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

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by
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ABSTRACT OF THESIS

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Recollection and familiarity are independent processes that contribute to memory performance. Recollection is dependent on attentional control, which breaks down in early-stage Alzheimer disease (AD), whereas familiarity is independent of attention. The present 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 older adults (N = 519) and the extent to which recollection discriminates these individuals from individuals with very mild symptomatic AD (N = 64). 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. 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 improvement in recollection over time. Finally, presence of amyloid

plaques, as imaged by PIB-PET, was related to less improvement in recollection over time. These findings suggest that attention-demanding memory processes, such as recollection, may be particularly sensitive to both symptomatic and preclinical AD pathology.

Chapter 1: Introduction

Alzheimer 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 & Kopelamn, 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 reviews, 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). Interestingly, structural equation models reveal that individual age differences in memory ability 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 asymptomatic 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 not directly estimated, but were inferred using a remember-know procedure (e.g., McCabe, Roediger, McDaniel, & Balota, 2009). In the studies that directly 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 effects 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 one of the foci of the present study is on early stage symptomatic AD, one aspect of the Koen and Yonelinas meta-analysis that is 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), while 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 symptomatic AD, 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 due in part to different approaches for estimating recollection and familiarity, e.g., using remember/know judgments, as opposed to direct estimates via PDP

procedures, or different criteria for diagnosis, e.g., 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, e.g., 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 recall task (Craik, 1983). If attentional control plays a role in the memory changes in aging and symptomatic AD, it might be more informative to examine memory processes in a free or cued recall task. Finally, because of relatively small sample sizes in previous studies, i.e., from 7 to 32 individuals with aMCI or AD in each study, it is important to examine these process estimates in a larger, well-characterized sample.

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 non-demented older adults. Clinically, the stage of progressed AD biomarkers in the absence of AD symptoms or 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 magnetic resonance imaging (MRI) (Sperling et al., 2011). Correlations between these preclinical biomarkers and cognitive measures are small and

inconsistent (see Hedden, Oh, Younger, & Patel, 2013 for meta-analysis). Here we examined whether memory process estimates, particularly recollection, might be sensitive to these biomarkers.

The present study includes a large, longitudinal cohort of healthy aging (N = 519 individuals) and early stage symptomatic AD (N = 64 individuals) from the Charles and Joanne Knight Alzheimer Disease Research Center at Washington University in St. Louis. The participants are well-characterized with AD-related biomarkers, e.g., 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). These individuals typically have an average MMSE score around 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 age and 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 older 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 as a function of biomarker burden across time via longitudinal analyses.

In order to address these goals, we utilized a primed memory task that would allow for PDP estimates of recollection and familiarity, based on 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, i.e., 30 critical test trials vs. 60-90 trials. In fact, this task may be administered in approximately 10 minutes, which might facilitate use in clinical applications.

As shown in Figure 1, the current PDP memory task included an incidental encoding phase followed by a fragment-completion phase. During incidental encoding, participants made a judgment of relatedness about a series of word pairs, e.g., "knee bone," "arrow cage." Immediately afterward, participants completed a primed, cued fragment-completion task 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_." Each trial was primed with a stimulus that was *congruent* with the correct response, e.g., "bone," *incongruent* with the correct response, e.g., "bend," or *neutral*, i.e., "&&&&." Crucially, all incongruent primes were also valid completions of the stem and semantically related to the cue, but had not been presented during the incidental encoding phase. Thus, the incongruent condition was designed to prime a feeling of familiarity for an incorrect response. In a longer version of this task, Jacoby (1999a) found that healthy older adults were more likely than younger controls to falsely recall the incongruent prime words, resulting in 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 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 requires only simple instruction. Furthermore, since the paradigm demands explicit retrieval of the target, it should be particularly sensitive to changes in attentional control processes.

