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Review Article

Detecting cognitive changes in preclinical Alzheimer's disease: A review of its feasibility

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Abstract Significant progress has been made in characterizing the biological changes occurring in preclinical Alzheimer's disease (AD). Cognitive dysfunction has been viewed, however, as a late-stage phenomenon, despite increasing evidence that changes may be detected in the decades preceding dementia. In the absence of comprehensive evidence-based guidelines for preclinical cognitive assessment, longitudinal cohort and neuroimaging studies have been reviewed to determine the temporal order and brain biomarker correlates of specific cognitive functions. Episodic memory decline was observed to be the most salient cognitive function, correlating with high levels of amyloid deposition and hypoconnectivity across large-scale brain networks. Prospective studies point to early decline in both episodic and semantic memory processing as well as executive functions in the predementia period. The cognitive tests have, however, been principally those used to diagnose dementia. New procedures are required which target more finely the medial temporal lobe subregions first affected by clinically silent AD pathology.

Keywords: Cognition; Neuropsychology; Alzheimer's disease; Diagnosis; Preclinical markers

1. Introduction

Prospective clinical and biomarker studies have shown that Alzheimer's disease (AD) pathology is present decades before a clinical diagnosis of dementia is made [1–3], this preclinical period thus constituting a new window for both risk factor reduction and secondary prevention of AD [4,5]. Longitudinal models of the temporal order of these markers have hypothesized that amyloid-β (Aβ) accumulation to be the starting point in the disease process, followed by markers of neurodegeneration, that synergistically lead to cognitive decline [6,7]. This framework has served as the basis for operationalizing the preclinical stages of AD, where pathology precedes cognitive impairments that are purportedly only detectable near the tail end of this preclinical (prodromal) period,

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immediately antecedent to a diagnosis of mild cognitive impairment (MCI) [8]. This model is consistent with the fact that the clinical diagnosis of MCI/AD is centered on the establishment of dementia rather than on the underlying neuropathological changes. The design of secondary prevention trials targeting the preclinical period has thus been handicapped up to this point by the lack of proximal cognitive outcome markers. The cognitive tests currently used to describe AD, having been largely derived from comparisons of persons with and without dementia, are by definition inappropriate for preclinical studies. Such early cognitive changes, if they exist, are likely to be subtle, requiring highly sensitive tests that target specific brain regions affected early in the disease process.

An increasing number of studies are combining biological, neuroimaging, and cognitive biomarkers in large cohorts to determine whether sequentially cognitive changes follow on from biomarker changes or whether they may be detected at an earlier and parallel stage using conventional testing. The aim of the present review is to examine existing studies to determine whether any of the neuropsychological tests used have been able to detect either quantitative of qualitative cognitive signals and, if so, in which domains and at what point preceding clinical diagnosis. In this context, we first examine the functional, structural, and molecular neuroimaging studies for their association with cognitive changes, followed by a review of the longitudinal studies that have examined cognitive changes as measured by neuropsychological tests in cognitively normal (CN) populations followed to dementia. A consensus across studies of these changes is critical at this point not only to inform our understanding of the order of appearance of cognitive and pathological biomarkers of early AD but also to support the use of specific cognitive measures in clinical trials leading to the prevention of AD.

2. Methods

We examined the literature from 2000 to 2015 using the PubMed data base with MeSH terms and keywords from previous reviews. The review covered: (1) functional, structural, and molecular neuroimaging studies that investigated the cognitive correlates of these brain changes in early AD and (2) clinical and epidemiological studies that examined the longitudinal course of cognitive changes as measured by neuropsychological tests among aged CN populations who were followed to a diagnosis of dementia. To identify appropriate studies, we used the following search terms in PubMed: preclinical, Alzheimer, neuroimaging, positron emission tomography, amyloid beta, cognition, cognitive, neuropsychological tests. We identified further studies from reference lists in recent meta-analyses [9,10]. For imaging studies, we examined CN populations who were "at risk" for AD due to the presence of the apolipoprotein ε4 allele (*APOE* ε4), amyloid deposition, or the presence of suspected non-Alzheimer pathology (neurodegeneration markers without evident amyloidosis). Importantly, we excluded studies that followed individuals already identified as MCI since that is technically the "prodromal period" of AD. The final studies selected for this review had the following characteristics: (1) follow-up of at least 2 years, (2) a total sample size of 200 or more, unless imaging biomarkers were included, and (3) using recognized neuropsychological tests and not screening tests. A summary of these results can be found in Table 1 (review of imaging studies) and Table 2 (review of cognitive studies).

The studies were compared to determine the cognitive domains most sensitive to decline in preclinical AD, the neuropsychological tests used, and the study design (notably the origin and clinical characteristics of the subjects and longitudinal versus cross-sectional design). Given the considerable heterogeneity of these factors and our dual approach, a meta-analysis was not considered feasible.

3. Results

3.1. Structural brain changes in preclinical AD and cognitive correlates

A primary focus of structural neuroimaging studies in preclinical AD has been the hippocampus and related structures. Cross-sectional studies of hippocampal volume and its cognitive correlates [11–13] have shown no significant associations with composite memory scores in preclinical stages. Conversely, the only longitudinal study measuring changes in hippocampal volume [14], did find smaller bilateral hippocampal volumes at baseline and declining in association with a steeper downward slope on the Rey Auditory Verbal Learning Test (RAVLT) sum of trials 1–5 and RAVLT delayed recall over an 18-month period. Cross sectionally, this group also showed poorer performance on recent rather than remote name recognition using the famous name recognition task [14]. Observations of both temporal lobe and posterior cingulate cortex have shown changes in brain atrophy and cortical thickness associated with poor performance on composite scores of memory and executive functioning [12,13,15].

3.2. Functional brain changes in preclinical AD and cognitive correlates

Significant associations have been observed between hypometabolism in brain regions known to be affected in early AD (i.e., posterior cingulate and temporoparietal regions) and lower composite memory and executive scores [12,13], although this association has not always been found [11]. In addition to data on specific brain regions that are affected early in the disease process, other evidence suggests that cognitive decline may reflect large-scale changes across the brain in the default mode network (DMN), a set of brain regions that shows temporally

Table 1
Brain change in preclinical AD and cognitive correlates

First author (year)	Sample sizes	Study design (follow-up)	Mean ages (years)	Neuroimaging	Cognitive tests	Outcomes
Amyloid burden in preclinical AD and cognitive correlates						
Amariglio [27] (2012)	24 Aβ+ 97 Aβ−	C	75.5 72.7	PIB-PET DVR calculated in an aggregate of amyloid-vulnerable cortical ROI. Aβ+ if global mean PiB ≥1.25	Neuropsychological tests: MMSE, letter-number sequence, trails A and B, BNT, visual form discrimination test, and the 6-trial SRT Subjective cognitive complaints (SCC): composite score from 3 different questionnaires (the everyday cognition (E-Cog) scale, the memory functioning questionnaire (MFQ), 7 questions sum	A significant association was found between SCC composite score and amyloid deposition, after controlling for depression. In contrast, there was no significant relationship between the tests measuring memory and executive functions and amyloid deposition.
Doherty [26] (2015)	35 Aβ+ 74 Aβ−	C	63.3 59.5	PiB-PET (visual rating of PiB positivity) HV and amygdala volume Cortical thickness	Verbal ability: vocabulary and similarities subtests from the WASI, BNT, and reading subtest from the WRAT-3rd edition Visuospatial ability: block design and matrix reasoning subtests from the WASI and Benton Judgment of Line Orientation Speed and flexibility: Stroop test interference trial, TMT A and B Working memory: digit span and letter-numbering sequencing subtests from the WAIS-3rd edition Verbal learning and memory: RAVLT trials 3 to 5 and delayed recall trial Immediate memory: RAVLT trials 1 and 2	Aβ and cognition: the Aβ+ group showed lower scores on all six cognitive domains relative to Aβ − group, but differences were not significant. However, Aβ+ participants demonstrated significantly greater age-associated cognitive decline on speed and flexibility (age × Aβ rating $P = .034$). Aβ and structural MRI: the Aβ+ group exhibited significant cortical thinning in the entorhinal cortex compared with the Aβ− group.
Donohue [42] (2014)	ADNI 60 CN Aβ+ 37 CN Aβ− AIBL 114 CN Aβ+ 50 CN Aβ−	L (3 years)	 74.8 77.5 69.8 75.1	PIB-PET Aβ+ if SUVR>1,5 and a CSF Aβ42 level below 192 pg/mL PIB-PET Aβ+ if SUVR>1,5	Composite score: the ADCS-PACC FCSRT (free recall, 0–48 words), LM IIa subtest from the WMS (0–25 story units), the digit symbol substitution test score from the WAIS–revised (0–93 symbols), MMSE total score. ADCS-PACC will be implemented in the anti-amyloid treatment in asymptomatic Alzheimer's study (the A4 study).	In ADNI, Aβ+ participants showed more decline than did Aβ-participants with regard to the ADCS-PACC score at 24 months. In AIBL, the mean difference is significant at both 18 months and 36 months.
Doraiswamy [28] (2012)	10 Aβ+ 59 Aβ−	C/L (18 months)	77.3 68.5	Florbetapir PET (ROIs: frontal, temporal, and parietal cortices and anterior cingulate, posterior cingulate, and precuneus). PET images were visually scored as positive (Aβ+) or negative (Aβ−)	Language: Category verbal fluency (animals and vegetables) Executive function: DSST Verbal episodic memory: WMS-LM (immediate and delayed recall) Global cognition: MMSE, ADAS-Cog, CDR-SB	In CN, baseline Aβ+ scans were associated: 1) with significantly worse performance on DSST at baseline and WMS-LM (immediate and delayed recall) at baseline 2) with greater clinical worsening on the ADAS-Cog and CDR-SB over time.

