

## **Neuroimaging Correlates of False Memory in Alzheimer's Disease: A Preliminary Systematic Review**

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### **Abstract**

Alzheimer's disease (AD) is characterised by episodic memory impairment, but people also experience memory *distortions*, including false memories, which can impact on safety and reduce functioning. Understanding the neural networks that underpin false memories could help to predict the need for intervention and guide development of cognitive strategies to reduce memory errors. However, there is a relative absence of research into how the neuropathology of AD contributes to false memory generation. This paper systematically reviews the methodology and outcomes of studies investigating the neuroimaging correlates of false memory in AD. Four studies using structural imaging and three studies using functional imaging were identified. Studies were heterogenous in methodology and received mostly 'weak' quality assessment ratings. Combined, and consistent with neuroimaging findings in non-AD populations,

results from identified studies provide preliminary support for the hypothesis that medial temporal lobe and prefrontal cortex dysfunction may lead to generation of false memories in AD. However, the small number of studies and significant heterogeneity within them means further study is necessary to assess replicability of results.

Keywords: Alzheimer's disease; Neuroimaging; False Memory; Confabulation

### Highlights

- Few studies assess neuroimaging correlates of false memory in Alzheimer's disease
- There is significant heterogeneity in methodology of these studies
- Medial temporal lobe functional integrity correlated negatively with false memories
- Findings related to prefrontal cortex were more mixed

### 1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by impaired short term episodic memory, and an increased susceptibility to generate false memories (Budson et al., 2004; Budson et al., 2007). The term false memory is used to describe a broad range of phenomena, including misremembering of word lists, false recognition of novel stimuli and distortions in autobiographical memory (Schacter, 1999).

Confabulation (giving false information without being aware of it) is included in this spectrum and ranges from intrusions to more elaborate false beliefs relating to past experiences (Gilboa and Moscovitch, 2002).

The Deese-Roediger-McDermott (DRM) paradigm (Roediger and McDermott, 1995), which requires participants to distinguish previously presented words (e.g. medicine, sick, nurse) from highly related but not presented words (e.g. doctor) and unrelated and not presented words, is the most widely used tool to study false memory (Gallo, 2010). Healthy young adults consistently falsely recall the highly related words but not the unrelated words, indicating that this effect is more than simply a failure of episodic memory (Gallo, 2010). Results using the DRM in AD have been inconsistent (Balota et al., 1999; Budson et al., 2000; Budson et al., 2001; Budson et al., 2003; Gallo et al., 2004). However, use of the DRM in AD has demonstrated a greater susceptibility for false memory generation due to impaired recollection (item-specific memory) (Balota et al., 1999; Budson et al., 2001; Budson et al., 2003; Gallo et al., 2004), a proportionately lesser impairment and therefore overreliance on familiarity (gist memory) (Abe et al., 2011; Budson et al., 2000) and impaired memory verification and monitoring (Budson et al., 2002). AD participants consistently demonstrate more provoked confabulation than controls (Dalla Barba et al., 1999; Kern et al., 1992), with results from one paradigm suggesting that confabulation arises when over-learned information replaces poorly encoded information (Attali et al., 2008), possibly due to impaired monitoring (Gilboa and Moscovitch, 2017).

There has been a relative absence of research into the relationship between the neuropathology of AD and false memories. In non-AD populations, lesion and neuroimaging studies demonstrate that posterior medial temporal lobe (MTL) structures may be involved in distinguishing true from false memory, with a combination of frontal dysfunction and memory preservation required for false memory generation (Cabeza et al., 2001; Melo et al., 1999). Preserved functioning of the medial prefrontal cortex (PFC), which is involved in complex decision making, source attribution and veracity

monitoring, is also thought to be essential to false memory creation (Kim and Cabeza, 2006; Warren et al., 2014). Lesion studies have implicated a large number of regions in confabulation (Gilboa and Moscovitch, 2002). However, one relatively consistent finding is that some degree of preserved hippocampal function is required to generate confabulations (Dalla Barba and La Corte, 2015). Given the presence of AD pathology in the MTL, it is hypothesised that false memories may result from reduced function within MTL structures with some preservation of medial PFC leading to increased reliance on familiarity (Malone et al., 2019), and additional frontal dysfunction leading to impairment of memory veracity monitoring (Budson et al., 2002; Gold and Budson, 2008; Schnider, 2001).