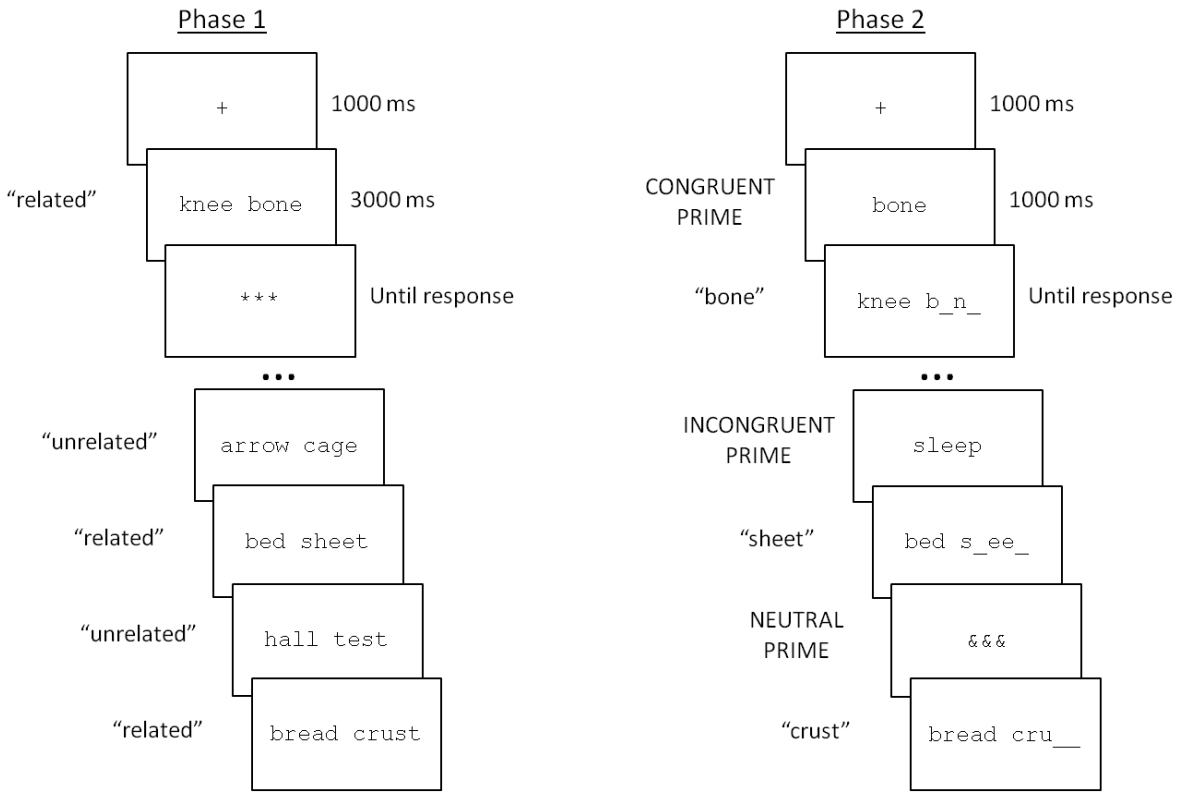

Figure 1. Illustration of PDP task design and example trials.

Chapter 2: Method

2.1 Participants

As noted, all participants were recruited by the Charles F. and Joanne Knight Alzheimer 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 for up to four study sessions over the course of up to 8 years. 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.

2.2 Annual Clinical, Psychometric, and Cognitive 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 diagnosis 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-hour 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). Measures of Associate Memory, FCSR free recall, and Logical Memory delayed recall were averaged together to form an episodic memory composite (see Aschenbrenner, Balota, Fagan, et al., 2015). 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. Table 2 presents the reliability of these scores over time in the full sample of CDR 0s and CDR 0.5s, as measured by intra-class correlation (ICC), using the "ICC" package in R (Wolak, Fairbairn, & Paulsen, 2012).

Participants also completed a separate battery of cognitive tests to assess attentional control. This battery included computerized versions of the Stroop color naming task (Spieler, Balota, & Faust, 1996; Stroop, 1935), the Simon task (Castel, Balota, Hutchison, Logan, & Yap, 2007; Simon, 1969), and a consonant-vowel/odd-even task-switching task (CVOE; Tse, Balota, Yap, Duchek, & McCabe, 2010). Accuracy on select conditions of these tasks, i.e., incongruent Stroop and Simon trials and CVOE switch trials, were standardized to previous norms from a similar cohort and averaged into a composite measure for each time point, as described by Aschenbrenner, Balota, Fagan, and colleagues (2015).