Duff [41] (2013)	15 CN 10 MCI	C	74.6	18F-flutemetamol PET	Measure of premorbid intellect: Wide-range achievement test-4 reading RBANS: tapping immediate and delayed memory, visuospatial perception, and construction, attention, and language	18F-flutemetamol uptake significantly correlated with the delayed memory index from the RBANS, with greater uptake being associated with lower memory scores. The delayed memory and amyloid associations seemed most influenced by the MCI subgroup (MCI r = −.65, CN r = −.17). Other RBANS indexes did not correlate with the global composite score of 18F-flutemetamol. WRAT-4 reading was significantly, but positively, correlated with 18F-flutemetamol uptake.
Ellis [39] (2013)	55 Aβ+ 123 Aβ− 76 *APOE* ε4+ 102 *APOE* ε4	L (18 months)	75.2 69.9 70.1 72.6	PiB-PET Aβ+ if SUVR ≥1.5 Neocortical Aβ burden = average SUVR of the area-weighted mean of frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions.	MMSE, CDR-SB, LM 1 and 2, CVLT-II total learning/short delay/long recall, RCFT 3-minute recall/30-minute recall/copy Stroop colors, stroop C/D, stroop dots Letter fluency, category fluency Category switching accuracy Digit span Digit symbol BNT	With neuropsychological performance at baseline controlled statistically, a larger decline was observed for paragraph recall and verbal recall, over short and long delays in Aβ+ than in Aβ− (with small to moderate differences). Aβ+ also showed greater decline in language function (category fluency and BNT). No differences between the high and low Aβ groups were detected for the rate of decline for visual memory, executive function, and attention or for the clinical rating of disease severity (CDR-SB).
Hedden [10] (2013)	Meta-analysis of amyloid-cognition relations in CN older adults			Here, focus on the 16 data sets (maximum of 1278 subjects) with independent cohorts using PiB. All the studies were cross sectional but one.	Episodic memory Executive function Working memory Global cognition	Only episodic memory had a significant relationship with amyloid burden.
Hollands [40] (2015)	65 Aβ+ 224 Aβ−	C/L (18 months)	73.5 68.4	PiB-PET Aβ+ if SUVR ≥1.5	Subjective memory impairment: memory complaint questionnaire, IQCODE (short form) Cogstate brief battery: Psychomotor functions: detection (DET) Visual attention: identification (IDN) Visual learning: one card learning (OCL) Working memory: one back (OBK) Learning/working memory composite score (OCLOBK) Psychomotor/attention composite score (DETIDN) Depressive anxiety symptoms Hospital anxiety and depression scale	Cross-sectional analyses showed no differences between Aβ+ and Aβ− groups for any subjective memory impairment or Cogstate brief battery measures. Long analyses showed moderate decline in learning and working memory (OCL and OCLOBK) over the 18 months in the Aβ+ group. No change over time in subjective or informant-rated cognitive impairment, depressive and anxiety symptoms, or cognition in either Aβ group.

(*Continued*)

Table 1
Brain change in preclinical AD and cognitive correlates (*Continued*)

First author (year)	Sample sizes	Study design (follow-up)	Mean ages (years)	Neuroimaging	Cognitive tests	Outcomes
Johnson [23] (2014)	83 Aβ− 36 Aβ+ 82 Aβi	C	59.3 62.8 60.1	PiB-PET (visual rating of PiB positivity) FDG-PET MRI	Global cognition: MMSE Verbal memory: RAVLT total, RAVLT long delay Visual memory: BVMT-R total, BVMT-R delay Language: COWAT Working memory: WAIS digit span total Executive functions: TMT A and B Task switching: WCST perseverative response Subjective memory impairment: IQCODE, memory self-rating	Groups did not differ on any of the cognitive measures. Nor did they differ on subjective cognitive complaints or symptoms of depression. However, the Aβ+ group exhibited greater metabolic activity in the medial thalamus bilaterally and the superior temporal gyrus bilaterally. Amyloid burden is accompanied by glucometabolic increases in specific areas, but not atrophy or cognitive loss.
Lim [30] (2014)	76 CN Aβ+ 244 CN Aβ−	L (3 years)	73.8 68.6	PiB-PET 18F-florbetapir 18-Fflutemetamol Aβ+ if: PiB and flutemetamol SUV ratio ≥1,5 Florbetapir SUV ratio t ≥ 1.1	Composite scores Verbal episodic memory: LM delayed recall, CVLT-II long delay recall, and CVLT-II d' Visual episodic memory: RCFT 30-minute delayed recall, Cogstate one card learning task, and Cogstate one back task Executive function: stroop colors/dots, letter fluency, category fluency switching (fruit/furniture) Language: category fluency (animals/boys' names), BNT Attention: digit symbol, Cogstate detection task, and Cogstate identification task Visuospatial: RCFT copy, and clock drawing	Relative to the CN Aβ− group, the CN Aβ+ group showed a significantly greater rate of decline over 36 months on the verbal episodic memory and visual episodic memory composites (with the magnitude of these differences considered as moderate). No differences in group mean slopes were observed between the CN Aβ+ and CN Aβ− groups on any of the other cognitive composite scores.
Lim [31] (2015)	36 Aβ+/*APOE* ε4− 48 Aβ+/*APOE* ε4+	L (54 months)	76 72	Aβ+ definition: - In PIB studies when SURV ≥1.5 - In florbetapir when SURV ≥1.11 - In flutemetamol when SURV ≥0.62	Global cognition: MMSE, CDR Verbal episodic memory: LM test Cogstate brief battery: psychomotor functions: detection (DET) Visual attention: identification (IDN) Visual learning: one card learning (OCL) Working memory: one back (OBK) Learning/working memory composite score (OCLOBK) Psychomotor/attention composite score (DETIDN)	Aβ+ ε4 carriers showed faster decline on measures of verbal memory, visual learning, and a composite measure of learning and working memory (the one card learning task, the OCLOBK composite and the logical memory delayed recall task). Aβ+ ε4 carriers also showed a trend to decline on the composite measure of attention and processing speed.
Mormino [32] (2014)	284 Aβ−/*APOE* ε4− 71 Aβ−/*APOE* ε4+ 68 Aβ+/*APOE* ε4− 67 Aβ+/*APOE* ε4+	L (1.5 years)	74.5 70 78 75	PiB for HABS/AIBLA Florbetapir for ADNI	Global cognition MMSE Verbal Episodic Memory LM (immediate and delayed recall scores)	After adjustment for age, education, and sex, Aβ+/*APOE*+ showed significant greater decline in LM (immediate and delayed recall) and MMSE compared to all others groups (Aβ−/APOE−, Aβ−/*APOE*+, Aβ+/APOE−).

