Process Dissociation Analyses of Memory Changes in Healthy Aging, Preclinical, and Very Mild Alzheimer Disease: Evidence for Isolated Recollection Deficits

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Objective: Recollection and familiarity are independent processes that contribute to memory performance. Recollection is dependent on attentional control, which has been shown to be disrupted in early stage Alzheimer's disease (AD), whereas familiarity is independent of attention. The present longitudinal study examines the sensitivity of recollection estimates based on Jacoby's (1991) process dissociation procedure to AD-related biomarkers in a large sample of well-characterized cognitively normal middle-aged and older adults ($N = 519$) and the extent to which recollection discriminates these individuals from individuals with very mild symptomatic AD ($N = 64$). *Method:* Participants studied word pairs (e.g., knee bone), then completed a primed, explicit, cued fragment-completion memory task (e.g., knee b_n_). Primes were either congruent with the correct response (e.g., bone), incongruent (e.g., bend), or neutral (e.g., &&&). This design allowed for the estimation of independent contributions of recollection and familiarity processes, using the process dissociation procedure. *Results:* Recollection, but not familiarity, was impaired in healthy aging and in very mild AD. Recollection discriminated cognitively normal individuals from the earliest detectable stage of symptomatic AD above and beyond standard psychometric tests. In cognitively normal individuals, baseline CSF measures indicative of AD pathology were related to lower initial recollection and less practice-related improvement in recollection over time. Finally, presence of amyloid plaques, as imaged by PIB-PET, was also related to less improvement in recollection over time. *Conclusions:* These findings suggest that attention-demanding memory processes, such as recollection, may be particularly sensitive to both symptomatic and preclinical AD pathology.

General Scientific Summary
Recollection is a controlled process of memory retrieval, as opposed to familiarity, which is automatic. An estimate of recollection, derived from a 10-min computer-based memory task, outperformed a majority of other behavioral measures in correctly discriminating between cognitively normal individuals from those with the earliest detectable stage of dementia. Recollection was also uniquely related to the accumulation of Alzheimer's disease pathology, that is, amyloid plaques and neurodegeneration, in presymptomatic, cognitively normal individuals.

Keywords: Alzheimer's disease, amyloid, episodic memory, recollection, tau

Alzheimer's disease (AD) is traditionally characterized by a deficit in episodic memory processes and there is clear evidence that these deficits are the prominent clinical feature of the disease throughout its progression (for review, see Carlesimo & Oscar-Berman, 1992; R. G. Morris & Kopelman, 1986). In addition to episodic memory, there is accumulating evidence that early stage symptomatic AD is also marked by changes in executive function and/or attentional control processes that might contribute to changes in memory performance (for review, see Balota & Duchek, 2015; Faust & Balota, 2007; Perry & Hodges, 1999). This proposal runs parallel to research in the domain of healthy aging, where it has been repeatedly demonstrated that certain age-related memory deficits may be mimicked in younger adults under conditions of divided attention (e.g., Balota, Burgess, Cortese, & Adams, 2002; Benjamin, 2001; Castel & Craik, 2003; Jacoby, 1999b). Moreover, structural equation models reveal that individual age differences in memory performance are mediated by an executive/attention factor, composed of executive functioning and working memory measures (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010). The critical role of attention/executive processes in the study of memory changes in both healthy aging and AD is in accord with longstanding theoretical frameworks that emphasize the relationship between attention and memory systems (e.g., Craik & Lockhart, 1972; Hasher & Zacks, 1979; Jacoby, 1991). In this light, if changes in attention processes are hypothesized to contribute to AD-related memory changes, then one might predict that memory tasks and processes that are highly dependent on such processes should be particularly sensitive to biomarkers of presymptomatic AD in healthy control individuals and in discriminating healthy aging from the earliest stages of symptomatic AD.

One theoretical framework that has been critical in identifying contributions of attention to memory performance is Jacoby's (1991) dual process theory. This model proposes that at least two cognitive processes contribute independently to performance on a given memory task: *recollection*, which is intentionally guided and highly dependent upon attentional control, and *familiarity*, which is automatic and independent of attentional control. Importantly, Jacoby (1991) developed experimental paradigms to isolate the contributions of each process to overall performance via the process dissociation procedure (PDP). A PDP task includes congruent conditions, in which reliance upon either process would lead to the same response, and incongruent conditions, in which the two processes lead to conflicting responses. With such a design, one can estimate the independent contributions of recollection and familiarity for a single memory task. As predicted by the dual process model, under conditions of divided attention at encoding or retrieval, estimates of recollection are decreased, while estimates of familiarity remain consistent (Jacoby, 1991, 1998; Jacoby, Toth, & Yonelinas, 1993; for review, see Yonelinas & Jacoby, 2012), confirming that recollection is highly dependent upon attentional control.

If recollection is indeed dependent upon attentional control systems, one would predict a relatively large recollection deficit among individuals who exhibit deficits in such systems, such as aging or dementing populations. Koen and Yonelinas (2014) recently presented a meta-analysis of recollection and familiarity estimates as a function of healthy aging, amnestic mild cognitive impairment (aMCI), and AD. Interestingly, healthy aging was associated with significant reductions of *both* recollection and familiarity. However, the mean effect size of age on recollection was approximately three times larger than the effect on familiarity. Furthermore, the effect of age on familiarity was only significant for a subset of studies in which processes were inferred using a self-report remember/know procedure (e.g., McCabe, Roediger, McDaniel, & Balota, 2009). In the studies that employed a PDP (e.g., Jacoby, 1999b) or receiver operating characteristic (ROC) approach (e.g., Healy, Light, & Chung, 2005), there was no deficit in the more automatic familiarity process. In contrast to the inconsistent effect of age on familiarity estimates, the effect of age on recollection was significant across all three estimation procedures (Koen & Yonelinas, 2014). AD, like healthy aging, was associated with significant reductions of both recollection and familiarity. Unlike healthy aging, however, the effect sizes were similar in magnitude across the two processes. This finding is somewhat surprising given the above evidence of deficits in both attention and memory in early stage symptomatic AD. If indeed attention contributes to the memory deficit, one would a priori expect AD status to produce a larger deficit in recollection than in familiarity.

Because the present study is partially focused on early stage symptomatic AD, one aspect of the Koen and Yonelinas meta-analysis of particular interest is that aMCI was associated with a deficit in recollection, but not in familiarity. Indeed, the mean effect of aMCI on familiarity only approached significance for a subset of studies that tested individuals with both single-domain and multiple-domain diagnoses of aMCI (e.g., Wolk, Mancuso, Kliot, Arnold, & Dickerson, 2013), whereas the mean effect size was near zero and slightly positive for studies that examined only single-domain aMCI (e.g., Anderson et al., 2008).

It is clear that estimates of recollection are sensitive to healthy aging and dementia, however there appears to be some inconsistency regarding the relative contributions of familiarity in these populations, which merits further investigation. As noted above, this inconsistency may be attributable in part to different approaches for estimating recollection and familiarity, for example, using remember/know judgments based on self-report, as opposed to PDP procedures based on memory task performance, or different diagnoses of dementia, for example, single-domain aMCI, multiple-domain aMCI, or AD. In addition, task complexity may play a part in this variability. It is possible that some of the more severe AD participants may not fully understand complex task instructions and hence produce deficits in both recollection and familiarity. Other procedural details of the memory task may play a role as well. Studies reported in the Koen and Yonelinas meta-analysis estimated recollection from performance on a variety of recognition tasks, for example, memory inclusion and/or exclusion, or discrimination of intact, rearranged, and novel paired associates. Such recognition tasks might not engage controlled processes to the same extent as a free or cued-recall task (Craik, 1983). If attentional control plays a role in the memory changes that occur in aging and symptomatic AD, it might be more informative to examine memory processes using a free or cued recall task. Finally, because of relatively small sample sizes in previous studies, that is, from 7 to 32 individuals with aMCI or AD in each previous study, it is important to examine these process estimates in a larger, well-characterized sample.

In addition to the behavioral evidence regarding the influence of age, MCI, and AD on retrieval process estimates, there has also

been evidence that distinct neural substrates that are influenced by AD pathology influence both recollection and familiarity. Specifically, recollection has been associated with the hippocampus, whereas familiarity has been associated with the anterior parahippocampal gyrus, including entorhinal and perirhinal cortices (Bowles et al., 2010; Davachi, Mitchell, & Wagner, 2003; Wolk, Dunfee, Dickerson, Aizenstein, & Dekosky, 2011; for review, see Diana, Yonelinas, & Ranganath, 2007; but also see Wais, Squire, & Wixted, 2010). Because early stage AD tau pathology begins in medial perirhinal cortex, continuing into entorhinal, and then hippocampal areas (Braak & Braak, 1991; Taylor & Probst, 2008), one may expect disruptions in both recollection and familiarity processes. However, as noted above, this effect may depend on the tasks used to measure recollection and familiarity, along with the severity of disease progression.

In addition to discriminating healthy aging from early stage symptomatic AD, memory process estimates might change as a function of biomarkers of asymptomatic AD pathology in nondemented individuals. In current disease staging, the presence of AD biomarkers in the absence of AD diagnosis is defined as "preclinical AD" (Albert et al., 2011; J. C. Morris et al., 2014; Sperling et al., 2011). Physiologically, this stage is marked by amyloid plaque deposits, which can be detected by measuring amyloid β_{42} ($A\beta_{42}$) in the cerebral spinal fluid (CSF) or via positron emission tomography with the Pittsburgh Compound B radiotracer (PIB-PET), and progressive neuronal degeneration, which can be detected by measuring tau in the CSF or regional brain atrophy via MRI (Sperling et al., 2011). Correlations between these preclinical biomarkers and standardized neuropsychological measures are relatively small and are somewhat inconsistent (for meta-analysis, see Hedden, Oh, Younger, & Patel, 2013). Here we examined whether memory process estimates, particularly recollection, might be sensitive to these biomarkers.