False memories in AD impact on safety (for example when an individual incorrectly remembers turning off the oven or taking medication), reduce functional ability and increase caregiver distress (Mills et al., 2006; Seltzer et al., 1997; Steeman et al., 1997). Cognitive strategies to reduce false memories are being explored, but have thus far been largely unsuccessful (Malone et al., 2019). An increased understanding of the neural underpinnings of false memory would guide further development in this area. This review therefore aims to systematically review existing studies investigating the neuroimaging correlates of false memory in AD.

## **2. Methods**

No ethical approval was required. Data was gathered and findings were reported according to PRISMA systematic review guidelines (Moher et al., 2009).

### *2.1 Literature search*

An electronic database search (Embase, Embase Classic, Medline, PsycINFO, Web of Science) was completed on December 18<sup>th</sup> 2018 using the search terms (AD OR Alzheimer\*) AND (False memor\* OR false recall OR false recognition OR false alarm\* OR false positive\* OR confab\* OR intrusion\* OR DRM OR Deese Roediger McDermott OR Deese-Roediger-McDermott) AND (Imaging OR neuroimaging OR MRI OR fMRI OR magnetic resonance OR functional magnetic resonance OR PET OR Positron emission tomography OR positron-emission tomography OR CT OR computed tomography OR computerised tomography).

### *2.2 Inclusion and exclusion criteria*

Studies were included if they were published in peer reviewed papers, in English; carried out in human subjects with diagnosed AD; and included a measure of false memory (defined above) in relation to a neuroimaging measure (brain structure, functioning or metabolism). Studies were excluded if they contained no analysis of relationship between false memory task performance and neuroimaging or included patients with other forms of dementia or mild cognitive impairment (MCI) in the sample. Case reports, poster abstracts and dissertations were excluded. Reviews were excluded but reference lists from relevant reviews were screened.

### *2.3 Data extraction*

Authors EM and SRa independently screened titles and abstracts, followed by full article texts, and extracted data to a pre-defined excel spreadsheet. This included study characteristics (inclusion and exclusion criteria, imaging modality), demographics (sex, mean age, ethnicity, handedness, mean years of education, medication status), clinical characteristics (AD diagnostic criteria, mean cognitive score, mean years since diagnosis), relevant outcomes (false memory task results, neuroimaging correlates).

Discrepancies were resolved through discussion, or in consultation with a third author (SRc). Demographic characteristics of the studies (when specified) were then combined as weighted pooled means and pooled proportions.

#### *2.4 Quality assessment*

EM and SRa independently evaluated the quality of each study using a modified version of the Effective Public Health Practice Project (EPHPP) tool for quality assessment (Thomas et al., 2004), see supplementary material. Studies were rated in the following areas: selection bias, study design, false memory task, neuroimaging methodology and statistical analysis. Section D (blinding), F (withdrawals and drop-outs) and G (intervention integrity) were excluded as they are specific for randomised controlled trials and inappropriate for the studies included in this review. Scores in each subsection were used to provide an overall rating of 'strong' (no weak ratings in any section), 'moderate' (only one weak rating), or 'weak' (two or more weak ratings), and an overall score was given (5 to 14 points) based on the rating of each category (strong = 1, weak = 3), with lower scores indicating better methodological quality. Any disagreements were resolved through discussion.

### **3. Results**

#### *3.1 Literature search and study selection*

Database searches identified 837 potential studies, with manual search of relevant review references yielding a further 32 results. Of the 617 studies remaining after duplicate removal, seven met the criteria for data extraction (see PRISMA flow chart, Figure 1). Inter-rater reliability was high, with 97.8% agreement,  $\kappa = 0.76$ . Study characteristics, main findings and quality assessment are shown in Table 1 and summarised below.

### *3.2 Characteristics of included studies*

The majority of studies (n = 4) received a 'weak' rating on quality assessment, with the remaining three studies rated as 'moderate'. Across scoring categories, five studies had a 'weak' rating for selection bias; two studies had a 'weak' rating for study design; no study received a 'weak' rating for either false memory task or neuroimaging methodology; three studies received a 'weak' rating for analysis.