Perrotin [24] (2012)	11 Aβ+ 28 Aβ−	C	75.7 71.9	PiB-PET (Global PiB uptake index in cortical ROIs known to be associated with Aβ deposition early in AD + PiB indices in 5 a priori ROIs: the medial PFC and ACC; the lateral PFC; the precuneus, PCC, and isthmus cingulate cortex (ICC); the medial temporal lobe; and the lateral temporal lobe). Aβ+ if PiB uptake ≥1,46	Episodic memory (CVLT-II, visual reproduction Subtest of the WMS–R) Executive abilities (Stroop color word test, digit span forward and backward subtests of the WAIS-R, and the listening span test) Fluency (letter fluency subtest of the controlled word association test, category fluency test). Subjective cognition: self-reported (consisted of asking subjects to rate their memory relative to other people of the same age and relative to themselves 20 years ago).	Aβ+ participants showed significantly lower performance on episodic memory (CVLT, immediate recall) compared to Aβ− and were less confident about their memory abilities compared to others their age. No correlation with Aβ deposition and report of their own memory 20 years ago. Results were independent of demographic variables and depression. The ROI approach suggests that the pattern of PiB uptake in the right medial anterior and posterior cortices is related to reduced general memory ability confidence relative to other people of the same age.
Pietrzak [33] (2015)	84 CN Aβ+ 249 CN Aβ−	L (54 months)	70.0	PiB-PET Florbetapir 18 F Flutemetamol 18 F	Composite scores Verbal memory: LM delayed recall, delayed recall, d' of CVLT second edition Visuospatial: copy and clock drawing test (RCFT) Visual memory: 3-minute and 30-minute delayed recall of the RCFT, Cogstate OCL task Executive function: letter fluency (FAS), category switching (fruit/furniture), Cogstate one back tests Language: category fluency test, BNT Attention: digit span, Cogstate detection, Cogstate identification test Global cognition: averaging scores across these cognitive domains	Significant effect of Aβ status on global cognition and all component aspects of cognition over time except attention and visuospatial function. CN Aβ+ with elevated anxiety symptoms had a greater decrease in these cognitive domains than CN Aβ+ with nonelevated anxiety symptoms.
Roe [34] (2013)		L (3.7 years)	67.8	PiB-PET: The mean cortical BP (MCBP) is obtained by taking the mean of the BPs from the prefrontal cortex, gyrus rectus, lateral temporal cortex, and precuneus	Verbal episodic memory: SRT–free recall subtest Language: animal naming Executive functions: TMT A and B Global cognition: global composite psychometric score, CDR, MMSE.	Correcting on age, sex, education, and *APOE* ε4 status, increased MCBP was significantly associated with an increased risk of decline in global cognition (CDR and global composite score) and in verbal episodic memory (SRT).
Song [25] (2015)	23 Aβ+ 27 Aβ−	C	71.4	Florbetapir 18 F Visual assessment of cortical Aβ load (frontal, temporal, parietal, anterior cingulate, PC, and precuneus) Aβ+ level (visually rated) ≈ SUVR ≥1.10	CVLT-II WMS visual reproduction (immediate and delayed recall) D-KEFS (trials, verbal fluency, semantic fluency) Boston object naming correct, WAIS–digit symbol	No significant effects of cortical Aβ load on any neuropsychological scores.

(*Continued*)

Table 1
Brain change in preclinical AD and cognitive correlates (*Continued*)

First author (year)	Sample sizes	Study design (follow-up)	Mean ages (years)	Neuroimaging	Cognitive tests	Outcomes
Sperling [29] (2013)	11 Aβ+ 67 Aβ−	C	75.6 68.4	Flobertapir-PET (ROIs: frontal, temporal, and parietal cortices, anterior and posterior cingulated, and precuneus): Continuous and dichotomization (Aβ+ and Aβ− groups were determined by visual rating)	Global cognition: ADAS Executive functions: DSST Language: verbal fluency (vegetables, animals) Verbal episodic memory: WLM (immediate and delayed recall)	Adjustment for age, education. Aβ as a continuous variable: higher amyloid burden (SUVR) was significantly associated with worse performance on both memory measures (immediate and delayed). Aβ as a dichotomized variable: the Aβ+ subjects performed worse on WLM-I and WLM-D than Aβ− subjects.
Stonnington [35] (2014)	14 CN Decliners 14 CN nondecliners	L (12 years)	66.5	PiB-PET	Memory: AVLT (short-term memory; long-term memory; or percent recall), SRT free recall, complex figure test recall, and visual retention test total correct. Executive: WAIS-revised freedom from distractibility, COWAT, WCST (categories completed, total errors, or perseverative errors), and paced auditory serial attention task (3- and 2-second administration).	CN decliners evidenced decline in scores on 2 different memory tests and/or 2 different executive function tests (annual mean change at least of 2 SD beyond the decline of the entire group). Greater fibrillary Aβ burden was found in the decliners compared to nondecliners at several areas, particularly the temporal pole, paracentral lobule, and occipital region, with the strongest effect in the right temporal pole and the left occipital lobe.
Villemagne [36] (2013)	74 CN Aβ− 38 CN Aβ−	L (3.8 years)	71.2	PiB-PET GM volume HV Volumes were normalized for ICV	Composite episodic memory score RCFT long delay, CVLT-II long delay, and LM II. Composite nonmemory score BNT, letter and category fluency, DSF, DSB, digit symbol coding, and RCFT copy	Over time, CN with high ^{11}C-PiB retention showed significant increased rate of Aβ deposition (SUVR per year), episodic memory and nonmemory declines, as well as significant greater hippocampus and GM atrophy (vs. CN with low ^{11}C-PiB retention).
Yotter [37] (2013)	13 Stable 13 Decliners	L (12 years)	75.7 80.7	PiB-PET ROIs = L and R sensorimotor areas, L and R temporal areas, L and R precuneus, L and R frontal areas	Verbal episodic memory CVLT (immediate free recall)	No significant differences in mean cortical amyloid load between the two groups. However, the temporal lobe and the sensorimotor cortices were relatively spared in the stable group, whereas these 2 regions were affected earlier in the declining group (bottom 20% CVLT slop scores). CC: the spatial pattern of amyloid deposition is related to cognitive performance.

Functional brain changes in preclinical AD and cognitive correlates

Fleisher [19] (2009)	17 FH+/*APOE* ε4+ 12 FH−/*APOE* ε4−	C	58.6 57.6	fMRI task and resting-state DN analysis	1) fMRI associative encoding task Interleaved blocks of memorizing pairs of faces and names, and periods of rest. Postscan testing: percent recall scores were calculated to verify attention to the scanning task and evaluate encoding capabilities in both risk groups 2) Neuropsychological testing Language: BNT, verbal fluency Working Memory: WAIS-R digit span forward and backward Verbal episodic memory: CVLT, WMS-R LM test Executive functions: TMT A and B, WAIS-R digit symbol test Visuospatial: clock drawing	NP × groups: no group differences in measures of neurocognitive scores, except higher scores on category fluency in CN FH−*APOE* ε4−. No group differences on the postscan recall task of face-name pairs. NP × MRI in high-risk group: worse performance in the high-risk group on category fluency testing was associated with increased temporal and prefrontal cortex resting connectivity, while associated with decreased connectivity in the precuneus and orbital frontal lobes. Memory scores correlated with the degree of parietal deactivation during encoding.
Kennedy [20] (2012)	127 CN	C	30–89	fMRI task Florbetapir PET (precuneus, a critical component of the memory system).	fMRI memory encoding task: participants viewed images of outdoor landscape scenes and have to determine whether there was water present in the scene. Images were presented for 3 seconds each and jittered so that it is ranged between 4 and 14 seconds. Processing speed: WAIS-II digit symbol Language: COWAT Working memory: operation span Reasoning: Raven's progressive matrices	During the encoding task: as Aβ in the precuneus increased, activation decreased in multiple regions of the prefrontal cortex (which are part of a frontotemporal memory network), and suppression decreased in DN regions (bilateral superior/medial frontal and lateral temporal cortex). In individuals with the most elevated Aβ (n = 18, >60 years), altered prefrontal and temporal activation is associated with poorer performance on processing speed, language and fluid reasoning.
Song [21] (2015)	13 *APOE* ε4+ 34 *APOE* ε4−	L (1 year)	76 72	fMRI resting state	MMSE MoCA WHO-UCLA AVLT CDR	In *APOE* ε4+, positive correlation between left parahippocampal gyrus and medial prefrontal cortex functional connectivity and baseline MMSE scores but negative correlation between increased functional connectivity and cognitive performance at follow-up.
Westlye [22] (2011)	33 *APOE* ε4+ 6 *APOE* ε4−	C	62.6 64.4	fMRI resting state	CVLT-II	Increased hippocampal synchronization in *APOE*+ relative to *APOE* ε4− in a resting-state network spanning the posterior DMN (extended effects into the PCC, parietal, and parahippocampal regions). Negative relationship between memory performance and resting hippocampal synchronization.