The present study includes a large, longitudinal cohort of cognitively normal adults and individuals with early stage symptomatic AD. The participants are well-characterized with AD-related biomarkers, for example, apolipoprotein E (APOE) genotype, CSF estimates of $A\beta_{42}$ and tau, and PIB-PET imaging, available for most participants. By defining the current AD sample using the Clinical Dementia Rating (CDR) scale, we can focus on the earliest detectable stage of symptomatic AD in participants who have a CDR of 0.5 (indicating very mild dementia). Importantly, we apply strict diagnostic criteria to include only individuals with early stage symptomatic AD, as opposed to mixed etiologies or uncertain causes for early cognitive decline. Individuals with a CDR of 0.5 typically have an average MMSE score of 26 to 27 and are very likely to progress to a higher CDR level. The CDR has been shown to be very accurate (93%) in identifying very mild AD (CDR 0.5), as confirmed by subsequent autopsy (Berg et al., 1998; Storandt, Grant, Miller, & Morris, 2006).

There are four goals in the present study. First, we developed a relatively simple paradigm that affords the use of the PDP to obtain estimates of recollection and familiarity in their relative contributions to the memory deficits observed in both healthy aging and symptomatic AD. Second, we examined the extent to which recollection estimates account for AD effects above and beyond standard psychometric measures. Third, because of the large and well-characterized sample, we were able to examine whether recollection (or familiarity) is sensitive to preclinical

biomarkers of AD pathology in cognitively normal adults. Fourth, because we have multiple measures of recollection and familiarity across time for individuals, we were able to examine the change in the recollection and familiarity estimates across time as a function of biomarker burden via longitudinal analyses. Because these longitudinal estimates were derived from identical tasks, they may exhibit a practice effect benefit from repeated exposures. Importantly, reduced episodic memory practice effects in similar samples have previously been shown to relate to preclinical AD and to predict AD conversion (Hassenstab et al., 2015).

To address these goals, we utilized a primed memory task that allows for PDP estimates of recollection and familiarity, based on a modification of a procedure previously used by Jacoby (1999a). The current version of the task was unique in that it was much shorter than prior PDP tasks of a similar type, that is, 30 critical test trials versus 60–90 trials. In fact, this task may be administered in approximately 10 min, which might facilitate use in clinical applications.

As shown in Figure 1, the current PDP memory task included two phases. First, participants incidentally encoded (via relatedness decisions) related and unrelated word pairs (e.g., knee bone, arrow cage). Next, participants completed a primed, cued fragment-completion task for the related pairs with explicit recall instructions. Participants were instructed to complete a cued word fragment based on their memory for the prior related word pairs (e.g., bone for knee b_n_). Immediately before the onset of each cued fragment, participants were presented a prime word that was *congruent* with the correct response (e.g., bone), *incongruent* with the correct response (e.g., bend), or *neutral* (i.e., &&&). Thus, the congruent condition was designed to prime familiarity for a correct response, while the incongruent condition was designed to prime familiarity for an incorrect response, which might bias participants to commit intrusion errors.

In a longer version of this task with slightly different instructions at retrieval, Jacoby (1999a) found that healthy older adults were more likely than younger controls to falsely recall the incongruent prime words, as evidenced by a higher intrusion rate. He did not report estimates of recollection and familiarity for individual participants, but application of the PDP to mean performance revealed a greater estimate of recollection in younger adults than in older adults and similar estimates of familiarity in each age group. This task is also conceptually similar to an earlier paradigm that manipulated the familiarity signal by establishing "habitual" associations in a prestudy training phase, for example, training on 15 presentations of "knee bone" and 5 presentations of "knee bend" (Hay & Jacoby, 1996). Process estimates from similar variants of that paradigm have demonstrated process-specific age-related deficits in recollection, but not in familiarity (Anderson & Craik, 2006; Guerdoux, Dressaire, Martin, Adam, & Brouillet, 2012; Hay & Jacoby, 1999). Of particular interest to the present study, Guerdoux and colleagues (2012) used this later paradigm to obtain process estimates in healthy control, aMCI, and AD individuals, and found only a deficit in recollection and not in familiarity.

The current paradigm is ideally suited to obtain estimates of the relative contributions of recollection and familiarity in healthy aging and very mild AD because the task is mostly automated, relatively brief, and is well-understood by the participants. Furthermore, because the paradigm demands explicit retrieval of the
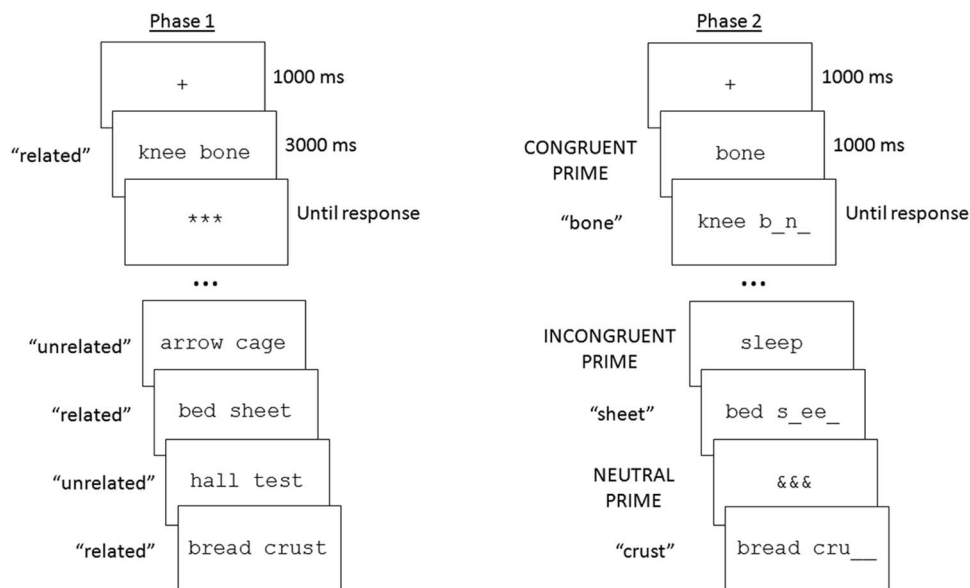
Figure 1. Illustration of PDP task design and example trials.

target, it should be particularly sensitive to changes in attentional control processes.

Method

Participants

All participants were recruited by the Charles F. and Joanne Knight Alzheimer's Disease Research Center at Washington University in St. Louis, as part of one of two longitudinal studies: the Healthy Aging and Senile Dementia Program Project or the Adult Children Study Program Project. In total, 583 individuals participated in this study over the course of up to 8 years, including 519 individuals with a CDR of 0 at baseline, indicating no dementia, and 64 individuals with a CDR of 0.5 at baseline, indicating the earliest detectable stage of dementia. All participants with a CDR of 0.5 only included individuals with a diagnosis of symptomatic AD, and so we excluded all individuals diagnosed with non-AD, uncertain, or mixed etiologies, such as frontotemporal contributions to the dementia. Aging effects were tested by dividing the sample of CDR 0 participants into three age groups: 45–59 years, 60–74, and 75–95. These age groups were selected to obtain relative equivalence of both the number of individuals and the range of ages represented in each group. Basic demographic measures of the sample are reported in Table 1. Research methods were approved by the Washington University Human Research Protection office. Written informed consent was obtained from all participants.

Annual Clinical and Psychometric Batteries

Each participant was assessed by a trained clinician using the Clinical Dementia Rating (CDR) scale (John C Morris, 1993). At each assessment, participants were assigned a CDR rating: 0 for cognitively normal, 0.5 for very mild dementia, 1 for mild dementia, 2 for moderate dementia, or 3 for severe dementia. A clinical diag-

nosis of AD in individuals who are CDR 0.5 or greater was based on NINCDS-ADRDA criteria (McKhann et al., 1984). In this report, we are most interested in describing very mild symptomatic and asymptomatic AD, so we focus on individuals with CDR ratings of 0 or 0.5.

Participants also annually completed a 2-hr battery of psychometric tests to assess cognitive performance. This battery included: several measures of memory, including the Logical Memory, Digit Span, and Associate Memory subtests of the Wechsler Memory Scale (WMS-R; Wechsler, 1987), and the Free and Cued Selective Reminding test (FCSR; Grober, Buschke, Crystal, Bang, & Dresner, 1988); measures of attention and processing speed, including WMS Mental Control (Wechsler & Stone, 1973), Letter-Number Sequencing (Wechsler, 1997), and Digit Symbol of the Wechsler Adult Intelligence Scales (WAIS–R Wechsler, 1981); measures of semantic/lexical retrieval, including the Animal Naming Test (Goodglass & Kaplan, 1983), the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1976), and the Word Fluency Test S-P (Thurstone & Thurstone, 1947); as well as measures of visuomotor ability (Trail Making A & B; Armitage, 1946); and working memory capacity (Reading Span; Engle, Tuholski, Laughlin, & Conway, 1999). The tasks included in the psychometric battery differed between the two longitudinal cohorts and, thus, some tasks were administered to only a subset of the current sample. All participants also completed the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975). Average baseline psychometric test scores are presented in Table 1 as a function of age and CDR status.