2.3 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 present, i.e., ε24, ε34, and ε44, while ε4- individuals were those without a single ε4 allele present, i.e., 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, 20-30 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

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)	.38
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)	.26
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)	.28
% APOE ε4 positive	40%	36%	25%	54%		
CSF $A\beta_{42}$ (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)	.10
PIB-PET MCBP	0.05 (0.07)	0.15 (0.21)	0.24 (0.32)	0.43 (0.32)	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)	.71
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

Table 1. Demographic, psychometric, and biomarker measures, mean (SD), at initial test grouped by age and CDR status. *F*(df) reports the univariate *F* statistic for the effect of CDR status, controlling for age as a continuous covariate. * Age was not controlled as a covariate.

[formerly Innogenetics], Ghent, Belgium). Baseline levels of CSF biomarkers, $A\beta_{42}$ and tau, are presented in Table 1.

Variable	ICC	95% LB	95% UB	N	k	σ^2_w	σ^2_a
WMS Logical Memory immediate	0.65	0.57	0.72	441	1.47	6.73	12.77
WMS Logical Memory delayed	0.74	0.68	0.79	441	1.47	6.74	19.64
WMS Digit forward	0.62	0.53	0.69	439	1.47	0.43	0.70
WMS Digit backward	0.45	0.34	0.55	439	1.47	0.78	0.65
WMS Associate Memory	0.72	0.65	0.77	438	1.47	4.46	11.26
FCSR free recall	0.69	0.63	0.74	562	1.54	16.23	36.02
FCSR total	0.79	0.75	0.83	562	1.54	1.51	5.71
WMS Mental Control	0.54	0.44	0.62	441	1.47	1.43	1.67
WAIS Letter Number Sequencing	0.71	0.64	0.76	480	1.45	2.18	5.38
WAIS-R Digit Symbol	0.87	0.84	0.90	434	1.44	17.55	117.78
Animal Naming	0.69	0.63	0.74	570	1.54	10.90	24.42
Boston Naming	0.83	0.78	0.86	441	1.47	6.19	29.39
Word Fluency S-P	0.71	0.64	0.77	441	1.47	29.76	73.64
Trail Making A	0.74	0.68	0.78	570	1.54	62.71	174.92
Trail Making B	0.79	0.74	0.82	570	1.54	305.94	1129.02
Reading span	0.42	0.28	0.54	423	1.36	0.41	0.30
Attentional control composite	0.72	0.66	0.77	584	1.50	0.71	1.83
Episodic memory composite	0.74	0.69	0.79	570	1.54	0.20	0.57
MMSE	0.66	0.60	0.71	570	1.54	0.98	1.91
Recollection	0.63	0.57	0.69	595	1.55	0.03	0.05
Familiarity	0.18	0.05	0.29	578	1.50	0.05	0.01

Table 2. Reliability of psychometric tests and current PDP task measures. Measures reported include intra-class correlation (ICC), 95% confidence interval, number of individuals (N), average number of observations per individual (k), variance within individuals (σ^2_w), and variance among individuals (σ^2_a).

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 calculated 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.

2.4 Behavioral PDP Memory Task

Word stimuli 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 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 verbal 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). 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 30 related word pairs presented during the incidental encoding phase, e.g., "knee b_n_." The type of prime was manipulated within subjects in 3 conditions: congruent with the correct response, e.g., "bone," incongruent with the correct response, e.g., "bend," or neutral symbols, i.e., "&&&." 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.

2.5 Data Aggregation

For each administration of the PDP task, performance was matched with a set of demographic, behavioral, and physiological measures from that individual, within 1 year before or after the CDR rating, within 2 years before or after the psychometric and attentional control batteries, and within 3 years before or after the CSF estimates and the PIB-PET scans. The mean time intervals between the PDP task and each of these measures are reported in Table 1.

Chapter 3: Results

We first tested the effects of healthy aging and very mild symptomatic AD on task performance, then on PDP estimates of recollection and familiarity. 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 the number of individuals and the range of ages represented in each group. Other groupings of age, e.g., 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 to CDR 0.5s with age as a covariate. We then compared the recollection estimates to a battery of standard psychometric tests in their accuracy in classifying individuals as CDR 0 vs. CDR 0.5. We also 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 via longitudinal analyses. These biomarkers included APOE genotype, CSF measurements 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 rating was unable to be matched.