(*Continued*)

Table 1
Brain change in preclinical AD and cognitive correlates (*Continued*)

First author (year)	Sample sizes	Study design (follow-up)	Mean ages (years)	Neuroimaging	Cognitive tests	Outcomes
Structural brain changes in preclinical AD and cognitive correlates						
Besson [11] (2015)	12 MRI+ 42 MRI− 12 FDG+ 42 FDG− 20 ND+ 34 ND−	C	67.0 65.5 65.0 66.0 65.6 65.9	MRI biomarker: HV FDG biomarker: FDG-PET (posterior cingulate and temporoparietal region) ND biomarker: MRI + FDG biomarkers Amyloid biomarker: Florbetapir–PET	Composite scores (average after z-transformation) Global cognition: MMSE, Mattis dementia rating scale Verbal episodic memory: immediate and delayed free recall of the FCSRT, (encoding, storage, retrieval) paradigm Visual episodic memory: free recalls from 2 lists of 8 graphic signs Executive function: letter verbal fluency, digit span test, TMT (difference between parts B and A), and stroop test. Processing speed: times to perform TMT part A and the color naming of the stroop test. Semantic memory: animal fluency, semantic (names) autobiographical memory task. Total score: average of the 6 composite scores	The MRI+ group showed lower performance in the executive function composite score compared with the MRI− group.
Doré [15] (2013)	64 Aβ− 29 Aβ+ (SUVR ≥1.4)	C/L (36 months)	72 78.2	PiB-PET Cortical thickness estimation of temporal lobe, precuneus and posterior cingulate gyrus (PPC), hippocampus	Composite episodic memory score by averaging: LM CVLT-II long delay recall	Cross-sectional analysis: PPC and hippocampus were significantly more atrophic in the CN Aβ+ group versus the CN Aβ − group. Correlation between cortical thickness and episodic memory: no significance in the CN Aβ− group/in the CN Aβ+ group, significant association between episodic memory scores in the temporal lobe and PCC of the right hemisphere. Cortical thickness in the hippocampus was not significantly associated with episodic memory in the 2 groups. Longitudinal analysis: The rate of atrophy in the CN Aβ+ group was significantly faster in both the temporal lobe and hippocampus.
Seidenberg [14] (2013)	27 declining in episodic memory 51 stable in episodic memory	L (18 months)	73	L.HV and R.HV	Semantic memory (at baseline) FNRT: recent famous name, remote famous name, nonfamous name (time-limited temporal gradient: in AD and MCI, better performance for recognition of remote memory than recent memory, object naming, category fluency). Episodic memory (longitudinal measures) The definition of memory decline over the follow-up period was based on the extent of reduction from baseline performance on three outcome indices: Mattis dementia rating scale-2 (DRS-2) total score, RAVLT sum of trials 1–5, and RAVLT delayed recall.	This person-semantic identity task was able to identify cognitively intact elders most likely to exhibit future episodic memory decline. Participants showing an episodic memory decline had poorer baseline performance for recent famous names but not remote famous names. Baseline L.HV and R.HV were significantly smaller in the declining group. The propensity for better accuracy for remote than recent names was related to HV.

Toledo [12] (2015)	SCI groups: Executive (n = 51) Memory (n = 66) Multidomain (executive + memory SCI) (n = 27) SMC (n = 71) CN n = 307	C/L (6 years)	77.3 75.0 78.0 71.6 73.9	Cortical gray matter volumes aHV MRI-SPARE-AD FDG-PET	Composite score of memory: RAVLT, ADAS-Cog, MMSE, LM I of the WMTR Composite score of executive functions: WAIS-R digit symbol substitution, digit span backwards, trails A and B, category fluency, and clock drawing. Cutoffs for the groups of SCI in memory and executive performances were calculated with scores in 81 CN (clinically stable after at least 7 years of follow-up) using the fifth percentiles. Multidomain SCI: presence of abnormal values in memory and executive scores.	Cross sectionally, compared with CN participants: 1) MRI-SPARE-AD revealed increased brain atrophy in participants with SMC and memory and multidomain SCI. (participants with multidomain CI showed larger atrophy than those with memory SCI involving similar areas. Participants with SMC showed atrophy that mainly affected the frontal pole and orbitofrontal cortex). 2) The multidomain SCI group presented greater posterior cingulate FDG-PET hypometabolism 3) The aHV showed no overall differences between groups. Longitudinal analyses: 50% of the participants with executive, memory, and multidomain SCI progressed to MCI or dementia at 7, 5, and 2 years, respectively.
Wirth [13] (2013)	7 GM thickness+ 65 GM thickness− 6 FDG-PET+ 66 FDG-PET− 8 HV+ 64HV−	C	74.9	PiB-PET HV, glucose metabolism, and GM thickness from cortical AD− affected regions, WMH.	Composite measure (average after z-transformation) of: Memory function: CVLT, LMT, visual reproduction delayed recall recognition test Executive functions: stroop test, COWAT, TMT, digit symbol coding test	Adjustment on age, sex, and education. Poorer cognitive abilities were detected in participants with abnormal (n = 7) compared with normal cortical thickness in memory and executive function. Participants with abnormal FDG-PET (n = 6) also exhibited lower executive functions and lower memory. The same association was not found for the participants with abnormal HV (n = 8). Neurodegenerative biomarkers were not significantly related to continuous PiB retention but significantly associated with WMH.

Abbreviations: AD, Alzheimer's disease; PIB-PET, Pittsburgh Compound B–positron emission tomography; ROI, region of interest; ADNI, Alzheimer's Disease Neuroimaging Initiative; CN, cognitively normal; MCI, mild cognitive impairment; *APOE*, apolipoprotein E; MRI, magnetic resonance imaging; FDG, fluorodeoxyglucose; SMC, subjective memory complaints; HV, hippocampus volume; C, cross sectional; PFC, prefrontal cortex; PCC, posterior cingulate cortex; HABS, Harvard Aging Brain Study; MMSE, Mini-Mental State Examination; BNT, Boston naming test; SRT, selective reminding test; ADCS-PACC, Alzheimer's Disease Cooperative Study Preclinical Alzheimer Cognitive Composite; FCSRT, free and cued selective reminding test; LM, logical memory; WMS, Wechsler memory scale; WAIS, Wechsler adult intelligence scale; DSST, digit symbol substitution test; ADAS, Alzheimer's disease assessment scale; WASI, Wechsler abbreviated scale of intelligence; WRAT, wide-range achievement test; TMT, trail making test; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; CVLT, California verbal learning test; BVMT, brief visuospatial memory test; COWAT, controlled oral word association test; WCST, Wisconsin card sort test; IQCODE, Informant Questionnaire On Cognitive Decline in the Elderly; D-KEFS, Delis-Kaplan Executive Function System; WLM, logical memory from Wechsler; FNRT, famous name recognition task; DVR, Distribution Volume Ratio; AIBL/AIBLA, Australian Imaging, Biomarkers, and Lifestyle Study of Aging; FH, Family History; SUVR/SURV, standardized uptake value ratio; SCI, Subtle Cognitive Impairment; GM, Gray Matter; L, Longitudinal; WMH, White Matter Hyperintensities; SPARE, Spatial Pattern for Recognition of Early AD; DN, Default Network; ICV, Intracranial Volume; PC, Posterior CingulateCortex; BP, Binding potential; ACC, anterior cingulate cortex; RCFT, Rey complex figure test; DSF, Digit Span Forward; MoCA, Montreal Cognitive Assessment; WHO-UCLA AVLT, World Health Organization-University of California-Los Angeles auditory verbal learning test; CDR, Clinical Dementia Rating Scale; LMT, Logical Memory Test; CI, Cognitive Impairment; ND, neurodegeneration; OCLOBK, one card learning and one back.

Table 2
Longitudinal studies of cognitive changes in preclinical AD

First author (year)	Sample sizes (end of study)	Follow-up	Mean ages (years)	Cognitive tests	Outcomes
Cognitively normal populations at baseline followed to diagnosis					
Amieva [61] (2005)	215 AD 1050 Controls	9 years	Diagnosis: AD: 79 Controls: 72	-Abstract reasoning: -WAIS-R similarities -Global: MMSE -Semantic memory/verbal: -IST -Visuospatial/working memory: -BVRT	Lower baseline performance was observed across all tests for those who went on to develop AD 9 years later. Impairments in abstract reasoning and visuospatial/working memory were among the most predictive.
Amieva [69] (2008)	350 AD 350 Controls	14 years	Diagnosis: AD: 86 Controls: 86	-Abstract reasoning: -WAIS-R similarities -Global: MMSE -Semantic memory/verbal: -IST -Visuospatial/working memory: -BVRT	Twelve years prior to diagnosis, individuals showed declines in semantic memory, followed by abstract reasoning/conceptual knowledge 2 years later global cognition and visuospatial/working memory impairments appeared about 8–9 years prior to diagnosis and co-occurred with subjective memory complaints and depressive symptoms. About 2 years later, subjects started to become dependent in their activities of daily
Bilgel [44] (2014)	149 impaired (Cog decline, MCI, AD) 746 Controls	~6 years	Baseline: Impaired: 78 Controls: 68	-Episodic memory (verbal): -CVLT -Episodic memory (visual): - BVRT - Global: BMS, MMSE	Immediate recall for verbal episodic memory was first to show decline followed by delayed recall. The visual episodic memory test declined only slightly thereafter, with global cognition the last to reflect change.
Blacker [45] (2007)	MCI: 235 (69 convert to AD) Controls: 107 (46 convert to MCI)	5 years	Baseline: MCI: 73 Controls: 71	- Episodic memory (verbal): - CVLT - SRT - Executive function: - TMT A and B - Self-ordering test - Alpha span test - Semantic memory/verbal: - COWAT	Healthy normal subjects with lower scores on episodic memory show an increased risk of progressing to MCI in 5 years. Executive functions were also predictive of decline but not as significant. Similar outcomes were found with progression from MCI to AD as well.
Chen [55] (2000)	120 AD 483 Controls	10 years	Follow-up: AD: 78 Controls: 75	- Episodic memory (verbal): - 10-item list learning and memory - WLM - Executive function: TMT A and B - Global: clock drawing, MMSE - Semantic memory/verbal: - Letter and category fluency - CERAD version of BNT - Visuospatial: CERAD praxis	The combination of measures of delayed recall and executive function produced the greatest differentiation between cases and control.

