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Review Article

Current understanding of magnetic resonance imaging biomarkers and memory in Alzheimer's disease

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Abstract Alzheimer's disease (AD) is caused by a cascade of changes to brain integrity. Neuroimaging biomarkers are important in diagnosis and monitoring the effects of interventions. As memory impairments are among the first symptoms of AD, the relationship between imaging findings and memory deficits is important in biomarker research. The most established magnetic resonance imaging (MRI) finding is hippocampal atrophy, which is related to memory decline and currently used as a diagnostic criterion for AD. While the medial temporal lobes are impacted early by the spread of neurofibrillary tangles, other networks and regional changes can be found quite early in the progression. Atrophy in several frontal and parietal regions, cortical thinning, and white matter alterations correlate with memory deficits in early AD. Changes in activation and connectivity have been detected by functional MRI (fMRI). Task-based fMRI studies have revealed medial temporal lobe hypoactivation, parietal hyperactivation, and frontal hyperactivation in AD during memory tasks, and activation patterns of these regions are also altered in preclinical and prodromal AD. Resting state fMRI has revealed alterations in default mode network activity related to memory in early AD. These studies are limited in part due to the historic inclusion of patients who had suspected AD but likely did not have the disorder. Modern biomarkers allow for more diagnostic certainty, allowing better understanding of neuroimaging markers in true AD, even in the preclinical stage. Larger patient cohorts, comparison of candidate imaging biomarkers to more established biomarkers, and inclusion of more detailed neuropsychological batteries to assess multiple aspects of memory are needed to better understand the memory deficit in AD and help develop new biomarkers. This article reviews MRI findings related to episodic memory impairments in AD and introduces a new study with multimodal imaging and comprehensive neuropsychiatric evaluation to overcome current limitations.

Keywords: Alzheimer's disease; Dementia; Magnetic resonance imaging; Memory; Biomarker

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder resulting from pathological changes which typically spread through brain networks in a predictable pattern. AD pathology leads to early decline in memory, and some pathology can be detected years before measurable cognitive or functional change. At present, there are no disease-modifying treatments, and symptomatic treatment is limited in efficacy. Trials of novel therapeutics increasingly target the earliest brain changes, when a disease-modifying trajectory could potentially result in reduction or elimination of clinical impact. Memory measures remain an important way of assessing such clinical impact and are required in clinical trials in the United States [1].

Accurate diagnosis of AD was, until recently, confirmed only at autopsy. Today, there are several imaging biomarkers measuring neurodegeneration and amyloid β (Aβ) deposition in the brain to support the diagnosis [2]. Atrophy on

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structural magnetic resonance imaging (MRI), hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET), and increased levels of craniospinal fluid (CSF) total and phosphorylated tau are used to assess neurodegeneration. CSF Aβ42 and Aβ PET, on the other hand, are used to assess Aβ pathology. Preclinical studies focus on groups at risk for AD, as defined by the apolipoprotein E (APOE) status or examine cognitively normal control (CNC) performance in the context of other AD biomarkers, such as CSF Aβ. Large, shared, multisite, longitudinal multimodal data sets such as the AD Neuroimaging Initiative and similar studies initiated in Asia, Europe, and Australia allow for widespread exploration of structural and functional magnetic resonance imaging (fMRI) and PET data in addition to clinical, cognitive, and fluid biomarker data across the spectrum of disease. While there are several limitations, these data sets are an important resource in understanding imaging biomarkers in AD.

Memory is a complex construct. AD has an early and specific impact on episodic memory (i.e., the ability to learn and remember new information) [3], which can broadly be subdivided into encoding (or learning), recall, and recognition. Different types of stimuli (e.g., words, faces, and shapes) and memory tests (e.g., single trial and multi-trial presentations, free and prompted recall) can be used to detect deficits in these aspects of memory, and typically used measures often differ between clinical and research settings. Nonetheless, many studies of AD MRI biomarkers and biomarker candidates have included memory measures as correlates or validating factors.

At present, despite exploration of imaging biomarkers for AD, few have become widely accepted and approved for clinical use, and most remain experimental. In this targeted review, we focused on MRI studies. Following the conceptualization of AD as a biological and clinical continuum by Aisen et al [4], we assessed the MRI findings within preclinical (clinically normal individuals with evidence of AD pathology), and clinical (mild cognitive impairment [MCI] or prodromal AD, and AD dementia [ADD]) phases of AD. The transition between these phases is subtle, and individuals may report cognitive decline even when neuropsychological testing does not suggest any impairment. As episodic memory is the first cognitive domain to be affected along the course of AD, we aimed to investigate the association between MRI findings and episodic memory performance specifically. Current diagnostic criteria of MCI (prodromal AD) and ADD are based on clinical history, neuropsychological testing, and neurologic and psychiatric examinations [5,6]. Imaging methods, CSF, and blood tests are used only to support the diagnosis and to exclude other dementia causes. Nevertheless, subtle findings on MRI have been reported years before the onset of clinical symptoms. Thus, imaging findings correlating with the clinical profile may help identify underlying mechanisms and therapeutic targets for the debilitating memory deficit in AD.

2. Structural MRI

Aging is associated with a slow decline in both white matter (WM) and gray matter (GM) volumes, and this atrophy rate is increased in AD [7]. Although GM atrophy has been more frequently assessed in AD, structural MRI approaches also allow for the assessment of cortical thickness, as well as shape and WM alterations. This section will focus on studies investigating the relationship between episodic memory performance and structural changes in GM and WM using different imaging analysis approaches (Table 1). Structural differences between CNC and participants within AD spectrum without any episodic memory associations are beyond the scope of this review and will not be discussed.

2.1. GM changes

Hippocampal atrophy is included in the 2011 National Institute on Aging criteria for ADD and MCI due to AD [3,5]. Before the advent of Aβ PET imaging, hippocampal volumetric changes that can be determined noninvasively and relatively cheaply using MRI were one of the earliest detectable imaging changes in AD. These changes can be quantified using NeuroQuant, an Food and Drug Administration-approved imaging processing tool [42]. Decline in hippocampal volume and thickness has been consistently associated with memory deficits in AD continuum. In preclinical AD, hippocampal and entorhinal cortex volume, and hippocampal and parahippocampal thickness have been associated with verbal memory [9,12,30]. There have also been reported associations between reduced medial temporal lobe (MTL) volume in CNC with AD risk factors and future memory decline [8]. Further along the course of the disease, in MCI and ADD, decline in hippocampal volume and MTL thickness was associated with worsening in verbal memory [13,16,19,21,23–27,29,33–35,39,40]. Although less extensively studied, visual memory has been associated with hippocampal volume in amnestic MCI (aMCI) [39]. Studies of hippocampal subregions revealed that CA1 volume declines within hippocampus were particularly related with recall performance in aMCI and ADD [26,29,37].

With time, GM changes in AD spread outside the MTL. Extratemporal regions implicated in episodic memory decline include the posterior cingulate gyrus (PCG)/precuneus [28,30,31] and middle frontal gyrus [27,28]. Both atrophy and thinning of these regions were associated with memory decline. In MCI patients, who converted to ADD over time, decreased inferior frontal gyrus volume was associated with the verbal memory decline [38], suggesting extratemporal involvement may be predictive of disease progression.

2.2. WM changes

While AD is a disease primarily associated with GM loss, concomitant WM change has a role in cognitive expression.