3.1 Memory Performance in Healthy Aging

Figure 2 displays the proportion of each response type (correct, intrusion, or other error) at the initial PDP test as a function of age (top panel) and CDR status (bottom panel). We first tested the effects of healthy aging on memory task performance in a 3 x 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, including random word responses and time-outs. 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.

We also analyzed "other" errors. These 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, $F(2,516) = 3.98$, $p = .02$, $\eta_p^2 = .02$, 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, $F(4,1032) = 0.51$, $p = .73$, $\eta_p^2 < .01$.

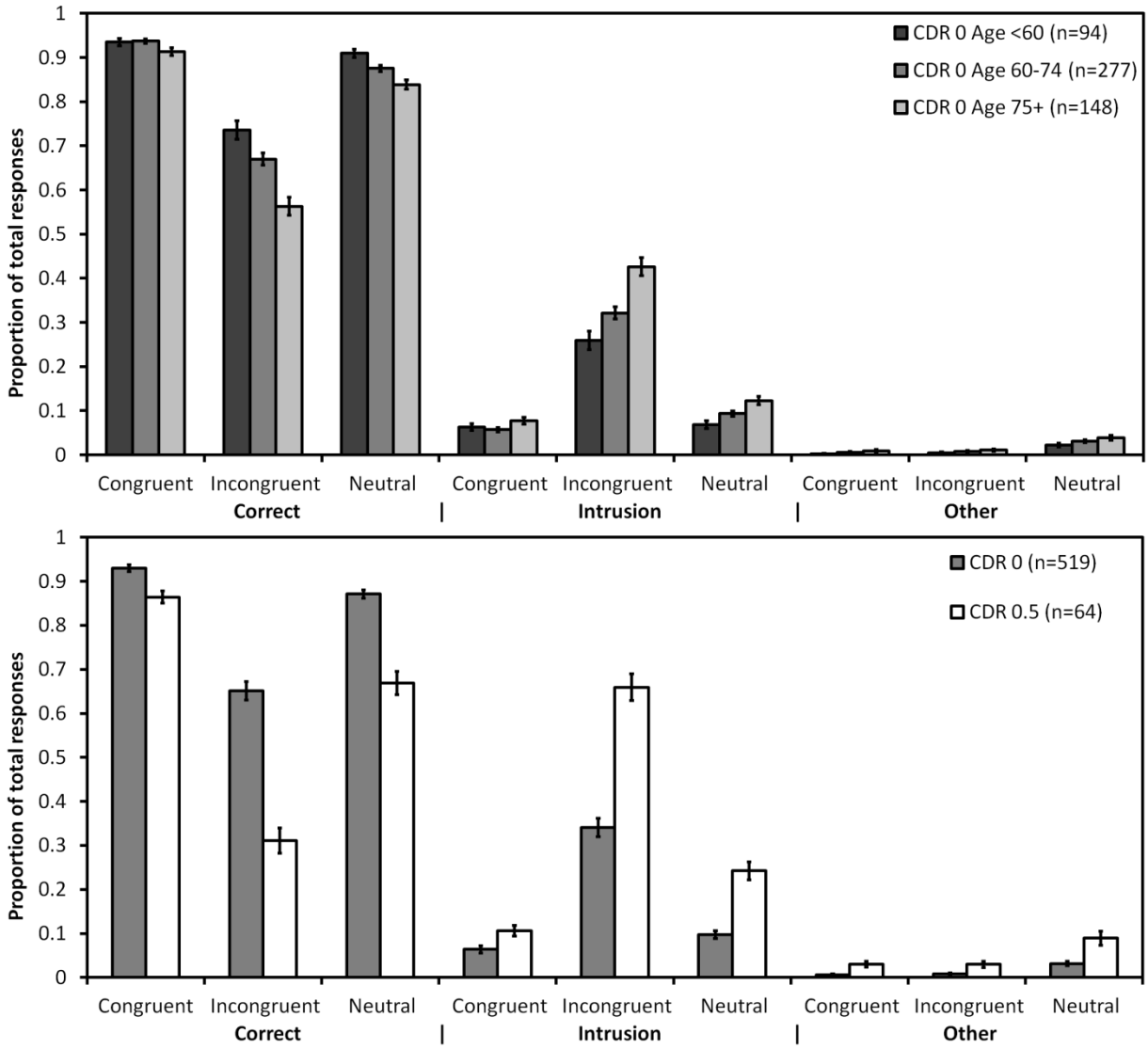

Figure 2. Mean proportion (+/- standard error of the mean) of correct responses, intrusions, and other errors as a function of trial type, age group (top panel) and AD group (bottom panel) on the baseline PDP task.