Mean age of participants was  $70.4 \pm 8.7$  (reported in n = 6 studies), 55.3% of participants were female (n = 5), mean Mini Mental State Examination (MMSE) score was  $21.7 \pm 3.8$  (n = 5) and participants had spent on average  $11.7 \pm 3.2$  years in education (n = 3).

Duration of AD and handedness were reported in two studies (mean  $34.4 \pm 25.9$  months, 90.9% right handed) and race in one study (Weiner et al., 2011), with the majority (85.1%) of participants being of white ethnicity. Medication status was partially reported by four studies. Four studies did not report medical or psychiatric history of participants or include this in inclusion/exclusion criteria. Information on recruitment setting was included by four studies, two of whom recruited participants via outpatient clinics, one from hospitals, and one from both inpatient and community sites. None of the studies provided detail of whether or not participants were living independently. The majority of studies (n=6) used a cross-sectional methodology.

Most studies (n = 5) investigated intrusion errors on the California Verbal Learning Test (CVLT, n = 3) or Grober and Buschke's test (n = 2) (Fox et al., 1998; Grober and Buschke, 1987). Two studies investigated more elaborate confabulatory responses using a specifically developed Modified Confabulation Battery (MCB) (Lee et al., 2009), a prose memory test (Morris et al., 2014) or verbal recall tests from the Consortium to Establish

a Registry for Alzheimer's Disease (CERAD) (Lamberty et al., 1995). Two studies investigated false positive errors on Grober and Buschke's test or Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996). One study investigated correlates of 'visuospatial confabulation' in response to the Rey-Osterrieth Complex Figure (ROCF) (Osterrieth, 1944; Rey, 1941).

Four studies investigated structural neuroimaging correlates of a false memory measure, three using magnetic resonance imaging (MRI) (Deweert et al., 1995; Lee et al., 2009; Weiner et al., 2011) and one using diffusion tensor imaging (DTI) (Flanagan et al., 2016). Each of the three remaining identified studies employed a different functional neuroimaging technique including connectivity analysis using resting-state functional MRI (fMRI) (Venneri et al., 2017), positron emission tomography (PET) using the  $^{18}\text{F}$ -fluoro-2-deoxyglucose ( $^{18}\text{FDG}$ ) tracer (Desgranges et al., 2002) and single photon emission computed tomography (SPECT) using the  $^{123}\text{I}$  N-isopropyl-p-iodoamphetamine (IMP) tracer (Reed et al., 1993).

### *3.3 Neuroimaging methodology*

#### *3.3.1 Structural MRI*

All three studies used T1 weighted coronal contiguous acquisition protocols. One study (Deweert et al., 1995) provided no detail of magnetic field strength and little further detail of the imaging protocol used, but Lee et al. (2009) and Weiner et al. (2011) used 1.0 Tesla (T) and 1.5T respectively. Lee et al. (2009) used rapid acquisition and employed a 3D, spoiled gradient recalled sequence. Three different scanners were used by Weiner et al. (2011), and variously used 3D magnetization-prepared rapid gradient echo; spoiled gradient recalled echo; and turbo field echo sequences. The imaging data was co-registered either to other study participants or to an anatomical template in two of the

studies – the Montreal Neurological Institute-152 (MNI-152) (Lee et al., 2009) and a hippocampal template developed by Csernansky et al. (1998) (Weiner et al., 2011). Only one study (Lee et al., 2009) gave information on slice thickness, voxel size or spatial smoothing of images. Slice thickness was 1.5mm, with voxel size 1.02x1.02x1.50mm, and images were smoothed using a Gaussian kernel of 10mm full-width half-maximum (FWHM) prior to VBM with SPM2 running in MATLAB, with a statistical threshold of  $p < 0.001$  uncorrected for multiple comparisons, rejecting cluster sizes less than 27mm x 3.

Two of the studies used a region-of-interest (ROI) analysis, and one study used voxel-based-morphometry (VBM). Deweer et al. (1995) completed a ROI analysis, manually tracing the hippocampus, amygdala and caudate nucleus, although identifying the ventricles using a semi-automated approach. The volume of each structure was then calculated from surface area by multiplying by inter-slice thickness. Weiner et al. (2011) also completed a ROI analysis, calculating volume change of left and right hippocampus, ventricles and total brain volume between scans at baseline, 24 and 48 weeks. Scans were co-registered to each other to provide a measure of volume change in total brain volume and ventricular volume via the boundary shift interval (Freeborough and Fox, 1997). Hippocampal volume was measured using a semi-automated technique, using a high-dimensional brain mapping tool.