Table 1
Structural MRI correlates of episodic memory

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
Preclinical AD				
Jagust, et al 2006 [8]	60 CNC (6 dementia or MCI converters) (2-year follow-up)	Word list	HC and entorhinal cortex volumetry/ FDG-PET	HC and entorhinal cortex volume predicted delayed recall decline over time.
Lind, et al 2006 [9]	30 APOE ε4 carrier, 30 noncarrier CNC	Word categorization task	HC volumetry	R HC volume negatively correlated with number of false alarms in APOE ε4 carriers.
Westlye, et al 2012 [10]	31 APOE ε4 carrier, 61 noncarrier CNC (3-4 year follow-up)	CVLT-II	Entorhinal cortex, parahippocampal gyrus thickness and WM volumetry, DTI	Entorhinal WM FA positively correlated with memory in the APOE ε4 carriers.
Zhuang, et al 2012 [11]	193 CNC (20 aMCI converters in 2 years)	Logical Memory, RAVLT	VBM, DTI	Lower baseline L parahippocampal cingulum, inferior temporal lobe WM, parahippocampal gyrus, thalamus FA associated with worse verbal memory decline. L parahippocampal gyrus WM was predictive of subsequent memory decline.
Dowell, et al 2016 [12]	21 APOE ε4 carrier, 20 noncarrier young CNC, and 17 APOE ε4 carrier, 20 noncarrier mid-age CNC	Word list	HC and parahippocampus thickness, WM volumetry	Parahippocampal thickness positively correlated with memory in young APOE ε4 carriers.
MCI				
Chetelat, et al 2003 [13]	21 aMCI	Word list	VBM/FDG-PET	HC volume positively correlated with memory.
Stoub, et al 2006 [14]	40 aMCI, 50 CNC	East Boston Story, WMS-R, CERAD-WL	HC and entorhinal cortex volumetry, WM VBM	Entorhinal cortex, HC and total parahippocampal WM were significant predictors of memory.
Goldstein, et al 2009 [15]	14 aMCI, 9 CNC	CERAD-WL, Story A of Logical Memory, BVMT-R	DTI	Temporal and whole brain apparent diffusion coefficient negatively, whole brain FA positively correlated with verbal memory in aMCI.
Wang, et al 2009 [16]	10 MCI (4 ADD converters in 3 years), 12 CNC	CERAD-WL, Logical Memory	HC, parahippocampal gyrus, amygdala volumetry, lobar masking method for frontal, lateral temporal, parietal occipital ROIs/SPECT	MTL volume positively correlated with memory.
Zhuang, et al 2012 [17]	76 aMCI, 51 naMCI, 206 CNC	Logical Memory, RAVLT, Benton Visual Retention Test	HC DBM, fornix DTI	L fornix radial diffusivity negatively correlated with verbal memory.
Meyer, et al 2013 [18]	25 aMCI	CERAD, CANTAB, WMS-R	VBM	Temporal WM volume positively correlated with pattern recognition. Parahippocampal gyrus and L precuneus WM volume positively correlated with story recall.
Fujishima, et al 2014 [19]	186 MCI, 136 CNC	Logical Memory II	Cortical thickness, WMH probability map of the whole brain	L entorhinal cortex thickness positively; WMH volume in the posterior periventricular regions and near the R anterior horn of the lateral ventricle negatively correlated with memory.
Remy, et al 2015 [20]	22 aMCI, 15 CNC	RCFT, DMS48 test	HC volumetry, DTI	L uncinate fasciculus FA positively correlated with recognition.
Peter, et al 2016 [21]	20 MCI, 20 CNC	Verbal Learning and Memory Test	HC and basal forebrain cholinergic system volumetry	HC volume positively correlated with memory.

(Continued)

Table 1
Structural MRI correlates of episodic memory (*Continued*)

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
Gyebnar, et al 2018 [22]	18 aMCI, 20 naMCI, 27 CNC	CANTAB, RAVLT	Voxel- and ROI-based DTI	Voxel-based: R inferior frontal gyrus pars triangularis FA negatively correlated with visual memory. L parahippocampal gyrus MD negatively correlated with verbal memory. ROI-based: Left cingulum MD negatively correlated with verbal memory, and L stria terminalis/crus of the fornix MD positively correlated with visual memory.
ADD				
Deweer, et al 1995 [23]	18 ADD	WMS, CVLT, Grober and Buschke test	Hippocampal formation, amygdala, caudate nucleus, and ventricle volumetry	Hippocampal formation volume positively correlated with memory.
Kramer, et al 2005 [24]	13 ADD, 11 frontotemporal dementia, 10 semantic dementia, 8 CNC	CVLT	HC, frontal, anterior temporal lobes, and posterior cortex volumetry	HC volume was the only predictor of delayed recall.
Sarazin, et al 2010 [25]	35 ADD	The Free and Cued Selective Reminding Test	VBM, HC volumetry, and three-dimensional hippocampal surface-based shape analysis	VBM: L MTL, and thalamus volume positively correlated with total recall. Automatic hippocampal volumetry: L HC volume positively correlated with total recall. Three-dimensional hippocampal surface-based shape analysis: HC CA1 field volume positively correlated with free and total recall.
Yakushev, et al 2010 [26]	20 ADD, 18 CNC	CERAD	HC volumetry and diffusivity	L body-tail volume positively correlated with recall in ADD. L head diffusivity negatively correlated with delayed verbal recall.
Wolk, et al 2011 [27]	146 ADD	RAVLT, Logical Memory, ADAS-Cog-Word list	Rostral MTL, rostral inferior temporal gyrus, temporal pole, angular gyrus, supramarginal gyrus, superior parietal lobule, precuneus, superior frontal gyrus, inferior frontal sulcus/caudal middle frontal gyrus thickness	HC, MTL, caudal middle frontal gyrus, temporal pole thickness positively correlated with memory.
Irish, et al 2012 [28]	11 ADD, 11 semantic dementia, 10 CNC	Modified version of the past–future task	VBM	R frontal pole, R PCG and precuneus, L inferior temporal and L middle frontal gyri volume positively correlated with past retrieval in ADD and CNC.
Kerchner, et al 2012 [29]	9 ADD	HVLT-R, BVMT-R, Logical Memory	CA1-SP, CA1-SRLM, and entorhinal cortex thickness; DG/CA3 and hippocampal cross-sectional area (proxy for total HC volume) volumetry	CA1- SRLM and entorhinal cortex width, HC volume positively correlated with recall.
Dore, et al 2013 [30]	40 ADD, 93 CNC	CVLT-II, Logical Memory II	HC, temporal lobe, precuneus and PCG thickness combined with a voxel-based approach/PiB PET	R temporal lobe and R precuneus/PCG thickness positively correlated with memory in CNC with high PiB retention. HC thickness positively correlated with memory in both CNC groups.

(*Continued*)

Table 1
Structural MRI correlates of episodic memory (*Continued*)