3.2 Memory Performance in Very Mild Symptomatic AD

Turning to the effects of CDR status on memory task performance, we conducted a 2 (CDR: 0 or 0.5) x 3 (condition: congruent, incongruent, or neutral) mixed-model analysis of covariance (ANCOVA), controlling for the effect of age as a continuous covariate. 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 intrusions, there was a significant main effect of CDR status, $F(1,580) = 126.98$, $p < .001$, $\eta_p^2 = .18$, 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 intrusions 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 intrusion errors, and to a much smaller extent, by other errors, including random word responses and failures to respond.

3.3 Estimates of Recollection and Familiarity using the PDP

In the current paradigm, the independent memory processes, recollection and familiarity, may lead to a consistent response (on congruent trials) or conflicting responses (on incongruent trials). Thus, this paradigm was ideally suited to use the following equations (see Jacoby, 1991) to obtain estimates of recollection and familiarity:

$$Recollection = P(correct|congruent) - P(intrusion|incongruent)$$

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

Since 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), excluding recollection estimates of 1.00, for which a corresponding familiarity estimate was not calculated.

Because when recollection estimates of 1.00, the familiarity estimate is undefined, recollection estimates of 1.00 were also excluded from Figure 3 and from the ANOVA and ANCOVA analyses of process estimates. For subsequent regression analyses, in which we focused specifically on recollection, we included 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.

The effects of healthy aging on memory process estimates were tested in the CDR 0 sample using a 3 x 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, $F(2,487) = 0.12$, $p = .89$, $\eta_p^2 < .01$.