### *3.3.2 DTI*

Flanagan et al. (2016) completed a DTI analysis. Two DTI-weighted sequences were acquired for each participant using 3T magnetic field strength, 32 gradient directions and 2.5x2.5x2.5mm voxel size. Images were co-registered to the MNI template. A ROI

analysis was then conducted using a mask for the fornix, created using the JHU White-Matter Tractography Atlas.

### *3.3.3 fMRI Connectivity Analysis*

Data for the fMRI connectivity analysis conducted by Venneri et al. (2017) were acquired at two different sites. In Italy, 18 participants had two resting-state fMRI echoplanar sequences (voxel dimensions 3.28x3.28x6.0mm) and a complementary 3D anatomical T1-weighted scan (1.1x1.1x6mm voxels) acquired on a 1.5T scanner. In the UK, the remaining 18 participants underwent resting-state fMRI sequences (voxel dimensions 1.8x1.8x4mm) and 3D T1-weighted anatomical scan (0.9x0.9x1.0mm voxels) on a 3T scanner.

Analysis was completed with VBM using SPM12b running in MATLAB. Images were co-registered to MNI space and smoothed with a Gaussian kernel of 6mm FWHM.

Connectivity maps were created using a main seed of interest in the inferior-dorsal portion of the right orbitolateral PFC, contralateral homologous seed in the left orbitolateral PFC as an anatomical control and a third seed in the calcarine cortex as a methodological control – all generated using the WFU PickAtlas toolbox. Only clusters surviving family wise error (FWE) correction at  $p < 0.05$  were considered for interpretation.

### *3.3.4 PET*

Desgranges et al. (2002) investigated resting-state brain glucose utilization (CMRG1c) using FDG-PET. Images were collected from 50 minutes post injection, with 63 septa out planes acquired, (slice thickness 2.43mm, lateral resolution 2.2x2.2mm) with slices positioned parallel to the canthomeatal line. 3-5mCi of  $^{18}\text{F}$ FDG were injected via radial

artery catheter and serial sampling used to determine the time course of  $^{18}\text{F}$ FDG in plasma and average plasma glucose. CMRG1c values were normalised using the cerebellar vermis as a control region. Images were processed using SPM99 in MATLAB, co-registered to a Talairach atlas and smoothed using a 3D Gaussian filter of 14mm. Only voxels with normalised CMRG1c values above 40% of the mean for the whole brain were selected for analysis. A hypothesis-driven ROI analysis was completed, including the right PFC and left hippocampal region, with clusters considered as significant at  $p < 0.05$ , corrected for multiple tests using the small volume corrections routine of SPM99. To test specificity of the results, a further whole brain analysis was completed, with significance threshold of uncorrected  $p < 0.01$ .

### *3.3.5 SPECT*

Reed et al. (1993) used SPECT to measure regional cerebral blood flow (rCBF), using the tracer  $^{123}\text{I}$  N-isopropyl-p-iodoamphetamine (IMP). Images were collected from 10 minutes after injection of a 5mCi bolus of IMP. Two tomographic levels were studied for 20 minutes each, corresponding to 5 and 7cm above and parallel to the orbitomeatal line. A ROI approach was used to investigate frontal cortex, orbitofrontal cortex (OFC), parietal, temporal and occipital cortices. rCBF values (activity/ $\text{mm}^2$ ) were normalised using the occipital cortex as control. No information was provided regarding co-registration or smoothing.

### *3.4 Central Findings*

Measures of volume, connectivity, perfusion and metabolism of medial temporal structures all correlated negatively with measures of false memory, although there was no consensus regarding lateralisation. In terms of structural imaging, the volume of both hippocampal formation and amygdala correlated negatively with intrusions and

false positive errors respectively (Deweer et al., 1995), and the volume of the bilateral medial temporal lobe and right middle temporal gyrus correlated negatively with confabulation (Lee et al., 2009). Functional imaging also revealed findings related to MTL regions, with reduced connectivity between right OFC and right hippocampus and uncus and between left OFC and left parahippocampal and fusiform gyri in those patients with confabulation (Venneri et al., 2017). Further, hypoperfusion of the right temporal lobe correlated with false positive errors (Reed et al., 1993), and hypometabolism in left entorhinal and left perirhinal regions correlated with intrusion errors (Desgranges et al., 2002).