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
Irish, et al 2013 [31]	10 ADD, 10 frontotemporal dementia, 10 CNC	Modified version of the past–future task	VBM	L PCG volume positively correlated with past retrieval in ADD and CNC.
MCI and ADD				
Fellgiebel, et al 2005 [32]	17 aMCI, 25 ADD, 21 CNC	Delayed verbal recall test	DTI	PCG bundle FA positively, MD negatively correlated with memory.
Leube, et al 2008 [33]	21 MCI, 12 ADD, 29 CNC	Verbal learning and memory test	VBM	HC, L perirhinal cortex, L parahippocampal gyrus, L ventral anterior cingulate and R posterior entorhinal cortex, R middle temporal gyrus volume positively correlated with memory.
Sexton, et al 2010 [34]	8 MCI, 7 ADD, 8 CNC	HVLT-R, RCFT	HC volumetry, cingulum and fornix DTI	HC volume, L crus of the fornix FA positively; cingulate gyrus MD negatively correlated with memory.
Molinuevo, et al 2011 [35]	24 aMCI, 27 MCI (ADD converters in 2 years), 31 ADD, 27 CNC	CERAD-recall of constructional praxis, delayed text memory, memory alteration tests	VBM	L lateral, medial, inferior, and R medial, inferior gyri volume positively correlated with memory over time. L medial temporal gyrus positively correlated with delayed text memory.
Bosch, et al 2012 [36]	16 aMCI, 15 ADD, 15 CNC	CERAD-recall of constructional praxis, Grober and Buschke test	DTI	Whole brain FA positively correlated with memory.
Kerchner, et al 2013 [37]	15 aMCI, 11 ADD, 9 young CNC, 18 old CNC	HVLT-R, BVLT-R, Logical Memory	CA1-SP, CA1-SRLM, and entorhinal cortex thickness; DG/CA3 and hippocampal cross-sectional area volumetry	CA1-SRLM width positively correlated with recall in aMCI.
Defrancesco, et al 2014 [38]	14 MCI, 13 MCI (ADD converters), 28 CNC	CERAD-WL, CERAD-figural memory	GM and WM VBM, MD reflected by apparent diffusion coefficient maps	L putamen and inferior frontal gyrus volume positively correlated with verbal memory in ADD converters.
Bonner-Jackson, et al 2015 [39]	82 aMCI, 13 naMCI, 72 other neurological disorders, 34 ADD, 25 CNC	HVLT-R, BVMT-R	HC volumetry	Bilateral HC volume positively correlated with memory. HC volume positively correlated with non-verbal memory in aMCI.
Gomar, et al 2017 [40]	9 aMCI, 9 ADD, 44 CNC	Relational and item-specific encoding task	Entorhinal, perirhinal, parahippocampal cortices thickness, HC volumetry	HC volume, perirhinal and parahippocampal thickness predicted encoding performance.
Reas, et al 2017 [41]	12 MCI, 13 ADD, 31 CNC	WMS-R, CVLT, CERAD	Restriction spectrum imaging in fiber tracts, HC and entorhinal cortex GM; DTI	Fornix, uncinated, inferior fronto-occipital, inferior longitudinal and arcuate fasciculi neurite density positively correlated with recall. HC and entorhinal cortex isotropic free water diffusion negatively correlated with memory.

Abbreviations: MCI, mild cognitive impairment; APOE ε4, apolipoprotein E ε4; CNC, cognitively normal control; aMCI, amnestic mild cognitive impairment; ADD, Alzheimer's disease dementia; naMCI, nonamnestic mild cognitive impairment; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; WMS-R, Wechsler Memory Scale-Revised; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CERAD-WL, CERAD-Word list; BVMT-R, Brief Visuospatial Memory Test-Revised; CANTAB, Cambridge Neuropsychological Test Automated Battery; RCFT, Rey Complex Figure Test; DMS48, delayed matching to sample-48 items; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; HVLT-R, Hopkins Verbal Learning Test-Revised; HC, hippocampus; FDG-PET, fluorodeoxyglucose positron emission tomography; WM, white matter; DTI, diffusion tensor imaging; VBM, voxel-based morphometry; ROI, region of interest; SPECT, single-photon emission computed tomography; DBM, deformation based morphometry; WMH, white matter hyperintensity; MTL, medial temporal lobe; CA, cornu ammonis; CA1-SP, CA1-stratum pyramidale; CA1-SRLM, CA1-stratum radiatum/stratum lacunosum-moleculare; DG/CA3, dentate gyrus/CA3; PCG, posterior cingulate gyrus; PiB PET, Pittsburgh compound B PET; GM, gray matter; MD, mean diffusivity; R, right; L, left; FA, fractional anisotropy.

Table 2
Task-based fMRI correlates of episodic memory

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
Preclinical AD				
Han, et al 2007 [45]	12 APOE ε4 carrier, 13 noncarrier CNC	Word pair association	Whole brain, ROI (HC)/HC volumetry	Increased R anterior cingulate, lingual, middle temporal, middle frontal gyri, PCG, precuneus and cerebellar tonsil activation in APOE ε4 carriers.
Quiroz, et al 2010 [46]	20 Presenilin 1 mutation carriers, 19 noncarrier CNC	Face-name association	Whole brain, ROI (HC)	Increased right anterior HC activation during encoding in presenilin 1 mutation carriers.
Adamson, et al 2011 [47]	10 APOE ε4 carrier, 11 noncarrier CNC	Spatial encoding	ROI (HC)	Reduced HC activation in APOE ε4 carriers.
Erk, et al 2011 [48]	19 subjective memory impairment, 20 CNC	Face-profession association	ROI (HC, DLPFC)	Reduced right HC activation, increased right DLPFC activation in subjective memory impairment group.
Chen, et al 2017 [49]	35 APOE ε4 carrier, 40 noncarrier CNC	Picture encoding	Seed ROI based on group cortical morphology differences and DMN/cortical thickness	Reduced precuneus deactivation, reduced postcentral, precentral, inferior occipital gyri, inferior parietal lobule activation in APOE ε4 carriers.
MCI				
Johnson, et al 2006 [50]	14 MCI, 14 CNC	Picture encoding	Reference group activation	Reduced R HC head and body, L lateral frontal, R inferior temporal lobe activation in MCI during novel pictures. Reduced R PCG/precuneus activation during previously learned items in MCI.
Petrella, 2006 et al [51]	20 aMCI, 20 CNC	Face-name association	Whole brain	Reduced frontal cortex, L cerebellum activation during encoding. Reduced frontal lobe, L HC; increased posterior frontal lobe activation during retrieval.
Heun, et al 2007 [52]	21 MCI, 29 CNC	Verbal encoding	Whole brain	Increased R superior, inferior and L middle frontal gyri activation in MCI.
Kircher, et al 2007 [53]	21 MCI, 29 CNC	Verbal encoding	Whole brain	Increased L HC, medial frontal, postcentral and cingulate gyri activation in MCI
Dannhauser, et al 2008 [54]	10 aMCI, 10 CNC	Verbal encoding	Whole brain	Reduced L ventrolateral PFC activation stretching into premotor cortex in aMCI.
Trivedi, et al 2008 [55]	16 aMCI, 23 CNC	Picture encoding	Whole brain, ROI (frontal cortex, MTL, PCG, inferior parietal cortex)	Reduced inferior frontal, R inferior parietal and parahippocampal cortex activation in aMCI during encoding. Reduced L inferior frontal cortex; increased R HC activation in aMCI during recognition.
Machulda, et al 2009 [56]	19 aMCI, 12 naMCI, 29 CNC	Scene encoding	Whole brain	Reduced temporoparietal and frontal activation in MCI during encoding. Reduced temporoparietal activation in aMCI during recognition.
Mandzia, et al 2009 [57]	14 MCI, 14 CNC	Object and animal encoding	ROI (HC and parahippocampal gyrus)	Reduced L superior and middle temporal, R middle temporal gyri, precuneus, L cuneus, anterior cingulate, R lentiform nucleus, caudate and putamen activation during deep encoding. Reduced L parahippocampal, fusiform, R middle temporal gyri, R inferior frontal, inferior parietal regions, caudate, L cerebellum, middle occipital gyrus and cuneus activation during shallow encoding. Reduced L HC, superior and middle frontal, R lateral inferior and medial frontal gyri, cingulate, L thalamus and middle occipital gyrus activation in during deeply encoded item recognition. Reduced L lentiform nucleus and putamen; increased L fusiform and superior frontal, R cingulate gyri activation during shallowly encoded item recognition.
Clement and Belleville, 2010 [58]	28 MCI, 12 CNC	Word pair association	Whole brain, ROI (HC)	Increased R dorsolateral, ventrolateral PFC, premotor and motor area activation MCI with higher cognition scores. Reduced R occipital lobe and L inferior parietal lobule; increased dorsal L inferior parietal lobule activation in MCI with lower cognition scores. Increased L temporal regions, R precentral gyrus,

(*Continued*)

Table 2
Task-based fMRI correlates of episodic memory (*Continued*)