Chen [47] (2001)	Same population as previously mentioned but examining performance across shorter intervals	1.5 and 3.5 years	Baseline:
			AD: 77
			Controls: 73
				- Episodic memory (verbal):
				  - 10-item list learning and memory
				  - WLM
				- Executive function: TMT A and B
				- Global: clock drawing, MMSE
				- Semantic memory/verbal:
				  - Letter and category fluency
				  - CERAD version of BNT
				- Visuospatial: CERAD praxis
					Episodic memory functions as well as executive functions showed impairments at both time points prior to diagnosis.

Elias [56] (2000)	109 AD
	967 Controls
		22 years	Baseline:
			AD: 75
			Controls: 72
				- Abstract reasoning:
				  - WAIS-R similarities
				- Attention:
				  - WAIS-R digit span F & B
				- Episodic memory (verbal):
				  - WLM
				  - WMS paired associate test
				- Global: MMSE
				- Semantic memory/verbal:
				  - COWAT
				- Visuospatial:
				  - WMS visual reproduction
					Deficits on episodic memory and abstract reasoning were the strongest predictors of AD up to 10 years prior to diagnosis.

Grober [57] (2008)	92 AD
	914 Controls (analyzed within-subject changes to AD diagnosis)
		15 years	Baseline: 80	- Episodic memory (verbal):
				  - FCSRT
				- Executive function:
				  - TMT A and B
				  - Letter and category fluency
				- Verbal IQ: AMNART
					Memory decline in preclinical AD was shown to decline first around 7 years prior to diagnosis, with second decline in 2–3 years before onset. Executive function decline, with some semantic memory components showed significant decline also right at this time, with verbal IQ declining at the time of diagnosis.

Hall [48] (2000)	35 AD 293 Controls	15 years	Baseline: AD: 79 Controls: 73	- Episodic memory (verbal): - SRT	Decline in episodic memory was observed 5 years prior to diagnosis.

Jungwirth [49] (2009)	22 AD
	457 Controls
		5 years	Baseline: 76	- Episodic memory (verbal):
				  - IDSR-7
				- Executive function:
				  - TMT A and B
				  - Alters-Konzentrations test
				- Processing speed:
				  - CERAD word list
				  - CERAD figures
				- Semantic memory/verbal:
				  - CERAD animal fluency
				  - BNT
				  - Aachener aphasia test
				- Visuospatial:
				  - Constructional praxis
				  - WAIS-R figures
					Performance on episodic memory and processing speed/executive function coupled with subjective memory complaints and *APOE* ε4 allele predicted AD within 5 years.

(*Continued*)

Table 2
Longitudinal studies of cognitive changes in preclinical AD (*Continued*)

First author (year)	Sample sizes (end of study)	Follow-up	Mean ages (years)	Cognitive tests	Outcomes
Kawas [59] (2003)	144 AD 1281 Controls (analyzed within-subject changes to AD diagnosis)	17 years (mean)	Last visit: 78	- Episodic memory (visual): - BVRT - Verbal IQ: WAIS-R vocabulary	Lower performance on episodic memory at baseline doubled the risk of developing AD 15 years prior to diagnosis. In contrast, verbal IQ alone did not predict AD risk.

Laukka [94] (2012)	286 AD
	63 Vascular AD (VaD)
	565 Controls
		10 years	Baseline:
			AD: 83
			VaD: 82
			Controls: 82
				- Episodic memory (verbal):
				  - 12-item list learning and memory
				  - WLM
				Global: clock reading
				- Semantic memory/verbal:
				  - Category fluency
				- Visuospatial:
				  - WAIS-R block design
					Significant deviation from normal aging began 10 years prior to an AD diagnosis with initial decline in visuospatial processing, followed by episodic memory recall at 9 years and recognition at 7 years, semantic memory at 7 years, and clock reading at 4.5 years. In contrast, preclinical VaD showed decline 6 years prior to diagnosis but at a more accelerated rate. Once preclinical VaD persons started to decline, they deteriorated at a faster rate than the preclinical AD persons. Word recognition was the task that best differentiated groups.

Saxton [63] (2004)	72 AD
	621 Controls
		8 years total (1.5–3.4 years, 3.5–5.0 years, 5.1–8.1 years)	Baseline:
			AD: 76.5
			Controls: 73
				- Episodic memory (immediate):
				  - WMS-R verbal, visual, general
				- Episodic memory (delayed):
				  - WMS-R delayed memory
				- Processing speed/attention:
				  - WMS-R concentration
				  - DSST
				  - TMT A and B
				- Semantic memory/verbal:
				  - WAIS-R vocabulary
				  - Letter and category fluency
				  - BNT
				- Visuospatial:
				  - WAIS-R block design
				  - WMS-R orientation
					Delayed recall and semantic memory measures showed the first decline from 5 to 8 years prior to diagnosis. Attention and visuospatial and immediate memory recall were the last to decline from 1.5 to 3.4 years prior to diagnosis.

Wilson [75] (2011)	462 AD
	1049 Controls (analyzed within-subject changes to AD diagnosis)
		16 years	Baseline: 76	- Episodic memory (verbal):
				  - CERAD word list
				  - East Boston story
				  - WLM
				- Processing speed:
				  - Number comparison
				  - Symbol digit modalities test
				- Semantic memory/verbal:
				  - Verbal fluency
				  - BNT
				  - Word recognition
				- Visuospatial:
				  - Judgment of line orientation
				  - Standard progressive matrices
				- Working memory:
				  - WAIS-R digit span F & B
				  - Digit ordering
				- Global: all measures
					For those who converted to AD, significant decline was first observed in semantic memory at 6.33 years prior to diagnosis, followed by working memory at 6.25 years, followed by perceptual speed at 5.83 years, followed by visuospatial processing at 5.41 years, and episodic memory at 5.25 years.

Wilson [64] (2012)	226 AD
	1013 Controls (comparisons across cohorts)
		10.2 years (mean)	Diagnosis:
			AD: 88
			Controls: 87
				- Episodic memory (verbal):
				  - CERAD word list
				  - East Boston story
				  - WLM
				- Processing speed:
				  - Number comparison
				  - Symbol digit modalities test
				- Semantic memory/verbal:
				  - Verbal fluency
				  - BNT
				  - Word recognition
				- Visuospatial:
				  - Judgment of line orientation
				  - Standard progressive matrices
				- Working memory:
				  - WAIS-R digit span F & B
				  - Digit ordering
				- Global: all measures
					Global cognitive function declined around 7.5 years before dementia that was observed at an accelerated rate at 2 years prior to diagnosis.

(*Continued*)

Table 2
Longitudinal studies of cognitive changes in preclinical AD (*Continued*)

First author (year)	Sample sizes (end of study)	Follow-up	Mean ages (years)	Cognitive tests	Outcomes
Followed to autopsy					

Johnson [62] (2009)	44 Autopsied
	134 Progressed
	310 Stable (controls)
		10 years	Baseline:
			Autopsied:
			84 Progressed: 80
			Controls: 74
				- Episodic memory (verbal):
				  - WLM
				  - WMS-R paired associate
				  - Information
				  - BNT
				- Visuospatial:
				  - Block design
				  - DSST
				  - TMT A
				  - BVRT
				- Working memory:
				  - Mental control
				  - Digit span F & B
				  - Letter fluency
				- Global: all measures
					Significant decline first observed in visuospatial processing 3 years before clinical diagnosis, followed by global cognitive decline at 2 years prior and working memory at 1 year before clinical diagnosis. The rate of decline accelerated closer to diagnosis, with the steepest slope being working memory.

Monsell [71] (2014)	131 AD neuropath (autopsy-confirmed)
	80 Controls (no AD neuropath)
		8 years	Range:
			60 to 90+
				- Episodic memory (verbal):
				  - WLM
				- Executive function:
				  - TMT A & B
				  - DSST
				- Semantic memory/verbal:
				  - BNT
				  - Animal and vegetable naming
				- Working memory:
				  - Mental control
				  - Digit span F & B
					Individuals with AD neuropathological change at autopsy showed annual decline in the executive function/working memory domain relative to persons without AD neuropathology.

Riley [95] (2011)	32 AD neuropath (autopsy-confirmed)
	89 Controls
		7.5 years	Baseline:
			AD: 80
			Controls: 75
				- Episodic memory (verbal):
				  - WLM
				  - CERAD word list memory
				- Semantic memory/verbal:
				  - BNT
				  - CERAD animal naming
				- Visuospatial:
				  - Constructional praxis
				- Global: all measures
					Although there were no significant differences in performance at baseline, the slopes for episodic memory (delayed), semantic memory, and visuospatial processing were significantly different between groups. Autopsy was used to confirm diagnosis.