APOE Genotyping, CSF Measurement, and PIB-PET Imaging

APOE genotyping was performed using standard procedures with TaqMan assays (Applied Biosystems, Foster City, CA) for both rs429358 (ABI#C_3084793_20) and rs7412 (ABI#C_904973_10). We defined ε4+ individuals as those with at least one ε4 allele

Table 1

Demographic, Psychometric, and Biomarker Measures, Mean (SD), at Initial Test Grouped by Age and CDR Status

Variable (units)	CDR 0 Age <60	CDR 0 Age 60–74	CDR 0 Age 75+	CDR 0.5	*F(df)*	*p*
N	94	277	148	64		
% Female	68%	61%	61%	42%		
Age (years)	54.04 (3.38)	68.10 (3.98)	79.92 (4.13)	75.03 (7.14)	24.64 (1,581)	<.001
Education (years)	16.25 (2.53)	15.57 (2.57)	15.39 (2.71)	15.11 (2.69)	0.78 (1,572)	.378
MMSE	29.45 (0.84)	29.08 (1.30)	28.50 (1.49)	26.15 (3.32)	134.55 (1,552)	<.001
WMS Logical Memory immediate	12.57 (4.12)	13.89 (3.76)	13.28 (4.44)	8.54 (4.64)	76.78 (1,426)	<.001
WMS Logical Memory delayed	13.00 (4.55)	12.99 (4.18)	12.19 (4.95)	5.62 (5.27)	119.04 (1,426)	<.001
WMS Digit forward	6.43 (0.98)	6.83 (1.04)	6.64 (1.10)	6.57 (1.06)	1.25 (1,424)	.264
WMS Digit backward	4.86 (1.46)	4.85 (1.20)	4.74 (1.15)	4.28 (1.14)	9.79 (1,424)	.002
WMS Associate Memory	14.50 (4.50)	14.45 (3.38)	13.33 (3.99)	9.86 (3.58)	64.48 (1,423)	<.001
FCSR free recall	33.15 (5.38)	31.41 (5.76)	28.97 (6.31)	18.52 (8.25)	174.51 (1,545)	<.001
FCSR total	47.87 (0.37)	47.82 (1.32)	47.63 (0.85)	42.79 (7.91)	161.02 (1,545)	<.001
WMS Mental Control	6.71 (1.80)	7.32 (1.77)	7.48 (1.71)	6.72 (1.97)	6.89 (1,426)	.009
WAIS-III Letter Number Sequencing	11.83 (2.61)	10.35 (2.54)	8.63 (2.42)	7.71 (3.27)	15.33 (1,372)	<.001
WAIS-R Digit Symbol	58.86 (12.19)	49.59 (10.12)	44.99 (10.78)	37.74 (12.95)	41.52 (1,418)	<.001
Animal Naming	24.50 (5.94)	21.51 (5.45)	18.38 (5.53)	15.95 (4.41)	27.49 (1,552)	<.001
Boston Naming	57.43 (3.60)	55.64 (4.92)	53.56 (6.82)	50.52 (7.75)	24.13 (1,426)	<.001
Word Fluency S-P	33.57 (11.83)	30.58 (9.75)	29.77 (10.63)	25.82 (10.02)	9.38 (1,426)	.002
Trail Making A	27.26 (9.13)	32.86 (13.46)	39.23 (14.10)	49.03 (28.47)	35.56 (1,552)	<.001
Trail Making B	58.79 (22.80)	78.67 (31.28)	101.26 (39.40)	116.85 (47.28)	30.59 (1,551)	<.001
Reading span	2.82 (0.67)	2.45 (0.72)	2.09 (0.56)	1.68 (0.61)	23.33 (1,287)	<.001
Psychometric interval (days)	196.4 (194.45)	86.70 (114.32)	62.80 (57.21)	59.36 (59.88)	1.16 (1,552)	.282
% APOE ε4 positive	40%	36%	25%	54%		
CSF Aβ$_{42}$ (pg/mL)	700.29 (230.65)	692.84 (259.62)	608.56 (304.98)	485.99 (228.86)	10.96 (1,346)	.001
CSF Tau (pg/mL)	204.64 (77.34)	285.98 (159.11)	392.64 (248.17)	589.29 (292.72)	54.63 (1,346)	<.001
Lumbar puncture interval (days)	280.99 (281.83)	194.64 (230.94)	265.94 (292.87)	142.46 (164.02)	2.80 (1,346)	.095
PIB-PET MCBP	.05 (.07)	.15 (.21)	.24 (.32)	.43 (.32)	9.94 (1,289)	.002
PIB-PET interval (days)	239.13 (227.32)	263.91 (263.49)	277.77 (226.39)	316.89 (369.05)	0.14 (1,289)	.712
Number of PDP assessments	1.69 (0.73)	1.75 (0.80)	1.45 (0.59)	1.30 (0.46)	8.52 (1,580)	.004
Time in Study (years)	2.51 (2.55)	2.34 (2.38)	1.41 (1.88)	0.91 (1.49)	9.05 (1,580)	.003

Note. *F(df)* reports the univariate *F* statistic for the effect of CDR status, controlling for age as a continuous covariate.

present, that is, ε24, ε34, and ε44, whereas ε4- individuals were those without a single ε4 allele present, that is, ε22, ε23, and ε33. The proportion of individuals identified as ε4+ is presented in Table 1.

Approximately once every 3 years, CSF was collected via lumbar puncture and analyzed using methods described previously (Fagan et al., 2007). After participants fasted overnight, 20- to 30-mL samples of CSF were collected, then aliquoted (500 μl) in polypropylene tubes, and stored at −84°C. Samples were analyzed after a single thaw using ELISA (INNOTEST, Fujirebio [formerly Innogenetics], Ghent, Belgium). Baseline levels of CSF biomarkers, Aβ$_{42}$ and tau, are presented in Table 1.

Approximately once every 3 years, amyloid burden was imaged with PIB-PET using methods previously described (Mintun et al., 2006). Regions of interest were segmented automatically using Freesurfer (Fischl, 2012). Mean cortical binding potential (MCBP) was averaged across the following regions: left and right lateral orbitofrontal, inferior parietal, precuneus, rostral middle frontal, superior frontal, superior temporal, and middle temporal. Cerebellum was used as the reference region. This Freesurfer-derived measure of MCBP is highly consistent with a manually derived MCBP and demonstrates excellent test–retest reliability (Su et al., 2013). Baseline MCBP is presented in Table 1.

PDP Memory Task

Approximately once every 3 years, participants completed the PDP memory task. Word stimuli for this task were developed

according to previously described norms (Jacoby, 1996, 1999b). Related word pairs were constructed such that the cue word had a strong semantic association with two target words (e.g., knee bone, knee bend). Furthermore, the two possible targets were constrained to include words with the same number of letters and with at least two identical letters in the same position, such that either target would be a valid completion of the same word fragment (e.g., b_n_). In total, 34 related and 14 unrelated word pairs were produced. All stimuli were presented in 18-point Courier font on a computer monitor using E-Prime (Psychology Software Tools, Pittsburgh, PA).

As noted, the PDP memory task consisted of two phases (see Figure 1). During incidental encoding (Phase 1), participants viewed a series of 40 word pairs, consisting of 30 related pairs (e.g., knee bone) and 10 unrelated pairs (e.g., arrow cage). Word pairs were presented in a random order. On each trial, the following sequence of events occurred: (a) a fixation cross appeared at the center of the screen for 1000 ms; (b) a word pair appeared for 3000 ms; (c) the participant read each word pair aloud and vocally identified if the words were related or unrelated; (d) the experimenter coded vocal responses with a button press. Four unscored buffer trials (including 2 related and 2 unrelated word pairs) were presented before and after the 40 test trials to minimize the influence of primacy and recency effects and to serve as memory targets for practice trials in the second phase.

Immediately after completing the incidental encoding phase, participants completed a primed, cued fragment-completion task with explicit recall instructions (Phase 2). The 30 related word pairs from Phase 1 were used as cued retrieval targets. Each trial consisted of the following: (a) a fixation cross presented at the center of the screen for 1000 ms; (b) a prime presented for 1000 ms; (c) a cue word paired with a word fragment, based on one of the related word pairs from Phase 1 (e.g., knee b_n_). The type of prime was manipulated within subjects in three conditions: congruent with the correct response (e.g., bone), incongruent with the correct response (e.g., bend), or neutral symbols (i.e., &&&). Crucially, all incongruent primes were also valid completions of the fragment and semantically related to the cue, but had not been presented during the incidental encoding phase. Participants were instructed to silently read each prime word, then use the cue and fragment to recall the word that was earlier paired with the cue. Participants were given up to 20 seconds for their responses. The experimenter coded all vocal responses. Participants were informed that all correct answers were related to the cue word and correctly completed the fragment, and that the prime words might be congruent or incongruent with the correct answer that was presented during the first phase of the experiment. Participants completed 10 congruent, 10 incongruent, and 10 neutral trials in a random order. These 30 trials were preceded by 4 unscored practice trials, based on the 4 related buffer trials presented in the incidental encoding phase.

In each longitudinal session, participants completed an identical version of the PDP task. The recollection estimate derived from the task demonstrated adequate test–retest reliability for a behavioral measure, ICC = .63, 95% C.I. = [.57, .69].

Data Aggregation

For each administration of the PDP task, dependent measures were matched to the temporally closest clinical (CDR rating within 1 year), psychometric (within 2 years), and physiological measures (CSF estimates and PIB-PET scans within 3 years) for that individual. The mean time intervals between the PDP task and each of these measures are reported in Table 1.