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
				dorsolateral PFC, L inferior and bilateral superior parietal lobules activation in the MCI with higher cognition scores compared with MCI with lower scores.
Clement, et al 2010 [59]	12 MCI, 10 CNC	Verbal encoding	Whole brain, ROI (HC)	Reduced occipital lobe, R middle and superior temporal gyri, R thalamus, R anterior cingulate, R medial frontal lobe; increased L ventrolateral PFC activation during encoding. Reduced medial frontal lobe; increased premotor area activation during retrieval.
Yassa, et al 2010 [60]	10 aMCI, 10 CNC	Picture encoding	ROI (L CA3/DG, CA1, subiculum, entorhinal cortex)	Increased CA3/DG and reduced entorhinal cortex activation.
Hampstead, et al 2011 [61]	18 aMCI, 16 CNC	Object-location association	Whole brain, ROI (HC)	Reduced ventral and dorsal visual streams, frontal areas, dorsal precuneus, HC, perirhinal cortex, PCG, retrosplenial cortex, thalamus; increased mid-precuneus and L temporoparietal junction activation.
Hanseeuw, et al 2011 [62]	16 aMCI, 16 CNC	Verbal encoding	Whole brain/HC volumetry	HC volume positively correlated with associative memory in aMCI. Reduced L anterior HC activation.
Lenzi, et al 2011 [83]	15 aMCI, 14 CNC	Verbal encoding, Story Recall	Whole brain, ROI (HC, L inferior temporal, R superior temporal gyri)/VBM	Increased R superior temporal gyrus activation. This activation negatively correlated with Story Recall.
Giovanello, et al 2012 [63]	12 aMCI, 12 CNC	Word pair association	Whole brain	Reduced R inferior and superior frontal gyri, increased anterior cingulate and inferior frontal gyrus activation.
Jin, et al 2012 [64]	8 aMCI, 8 CNC	Scene encoding, face-occupation and object-location association	Whole brain, ROI (MTL)	Reduced MTL; increased medial PFC, L precentral and superior motor area activation during scene encoding. Increased L angular gyrus, R cuneus/precuneus activation during face-occupation task. Reduced R Rolandic operculum, insula; increased precentral and postcentral gyri activation during the object-location task.
ADD				
Rombouts, et al 2000 [65]	12 ADD, 10 CNC	Picture encoding	Whole brain	Reduced activation in L HC and bilateral parahippocampal gyrus.
Kato, et al 2001 [66]	7 ADD, 8 young CNC, 8 old CNC	Picture encoding	Whole brain/ hippocampal formation and entorhinal cortex volumetry	Reduced R entorhinal cortex, supramarginal gyrus, prefrontal regions, L anterior inferior temporal lobe activation during encoding. Activations in these regions positively correlated with memory in the overall sample.
Gron, et al 2002 [67]	12 ADD, 12 major depressive disorder patients, 12 CNC	Geometric pattern encoding	Whole brain	Reduced parahippocampal gyrus, HC, temporal cortex, R anterior caudate; increased L middle frontal, R inferior frontal gyri and inferior parietal cortex activation.
Lustig, et al 2003 [68]	23 ADD, 32 young CNC, 27 old CNC	Verbal encoding	ROI (lateral parietotemporal, medial frontal, medial parietal/ PCG, L frontal region)	Reduced medial parietal/PCG deactivation.
Sperling, et al 2003 [69]	7 ADD, 10 young CNC, 10 old CNC	Face-name association	Whole brain/HC volumetry	Reduced hippocampal formation; increased medial parietal cortex, R PCG, superior frontal cortex activation during encoding. Increased superior frontal cortex activation during recall.
Golby, et al 2005 [70]	7 ADD, 7 CNC	Scene encoding	Whole brain, ROI (hippocampal gyrus, parahippocampal gyrus, entorhinal cortex, subiculum,	Reduced MTL, fusiform, lateral occipital activation.

(*Continued*)

Table 2
Task-based fMRI correlates of episodic memory (*Continued*)

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
			fusiform gyrus, calcarine cortex)	
Gould, et al 2005 [71]	12 ADD, 12 CNC	Visuospatial paired association	Whole brain	No differences.
Pariente, et al 2005 [72]	12 ADD, 17 CNC	Face-name association	Whole brain	Increased parietofrontal network activation during encoding. Reduced R HC, increased L parietal lobule and the L inferior frontal gyrus activation during recall.
Remy, et al 2005 [73]	8 ADD, 11 CNC	Verbal encoding	Whole brain/VBM, HC volumetry	Reduced inferior parietal cortex, inferior frontal gyrus, L precentral gyrus, R temporal associative area, L PCG, L perirhinal cortex, and cerebellum; increased medial cerebellum and L middle frontal gyrus activation during encoding. Reduced L inferior frontal and precentral gyri, R lenticular nucleus, R HC and retrosplenial cortex, R inferior parietal cortex, superior temporal gyrus and cerebellum; increased inferior temporal gyrus, L lateral middle and superior frontal gyri activation during recognition.
Gould, et al 2006 [74]	12 ADD, 12 CNC	Visuospatial paired association	Whole brain, ROI (bilateral inferior, middle, superior frontal gyri, medial prefrontal cortex)	Increased L medial and R lateral prefrontal cortex activation during encoding.
Pihlajamaki, et al 2008 [75]	15 ADD, 29 CNC	Face-name association	Whole brain, ROI (HC and medial parietal regions)	Whole brain: Increased middle and inferior prefrontal gyri, L superior parietal lobule, intraparietal sulcus and supramarginal gyrus activation. ROI: Increased L MTL activation. Reduced precuneus, R PCG, L lateral parietal cortex deactivation.
Peters, et al 2009 [76]	16 ADD, 16 CNC	Verbal encoding	Whole brain, ROI (inferior frontal, precentral, middle frontal gyri, insula, posterior parietal, caudate, cerebellum, inferior parietal sulcus, HC, parahippocampus)	Reduced middle frontal, L inferior frontal and transverse temporal gyri, R precuneus activation during encoding. Reduced supplementary motor area, superior frontal, precentral, supramarginal, L postcentral and R middle frontal gyri; increased fusiform gyrus activation during recognition.
MCI and ADD				
Machulda, et al 2003 [77]	9 MCI, 9 ADD, 11 CNC	Picture encoding	ROI (HC, parahippocampal and fusiform gyri)	Reduced MTL activation in MCI and ADD.
Dickerson, et al 2005 [78]	9 MCI, 10 ADD, 10 CNC	Face-name association	ROI (hippocampal formation, entorhinal cortex)/ MTL volumetry	Increased HC activation in MCI. Reduced HC and entorhinal activation in ADD.
Celone, et al 2006 [79]	15 low-CDR MCI, 12 high-CDR MCI, 10 ADD, 15 CNC	Face-name association	Whole brain, ROI (determined by regions contributing significantly to the independent components)	Increased HC and functionally connected neocortical regions activation, increased DMN deactivation in MCI group with low CDR. Reduced HC activation and DMN deactivation in MCI group with high CDR and ADD.
Hamalainen, et al 2007 [80]	14 MCI, 15 ADD, 21 CNC	Picture-name association	Whole brain	Increased thalamus and L ventral visual stream extending to the posterior parahippocampal gyrus and HC activation in MCI.
Petrella, et al 2007 [81]	34 aMCI, 13 ADD, 28 CNC	Face-name association, CVLT	Whole brain	Reduced MTL; increased the posteromedial cortex activation along the spectrum from CNC to ADD. Posteromedial cortex activation magnitude associated with CVLT.

(*Continued*)

Table 2
Task-based fMRI correlates of episodic memory (*Continued*)

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
Pihlajamaki and Sperling, 2009 [82]	30 MCI (10 APOE ε4 carriers), 15 ADD (9 APOE ε4 carriers), 29 CNC (8 APOE ε4 carriers)	Face-name association	ROI (PCG, retrosplenial and precuneal regions)	Reduced L precuneus in MCI; bilateral PCG/precuneus deactivation in ADD. Reduced R PCG and bilateral precuneus deactivation in APOE ε4 carrier CNC compared to noncarrier CNC; reduced cuneus deactivation in APOE ε4 carrier ADD compared to noncarrier ADD.