Three studies had findings related to prefrontal regions, with anterior cingulate volume correlating negatively with confabulation (Lee et al., 2009) and hypometabolism in the right dorsolateral PFC correlating with intrusion errors (Desgranges et al., 2002).

Findings related to connectivity of the PFC varied according to laterality, with increased connectivity of the left OFC (with right PFC and anterior cingulate), and reduced connectivity of right OFC (with MTL) in those with confabulations (Venneri et al., 2017).

#### **4. Discussion**

The small number of studies identified by this review and their significant heterogeneity both in terms of false memory measure and imaging methodology means that the results should be interpreted with caution. With these qualifications in mind however, there are some notable patterns in the data, and these findings overlap with neuroimaging data of false memory and confabulation in non-AD populations to implicate both MTL and PFC dysfunction in the generation of false memories.

Neuroimaging studies that have investigated false memory in non-AD populations have shown reduced MTL activity and increased PFC activity (including right dorsolateral PFC

and anterior cingulate) during retrieval of false versus true memories (see Dennis et al. (2015)). The finding of reduced metabolism and connectivity of PFC regions in those with false memory (Desgranges et al., 2002; Venneri et al., 2017) superficially conflicts with the evidence base, but changes due to age-related structural and functional decline may be relevant here. Older adults similarly show reduced MTL function in false memory, with a more mixed picture of PFC involvement (see Devitt and Schacter (2016)). Indeed, similar to the findings of Venneri et al. (2017), older adults have been shown to be more prone to false alarms when they fail to recruit frontoparietal networks (Fandakova et al., 2015). Reduced connectivity between right OFC and MTL (Venneri et al., 2017) could also lead to confabulation through dysfunction of the reality-monitoring mechanism suggested by Schnider (2003), whereby the posterior OFC suppresses activated memories not related to ongoing reality. Clearly, both MTL and PFC are large anatomical areas containing multiple structures with their own distinct functions and connected neural networks. However, due to a lack of replicated findings related to any one of these regions, in the current review it is difficult to draw any more specific conclusions.

#### *4.1 Methodological issues*

There are some relatively significant limitations within the reviewed studies which further impact on the strength of these findings. Over half of the papers received a 'weak' quality rating on risk of bias assessment. The majority of studies had a small sample size and may have been underpowered to detect differences and, significantly, the majority of studies did not report either medication status or medical or psychiatric history of participants. Of note, the study with the largest sample size ( $n = 40$ ) found no significant relationship between hippocampal volume and intrusions (Weiner et al., 2011). Sample selection was an issue in three studies, as Flanagan et al. (2016) included largely early onset cases of AD, which may affect generalisability of results. Reed et al.

(1993) included two patients with clinical depression, and Lee et al. (2009) included 13 patients with delusions. Neither Reed et al. (1993) nor Lee et al. (2009) recorded any control for these clear potential confounders during analysis. Indeed, few studies ( $n = 2$ ) controlled for any potential confounders (age, gender, general cognitive function, attention, executive functioning). Not controlling for baseline measures of cognitive function could particularly lead to misinterpretation of the results of the structural imaging studies (Deweer et al., 1995; Lee et al., 2009), where overall disease severity could be a significant factor related to both reduced medial temporal volume and increase in false memories. There is also cause for concern regarding interpretation of some of the reported p values, as only three of the studies corrected for multiple comparisons, despite the fact that only four of the studies were hypothesis-driven.

Methodological issues were also identified in relation to neuroimaging protocols. All of the studies involved co-registration of images to a pre-existing template, apart from Deweer et al. (1995) and Reed et al. (1993) who both completed their scanning in the early 1990s, prior to significant recent developments in neuroimaging analysis. However, several different templates were used and none of the studies assessed the precision of co-registration, and this is particularly relevant for study of small structures such as the parahippocampal gyrus (Venneri et al. (2017)). Further, none of the studies reported methods to account for head motion, which could have affected image quality.

#### *4.2 Limitations*

The main limitations of this review, as discussed previously, are the small number of studies and the significant heterogeneity, which makes it difficult to meaningfully extrapolate from the results. It is also true that by using a broad definition of false memory (to include false recognition, intrusion and confabulation) we have introduced

further heterogeneity. However, it is generally acknowledged that these phenomena share similar underlying mechanisms (Mendez and Fras, 2011; Van Damme and d'Ydewalle, 2010).