Results

Overview of Analyses

We first tested the effects of healthy aging and disease status (i.e., healthy controls vs. very mild symptomatic AD, CDR .5) on task performance, then on PDP estimates of recollection and familiarity. Although we tested the effects of age as a function of three groups, other groupings of age, for example, two-group median split or four groups, resulted in consistent interpretations of the age effects. Effects of very mild symptomatic AD were tested by comparing all CDR 0s with CDR 0.5s with age as a continuous covariate. We then compared the recollection estimates to a battery of standard psychometric tests in their accuracy in classifying individuals as CDR 0 versus CDR 0.5. Finally, we tested whether recollection estimates were sensitive to individual differences in preclinical biomarkers of AD pathology and risk in cognitively normal individuals (CDR 0s) both at baseline and in longitudinal analyses. These biomarkers included APOE genotype, CSF mea-

surements of $A\beta_{42}$ and tau, as well as the presence of amyloid burden, as imaged by PIB-PET. One participant was excluded from all analyses as an outlier for age (31 years). Another participant was excluded from all analyses because a concurrent CDR was unable to be matched.

Memory Performance as a Function of Healthy Aging

Figure 2 displays the mean proportion of each response type (correct, intrusion error, or other error) at the initial PDP test as a function of age (top panel) and CDR status (bottom panel). We tested the effects of healthy aging on memory task performance in a 3×3 mixed-model Analysis of Variance (ANOVA), with proportion of correct responses as the dependent variable, age as a between-subjects factor (<60 years, 60–74 years, or 75+ years), and condition as a within-subjects factor (congruent, incongruent, or neutral). Only CDR 0s were included in this analysis. As expected, this analysis revealed a main effect of age, $F(2, 516) = 23.37$, $p < .001$, $\eta_p^2 = .08$, a main effect of condition, $F(2, 1032) = 407.17$, $p < .001$, $\eta_p^2 = .44$, and an interaction between age and condition, $F(4, 1032) = 8.65$, $p < .001$, $\eta_p^2 = .03$. As shown in the top panel of Figure 2, older age was associated with a greater decrease in correct responses for incongruent trials compared with neutral or congruent trials.

The age effects on correct memory responses might be driven by differences in the proportion of intrusions of the critical/incongruent prime word or other errors. Analysis of the intrusion errors revealed a main effect of age, $F(2, 516) = 21.83$, $p < .001$, $\eta_p^2 = .08$, a main effect of condition, $F(2, 1032) = 443.23$, $p < .001$, $\eta_p^2 = .46$, and a reliable interaction between age and condition, $F(4, 1032) = 9.29$, $p < .001$, $\eta_p^2 = .04$. As shown in the top panel of Figure 2, older age was associated with a greater increase in intrusion responses for incongruent trials compared with neutral or congruent trials.

Other errors included trials in which the participant responded with a word that was neither the correct response nor the critical lure, as well as trials in which the participant did not respond within 20 seconds. For these errors, there was a significant main effect of age, $F(2, 516) = 3.98$, $p = .019$, $\eta_p^2 = .02$, and a main effect of condition, $F(2, 1032) = 49.46$, $p < .001$, $\eta_p^2 = .09$, but the interaction between age and condition was not significant, $F(4, 1032) = 0.51$, $p = .726$, $\eta_p^2 < .01$.

Memory Performance as a Function of CDR Status

A 2 (CDR: 0 or 0.5) $\times$ 3 (condition: congruent, incongruent, or neutral) mixed-model analysis of covariance (ANCOVA), controlling for the effect of age as a continuous covariate, was conducted on mean correct performance. This analysis revealed a main effect of CDR status, $F(1, 580) = 158.68$, $p < .001$, $\eta_p^2 = .22$, and an interaction between CDR status and condition, $F(2, 1160) = 34.82$, $p < .001$, $\eta_p^2 = .06$. As shown in the bottom panel of Figure 2, the group difference in performance between CDR 0s and 0.5s was greater for incongruent trials compared with neutral trials or congruent trials.

The effects of CDR status on intrusion and other errors were tested in separate ANCOVA models, using the factor structure described above for correct responses. For intrusion errors, there was a significant main effect of CDR status, $F(1, 580) =$
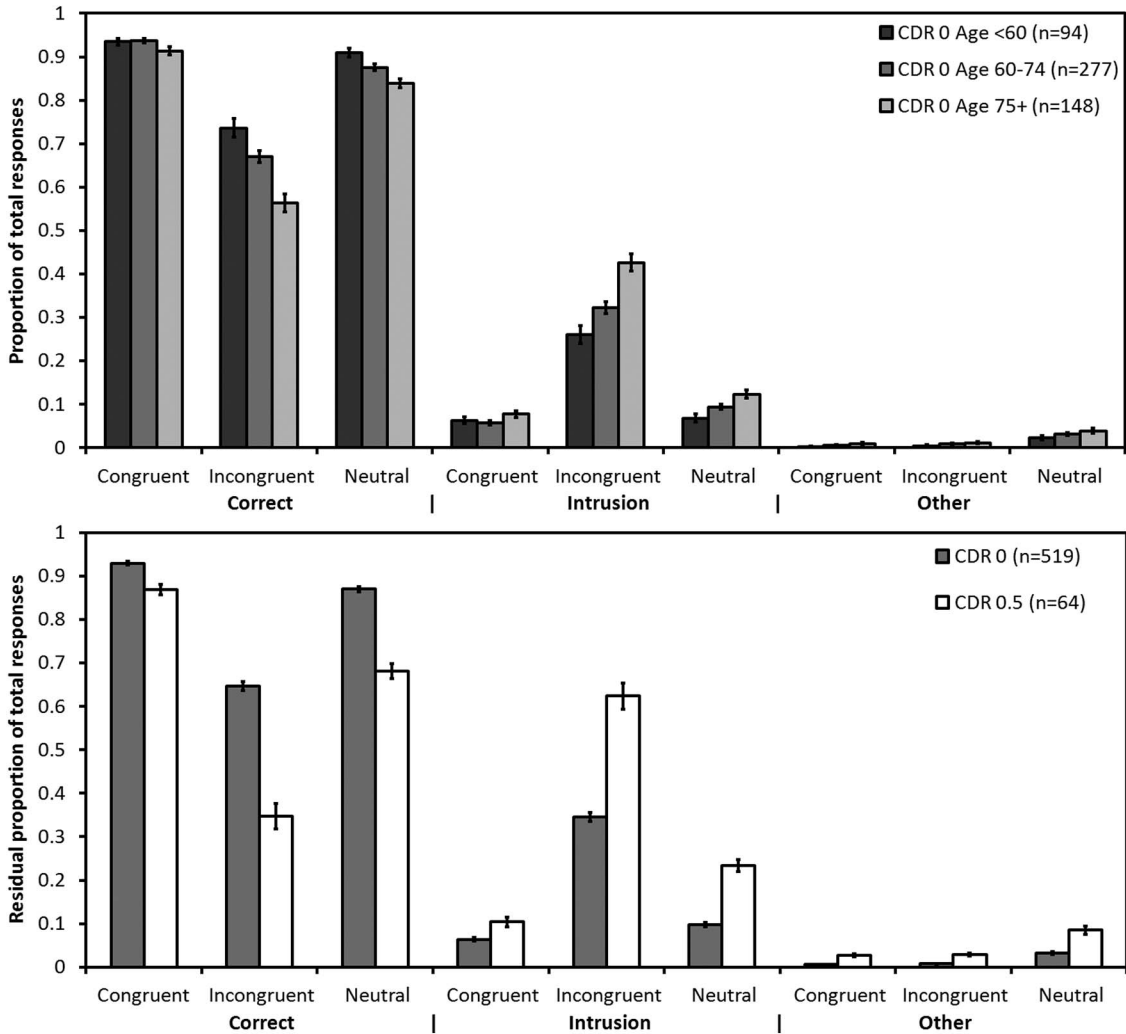
Figure 2. Mean proportion ($\pm$ standard error of the mean) of correct responses, intrusion errors, and other errors as a function of trial type, age group (top panel), and AD group (bottom panel) on the baseline PDP task. Values in the bottom panel are residual means, controlling for age.

126.98, $p < .001$, $\eta_p^2 = .18$, and an interaction between CDR status and condition, $F(2, 1160) = 36.76$, $p < .001$, $\eta_p^2 = .06$. As shown in the bottom panel of Figure 2, the group difference in intrusion responses between CDR 0s and 0.5s was greater for incongruent trials compared with neutral trials or congruent trials.

For other errors, there was a significant main effect of CDR status, $F(1, 580) = 46.95$, $p < .001$, $\eta_p^2 = .08$, and an interaction between CDR status and condition, $F(2, 1160) = 9.64$, $p < .001$, $\eta_p^2 = .02$. As shown in the bottom panel of Figure 2, the group difference in other errors between CDR 0s and 0.5s was greater for neutral trials compared with congruent trials or incongruent trials. Therefore, the present results indicate that, controlling for age, AD-related differences in task performance are strongly driven by intrusions of the primes in the incongruent condition, and to a much smaller extent, by other errors, including random word responses and failures to respond.

Estimates of Recollection and Familiarity Using the PDP

In the current paradigm, the following equations (see Jacoby, 1991) were used to obtain estimates of recollection and familiarity. Recollection was estimated by subtracting the probability of an intrusion on an incongruent trial (reflecting the failure of recollection and reliance on familiarity) from the probability of a correct response to a congruent trial (reflecting either successful recollection or reliance on familiarity):

$$Recollection = P(correct \mid congruent) - P(intrusion \mid incongruent)$$

Familiarity was then estimated by dividing the probability of an intrusion to an incongruent trial by the estimated probability of a failure of recollection:

$$Familiarity = \frac{P(intrusion \mid incongruent)}{1 - Recollection}$$

Because a recollection estimate of 1.00 would produce a familiarity estimate that is not defined, familiarity estimates were not calculated in cases where recollection was equal to 1.00 (approximately 6% of CDR 0s and 2% of CDR 0.5s). Figure 3 depicts the mean estimates of recollection and familiarity as a function of age (left panel) and CDR status (right panel).