Abbreviations: APOE ε4, apolipoprotein E ε4; CNC, cognitively normal control; MCI, mild cognitive impairment; aMCI, amnestic mild cognitive impairment; naMCI, nonamnestic mild cognitive impairment; ADD, Alzheimer's disease dementia; CDR, Clinical Dementia Rating; CVLT, California Verbal Learning Test; ROI, region of interest; HC, hippocampus; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; MTL, medial temporal lobe; PCG, posterior cingulate gyrus; DG, dentate gyrus; L, left; R, right; VBM, voxel-based morphometry; PFC, prefrontal cortex.

Diffusion tensor imaging metrics characterizing brain WM integrity are commonly affected in the AD continuum. Increased WM integrity for the whole brain was associated with better memory performance in CNC, MCI, and ADD, suggesting whole brain fractional anisotropy might be an overall marker of severity, rather than a specific measure [15,36].

Genetic status may mediate the relationship between MRI findings and cognition. In APOE ε4 carriers, loss of entorhinal WM integrity was related to worse memory performance [10]. However, other factors such as lower baseline MTL WM integrity have also been identified as predictors of memory decline in CNC converting to aMCI in 2 years [11], which can have the potential to be used as a biomarker for early diagnosis. MTL WM volume and integrity continued to have positive correlations with memory in aMCI and ADD [14,17,18,26,32,34]. Similar to GM changes, which include both MTL and extratemporal regions, precuneus WM volume reduction was also associated with worsened memory in aMCI [18]. Several fasciculi including uncinate, fornix, and cingulum, which are connected to medial temporal regions, were implicated in studies associating fiber density and memory [20,22,41]. In addition to these WM volume and integrity changes, Fujishima et al [19] reported that increased number of WMHs, pointing to increased vascular impairment, in the bilateral periventricular regions was related to worse recall performance in MCI.

Besides these more common MRI techniques, other approaches including diffusion kurtosis imaging, relaxometry, and magnetic transfer imaging may prove to be helpful in investigating WM integrity with high accuracy for whole brain mapping [43,44]. However, the number of studies using these approaches within the AD continuum is currently relatively small.

In summary, structural imaging studies show that hippocampal atrophy, which is closely related to episodic memory performance, is an established neurodegeneration biomarker in AD. Volume and cortical thickness of several additional regions, including PCG and precuneus, require further attention in terms of relationship to memory performance. WM changes, including loss of WM integrity in MTL and fasciculi connected to MTL assessed by formal diffusion tensor imaging metrics and hyperintensities in posterior regions of the brain, were also related to memory decline and should be assessed further in confirmed AD samples.

3. Functional MRI

fMRI is an indirect measure of brain activity relying on blood-oxygen-level dependent response, which is a proxy for neural activation. fMRI can be separated into task-based, when a participant is asked to engage in a task during scanning, or resting state, when the participant is asked to lie still without engaging in a task. In this section, we will summarize studies finding differences between those with preclinical or clinical AD and CNC, either on memory tasks during fMRI, or with resting state fMRI interpreted in relation to memory scores.

3.1. Task-based fMRI

Many studies have implemented task-based fMRI to investigate memory-related activation patterns in AD (Table 2). A variety of tasks have been used, most notably association tasks that pair two different stimuli (e.g., a face and a name). Whereas most studies include verbal stimuli, several studies use nonverbal stimuli (e.g., scene and picture encoding). Results of these studies support and extend the previously mentioned structural MRI findings.

3.1.1. Preclinical AD

Individuals with AD risk exhibit changes in blood-oxygen-level dependent responses even before the onset of memory deficits. These changes are nonlinear, with different activation patterns in MTL and heightened activation in frontal lobes sometimes reported. For example, reduced deactivation of PCG/precuneus [45,49,82], increased frontal activation [45], and altered MTL activation have all been reported, with one study reporting hyperactivation [45] and another reporting hypoactivation in preclinical APOE ε4 carriers [47]. Both presenilin 1 mutation carriers

and individuals with subjective memory impairment had hippocampal hypoactivation [46,48]. Frontal hyperactivation was also observed in individuals with subjective memory impairment [48]. These activation patterns in preclinical AD are suggestive of compensatory mechanisms within these regions which are capable of maintaining normal levels of cognition.

3.1.2. Mild cognitive impairment

Both hypoactivation [50,51,57,59,61,62,64,77] and hyperactivation [53,78,80,83] of the MTL during memory tasks have been reported in MCI. This difference may be a result of the particular memory process being assessed, as suggested by a study by Trivedi et al [55] reporting hypoactivation of parahippocampal cortices during encoding and hyperactivation of hippocampus during recognition in aMCI. A study showing CA3/dentate hyperactivation and entorhinal hypoactivation also suggested that discrepant findings in MTL may be caused by different activation patterns in MTL structures and hippocampal subregions [60]. The discrepancy may also be due to the mixed sample of MCI patients included in the studies. For example, MCI patients with lower dementia score as determined by Clinical Dementia Rating had hippocampal hyperactivation and decreased default mode network (DMN) deactivation, whereas the activation pattern was completely opposite in MCI patients with higher dementia scores [79].

Similar to MTL, while some studies show reduced PCG/precuneus activation [50,61,64], some report hyperactivation or reduced deactivation within these regions [53,81,82,84]. PCG/precuneus is part of the DMN, and hyperactivation of these areas is possibly due to reduced deactivation of the DMN while performing a task. Frontal cortex activation is usually reduced [50,51,54–57,59,61,63] while several studies show hyperactivation in several frontal regions including precentral gyrus [51,52,59,64]. Dividing the MCI sample into two groups depending on cognitive performance, Clement and Belleville [58] revealed that frontal activation during a verbal memory task was decreased in MCI patients with more cognitive decline. Temporoparietal regions are also reported to be affected with some studies showing hypoactivation of these regions during picture or scene encoding tasks [55–57,64] and some reporting hyperactivation [61]. These findings suggest that future studies may benefit from better defined samples instead of including different types of MCI (aMCI and naMCI) patients with various levels of dementia.

3.1.3. Alzheimer's disease dementia

In ADD, MTL hypoactivation [65–67,69,70,72,77–79,81] and PCG/precuneus hyperactivation [69,81] or reduced deactivation [68,75,82] are the most consistent findings. Affected regions are not limited to these more commonly reported areas in the brain. Activation in frontal regions including prefrontal and motor areas were altered during verbal or visual encoding and recognition [66,73,76]. Although results are not consistent, there seems to be a tendency for frontal hyperactivation [67,69,72,74,75].

Overall, task-based fMRI findings suggest that episodic memory tasks lead to MTL hypoactivation, frontal hyperactivation, and reduced PCG/precuneus deactivation in ADD. Although preclinical AD and MCI samples have activation differences within these regions, the results are not consistent yet to provide early diagnosis or disease-tracking biomarker candidates. The discrepancy of the results appear to be caused by inclusion of mixed patient samples, distinct verbal and visual memory tasks, and implementing different analysis methods for imaging. In conclusion, task-based fMRI seems like a promising tool which can detect early changes along the AD continuum requiring further investigations for biomarker research in AD.

3.2. Resting state fMRI

By its nature, resting state fMRI (rsfMRI) does not involve a task, but the connectivity metrics calculated from these data can be used to assess relationships with memory tasks completed outside of the scanner (Table 3). This technique allows the investigation of functional connectivity between two regions and/or within specific networks impaired in AD.