The current review focused solely on neuroimaging correlates, without including other studies of neural correlates (e.g. – electroencephalography) or neuropsychological correlates of false memory. While strict inclusion and exclusion criteria are a strength of this review, this led to the exclusion of studies in which AD participants were combined with MCI or control participants, which could have contained interesting insights. The exclusion of grey literature means that this review has missed unpublished results, which are more likely to have non-significant findings.

#### *4.3 Recommendation for future study*

Given the limited number of studies identified by this review, further investigation of the neural correlates of false memory in AD is clearly warranted to assess the replicability of the above findings. Suggestions for further study are outlined in Figure 2.

#### *4.4 Conclusions*

Few studies have explored the neuroimaging correlates of false memory in AD. This review provides initial support for pre-existing hypotheses that the MTL-PFC network of recollection, familiarity and veracity monitoring is involved in false memory generation in AD. However, further study is necessary to assess replicability of results.

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### Conflicts of interest

None to report.

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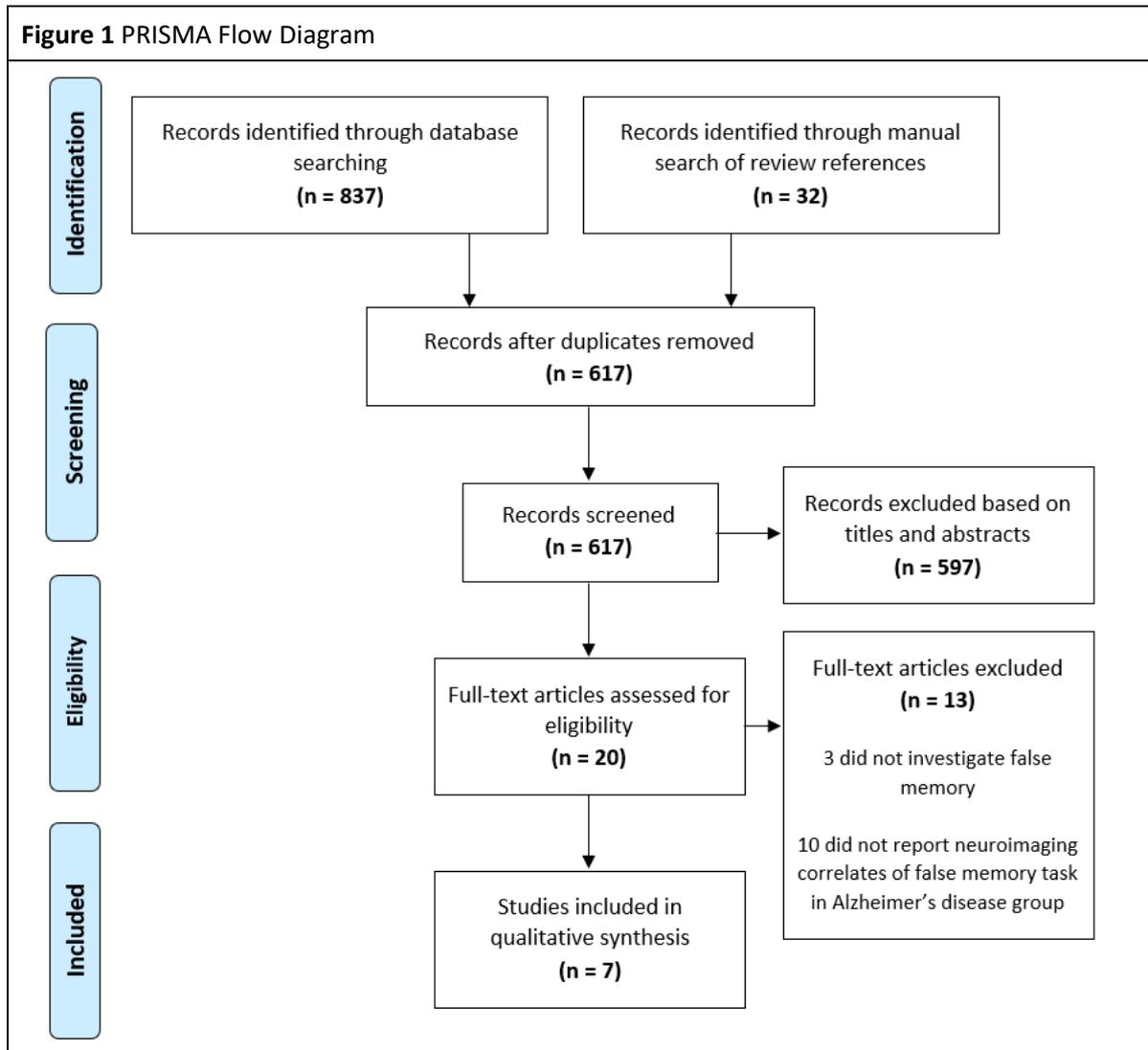
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**Figure 1** PRISMA Flow Diagram