The effects of healthy aging on memory process estimates were tested in the CDR 0 sample using a 3×2 mixed-model ANOVA, with process estimate as the dependent variable, age group as a between-subjects factor and process type as a within-subjects factor (recollection or familiarity). The interaction between age and process type was significant, $F(2, 487) = 7.45$, $p = .001$, $\eta_p^2 = .03$. As shown in the left panel of Figure 3, older age was associated with a greater change in recollection estimates than in familiarity estimates. Planned contrasts revealed that the age effect on recollection was significant, $F(2, 487) = 17.28$, $p < .001$, $\eta_p^2 = .07$, but the effect on familiarity was not, $F(2, 487) = 0.12$, $p = .892$, $\eta_p^2 < .01$.

The effects of very mild symptomatic AD on memory process estimates were tested in a 2×2 mixed-model ANCOVA, with process estimate as the dependent variable, CDR status as a between-subjects factor, process type as a within-subjects factor, and age as a continuous covariate. The interaction between CDR status and process type was highly significant, $F(1, 550) = 46.18$, $p < .001$, $\eta_p^2 = .08$. As shown in the right panel of Figure 3, the group difference between CDR 0s and 0.5s was greater for recollection estimates than it was for familiarity estimates. Planned contrasts revealed that, controlling for age, the AD group difference for recollection was significant, $F(1, 550) = 112.71$, $p < .001$, $\eta_p^2 = .17$, but the difference in familiarity was not, $F(1, 550) = 0.14$, $p = .707$, $\eta_p^2 < .001$.

The results from the PDP estimates are very clear. In a large, well-characterized sample, there are highly reliable effects of age and CDR status on the more attention-demanding recollection component, but there is no evidence of an effect of age or AD status on the more automatic familiarity component.[1]

Sensitivity of Recollection to CDR Status

Next we evaluated the utility of the recollection estimates[2] in discriminating between cognitively normal individuals and those with very mild symptomatic AD above and beyond standard psychometric tests, which have been useful in such discrimination in the extant literature (see Storandt, Botwinick, Danziger, Berg, & Hughes, 1984). To address this question, we ran a series of stepwise binary logistic regression models on participants at Time 1 with CDR status (0 or 0.5) as the dependent variable. In Step 1, we entered age, education, and one of the 17 psychometric measures described above and tested whether the measures were able to reliably classify CDR status. Each psychometric measure, with the exception of Digit Span forward, reliably classified CDR status, $\chi^2\text{s}(3) > 9$, $p\text{s} \leq .03$, Nagelkerke's $R^2\text{s} \geq .04$. In Step 2, we added recollection as a predictor and tested whether it reliably increased the classification accuracy of the previous model. Crucially, for each psychometric measure, adding recollection reliably increased classification accuracy in step 2, $\Delta\chi^2\text{s}(1) > 18$, $p\text{s} < .001$, ΔNagelkerke's $R^2\text{s} \geq .05$ (see the gray bars in Figure 4).

We then tested whether any of the psychometric measures offered discriminative utility for CDR status above and beyond

recollection. To do so, we ran another series of stepwise binary logistic regression models with CDR status as the dependent variable. In the first step, we entered age, education, and recollection. In each sample, this model reliably classified CDR status, $\chi^2\text{s}(3) > 55$, $p\text{s} < .001$, Nagelkerke's $R^2\text{s} \geq .33$. In the second step, we added one of the 17 psychometric measures. Adding the psychometric measures had mixed effects on classification accuracy in Step 2: 13 measures produced a significant improvement to the model, $\chi^2\text{s}(1) > 4.7$, $p\text{s} \leq .03$, Nagelkerke's $R^2\text{s} \geq .02$, and 4 measures produced a nonsignificant improvement, $\chi^2\text{s}(1) < 2.2$, $p\text{s} \geq .15$, Nagelkerke's $R^2\text{s} \leq .01$ (see the white bars in Figure 4).

We then compared the unique classification utility of recollection estimates to that of the psychometric measures by comparing model improvement measures, that is, $\Delta\chi^2\text{s}$, in Step 2, across the two models, that is, the recollection-second model versus the psychometric-second model. As shown in Figure 4, the improvements in classification accuracy for recollection after partialing each psychometric measure were greater than the corresponding improvements for each psychometric measure after partialing recollection for all but two cases: Logical Memory delayed recall and FCSR free recall. A nonparametric sign test revealed that the classification improvement for recollection over the psychometric measures ($N = 15$) was reliably greater than the classification improvement for psychometric measures over recollection ($N = 2$), $p = .002$. Thus, a recollection estimate from this 10-min, computerized task was a relatively useful discriminator of healthy aging from very mild symptomatic

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[1] It should be noted that the familiarity estimates were negatively skewed, with most estimates being 1.00. The skewness might limit statistical power for a test of differences in familiarity compared with a test of the more normal and more variable recollection estimate. Therefore, we also performed the same ANOVA for age effects on a subset of 244 CDR 0s in whom familiarity was less than one. Again, the interaction between age and process type was significant, $F(2, 241) = 7.05$, $p = .001$, $\eta_p^2 = .06$. Older age was associated with a greater change in recollection estimates ($M\text{s} = .57, .58, .43$) than in familiarity estimates ($M\text{s} = .62, .56, .65$). Planned contrasts revealed that the age effect on recollection was significant, $F(2, 241) = 10.02$, $p < .001$, $\eta_p^2 = .08$, as was the effect on familiarity, $F(2, 241) = 3.30$, $p = .039$, $\eta_p^2 = .03$. However, it is worth noting that this familiarity effect is marginally significant and importantly, is low for the middle aged group compared with the older age group. We also performed the same ANCOVA for symptomatic AD effects on a subset of 244 CDR 0s and 48 CDR 0.5s in whom familiarity was less than one. Again, the interaction between CDR status and process type was highly significant, $F(1, 289) = 51.73$, $p < .001$, $\eta_p^2 = .15$. The group difference between CDR 0s and 0.5s was greater for recollection estimates ($M\text{s} = .53, .16$) than it was for familiarity estimates ($M\text{s} = .60, .76$). Planned contrasts revealed that, controlling for age, the AD group difference for recollection was significant, $F(1, 289) = 79.97$, $p < .001$, $\eta_p^2 = .22$, as was the effect on familiarity, $F(1, 289) = 16.39$, $p < .001$, $\eta_p^2 = .05$. However, it is worth noting that this familiarity effect is in the opposite direction than that reported in some of the previous literature (see Koen & Yonelinas, 2014), and might reflect a dependence between the recollection and familiarity processes within this subset of the data. Indeed, when recollection is included as an additional covariate in the familiarity contrast, the AD group difference is no longer significant, $F(1, 288) = 3.25$, $p = .073$, $\eta_p^2 = .01$.

[2] Although we excluded recollection estimates of 1.00 from Figure 3 and from the ANOVA and ANCOVA analyses of process estimates because the corresponding familiarity estimates were undefined, for regression analyses, in which we focused specifically on recollection, we included those recollection estimates of 1.00. This inclusion served to avoid unnecessarily discarding data for tests that did not require complete pairs of recollection and familiarity estimates and to avoid biasing correlations by removing the highest performers.
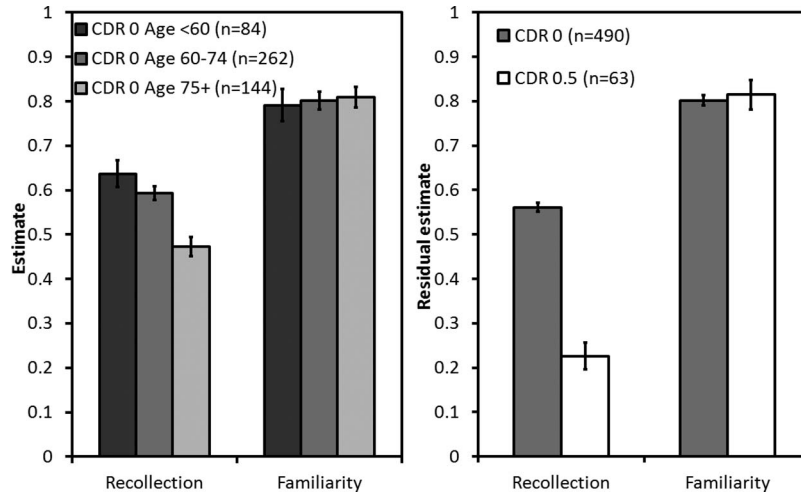
Figure 3. Mean estimates (±standard error of the mean) of recollection and familiarity as a function of age group (left panel) and AD group (right panel) on the baseline PDP task. Values in the right panel are residual means, controlling for age.

AD, and at the very least comparable with well-established psychometric memory measures.

Sensitivity of Recollection to Preclinical AD Biomarkers

If recollection estimates are sensitive to the earliest detectable stage of symptomatic AD, then these estimates might also be sensitive to individual differences in preclinical AD biomarkers within a cognitively normal population, as reflected by CSF measures or PIB-PET imaging. Moreover, since we estimated recollection multiple times longitudinally, this sensitivity might emerge in baseline recollection estimates and/or in change in recollection over time. We tested these hypotheses in hierarchical linear models

of recollection as predicted by biomarker measures, controlling for demographic variables. We completed these analyses on a sample of only CDR 0s, so that any effects could be attributable to preclinical variability in AD biomarkers and not a clinical diagnosis of symptomatic AD. In these models, we aimed to minimize the influence of extreme outliers in the recollection estimate, so we estimated each participant's slope of recollection over time. We removed two potential outlier individuals with recollection slopes greater than 5 standard deviations from the sample mean.