3.2.1. Preclinical AD

In APOE ε4 carriers, verbal memory decline was related to reduced anterior and posterior connectivity as shown by whole brain dynamic functional connectivity [87]. Studies using seed-based analysis reported that verbal memory decline was associated with reduced left medial temporal gyrus; and DMN and executive control network connectivity [85,86]. When episodic memory performance related to structural changes within DMN regions, reduced deactivation shown by task-based fMRI and connectivity decline of this network shown by rsfMRI are considered altogether, this network appears to play a significant role in AD and could be used for early diagnosis.

3.2.2. Clinical AD

The relationship between DMN connectivity reduction and episodic memory decline persisted in MCI [88,93,101,104] and ADD [100,101,104]. Longitudinal studies showed that the progression of memory decline in aMCI was related to the decline of functional connectivity between posterior cingulate cortex and other DMN regions [88], precentral gyrus [99], hippocampal formation [94], and hippocampus subregions [89]. Xie et al investigated the connectivity between regions with atrophy in aMCI and revealed that both atrophy of hippocampus, precuneus, insula, postcentral gyrus, and frontal regions and connectivity reduction between these regions were associated with worse memory performance.

Table 3
rsfMRI correlates of episodic memory

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
Preclinical AD				
Goveas, et al 2013 [85]	20 APOE ε4 carrier, 26 noncarrier CNC	RAVLT	Seed-based voxel-wise connectivity analysis (DMN-PCG, ECN-R dorsolateral PFC, Salience network-R orbital anterior insula)/VBM	DMN connectivity positively correlated with memory. ECN: Operculum clusters and R inferior/superior parietal cortex clusters negatively, R inferior temporal gyrus positively correlated with memory.
Matura, et al 2014 [86]	20 APOE ε4 carrier, 43 noncarrier CNC	Word list	Seed-based functional connectivity (L PCG)	L medial temporal gyrus connectivity positively correlated with recognition.
Quevenco, et al 2017 [87]	13 APOE ε4 carrier, 24 noncarrier CNC (2-year follow-up)	Verbal Learning and Memory Test	Whole brain dynamic functional connectivity/PiB PET	Anterior-posterior connectivity positively correlated with memory.
MCI				
Bai, et al 2011 [88]	26 aMCI, 18 CNC (20-month follow-up)	AVLT, RCFT	ICA	Reduced connectivity between PCG/precuneus and mean DMN independent components over time was correlated with episodic memory decline in the aMCI.
Bai, et al 2011 [89]	26 aMCI, 18 CNC (20-month follow-up)	AVLT, RCFT	Seed-based functional connectivity (HC subregions; CA, DG and subiculum)	Reductions in baseline hyperfunctional connectivity between the PCG/precuneus and mean DMN independent components in aMCI were positively correlated with memory decline over time.
Agosta, et al 2012 [90]	12 aMCI, 13 CNC	Babcock Story Recall, RAVLT, RCFT	ICA	No associations.
Liang, et al 2012 [91]	16 MCI, 16 CNC	CVLT	Seed-based functional connectivity (inferior parietal cortex, angular gyrus, supramarginal gyrus)/VBM	Angular gyrus and R precuneus connectivity negatively correlated with CVLT in MCI.
Xie, et al 2012 [92]	30 aMCI, 26 CNC	RAVLT, RCFT	Seed-based functional connectivity (insula subregions)	Intrinsic connectivity of insula positively correlated with memory in aMCI.
Wang, et al 2013 [93]	18 aMCI, 23 euthymic CNC, 16 CNC	CVLT-II	ICA/VBM	DMN connectivity positively correlated with CVLT-II. Positive correlations were most evident in the R HC, R hippocampal gyrus and R thalamus.
Dunn, et al 2014 [94]	24 aMCI, 33 naMCI	RAVLT	Seed-based functional connectivity (DMN-PCG, anteromedial prefrontal cortex; MTL-hippocampal formation, parahippocampal gyrus, retrosplenial cortex, posterior intraparietal lobule, ventromedial PFC; dorsal medial PFC subsystem-dorsomedial PFC, lateral temporal cortex, temporoparietal junction, temporal pole)/HC volumetry	PCG-hippocampal formation connectivity strength positively correlated with retrieval in aMCI.
Jacobs, et al 2015 [95]	18 aMCI, 18 CNC	Verbal word learning task	Seed-based functional connectivity (locus coeruleus)/GM volumetry	R locus coeruleus-L parahippocampal gyrus connectivity positively correlated with memory in aMCI.
Xie, et al 2015 [96]	30 aMCI, 26 CNC	Auditory Verbal Memory Test, RCFT	Seed-based functional connectivity (regions with atrophy in aMCI determined by VBM; bilateral precuneus and insula, L postcentral gyrus, medial frontal gyrus, middle frontal gyrus and HC)	GM volume and intrinsic connectivity positively correlated with memory.
Dillen, et al 2016 [97]	24 aMCI, 27 subjective cognitive impairment, 25 CNC	WMS-IV Logical memory and Design memory, Verbal learning memory test	Seed-based functional connectivity (retrosplenial cortex, PCG)/GM volumetry	Retrosplenial and frontal medial, L lateral occipital cortex connectivities positively correlated with verbal learning in MCI.

(*Continued*)

Table 3
rsfMRI correlates of episodic memory (*Continued*)

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
Franzmeier, et al 2017 [98]	44 Aβ + aMCI, 24 Aβ- CNC	RAVLT, ADAS, WMS Logical Memory I and II, MMSE	Seed-based functional connectivity (L frontal cortex)/FDG-PET	At low levels of L frontal cortex connectivity, lower precuneus hypometabolism was associated with worse memory; at high levels of L frontal cortex connectivity, the effect was reduced.
Zhang, et al 2017 [99]	32 aMCI, 40 CNC	AVLT	Seed-based functional connectivity (R PCG)	R PCG connectivity with the L and R central sulci, L precentral gyrus positively correlated with recall in aMCI.
ADD				
Balthazar, et al 2014 [100]	22 ADD, 26 CNC	RAVLT	Seed-based functional connectivity (PCG)	DMN connectivity positively correlated with memory scores in the overall sample.
MCI and ADD				
Binnewijzend, et al 2012 [101]	23 MCI, 39 ADD, 43 CNC (2.8 year follow-up; 7/23 MCI converted to ADD)	RAVLT	ICA	Regional connectivity within the DMN positively correlated with memory.
Pasquini, et al 2015 [102]	22 MCI, 21 ADD, 22 CNC	CERAD-WL	ICA	Local intrinsic functional connectivity of the HC negatively correlated with recall in ADD.
Zhang, et al 2016 [103]	76 aMCI, 19 ADD, 23 CNC	RAVLT, MMSE, ADAS, Logical Memory I and II	Functional connectivity between 18ROIs/Aβ PET, APOE ε4 status	Medial frontal gyrus and parahippocampus functional connectivity negatively correlated with memory in aMCI and ADD.
Contreras, et al 2017 [104]	21 aMCI, 8 ADD, 16 subjective cognitive decline, 13 CNC	CVLT-II	ICA (resting-state network, visual network, DMN and frontoparietal network)	DMN and frontoparietal network connectivity positively correlated with recall.

Abbreviations: APOE ε4, apolipoprotein E ε4; CNC, cognitively normal control; aMCI, amnestic mild cognitive impairment; MCI, mild cognitive impairment; naMCI, nonamnestic mild cognitive impairment; Aβ, amyloidβ; ADD, Alzheimer's disease dementia; RAVLT, Rey Auditory Verbal Learning Test; AVLT, Auditory Verbal Learning Test; RCFT, Rey Complex Figure Test; CVLT, California Verbal Learning Test; WMS, Wechsler Memory Scale; ADAS, Alzheimer's Disease Assessment Scales; MMSE, Mini–Mental State Examination; CERAD-WL, Consortium to Establish a Registry for Alzheimer's Disease-Word list; DMN, default mode network; ECN, executive control network; PCG, posterior cingulate gyrus; R, right; PFC, prefrontal cortex; VBM, voxel-based morphometry; L, left; PiB PET, Pittsburgh compound B positron emission tomography; ICA, independent component analysis; HC, hippocampus; DG, dentate gyrus; MTL, medial temporal lobe; HC, hippocampus; GM, gray matter; FDG-PET, fluorodeoxyglucose positron emission tomography; ROI, region of interest.