APOE genetic risk factor for AD					

Bretsky [66] (2003)	227 *APOE* ε4+
	738 *APOE* ε4−
		3 and 7 years	Baseline:
			ε4+: 74
			ε4−: 74
				- Abstract reasoning:
				  - WAIS-R similarities
				- Working memory:
				  - WAIS-R delayed spatial recog.
				- Episodic memory (verbal):
				  - WAIS-R delayed story recall
				- Semantic memory/verbal: BNT
				- Visuospatial:
				  - WAIS-R figures
				- Global: all measures
					At the 3-year follow-up, ε4+ carriers showed significant declines in both visuospatial and semantic memory/verbal abilities. At the 7 year follow-up, ε4 carriers showed further declines in these domains plus a global decrement compared to noncarriers.

Caselli [46] (2011)	71 *APOE* ε4/ε4
	194 *APOE* ε3/ε4
	356 Noncarriers
		∼6 years	Baseline:
			ε4/ε4: 56
			e3/ε4: 56
			Noncarriers: 57
				- Episodic memory (verbal):
				  - RAVLT
				- Executive function:
				  - Controlled oral word association
				  - DSST
				- Decision-making
				  - Iowa gambling test
				- Working memory:
				  - Paced auditory serial attention
				  - WAIS-R digit span F & B
				  - Mental arithmetic
				- Problem solving: WCST
					Preclinical episodic memory decline was observed in ε4+ carriers but not coupled with decline in executive function/frontal lobe measures. ε4/ε4 subjects showed a significant rate of decline on mental arithmetic tests.

Caselli [43] (2014)	Same population as previously mentioned but with additional cognitive measures	∼6 years	Baseline:
			ε4/ε4: 56
			e3/ε4: 56
			Noncarriers: 57
				- Episodic memory (verbal):
				  - RAVLT
				  - FCSRT
				- Episodic memory (visual):
				  - Complex figure test recall
				  - BVRT
				- Executive function:
				  - WAIS-R digit span F & B
				  - Mental arithmetic
				  - DSST
				  - WCST
				  - Paced auditory serial attention
				- Semantic memory/verbal:
				  - Controlled oral word association
				  - WAIS-R vocabulary similarities
				  - BNT
				  - Token test
				- Visuospatial:
				  - WAIS-R block design
				  - Complex figure test copy
				  - Facial recognition test
				  - Judgment line orientation test
				- Global: all measures
					Greater episodic memory decline over time was reported in ε4+ carriers versus noncarriers, but cross-sectional comparisons at beginning and end time points revealed nonsignificant effects.

Dik [65] (2000)	213 *APOE* ε4+ 653 *APOE* ε4−	3 and 6 years	Baseline: 72	- Episodic memory (verbal): - RAVLT - Global: MMSE	Although all subjects showed similar cognitive performance at baseline, subjective memory complaints and the presence of an ε4 allele predicted decline on all measures 6 years later.

(*Continued*)

Table 2
Longitudinal studies of cognitive changes in preclinical AD (*Continued*)

First author (year)	Sample sizes (end of study)	Follow-up	Mean ages (years)	Cognitive tests	Outcomes

Hofer [58] (2002)	94 *APOE* ε4+
	340 *APOE* ε4−
	(162 convert to probable dementia)
		7 years	Baseline: 76	- Episodic memory (verbal):
				  - Word recognition
				  - 3 word recall (with delay)
				  - Address recall (with delay)
				- Processing speed:
				  - Symbol-letter modalities test
				- Semantic memory/verbal:
				  - WAIS-R vocabulary
				  - WAIS-R similarities
				  - AMNART
					ε4 carriers showed lower baseline performance and greater change in episodic memory and speed measures over a 7-year period. Memory decline was seen even for those who did not convert to dementia status. A trend was seen for decrements in speed for those who did not convert.

Klages [50] (2003)	42 *APOE* ε4+ (10 convert to AD) 167 ε4− (17 convert to AD)	5 years	Baseline: ε4+: 76 ε4−: 77	- Episodic memory (verbal): - SRT	Regardless of genotype, individuals with lower memory scores at baseline showed an increase risk of developing AD in 5 years.

Mayeux [60] (2001)	80 *APOE* ε4+
	483 *APOE* ε4−
		7 years	Baseline: 76	- Abstract reasoning:
				  - WAIS-R similarities
				  - DRS identities and oddities
				- Episodic memory (visual):
				  - BVRT (multiple choice)
				- Episodic memory (verbal):
				  - SRT
				- Orientation: modified MMSE
				- Semantic memory/verbal:
				  - BNT
				  - COWAT
				  - Category naming
				  - Complex ideational material test
				  - Boston diagnostic aphasia test
				- Visuospatial:
				  - Rosen drawing test
				  - BVRT
					ε4+ carriers showed more rapid decline on memory at follow-up period of 7 years. ε4+ carriers with less than 10 years education showed an even more pronounced decline than those with more than 10 years education.

Riley [51] (2000)	34 *APOE* ε4+
	207
	APOE ε4−
		4 years	Baseline: 81	- Episodic memory (verbal):
				  - CERAD delayed word recall
				- Global: MMSE
				- Semantic memory/verbal:
				  - CERAD verbal fluency
				  - BNT
				- Visuospatial:
				  - Constructional praxis
					For individuals who were classified as cognitively intact at exam 1, the annual point change was significantly greater for global cognition and episodic memory recall for ε4+ carriers versus noncarriers. For individuals who were classified as cognitively impaired but not demented at exam 1, the annual point change was significantly greater for global cognition, semantic memory/verbal fluency, and episodic memory recall for ε4+ carriers versus noncarriers.

Salmon [53] (2013)	73 *APOE* ε4+ 213 *APOE* ε4−	4 years	Baseline:
			ε4+: 78
			ε4−: 79
				- Episodic memory (verbal):
				  - FCSRT
				  - NYU paragraph recall
				- Executive function:
				  - TMT A & B
				  - Cancellation test
				- Global:
				  - DSST
				  - Modified MMSE
				- Semantic memory/verbal:
				  - BNT
				  - CERAD animal fluency
					ε4+ carriers showed significant decline compared to noncarriers on episodic memory measures, executive functions, and semantic memory/verbal fluency.

Wilson [54] (2002)	158 *APOE* ε4+
	425 *APOE* ε3/ε3 86 *APOE* ε2/ε2, ε2/ε3
		5 years	Baseline:
			ε4+: 75
			ε3: 76
			ε2: 76
				- Episodic memory (verbal):
				  - CERAD word list memory
				  - WLM
				  - East Boston story
				- Semantic memory/verbal:
				  - BNT
				  - Verbal fluency
				  - Extended range vocabulary
				  - AMNART
				- Working memory:
				  - WAIS-R digit span F & B
				  - Digit ordering
				  - Alpha span test
				- Processing speed:
				  - Symbol digit modalities test
				  - Number comparison
				- Visuospatial:
				  - Judgment of line orientation
				  - Standard progressive matrices
					While the ε2 allele was protective for episodic memory, ε4+ carriers showed the greatest decline on episodic memory, followed by decline in semantic memory, and perceptual speed versus the other groups but not in working memory or visuospatial abilities.

Composite scores (cognitive measures only)					

Langbaum [80] (2014)	213 MCI/AD Convert
	413 Controls
		5 years	Last visit:
			Convert: 76
			Controls: 73
				- Composite score:
				- Episodic memory (verbal):
				  - WLM (delay)
				  - East BNT (immediate)
				- Global:
				  - MMSE orientation to time
				- Processing speed:
				  - Symbol digit modalities
				- Semantic memory/verbal:
				  - Fruits and vegetables fluency
				  - BNT
				- Visuospatial:
				  - Ravens progressive matrices
					Across three cohorts, the authors identified the ideal composite score that differentiated those who converted to MCI or AD diagnosis from those who remained cognitively normal. The most sensitive individual test score in this composite was the logical memory delayed recall.

(*Continued*)

Table 2
Longitudinal studies of cognitive changes in preclinical AD (*Continued*)

First author (year)	Sample sizes (end of study)	Follow-up	Mean ages (years)	Cognitive tests	Outcomes
Rajan [72] (2015)	442 AD 2125 Controls	18 years	Baseline: 73	- Composite score: - Episodic memory (verbal): - East BNT (immediate, delayed) - Executive function: - Symbol digit modalities - Global: - MMSE	Lower composite scores were associated with greater risk for development of AD. Decline was greatest in executive function and global cognition 13–17.9 years prior to diagnosis, a more robust finding than that of episodic memory. The risk for development of AD was greater in European Americans than African-Americans.