**Table 1** Summary of study characteristics and main findings

Author, year	n	Age, years	% female	% right handed	MMSE	Duration AD, months	Medication status	Measure of false memory	Summary of findings	Quality assessment (score)
Structural Magnetic Resonance Imaging (MRI)										
Deweer <i>et al.</i> , 1995	18	72.4 (1.5)	NR	NR	22.3 (0.9)	28.8 (3.6)	NR	Grober and Buschke test intrusions and false positives	HC formation volume correlates negatively with number of extra list intrusions, percentage of intrusions at cued recall and total recall ( $r=0.60$ , $p=0.009$ , slope=-16.8 (5.6); $r=0.62$ , $p=0.006$ , slope=-42.9 (13.5); $r=0.63$ , $p=0.005$ , slope=-43.8 (13.6) respectively). Amygdala volume correlates negatively with false positives ( $r=0.52$ , $p=0.03$ , slope=-14.4 (6.0)).	Weak (10)
								CVLT intrusions	HC formation volume correlates negatively with number and proportion of intrusions ( $r=0.54$ , $p=0.02$ , slope=-18.5 (7.3) and $r=0.63$ , $p=0.006$ , slope=-35.2 (11.0) respectively). Amygdala volume correlates negatively with number and proportion of extra list intrusions ( $r=0.49$ , $p=0.04$ , slope=-35.0 (16.0) and $r=0.54$ , $p=0.03$ , slope=-49.3 (19.9) respectively).	
Lee <i>et al.</i> , 2009	22	80.4 (6.2) <sup>†</sup>	86.4 <sup>†</sup>	NR	15.7 (4.6) <sup>†</sup>	NR	80.5% donepezil <sup>†</sup> 14.6% antipsychotic <sup>†</sup>	MCB	Volume of anterior cingulate, bilateral MTL and right MTG ( $p<0.001$ ) correlate negatively with semantic confabulation score.	Moderate (7)
Weiner <i>et al.</i> , 2011	40	75.3 (7.6) <sup>†</sup>	63.8 <sup>†</sup>	87.2 <sup>†</sup>	19.1 (3.7)	NR	All taking ChEI	CVLT intrusions	No significant correlation between change in HC volume and change in intrusions on CVLT after 24 weeks of add-on Memantine treatment.	Moderate (7)
Diffusion Tensor Imaging (DTI)										
Flanagan <i>et al.</i> , 2016	37	64.1 (7.5)	43.2	NR	24.0 (3.7)	37.1 (31.2)	NR	RAVLT false positive errors	No significant correlation between fornix integrity and false positives.	Moderate (8)
Functional MRI Connectivity Analysis										
Venneri <i>et al.</i> , 2016	Confabulators							‘Confabulatory tendencies’ on any of: ROCF (delayed recall), paired associates test, prose memory test (immediate or delayed) and CERAD learning and verbal recall	When compared to non-confabulators, confabulators had: <ul style="list-style-type: none"> <li>• Reduced connectivity between right OFC and MTA including right and left STG (<math>p=0.28</math>, 156 voxels, <math>Z=4.13^{\dagger}</math>, <math>p&lt;0.001</math>, 321 voxels, <math>Z=4.09^{\dagger}</math> respectively), right uncus and HC (<math>p=0.28</math>, 156 voxels, <math>Z=3.97</math> and <math>3.75^{\dagger}</math> respectively) and right and left insula (<math>p&lt;0.001</math>, 612 voxels, <math>Z=4.64^{\dagger}</math> and <math>p&lt;0.001</math>, 321 voxels, <math>Z=4.13^{\dagger}</math> respectively)</li> <li>• Reduced connectivity between left OFC and MTA including right and left STG (<math>p=0.005</math>, 230 voxels, <math>Z=4.23^{\dagger}</math> and <math>p&lt;0.001</math>, 491 voxels, <math>Z=4.89^{\dagger}</math> respectively) and left fusiform and PHG (<math>p&lt;0.001</math>, 326 voxels, <math>Z=4.24</math> and <math>4.15^{\dagger}</math> respectively)</li> <li>• Increased connectivity between right OFC and bilateral prefrontal areas including right SFG (<math>p&lt;0.001</math>, 1088 voxels, <math>Z=4.37^{\dagger}</math>) and left SFG and MFG (<math>p=0.008</math>, 200 voxels, <math>Z=4.03</math> and <math>3.74^{\dagger}</math> respectively)</li> <li>• Increased connectivity between left OFC and bilateral frontal areas including right SFG and left MFG (<math>p&lt;0.001</math>, 1329 voxels, <math>Z=4.51</math> and <math>4.48^{\dagger}</math> respectively)</li> </ul>	Weak (8)
	18	68.7 (10.6)	55.6	NR	21.5 (3.3)	NR	NR			
	Non-Confabulators									
	18	66.9 (11.5)	55.6	NR	22.3 (4.0)	NR	NR			