Decreased MTL connectivity with locus coeruleus [95], frontal medial cortex, and lateral occipital cortex [97] was associated with worse verbal memory scores. Focusing on insula subregions revealed that increased intrinsic connectivity of insula was also associated with better memory performance [92]. Combining both rsfMRI and FDG-PET approaches, Franzmeier et al [98] revealed an interaction between functional connectivity of frontal cortex and precuneus hypometabolism. With decreased frontal connectivity, precuneus hypometabolism was associated with reduced memory performance, whereas this association was lower at higher levels of frontal connectivity in aMCI. This study suggests that memory performance does not only rely on functional connectivity but also metabolism of DMN regions. Finally, in contrast to findings in aMCI, worse memory performance was associated with increased middle frontal gyrus and parahippocampus connectivity [103], and intrinsic hippocampal connectivity [102] in ADD.

To summarize, rsfMRI findings have revealed that MTL and DMN connectivity changes in AD are related to episodic memory. Reductions in DMN connectivity are closely related to memory decline, whereas MTL connectivity results are not that consistent throughout the AD continuum. Whereas preclinical and prodromal AD samples have reduced connectivity in association with worse memory performance, this pattern in reversed in ADD. Although DMN findings are rather consistent, there is still a need for more studies with sufficient power before rsfMRI can provide a reliable AD biomarker or tracking tool. Future studies may benefit from combining rsfMRI with other imaging techniques, including FDG-PET, and defining patient samples better by supporting the clinical criteria with established structural MRI, PET, and CSF findings.

4. Molecular MRI

Proton magnetic resonance spectroscopy can be used to assess changes in cell-specific metabolites, including choline, creatine, glutamine, glutamate, glutathione, N-acetyl aspartate (NAA), and myo-inositol. Levels of NAA, reflecting neuronal loss or dysfunction, decrease in AD; whereas

Table 4
Molecular MRI correlates of episodic memory

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
MCI				
Didic, et al 2010 [108]	28 aMCI, 28 CNC	DMS48	NAA/MI in hippocampal formation and perirhinal/entorhinal cortices	Anterior subhippocampal cortex and L anterior HC NAA/MI positively correlated with memory in the overall sample.
Duffy, et al 2014 [107]	54 MCI, 41 CNC	RAVLT	GSH in anterior and posterior cingulate	PCG GSH negatively correlated with memory.
ADD				
Chantal, et al 2002 [109]	14 ADD, 14 CNC	CVLT	NAA, Cho, Cr, MI in MTL	L HC NAA positively correlated with memory.
MCI and ADD				
Rami, et al 2007 [110]	27 aMCI, 35 ADD, 27 CNC	Text Memory Test, Wordlist Learning Test, Memory Alteration Test	MI/Cr ratio, NAA in PCG, L temporal pole and L posterior temporoparietal region	L temporal pole MI/Cr ratio negatively correlated with encoding. PCG NAA positively, MI/Cr ratio in all of the regions negatively correlated with memory alteration.
Foy, et al 2011 [111]	21 MCI, 39 ADD, 38 CNC	CERAD	NAA, MI, Cho, Cr + phosphocreatine in HC	NAA positively correlated with memory in MCI and ADD.
Lim, et al 2012 [112]	16 aMCI, 23 ADD, 22 CNC	Seoul Verbal Learning Test, HVLT-R	NAA/Cr ratio in PCG	NAA/Cr positively correlated with memory in the overall sample.
Watanabe, et al 2012 [113]	42 aMCI, 67 ADD, 54 CNC	WMS-R	NAA (N-acetylaspartate and N-acetylaspartylglutamate), MI in HC and PCG	HC NAA positively, MI negatively correlated with memory in the overall sample.
Jahng, et al 2016 [114]	24 aMCI, 24 ADD, 23 young CNC, 24 old CNC	Face-name association	Functional MRS; glutamine and glutamate complex, NAA, Cr, MI in PCG/precuneus	NAA and Cr highest in young CNC, and lowest in AD (AD < aMCI < old CNC < young CNC) during the task.

Abbreviations: aMCI, amnestic mild cognitive impairment; CNC, cognitively normal control; MCI, mild cognitive impairment; ADD, Alzheimer's disease dementia; DMS48, delayed matching to sample-48 items; RAVLT, Rey Auditory Verbal Learning Test; CVLT, California Verbal Learning Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; HVLT-R, Hopkins Verbal Learning Test-Revised; WMS-R, Wechsler Memory Scale-Revised; NAA, N-acetylaspartate; MI, myo-inositol; GSH, glutathione; Cho, choline; Cr, creatine; PCG, posterior cingulate gyrus; L, left; HC, hippocampus; MRS; magnetic resonance spectroscopy.

increased myo-inositol levels, reflecting glial cell activation, have been reported in MCI and AD [105,106]. Glutathione is an intracellular antioxidant in the brain and has yet to be extensively studied in AD [107]. In addition, there are only a few studies evaluating the association between these metabolite alterations and memory performance in particular (Table 4).

Levels of NAA in MTL have been consistently reported to have positive associations with verbal memory performance both in MCI and ADD [108,109,111–113]. In addition to the positive correlation between PCG NAA and verbal memory scores [110], NAA within this regions decrease along the AD continuum [114]. Levels of NAA were shown to decrease with age (as shown by the difference between young and old CNCs) and AD progression. Patients with ADD had the lowest NAA and creatine concentration, followed by aMCI patients, whereas young CNCs had the highest concentration in PCG/precuneus. As myo-inositol increases in AD, it also seems to be negatively correlated with verbal memory in MCI and AD [110,113]. These results suggest that increased neuronal dysfunction coupled with glial cell activation play a role in the verbal memory deterioration in MCI and AD. Elevated glutathione levels with decreased memory performance are suggestive of early compensation in MCI [107]. These molecules may prove to be markers to track disease progression with future longitudinal studies investigating the course of the levels of these molecules within specific regions in association with cognitive decline.

5. Arterial spin labeling MRI

Arterial spin labeling MRI measures cerebral blood flow (CBF), which is a more direct evaluation of brain physiology compared with the blood-oxygen-level dependent response measured by fMRI. A small number of studies on this MRI technique reported that the CBF alterations are associated with episodic memory within the AD continuum (Table 5).