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; *APOE*, apolipoprotein; MMSE, Mini-Mental State Examination; BNT, Boston naming test; WLM, logical memory from Wechsler; WAIS-R, Wechsler adult intelligence scale-revised; AMNART, American National Adult Reading Test; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; TMT, trail making test; FCSRT, free and cued selective reminding test; BVRT, Benton visual retention test; COWAT, controlled oral word association test; SRT, selective reminding test; DRS, dementia rating scale; RAVLT, Rey Auditory Verbal Learning Test; WCST, Wisconsin card sort test; DSST, digit symbol substitution test; IDSR, intracategorical delayed selective reminding test; WMS, Wechsler memory scale; IST, Isaacs set test.

correlated activity at rest and suppression of activity during task-related behaviors [16]. Given the close neuroanatomical relations between the loci of AD neuropathology and the areas that make up the DMN [17,18], it is possible that hypoconnectivity of this network may be implicated in early AD memory decline [16]. In this way, DMN dysfunction may constitute a relevant neuroimaging marker of cognitive decline in preclinical populations. This dysfunction may specifically manifest as a failure to suppress the DMN during task-related behaviors, causing excess neural noise that limits efficient cognitive processing. For example, while encoding associative face-name pairs, subjects who were characterized at risk for AD show decreased DMN deactivations compared to control groups for the medial prefrontal cortex, posterior cingulate cortex, and lateral parietal cortex [19,20]. These reduced DMN deactivations are also associated with lower performance in episodic memory [19], processing speed, verbal fluency, and fluid reasoning [20].

Other resting-state fMRI studies have reported competing increased and decreased functional connectivity across regions in at-risk individuals when compared to controls. Decreased functional connectivity has been localized to the posterior DMN in preclinical populations [19,21], with a tendency to be associated with lower episodic memory performance [19]. In contrast, increased functional connectivity has been observed in more anterior areas of the DMN [19,21,22] and may indicate a neuroadaptive function to maintain normal cognition [21]. However, this compensatory strategy does not appear to consistently preserve cognition, as indicated by the relationship between increased functional connectivity and lower performance in semantic memory for at-risk subjects [19] and episodic memory for *APOE* ε4 carriers [22]. The functional relevance of this compensatory process may thus be an important area for future studies in preclinical AD.

3.3. Amyloid burden in preclinical AD and cognitive correlates

Poorer performance in episodic memory has frequently been associated with increased amyloid burden, as recently confirmed in a meta-analysis that examined the association between amyloid load and cognitive performance in aged CN subjects using 16 data sets from mostly cross sectional studies (maximum of 1278 subjects) [10]. Individual cross-sectional studies have shown mixed results, however, depending on the neuropsychological test used and the method of amyloid estimation. Since this meta-analysis, most cross-sectional studies report no significant differences on visual episodic memory performance, assessed with the brief visuospatial memory test–revised and the Wechsler memory scale (WMS) visual reproduction test between persons with high and low amyloid deposition levels [23–25]. Verbal episodic memory performance as measured by the RAVLT (total and long delay recall) [23,26] or the

selective reminding test [27] was also unrelated to amyloid level. However, significantly poorer performance on the California verbal learning test (CVLT) has been reported in amyloid-positive (Aβ+) subjects, where amyloid was measured using the global Pittsburgh compound B uptake index [24] but not in another study that measured amyloid using visual ratings [25]. The test that yields the most consistent association with amyloid level is the WMS logical memory (LM) test [28,29]. Unlike the cross-sectional observations, longitudinal studies have consistently reported significantly greater episodic memory decline in Aβ+ participants, irrespective of the test used [30–37]. Individuals with the greatest performance decrements in this domain also showed significantly more amyloid burden in the temporal lobe [35,37].

Compared to episodic memory, there has been little exploration of semantic memory, this being restricted principally to tasks of category fluency and naming. Cross-sectional studies have not reported an association between performance on category fluency tasks and amyloid load [23–25,28,38], and longitudinal studies have detected only minimal impairment over time on the Boston naming test in association with increasing amyloid levels [33,39]. Studies of working memory also suggest this to be a domain less associated with amyloid deposition in early AD, with little to no differences being detected cross sectionally [23,27,30,31,33,40]. Small differences, however, were noted between Aβ+ and Aβ− subjects using the Cogstate one back and one card learning tasks over an 18-month [40] and 30-year period [31]. The small number of studies conducted in these areas and limitations in the range and type of cognitive stimuli used (insufficient exploration of semantic abilities and working memory tasks not adhering to its strictest definition as dual task performance) do not currently allow us to conclude as to the extent of early dysfunction in either semantic or working memory functions.

Most cross-sectional and longitudinal studies have not reported an association between amyloid burden and performance on executive tasks, regardless of the experimental design or testing procedure used [23–25,27,29,30,34,39]. Two studies have found differences either using Digit Symbol Substitution Symbol Test [28] or executive function composite score [33]. However, the testing procedures used in both studies have a significant episodic memory component, which could be driving this association. Only one study suggest that Aβ+ subjects might exhibit significantly greater age-associated cognitive decline on executive functions, assessed with stroop test interference trial and trail making test (TMT) A and B, relative to Aβ− subjects [26]. Finally, a number of studies have revealed a relationship between amyloid burden and cognitive composite scores derived by aggregating multiple neuropsychological tests. Cross-sectional correlations have been noted between the Repeatable Battery for the Assessment of Neuropsychological Status total score and the level of amyloid deposition [41], and Aβ+ subjects demonstrate greater decline on global scores for the Alzheimer's Disease Assessment Scale-Cognitive subscale [28] and on the Alzheimer's Disease Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC) at both 18 and 36 months relative to Aβ− subjects [42].

3.4. Cognitive changes in preclinical AD in prospective cohorts

Consistent with the imaging studies mentioned previously, episodic memory functioning is the most robust neuropsychological predictor of dementia in prospective studies [43–54], detectable between 7 and 15 years prior to diagnosis [55–60], as supported by recent meta-analyses [9,10]. Although this has been known for some time, recent studies have focused on qualifying the nature of this impairment. For instance, one recent study found that performance for immediate versus delayed episodic memory recall varies according to the temporal stage of disease progression [44]. Contrary to the common view that delayed memory recall is the most sensitive measure of early dementia, Bilgel et al. [44] found that immediate verbal recall measures in the CVLT were the first to decline in preclinical AD, followed by delayed verbal recall on the same test closer to a diagnosis of MCI, with visual memory measures from the Benton Visual Retention Test the last to change. While suggesting that evaluation of both immediate and delayed memory recall may provide information on distance to dementia [44], this finding has yet to be reproduced.

Other longitudinal studies have characterized episodic memory decline according to a change-point model with two inflection points, one being the initial slope that differentiates CN from preclinical disease states, followed by a steeper rate of decline approximately 2–3 years before a diagnosis of AD [57,61,62]. This second inflection point has been observed to parallel an upward swing in plasma Aβ and an acceleration in hippocampal atrophy [52], which taken together could improve the specificity of early diagnostics. Furthermore, accumulating evidence suggests that lower baseline performance for episodic memory (and other cognitive domains) as a predictor of dementia [45,59,61,63,64], is also moderated by the presence of the *APOE* ε4 allele [43,50,65], although these results are not always consistent [51,58,66]. In general, carriers of the *APOE* ε4 allele show lower baseline performance and steeper rates of decline than noncarriers [46,51,53,60,66], in contrast to the protective ε2 allele [54], with the caveat being that *APOE* individuals have not always been followed to diagnosis.

Within cohort studies, semantic memory impairments also appear early in this temporal sequence. Both episodic and semantic forms of memory are processed in the medial temporal cortex but in subregions that are affected at different stages of AD neurofibrillary degeneration,

which could affect the timing of these memory impairments. The starting point of this pathology is in the transentorhinal (perirhinal cortex), the structure responsible for semantic memory processing; this pathology then spreads to the entorhinal cortex and hippocampus, regions that are involved in episodic memory functions [17,67,68]. These findings would suggest that semantic memory impairments should in fact precede episodic memory dysfunction. At least two longitudinal studies suggest this is the case [61,69], although most report episodic memory as the first to decline (Table 1). However, assessment of semantic memory is often poor, being restricted to tasks which implicate multiple cognitive functions. As in episodic memory, semantic memory has been seen to be not only lower a decade before dementia onset but to show a downward inflection in parallel with an acceleration a few years before diagnosis in both plasmatic Aβ and hippocampal atrophy [52].

There appears to be some inconsistency between the progression of neural degeneration and the order in which specific memory subsystems decline. It should be noted, however, that many studies focus primarily on episodic memory, with other subsystems being largely neglected [9]. Second, the naïve assumption is often made that cognitive tests are highly specific to a given function, when in fact most implicate multiple cognitive processes. As a result, the same test has often been used to justify dysfunction in diverse cognitive domains. Neuropsychological testing can only assume that an individual with a given cognitive deficit will perform poorly on a specific test which implicates this ability; however, the contrary (that persons performing poorly on such a test can only have this specific cognitive deficit) is erroneous. Difficulties on any cognitive test may be attributable to a number of underlying deficits; the key cause only being identifiable from examination of performance on a wide range of stimuli. For example, underlying semantic deficits may be attributed to executive functions (concept formation) unless more specific cognitive stimuli are used which specifically target the perirhinal cortex [56,70].