Table 1 (Continued)

Author, year	n	Age, years	% female	% right handed	MMSE	Duration AD, months	Medication status	Measure of false memory	Summary of findings	Quality assessment (score)
Positron Emission Tomography (PET); <sup>18</sup> F-fluoro-2-deoxyglucose (FDG) tracer										
Desgranges <i>et al.</i> , 2002	19	72.9 (5.5)	63.2	100	22.6 (2.4)	NR	'Unmedicated'	Grober and Buschke test free recall intrusions Grober and Buschke test cued recall intrusions	Metabolism (CMRG1c) in right SFG (p<0.05, 445 voxels, Z=2.58), and left STG (p<0.01 uncorrected, 10 voxels, Z=2.36) correlates negatively with intrusions in free recall. Metabolism (CMRG1c) in left entorhinal cortex (p<0.05, 44 voxels, Z=2.72) and left perirhinal cortex (p<0.01 uncorrected, 14 voxels, Z=2.41) correlates negatively with intrusions in cued recall.	Weak (8)
Single Photon Emission Computed Tomography (SPECT); <sup>123</sup> I N -isopropyl-p-iodoamphetamine (IMP) tracer										
Reed <i>et al.</i> , 1993	20	71.0 (6.5)	50.0	NR	NR	NR	Excluded if taking antidepressants/antipsychotics	CVLTm intrusions	Right temporal lobe perfusion (rCBF) correlates negatively with false positive errors (p<0.05, r=-0.47).	Weak (10)

Notes: All included studies are cross-sectional. Values are reported as mean (SD) unless otherwise specified.

† demographic details are unavailable for subgroup who received imaging, therefore details of larger sample are provided.

‡ peak Z score

AD – Alzheimer's disease; CERAD - Consortium to Establish a Registry for Alzheimer's Disease; ChEI – Cholinesterase Inhibitor; CVLT – California Verbal Learning Test; HC – hippocampus; MCB – Modified Confabulation Battery; MFG – medial frontal gyrus; MTA – medial temporal area; MTG – medial temporal gyrus; MTL - medial temporal lobe; NR – not reported; OFC - orbitofrontal cortex; PHG – parahippocampal gyrus; RAVLT - Rey Auditory Verbal Learning Test; ROCF – Rey-Osterrieth Complex Figure; SD – standard deviation; SFG – superior frontal gyrus; STG – superior temporal gyrus

**Figure 2** Suggestions for Future Research Directions

- Exploratory voxel-based analyses and hypothesis-driven research in larger samples
- Future studies to control for variation in attention and upstream memory processes
- To explore the effect of, and consider controlling for, age, gender and APOE status on false memory and neuroimaging measures in AD
- To explore the relationship between neural correlates of false memory and AD biomarkers
- Use of the DRM to further explore this area, given the wealth of non-imaging studies using this tool to explore false memory in AD