1.53)	t(24)=.14, p=.89, Bm=33.44(8.04), Am=32.67(14.36)	t(24)=-1.07, p=.30, Bm=29.43(1.93), Am=30.67(1.15)	t(24)=-.72, p=.48, Bm=69.04(12.86), Am=74.67(11.72)
	AD	n=below cut off of 16: 14, at or above: 12	t(18.48)=2.01, p=.06, Bm=9.50(7.16), Am=5.25(3.17)	t(24)=1.21, p=.24, Bm=3.57(3.11), Am=2.25(2.34)	t(24)=1.11, p=.28, Bm=10.00(5.32), Am=7.67(5.33)	t(24)=.44, p=.66, Bm=16.93(5.54), Am=16.00(5.13)	t(24)=1.35, p=.19, Bm=23.00(6.74), Am=19.42(6.76)	t(24)=-.67, p=.51, Bm=22.36(16.08), Am=26.17(12.42)
CANTAB SRM	**Young**	Mean = 16.76	r=.39, p=.051	r=.22, p=.27	r=.60, p<.01	r=.42, p=.03	r=.18, p=.38	r=-.21, p=.30
	Old	Mean = 15.26	r=.29, p=.15	r=.57, p<.01	r=.58, p<.01	r=.11, p=.59	r=-.10, p=.61	r=.25, p=.23
	AD	Mean = 11.69	r=.51, p<.01	r=.43, p=.03	r=.57, p<.01	r=.42, p=.03	r=.33, p=.10	r=.33, p=.11
CANTAB PRM	**Young**	Mean = 22.34	r=.43, p=.03	r=.28, p=.16	r=.24, p=.25	r=.23, p=.25	r=.24, p=.23	r=.15, p=.46
	Old	Mean = 20.80	r=.32, p=.12	r=.41, p=.04	r=.45, p=.02	r=.38, p=.06	r=-.16, p=.45	r=.40, p=.046
	AD	Mean = 16.69	r=.52, p<.01	r=.65, p<.01	r=.66, p<.01	r=.40, p=.045	r=.41, p=.04	r=.33, p=.10
CANTAB SWM	**Young**	Mean = 6.88	r=-.31, p=.13	r=-.01, p=.95	r=-.03, p=.88	r=-.16, p=.42	r=-.18, p=.38	r=.24, p=.24
	Old	Mean = 19.07	r=-.42, p=.03	r=-.55, p<.01	r=-.21, p=.31	r=-.10, p=.63	r=.006, p=.98	r=.01, p=.95
	AD	Mean = 32.46	r=-.45, p=.02	r=-.39, p=.051	r=-.61, p<.01	r=-.19, p=.35	r=-.57, p<.01	r=-.01, p=.96
CANTAB CRT	**AD**	no ceiling effect, n=6 below cut-off of 46	r=.27, p=.19	r=.36, p=.07	r=.49, p=.01	r=.14, p=.50	r=.24, p=.23	r=-.08, p=.72

Note: Pearson's r correlations and independent t tests were used for the analyses; AD = Alzheimer's disease; KAT = Kitchen Arrangement Test; PAL: Paired Associates Learning; VPA= Verbal Paired Associates; IQ = Intelligence Quotient; CES-D_16 = Centre for Epidemiologic Studies Depression Scale_cut-off of 16; CANTAB = Cambridge Neuropsychological test Automated Battery; SRM = Spatial Recognition Memory; PRM = Pattern Recognition Memory; SWM = Spatial Working Memory; CRT = Choice Reaction Time; Ym = mean of yes, Nm = mean of no, Rm/Lm= mean of Right/of Left, Wm/Om= mean of White/Other, Fm= mean of females, Mm = mean of males, Bm = mean of below, Am = mean of above

Appendix 4n

Comparison of each binding task with each control task

Binding type	Binding task	vs. Control task	t-value	p-value
Spatial binding	KAT	SRM	1.29	.210
		PRM*	5.51	<.001
		SWM	0.43	.669
	Design	SRM	1.88	.072
		PRM*	3.22	.004
		SWM	2.69	.013
	PAL	SRM	5.94	<.001
		PRM	1.70	.102
		SWM	6.92	<.001
Non-spatial binding	VPA	SRM	2.34	.027
		PRM	2.34	.027
		SWM	2.87	.008
	Shape-Colour	SRM	4.33	<.001
		PRM	2.68	.013
		SWM	5.07	<.001
	Face-Name	SRM	8.00	<.001
		PRM	3.12	.004
		SWM	7.28	<.001

Note: KAT: The Kitchen Arrangement Test; PAL: Paired Associates Learning; VPA: Verbal Paired Associates; SRM: Spatial Recognition Memory; PRM: Pattern Recognition Memory; SWM: Spatial Working Memory.
*Performance worse on PRM than KAT and Design, so PRM better diagnostic test in this context.

Appendix 4o

Comparison of each binding task with every other binding task

Binding task	vs. every other binding task	t-value	p-value
Face-Name	KAT	10.195	<.001
	Design	8.47	<.001
	PAL	1.44	.163
	VPA	8.60	<.001
	Shape-Colour	1.04	.311
Shape-Colour	KAT	4.81	<.001
	Design	3.97	.001
	PAL	2.15	.004
	VPA	3.39	.002
VPA	KAT	4.54	<.001
	Design	1.13	.268
	PAL	3.56	.002
PAL	KAT	8.60	<.001
	Design	4.76	<.001
Design	KAT	4.72	<.001

Note: KAT: The Kitchen Arrangement Test; PAL: Paired Associates Learning; VPA: Verbal Paired Associates; SRM: Spatial Recognition Memory; PRM: Pattern Recognition Memory; SWM: Spatial Working Memory.