In the following analyses, we present two sections. First, we examine the relationship between the CSF biomarkers and recollection estimates both at baseline and longitudinally. Second, we examine the relationship between PIB and recollection both at
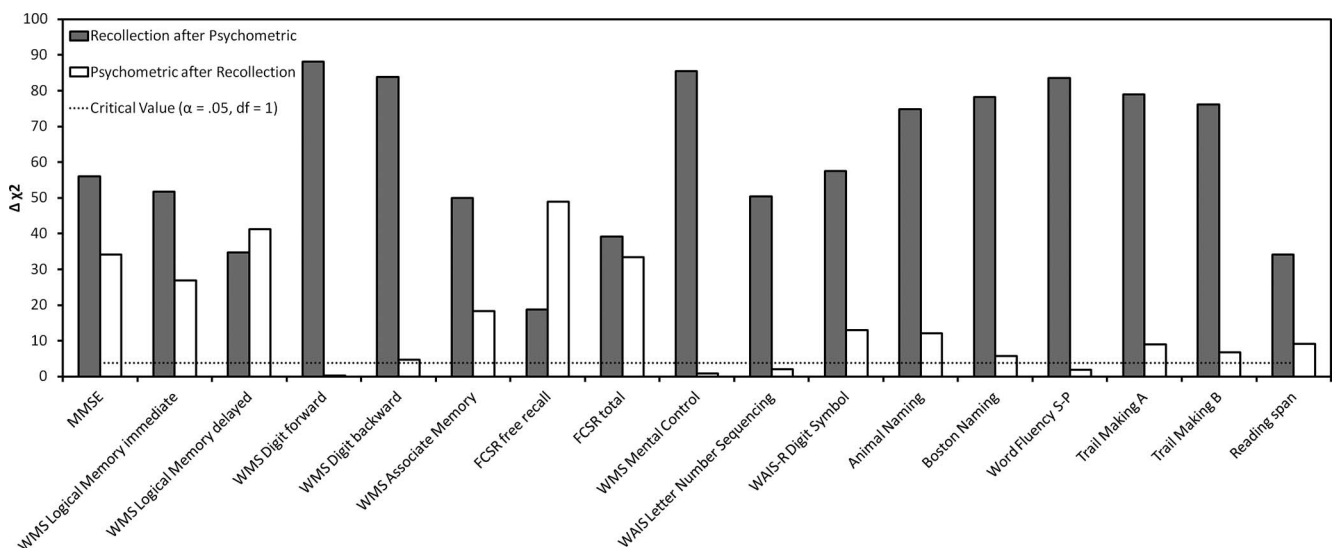

Figure 4. Comparison of the recollection-second (gray) and psychometric-second (white) models in improvements to classification accuracy (reported as $\Delta\chi^2$) in step 2 of the binary logistic regression analyses. Dotted line is the critical $\Delta\chi^2$ value for the addition of a single parameter ($df = 1$) with α set to .05.

baseline and longitudinally. We present the analyses on CSF biomarkers and on the PIB biomarker as separate analyses for two reasons: First, although there is overlap in individuals who have both PIB and CSF measures, when we impose our constraints regarding the timing of the biomarker measurements, the inclusion of only participants with both biomarkers reduces our sample size by 34% in the following CSF analyses and by 24% in the following PIB analyses. Hence, to maximize the sample, and reduce intercorrelated variables in the analyses (CSF $A\beta_{42}$ and PIB MCBP are correlated at $r = -.50$), we report these as separate analyses.

Sensitivity of recollection to CSF biomarkers. We first examined the sensitivity of recollection to CSF biomarkers, including measures of $A\beta_{42}$ and tau. These analyses were performed on a subset of individuals who had completed a lumbar puncture within 3 years of the baseline PDP estimate. We corrected for nonnormality in the tau measurement by applying a natural log transform as performed by Aschenbrenner, Balota, Tse, and colleagues (2015). No observations were identified as potential outliers for $A\beta_{42}$ or log-transformed tau (all cases were less than 3.5 standard deviations from the respective sample means). The final CSF model dataset included a total of 562 observations from 320 unique individuals (141 with one test, 122 with two tests, 51 with three tests, and 6 with four tests).

Hierarchical linear models were analyzed using the "nlme" package in R (Pinheiro, Bates, DebRoy, & Sarkar, 2014). We first calculated the intraclass correlation (ICC) in an unconditional random-intercept model to describe the variability of the recollection estimates in this sample. The ICC for this sample was .55, indicating that 55% of variability in recollection estimates was driven by interindividual differences, leaving 45% driven by intraindividual change over time. We then added time as a level 1 predictor to begin accounting for this variability. The fixed effect of time was marginally significant, $\beta = .03$, $SE = .02$, $p = .055$. Recollection marginally increased over time, likely a result of a practice effect from repeated exposure to the task and materials. The random effect 95% confidence interval was $-.14$ to $.20$, indicating the range of 95% of the slopes predicted in the sample. We then added demographic and CSF biomarker predictors of recollection. These predictors included baseline age, education, APOE genotype, sex, baseline values of CSF $A\beta_{42}$ and tau, as well as all two- and three-way interactions among time, $A\beta_{42}$, and/or tau. These predictors were always retained as they were necessary to test our a priori hypotheses. We then added the two-way interactions between each level 2 demographic predictor and time to test for cross-level effects. Only the interaction between time and sex was significant, and thus all other cross-level demographic interactions were removed from the model. This approach was taken to test our hypotheses and avoid forming overly complex models or overfitting the data.

The final parameter estimates are displayed in Table 2. In this model, time had a significant positive relationship with recollection, $\beta = .06$, $p = .021$. Confirming our previous analysis, baseline age was negatively related to the recollection estimate in the initial test, $\beta = -.21$, $p < .001$. Additionally, years of education were positively related to initial recollection estimate, $\beta = .06$, $p = .001$. APOE status was not related to recollection, $\beta = .02$, $p = .873$. Sex was positively related to initial recollection, $\beta = .49$, $p < .001$, indicating that females had higher initial recollec-

Table 2

Hierarchical Linear Model Parameters of CSF Biomarkers Predicting Recollection

Variable	Estimate (SE)	df	t	p
Intercept	−.33 (.09)	321	−3.72	<.001
Time	.06 (.02)	228	2.33	.021
Age	−.21 (.05)	321	−4.21	<.001
Education	.06 (.02)	321	3.33	.001
APOE	.02 (.10)	321	.16	.873
Sex	.49 (.11)	228	4.64	<.001
$A\beta_{42}$	.14 (.06)	321	2.41	.016
Tau	−.06 (.06)	321	−.93	.356
Time × Sex	−.06 (.03)	228	−1.99	.048
$A\beta_{42}$ × Tau	−.09 (.06)	321	−1.60	.111
Time × $A\beta_{42}$	−.01 (.02)	228	−.47	.639
Time × Tau	.00 (.02)	228	.01	.990
Time × $A\beta_{42}$ × Tau	.06 (.02)	228	3.23	.001

Note. Time was defined as years after initial test and was allowed to vary randomly within individuals. Age was defined as age at initial test. Education was centered at 16 years, the sample mean. APOE status was coded as 0 for absence and 1 for presence of an ε4 allele. Sex was coded as 0 for male and 1 for female. CSF biomarkers were baseline values at the time of the first PDP estimate, within 3 years. CSF tau was corrected for nonnormality using a natural log transform. Recollection, baseline age, and CSF biomarkers were standardized within the sample.

tion estimates than males. Additionally, the time × sex interaction was marginally significant, $\beta = -.06$, $p = .048$, indicating that females had marginally lower increases in recollection over time than males did.

The CSF biomarker predictors were most critical to our hypotheses. The model revealed that baseline level of $A\beta_{42}$ was positively related to initial recollection estimate, $\beta = .14$, $p = .016$ (see Figure 5). This effect is in the predicted direction, because low levels of $A\beta_{42}$ in the CSF are associated with accumulation of amyloid plaques in the brain (Fagan et al., 2006), and hence more AD pathology. In contrast, baseline level of tau was not related to initial recollection estimate, $\beta = -.06$, $p = .356$, nor was the interaction between baseline tau and $A\beta_{42}$, $\beta = -.09$, $p = .111$.