An emerging finding from prospective studies is that executive dysfunction is observed in preclinical phases [45,56,71–73], controlled by the prefrontal cortex [74]. Several studies have found that performance on the timed TMT differentiates preclinical AD from healthy controls [45,47,72,73]. In fact, Rajan et al. [72] reported that a loss in executive functions, as measured by the Symbols Digits Modalities Test, could be detected as early as 18 years prior to diagnosis, in a sample of 2000 people comprised of African and European Americans. Indeed, four tests of attention and executive function (digit letter test, TMT part B, digit symbol substitution test, and identical pictures test) have been shown to have the highest discriminatory power between individuals who convert to AD and those who remain CN [73]. A decline in other executive functions, notably response inhibition, has also been observed in preclinical phases [71,75]. Still other studies have observed executive impairments closer to a dementia diagnosis, upward of 3 years [49,55,57,62,63].

This pattern of deficits in executive and attention tasks coupled with episodic and semantic memory decline is consistent with the view that underlying cognitive processes are multiple-interacting neural networks, including the medial temporal memory complex and prefrontal cortical executive system [76,77]. It is possible then that AD pathophysiology in one network affects downstream cognitive functions associated with other networks. In this case, a breakdown in attentional processes or heightened sensitivity to interference, potentially triggered by the AD cholinergic deficit [73], may in turn prevent encoding of memories, which manifest as an episodic memory recall deficit [78,79]. Although disruption in these same processes have been reported in normal aging, it appears that individuals on the long trajectory of AD, experience more rapid acceleration of decline due to cerebrovascular disease, neurotransmitter depletion, and structural brain changes [76]. The multitude of factors that affect these neural systems may contribute to more global cognitive decline.

3.5. *Global cognitive decline measured with composite scores*

While cognitive psychologists have sought to identify highly specific cognitive subsystems which parallel underlying brain changes in order to better understand disease progression, there has been interest in relation to clinical trials in the possibility of composite cognitive test scores increasing sensitivity to preclinical AD and thus providing a better outcome measure for intervention. Composite scores are derived from either (1) a priori hypotheses about which cognitive domains are most affected early in the disease process, such as ADCS-PACC, which is weighted toward episodic memory and executive function [42] or (2) cognitive performance data in clinical cohorts, as proposed by the Alzheimer's Prevention Initiative (API) trial [80]. In the latter case, the API composite was comprised of seven test scores (category fluency [fruits and vegetables], Boston naming test, LM-delayed recall, east Boston naming test-immediate recall, Ravens progressive matrices subset, symbol digit modalities, and Mini-Mental State Examination orientation to time) that showed the greatest mean-to-standard deviation ratios of change over time when tested in independent cohorts that converted to mild cognitive impairment (MCI) or AD across a 2- to 5-year time frame, after controlling for age and practice effects [80]. These composites are now being used as primary end points in secondary prevention trials involving presenilin 1 E280A mutation carriers in the API trial [81] or individuals that show early amyloid accumulation in the anti-amyloid treatment in asymptomatic Alzheimer's trial [42]. The US Food and Drug Administration has recently approved these types of

composite scores in an attempt to accelerate approval of disease-modifying drugs [82].

Although this strategy has merit, it is important to point out that the results depend on the specific tests used in the composite, the order of presentation of these tests, for which interference could have an effect, and whether the cohorts studied are representative across geographic, cultural, and socioeconomic sectors. It may be the case that multiple combinations from various different tests are useful for consideration as long as they cover the cognitive domains affected in preclinical stages. Derivation of composite scores from batteries whose primary purpose is to differentiate normal aging from early AD trajectories may be worth exploring further, such as with the RBANS [83].

4. Discussion

Taken together, the studies reviewed previously clearly indicate that cognitive changes are detectable years before, rather than beginning with, a clinical diagnosis of MCI. However, the temporal sequence of these cognitive changes and the corresponding biomarkers that track cognitive impairment has yet to be fully characterized. The most consistent findings across longitudinal studies indicate performance decrements in episodic and semantic memory, as well as executive functions as being the first to emerge in the absence of dementia, in accordance with previous reviews [78,79]. However, as we indicate previously, decline in these same domains is not always coupled to brain biomarker changes. What is apparent is the relationship between episodic memory decline and increasing levels of amyloid deposition across time, other observations being less consistent and dependent both on type of test used and study design.

The reasons for this ambiguity are multifold. First, longitudinal studies examining the relationship between brain changes and their cognitive correlates in large preclinical AD cohorts are relatively scarce. The search strategy on PubMed provided numerous studies which investigated the brain changes in preclinical AD without exploring their cognitive correlates or studies which reported an association between brain changes and cognition in CN, MCI, or AD patients and not in preclinical AD populations as defined here. Second, for most of the studies that characterized at-risk populations, the trajectory for these populations is largely unknown. It is highly probable that a significant number of these individuals, defined as preclinical AD, do not convert to clinical AD. Identifying persons at high risk of developing AD is a challenging task, and the currently used criteria [8,84] have variable predictive value. Recently, it has been demonstrated that administration of pharmacological (anticholinergic drugs) [85,86] and cognitive stressors [87] in conjunction with cognitive testing may improve preclinical detection. Such stressors appear to reveal cognitive deficits in healthy older people with subjective memory complaints, a familial history of AD, or presence of amyloid who, under normal testing conditions, perform within normal limits.

Furthermore, it is yet to be determined if the criteria for preclinical AD staging [8] can clarify our understanding of AD disease progression. One recent study attempted to do so by characterizing ADNI subjects according to their scores on memory, executive function, or multidomain tests and comparing their neuropsychological profiles against preclinical AD biomarker stages [12]. They found distinct cognitive and biomarker profiles across stages and argued for longitudinal studies to quantify biomarker cutpoints to establish the clinical meaningfulness of these preclinical stages and their outcomes [12]. This type of approach could be helpful to understand the causal links between neuropathological markers and the cognitive changes that ensue.

With the new wave of secondary prevention trials, we are forced to rethink how best to define "CN" individuals into various at-risk groups according to their cognitive performance. The increasing use of neuroimaging biomarkers and characterization of neural networks paired with cognitive tests which are known to be specific to certain brain regions and functions, notably hippocampal subregion volume and interhemispheric/intrahemispheric functional connectivity, is already providing better prediction of progression [88]. Moreover, there has been a tendency to focalize on the episodic memory functions of the hippocampal formation while neglecting its other pivotal roles, notably in spatial navigation, spatial memory, and the integration of spatial location with episodic memory [89]. There have been few attempts to develop new testing procedures targeting specific regions such as the entorhinal cortex, precuneus, and retrosplenial cortex, although they are the regions in which both tau and Aβ pathology both initially co-occur [90,91]. There is a clear need for increased collaboration between researchers in clinical studies of AD and cognitive neuroscientists developing innovative methods for the investigation of specific regional brain functions. This level of specificity in cognitive testing have been well developed within the context of normal cognition [92] but has only recently been considered theoretically within the context of AD [93].

In conclusion, it would appear that there is ample evidence that cognitive changes may be detected within the preclinical period but that they only partially map at present to brain biomarker studies. While deterioration may be present at a subtle level over a decade before dementia is diagnosed, this downward trend is amplified by the upward sigmoidal swing in brain biomarkers. While the present review indicates some of the existing testing procedures which have been able to provide some very early signal detection (notably episodic and semantic memory), other areas such as so-called executive functioning are currently measured in such a wide variety of ways and subsume too many other cognitive abilities to be meaningfully interpreted. It is evident that more region-specific cognitive measures need to be developed and that these are furthermore likely to be most performant within a longitudinal rather than cross-sectional study design.

RESEARCH IN CONTEXT

1. Systematic review: While it has been generally assumed that cognitive dysfunction emerges only in the prodromal phase of AD, clinical trials are nonetheless being developed with cognitive outcomes largely derived from tests used to diagnose dementia. There is a need to consider available empirical evidence to inform cognitive test selection in the preclinical phase. To this end, a review of biomarker and clinical prospective studies was undertaken using the PubMed database.
2. Interpretation: Tests of episodic memory were observed to be the most robust indicators, correlating with high levels of amyloid deposition and hypoconnectivity across large-scale brain networks. Prospective studies further indicate the importance of semantic memory processing and executive functions.
3. Future directions: The range of tests used has been limited, notably lacking measures targeting specific brain areas first showing brain biomarker change. Future research would benefit from a closer association with the cognitive neurosciences.

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