Decreases in MTL CBF are detected even in the preclinical phase in individuals with AD risk [115]. Structures of MTL and PCG/precuneus CBF are closely associated with verbal memory performance in this sample of individuals. Individuals with positive Aβ, subjective cognitive decline, and APOE ε4 carriers have a decline in verbal memory performance coupled with increased CBF

Table 5
Arterial spin labeling MRI correlates of episodic memory

Author, year	Study groups	Episodic memory test	Imaging analysis method	Imaging correlates of episodic memory
Preclinical AD				
Fleisher, et al 2009 [115]	13 CNC (positive family history of AD and at least one copy of the APOE ε4; high risk), 10 CNC without these risk factors	Face-name association	CBF and BOLD signal response in MTL	Decreased CBF and BOLD response during encoding in the high risk group.
Bangen, et al 2014 [116]	16 CNC with high, 55 with low vascular risk	CVLT-II	CBF in caudate, thalamus, MTL, posteromedial and frontal cortices	Trend for positive correlation between MTL CBF and memory in high vascular risk group.
Zlatar, et al 2016 [117]	21 APOE ε4 carrier, 38 noncarrier CNC	WMS-R, CVLT-II	Voxel-wise analysis	R anterior cingulate, L HC, parahippocampal gyrus, insula, putamen, middle temporal, supramarginal, R middle and superior temporal gyri CBF negatively correlated with verbal memory in APOE ε4 carriers.
Bangen, et al 2017 [118]	15 Aβ+, 47 Aβ- CNC (florbetapir PET)	AVLT	CBF in HC, PCG, precuneus and postcentral gyrus	HC, PCG and precuneus CBF negatively correlated with recall in Aβ+ CNC.
Hays, et al 2017 [119]	35 subjective cognitive decline, 35 CNC	CVLT-II, WMS-R	Voxel-wise analysis	PCG, corpus callosum, HC, L medial and inferior temporal, fusiform gyri, R inferior frontal gyrus CBF negatively correlated with verbal memory in subjective cognitive decline CNC.
Preclinical AD and MCI				
Bangen, et al 2012 [120]	16 MCI (8 APOE ε4 carriers), 29 CNC (14 APOE ε4 carriers)	Picture encoding	CBF and BOLD signal response in MTL	No CBF or BOLD difference between CNC and MCI; and APOE ε4 carriers and noncarriers.
Wierenga, et al 2012 [121]	20 MCI (9 APOE ε4 carriers), 40 CNC (13 APOE ε4 carriers)	WMS-R, CVLT-II	Whole brain CBF	L parahippocampal and fusiform gyri CBF positively correlated with verbal memory in APOE ε4 carriers.
MCI				
Xu, 2007 et al [122]	12 aMCI, 14 CNC	RAVLT, scene encoding	Voxel-wise analysis	Reduced R precuneus, cuneus and PCG CBF during the task. CBF positively correlated with RAVLT in the overall sample.
Xie, 2016 et al [123]	65 aMCI, 62 CNC	Scene encoding	Voxel-wise analysis and CBF in PCG, precuneus, HC, parahippocampal gyrus	Reduced MTL, temporal pole, precuneus, PCG, L lingual and fusiform gyri, cuneus, superior occipital lobe CBF during the task.

Abbreviations: CNC, cognitively normal control; AD, Alzheimer's disease; APOE ε4, apolipoprotein E ε4; Aβ, amyloidβ; MCI, mild cognitive impairment; aMCI, amnestic mild cognitive impairment; CVLT-II, California Verbal Learning Test-II; WMS-R, Wechsler Memory Scale-Revised; AVLT, Auditory Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; CBF, cerebral blood flow; BOLD, blood-oxygen-level dependent; MTL, medial temporal lobe; HC, hippocampus; PCG, posterior cingulate gyrus; R, right; L, left.

[117–119]. Although there are no directional data regarding this association, this may be suggestive of a compensatory response within these regions aimed toward improving the performance.

In line with other MRI approaches, MCI patients show decreased CBF responses in MTL and PCG/precuneus, which correlate with the verbal memory performance [122,123]. Superior occipital lobe CBF is reduced when tasks demanding visual encoding are used [123].

Owing to diversity of the episodic memory tests used in the current studies, and the small number of studies to date, conclusions about how arterial spin labeling relates to episodic memory across the AD process would be premature. However, results to date suggest that arterial spin labeling magnetic resonance imaging holds a potential to provide biomarkers which can be used in early diagnosis and progression of AD.

6. Limitations and future directions

Existing literature suggests that MRI, widely available in clinical and research settings, may offer several potential biomarkers related to episodic memory impairment in AD. Structural and functional alterations in different regions may increase the predictive value of hippocampal atrophy assessed by MRI for AD diagnosis. As MRI findings

correlate with episodic memory deficits, they have the potential to offer more insight into the etiology of the disease and more utility for tracking progression over time.

Nevertheless, there are several limitations to using MRI in AD. Imaging is expensive, requires skilled staff for acquisition and analysis, and is time consuming. In most of the studies, cohort sizes tend to be small, limiting confidence in results [28,31,65,67,69–74,77–81,124,125]. The existence of large shared data sets such as AD Neuroimaging Initiative mitigates this to some extent and has been extremely useful in better understanding structural aspects of the disease. However, AD Neuroimaging Initiative is also limited in functional imaging data as it includes only rsfMRI and no task-based sequences. In addition, the neuropsychological battery includes only verbal memory testing. This is also true of many clinical research studies that limit our understanding of the relationship between rsfMRI and nonverbal measures. This differs from the task-based literature, where many tasks found to differentiate between AD and other cohorts involve nonverbal stimuli such as faces and scenes.

Another limitation is the use of clinical criteria for probable AD in most of the mentioned studies. For example, only a few used hippocampal atrophy, CSF Aβ, or PET to support the AD diagnosis [20,26,41,73,78,80,90,95,97,98]. Remy et al [20] included hypometabolism assessed by FDG-PET, medial temporal atrophy shown by MRI, and the level of phospho-tau and Aβ-tau index to confirm the AD diagnosis within their patient sample. The rest of the studies included in our review relied only on clinical criteria. Without the integration of supporting biomarkers, the positive predictive value of clinical diagnostic criteria is rather limited with poor negative predictive value [126]. If biomarkers revealing Aβ deposition and neurodegeneration are present at the same time as clinical criteria, likelihood of AD dementia is significantly increased [127]. Thus, whenever possible, these biomarkers should be implemented to reliably define study samples.

Although investigating differences on a whole brain level may help discover other regions implicated in episodic memory performance, these analyses may not be efficient in detecting subtle changes. Compared with region-of-interest analyses, whole brain analyses require spatial blurring and corrections for multiple comparisons leading to decline in power to detect small changes [45]. More powerful analysis methods should be favored in biomarker research to obtain more reliable results.

Moving forward, it seems that multimodal biomarker studies that use both Aβ and/or tau PET ligands and both structural and functional MRI might become more common in AD. Our own research supported by a Center for Biomedical Research Excellence award from the National Institute of General Medical Sciences will use Aβ PET, resting state fMRI, and neuropsychological testing including verbal, nonverbal, and navigational memory techniques in an attempt to fill some of the gaps in the current understanding of AD. Future work building from the current protocol will incorporate task-based fMRI to further understand task-based network connectivity in relation to the Aβ status and neuropsychological performance. Using multimodal imaging and including nonverbal memory tests in addition to verbal tests will expand on previous imaging studies. Navigational tasks used in animal studies are rarely implemented in human research, limiting the translational value of these studies. Thus, by using navigational tasks, we aim to overcome this existing limitation.

7. Conclusions

Several MRI and fMRI metrics, including hippocampal atrophy, hold the potential to become AD biomarkers and may be more relevant to the preclinical stages. However, most imaging studies include only one modality with either verbal or nonverbal memory tasks, which prevent generalized conclusions to be drawn from their findings. Investigating the underlying pathology of AD through the combination of multimodal imaging and extensive neuropsychological evaluation may help in early diagnosis and in testing the effectiveness of novel therapeutics. Longitudinal studies with larger participant samples, where clinical AD diagnosis has been supported by multiple biomarkers, could provide a better understanding of the disease.

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RESEARCH IN CONTEXT

1. Systematic review: Memory impairments are among the most common and early symptoms of Alzheimer's disease (AD). Structural and functional changes assessed by magnetic resonance imaging are related to memory performance.
2. Interpretation: Magnetic resonance imaging findings in AD associated with memory performance can be used as potential biomarkers in the future. However, current conflicting results are probably due to the fact that most studies use limited memory tests in small patient samples with probable AD diagnosis.
3. Future directions: More extensive neuropsychological batteries should be implemented in larger patient groups with multimodal imaging. The diagnosis for AD should be supported by currently available biomarkers to achieve more reliable results.

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