Turning to longitudinal change in recollection, the model revealed a significant interaction among time, $A\beta_{42}$, and tau, $\beta = .06$, $p < .001$. This interaction is depicted in Figure 6, in which predictions are plotted in separate panels for individuals with abnormal (lower) baseline CSF $A\beta_{42}$, as defined by Vos et al. (2013), using the Youden index, as values less than 459 pg/mL, and for individuals within the normal (higher) range. In these longitudinal plots, the positive slope of recollection over time likely reflects a practice effect, resulting from repeated exposures to the task. When $A\beta_{42}$ was abnormal, as CSF tau increased (indicating more progressed AD pathology), recollection was less likely to increase over time, perhaps reflecting an attenuated practice effect in those individuals. However, when $A\beta_{42}$ was normal, the relationship between CSF tau and recollection slope was weaker. Practice effects have been noted in similar samples for other repeated episodic memory tasks (see Aschenbrenner, Balota, Fagan, et al., 2015; Galvin et al., 2005; Hassenstab et al., 2015). The episodic memory practice benefit has previously been associated with a decreased risk of progression to symptomatic AD (Hassenstab et al., 2015). To summarize, in the current cognitively normal preclinical sample, CSF $A\beta_{42}$ and tau, both biomarkers of
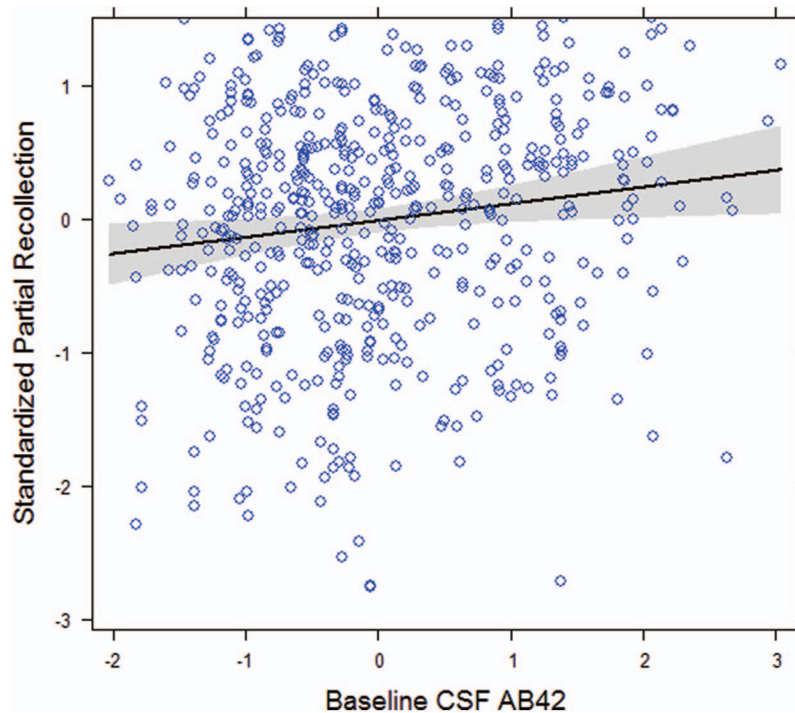
Figure 5. Relationship between recollection and CSF Aβ₄₂. Points are model residuals. Line is the model prediction. Shaded area is the 95% confidence region. See the online article for the color version of this figure.

AD pathology, produced an interactive influence on recollection across time.

Sensitivity of recollection to PIB-PET. We then tested whether recollection was related to presence of amyloid plaques as observed by PIB-PET imaging. These analyses were performed on a subset of observations in which the baseline PDP estimate had been completed within 3 years of a PIB-PET scan. MCBP within this sample was highly skewed with several potential outliers. One conservative, but informative, approach to testing the effects of amyloid plaque is to categorically identify the presence (PIB+) or absence of amyloid plaques (PIB−) using a threshold value of MCBP. We defined PIB+ individuals as those with MCBP greater than .23 and PIB− individuals with MCBP less than or equal to .23. This threshold value was taken from Gordon et al. (2015), who dichotomized PIB positivity in a similar cohort using the Youden index (as performed by Vos et al., 2013). The final PIB-PET model dataset included a total of 501 observations from 278 unique individuals (116 with one test, 106 with two tests, 51 with three tests, and 5 with four tests). We repeated the same modeling procedures described in the CSF model above, substituting PIB positivity for CSF measures as a biomarker predictor. The ICC of recollection in this sample was .53. Again, there was a marginally significant fixed effect of time, β = .03, *SE* = .02, *p* = .101, as well as a significant random effect of time, 95% C.I. = [−.09, .14]. The final model parameters are presented in Table 3. Importantly, PIB positivity was not related to baseline recollection, β = .00, *p* = .991, but it significantly interacted with time to predict change in recollection, β = −.10, *p* = .021. As shown in Figure 7, in individuals who were PIB− at baseline, recollection tended to slightly increase over time, whereas in individuals who were PIB+, recollection decreased over time.

Discussion

The results from the present study yielded a number of noteworthy results. Specifically, using a short 10-min procedure that affords retrieval process estimates in a large cohort of participants, an estimate of recollection, but not familiarity, is (a) sensitive to healthy aging, (b) particularly sensitive to early stage symptomatic AD, compared with standard psychometric measures, and (c) sensitive to biomarkers of preclinical AD pathology and risk in cognitively normal individuals both at baseline and as a function of longitudinal change. Below, we discuss how these results are informative to individual and group differences in memory processes, the relationships between AD biomarkers and cognition, the role of attention in memory, and the potential applied utility of recollection estimates.

Memory Processes in Healthy Aging and Early Stage Symptomatic AD

The current finding of a large age-related deficit in recollection, but not in familiarity, is consistent with the meta-analysis of age effects on process estimates (Koen & Yonelinas, 2014). Across 20 studies in which processes were estimated with PDP (13 studies) or ROC procedures (7 studies), recollection reliably decreased in healthy aging, while familiarity exhibited no deficit. The present study is unique, however, in that it replicated the effects of healthy aging on process estimates in a much less extreme age comparison. Most prior studies of these effects, as summarized by Koen and Yonelinas (2014), have compared younger adult samples (typically undergraduate students; mean sample age = 21.47, range = 18.90–30.00) with older adult samples (typically recruited from
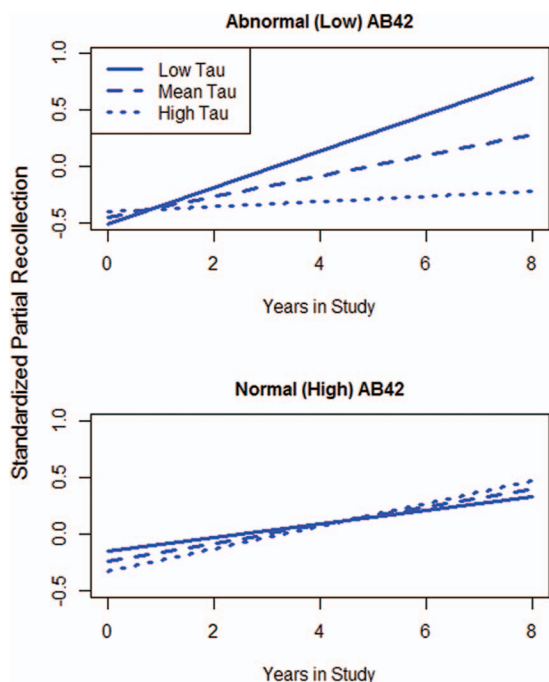
Figure 6. Interaction between Aβ₄₂, tau, and time on recollection. Regression lines of recollection, predicted by time, are plotted separately for mean levels of tau, as well as 1 standard deviation above and below the mean, for individuals with abnormal levels of $A\beta_{42}$ (<459 pg/mL, upper panel) and those with normal levels (≥459 pg/mL, lower panel). See the online article for the color version of this figure.

the community; mean sample age = 71.14, range = 60.61–77.00). By contrast, the present study compares three age groups (45–59 years, 60–74, and 75–95), recruited from the community, ranging from middle-aged to older adults. Furthermore, in both of the present hierarchical linear models for CSF and PIB biomarkers, we demonstrate continuous negative effects of age on recollection, controlling for AD biomarkers. To our knowledge, no other study

Table 3

Hierarchical Linear Model Parameters of PIB Positivity Predicting Recollection

Variable	Estimate (*SE*)	*df*	*t*	*p*
Intercept	−.16 (.10)	280	−1.62	.107
Time	.02 (.02)	212	.94	.350
Age	−.24 (.05)	280	−4.56	<.001
Education	.06 (.02)	280	3.29	.001
APOE	−.24 (.12)	280	−1.96	.051
Sex	.29 (.11)	280	2.78	.006
PIB	.00 (.15)	280	−.01	.991
Time × APOE	.06 (.03)	212	1.65	.100
Time × PIB	−.10 (.04)	212	−2.33	.021

Note. Time was defined as years after initial test and was allowed to vary randomly within individuals. Age was defined as age at initial test. Education was centered at 16 years, the sample mean. APOE status was coded as 0 for absence and 1 for presence of an ε4 allele. Sex was coded as 0 for male and 1 for female. PIB was coded as 0 for baseline MCBP ≤ .23 and 1 for > .23. Recollection and baseline age were standardized within the sample.
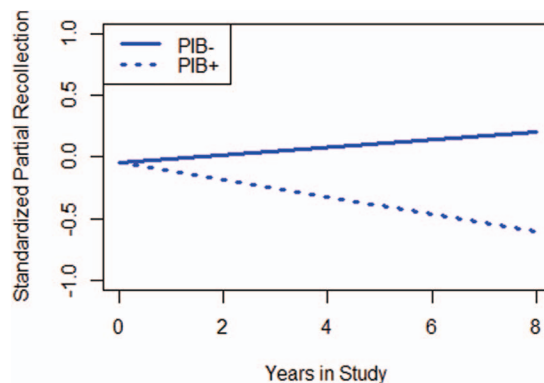

Figure 7. Interaction between PIB positivity and time on recollection. Regression lines of recollection, predicted by time, are plotted separately for individuals who were PIB+ (MCBP > .23) and those who were PIB− (MCBP ≤ .23). See the online article for the color version of this figure.

has examined age effects on process estimates within such a narrow age range. Nor have previous studies controlled for the possible contribution of preclinical AD pathology to the effect of age on memory processes. The current findings suggest that an age-related, process-specific deficit in recollection continues even in advanced healthy aging above and beyond the effects of preclinical AD pathology.

The current analyses also indicate that very mild symptomatic AD is associated with a large deficit in recollection, but no change in familiarity. This finding is also consistent with aspects of the meta-analysis of the effect of aMCI on process estimates (Koen & Yonelinas, 2014). In terms of dementia severity, the current CDR 0.5 sample (mean MMSE = 26.15, *SD* = 3.32) is a better match to the aMCI population reported in the meta-analysis (mean sample MMSE = 27.61, range = 25.50–28.50) than to the more advanced AD population (mean sample MMSE = 22.23, range = 17.00–24.90). Across 9 studies of single- and/or multiple-domain aMCI reported in the meta-analysis, recollection reliably decreased in aMCI, compared with healthy controls, while familiarity had only a marginal deficit. Only those studies that included multiple-domain diagnosis aMCI have reported familiarity deficits (see Ally, Gold, & Budson, 2009; Wolk et al., 2013; Wolk, Signoff, & DeKosky, 2008). Multiple-domain diagnosis of aMCI differs from a single-domain diagnosis in that the impairment is in at least one other cognitive domain, in addition to memory (Winblad et al., 2004). Interestingly, when studied exclusively, individuals with single-domain aMCI do not exhibit a reliable familiarity deficit (see Anderson et al., 2008; Serra et al., 2010). Finally, it is worth noting that the current CDR 0.5 sample (63 individuals afforded estimates of familiarity) is much larger than any previous sample in which a familiarity deficit was found (11 individuals with aMCI in Ally et al., 2009; 32 in Wolk et al., 2013, 16 in Wolk et al., 2008). Therefore, the present study affords increased sample size to detect a familiarity deficit, and yet no evidence of such a deficit was found.

It is also important to consider the unique characteristics of the current task in understanding any potential inconsistencies in dementia-related effects on familiarity. To our knowledge, no other study has tested the effect of symptomatic AD on memory

process estimates using a cued fragment completion recall task. The current findings regarding recollection estimates are largely consistent with previous studies in which processes were estimated from recognition, but it is likely that interpretations of familiarity estimates may vary depending on the task used for estimation. Specifically, recognition performance is more likely to be influenced by familiarity processes (e.g., Mandler, 1980). Furthermore, in most other PDP paradigms, the familiarity signal originates from a previous encoding phase, temporally and contextually separated from the retrieval attempt. Past findings of an aMCI-related familiarity deficit have employed such paradigms (Wolk et al., 2013, 2008; but see Serra et al., 2010; Troyer et al., 2012). By contrast, in the current paradigm, familiarity originates from a prime, presented immediately before the retrieval attempt. In this regard, the present paradigm is more similar to one used by Anderson and colleagues (2008), in which the familiarity signal originated from repeated stimuli within a continuous recognition task, separated by a lag of up to 12 trials. Consistent with the present findings, familiarity did not differ between individuals with aMCI and controls in that study. In the current paradigm, the highly salient primes might "capture" a retrieval attempt in a way that items made familiar at encoding might not (Jacoby, Bishara, Hessels, & Toth, 2005). Thus, it is possible that encoding-driven familiarity processes might in fact decline in AD (as suggested by Wolk et al., 2013, 2008), whereas retrieval-driven familiarity remains intact.

Cognitive Correlates of Preclinical AD Biomarkers

The present analysis of preclinical AD biomarkers showed that the initial estimate of recollection is sensitive to individual differences in CSF $A\beta_{42}$. Additionally, change in recollection over time is sensitive to the interaction between CSF $A\beta_{42}$ and tau, and to the presence of amyloid plaques detected by PIB-PET imaging. Because recollection is highly dependent upon executive/attentional control systems, it is likely sensitive to preclinical biomarkers in ways that other memory measures are not. Indeed, composite measures of both episodic memory and attentional control demonstrate sensitivity to preclinical AD biomarkers in a similar sample (Aschenbrenner, Balota, Fagan, et al., 2015). Furthermore, a recent meta-analysis reported small, but reliable correlations between preclinical measures of amyloid (including PIB, CSF, etc.) and both episodic memory and executive function (Hedden et al., 2013). Thus, recollection is likely tapping memorial, as well as attentional domains, both of which might be particularly disrupted in preclinical AD.

Relationship Between Attention and Memory Systems

One model of memory impairment in preclinical AD posits that the preferential accumulation of amyloid in areas of the default mode network directly influences the integrity of memory network areas through neuronal atrophy and metabolic disruption (Buckner et al., 2005). However, several longstanding cognitive models of memory recognize that memory is not an entirely isolated system and is, in fact, highly dependent upon executive and attentional control systems (Craik & Lockhart, 1972; Hasher & Zacks, 1979; Jacoby, 1991). Thus, attentional/executive control systems likely contribute to the memory deficits that arise in preclinical AD

(Balota & Duchek, 2015). In the present study, we conclude that attention-dependent recollection, but not automatic familiarity, is particularly sensitive to biomarkers of AD pathology and risk in asymptomatic individuals. Thus, the role of attentional systems should not be ignored in the study of preclinical AD and its effects on memory systems. Indeed, just as in the Stroop color-naming task (Stroop, 1935), one needs to exert control over the readily available Word dimension in the incongruent condition, in the present paradigm, one needs to exert control over the readily available incongruent prime information. Attentional control is important in both contexts, whereas the relative strength of the competing pathways likely varies across tasks. In this light, it is noteworthy that Spieler, Balota, and Faust (1996) applied the process dissociation procedure to Stroop performance and found that the Color (attention driven) estimate was impaired in very mild AD, compared with healthy controls, whereas there was no difference in the Word (automatic) component between those two groups, consistent with the current application of the PDP to a controlled memory task.

Clinical Utility of Recollection

The results from the binary logistic regression analyses indicate that a recollection estimate improves the identification of the earliest detectable stage of symptomatic AD above and beyond standard psychometric tests. Such a measure might aid in the diagnosis of AD. The current behavioral task was relatively quick, lasting about 10 min, is entirely computer-based, and can be automatically scored. Thus, it would be very easy to administer in a clinical setting.

It is worth noting that the recollection estimate provided less unique discrimination of CDR status than the Free and Cued Selective Reminding test (FCSR) free recall portion (Grober et al., 1988) and comparable discrimination to the WMS Logical Memory (WMS-LM) delayed recall units (WMS-LM; Wechsler, 1997). We further compared these measures in their sensitivity and specificity for CDR classification by calculating optimal cutoff points for each measure based on the Youden index. For recollection estimates, sensitivity was .77 and specificity was .86 for a Youden index of .63. In comparison, the Youden index of FCSR free recall was comparable (.64), but sensitivity was higher (.91) and specificity was lower (.73) than recollection. Finally, WMS-LM delayed recall had a lower Youden index (.54) than recollection with comparable, but lower, sensitivity (.71) and specificity (.83).

Unlike the recollection estimate, FCSR and WMS-LM currently lack computer implementation and instead must be manually administered and scored. Furthermore, the current PDP task is comparable in duration with FCSRT (12–15 min; National Institute on Aging) and is much shorter than the retention interval of 30 to 40 min required for the delayed WMS-LM (Wechsler, 1997). Finally, the test–retest reliability of recollection estimates within the full sample (ICC = .63, 95% C.I. = [.57, .69]) is comparable with that of FCSRT recall (ICC = .69, 95% C.I. = [.63, .74]), but, as expected, is lower than that of the much longer WMS-LM delayed recall (ICC = .74, 95% C.I. = [.68, .79]).

Interestingly, the FCSR free recall and WMS-LM delayed recall, like recollection, both involve strong components of controlled recall. It is possible that recollection estimates, FCSR, and WMS-LM are tapping similar processes, particularly memory re-

trieval processes that are highly dependent on executive and/or attentional control processes. If these processes are influenced by very mild symptomatic AD, then it is not surprising that such measures would be particularly useful in identifying CDR 0.5s. However, we would argue that no task is process pure and that FCSR and WMS-LM are likely not tapping *identical* processes to recollection. Indeed, recollection is only modestly correlated with FCSR free recall ($r = .52$) and with WMS-LM delayed recall ($r = .45$) in the current sample. It is noteworthy that the recollection estimate was measured in a different battery than the FCSR and WMS-LM tasks, with an average interval of 94.2 days between the two batteries, and so the correlations to those measures will be reduced. Hence, as expected, the correlation between FCSR free recall and WMS-LM delayed recall is higher ($r = .62$). Furthermore, in the logistic regression models, adding recollection significantly improves CDR classification accuracy *controlling for FCSR or WMS-LM* and vice versa (see Figure 4), suggesting that each measure is capturing a significant portion of unique variance within the sample. Therefore, recollection estimates, FCSR, and WMS-LM might each be indicative of *similar, but different*, processes or combinations of processes underlying memory performance.

As noted, FCSR and WMS-LM both employ a self-initiated free-recall task, which might be more sensitive to very mild symptomatic AD than the cued fragment-completion phase in the current PDP task. Perhaps a recollection estimate obtained from a task requiring more self-initiated retrieval processes might be even more sensitive to CDR status. Future studies might test this possibility by employing a cued recall task instead of cued fragment completion task. Discrimination of CDR status and/or test–retest reliability might also be improved in the current task by increasing the number of trials or by adding a delay between the encoding and retrieval phases. Although one advantage of the current task is its brevity, potential gains in diagnostic utility might be worth increasing the length of an already-short task.

An important potential clinical advantage of the current recollection estimate is its unique biomarker sensitivity. Of the two psychometric measures that performed as well or better than recollection in classifying CDR status, the only reliable CSF or imaging effect was CSF tau predicting baseline performance on WMS-LM delayed recall, $\beta = -.17$, $SE = .07$, $p = .020$. Across the full battery of 17 psychometric measures, neither the time $\times$ Aβ_{42} $\times$ tau nor the time $\times$ PIB interaction was significant in any model. Thus, the current recollection estimate appears to possess unique longitudinal sensitivities to preclinical AD biomarkers, and should be considered as a target for future research relating biomarkers to cognition in preclinical AD.

Conclusion

In summary, the present results suggest that recollection is a sensitive cognitive marker of age, very mild symptomatic AD, and preclinical AD pathology. Recollection may exhibit this role because it places a high demand on executive or attentional control systems. Moving forward, recollection, or other attention-demanding memory processes, might prove particularly useful in describing and detecting both symptomatic and asymptomatic AD pathology.

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