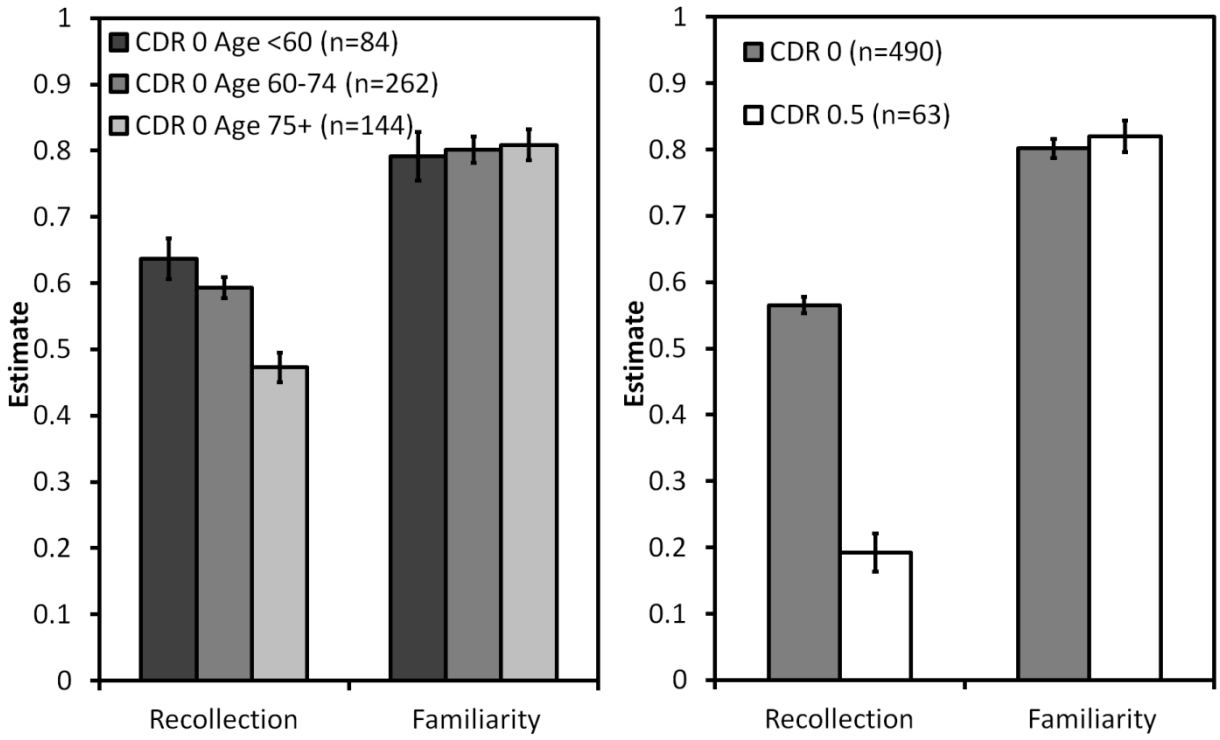

Figure 3. Mean estimates (+/- standard error of the mean) of recollection and familiarity as a function of age group (left panel) and AD group (right panel) on the baseline PDP task.

The effects of very mild symptomatic AD on memory process estimates were tested in a 2 x 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, $F(1,550) = 0.14$, $p = .71$, $\eta_p^2 < .001$.

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 to 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*s = .57, .58, .43) than in familiarity estimates (*M*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, $F(2,241) = 3.30$, $p = .04$, $\eta_p^2 = .03$. However, it is worth noting that this familiarity effect is marginally significant and importantly, is low for the middle aged group compared to 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*s = .53, .16) than it was for familiarity estimates (*M*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, $F(1,288) = 3.25$, $p = .07$, $\eta_p^2 = .01$.

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.

3.4 Sensitivity of Recollection to CDR Status

Next we evaluated the utility of the recollection estimates 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 the first step, we entered age, education, and one of the 19 psychometric measures and cognitive composites described above and tested whether the measures were able to reliably classify CDR status. In the second step, we added recollection as a predictor and tested whether it reliably increased the classification accuracy of the previous model. As shown in Table 3a, each psychometric measure, except Digit Span forward, when modeled with age and education, reliably classified CDR status in step 1, χ^2s(3) > 9, ps ≤ .03, Nagelkerke's R^2s ≥ .04. Crucially, for each psychometric measure, adding recollection reliably increased classification accuracy in step 2, Δ χ^2s(1) > 18, ps < .001, Δ Nagelkerke's R^2s ≥ .05.

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 the second step, we entered one of the 19 psychometric or composite measures. As shown in Table 3b, age, education, and recollection reliably classified CDR status in step 1 for each sample, χ^2s(3) > 55, ps < .001, Nagelkerke's R^2s ≥ .33. Adding the psychometric measures had mixed effects on classification accuracy in step 2:

	For age, education, and X			For recollection, after partialling out age, education, and X		
Variable	$\chi^2(3)$	*p*	R^2	$\Delta\chi^2(1)$	*p*	ΔR^2
WMS Logical Memory immediate	69.03	<.001	.27	51.69	<.001	.17
WMS Logical Memory delayed	100.41	<.001	.37	34.78	<.001	.11
WMS Digit forward	3.29	.35	.01	88.19	<.001	.33
WMS Digit backward	12.10	.007	.05	83.81	<.001	.31
WMS Associate Memory	63.03	<.001	.25	49.95	<.001	.17
FCSR free recall	133.21	<.001	.45	18.70	<.001	.05
FCSR total	97.17	<.001	.34	39.14	<.001	.12
WMS Mental Control	9.22	.03	.04	85.48	<.001	.32
WAIS Letter Number Sequencing	29.42	<.001	.17	50.39	<.001	.26
WAIS-R Digit Symbol	40.41	<.001	.17	57.55	<.001	.21
Animal Naming	50.81	<.001	.18	74.82	<.001	.23
Boston Naming	21.38	<.001	.09	78.20	<.001	.28
Word Fluency S-P	12.25	.007	.05	83.54	<.001	.31
Trail Making A	43.65	<.001	.15	78.89	<.001	.25
Trail Making B	43.91	<.001	.15	76.20	<.001	.24
Reading span	30.69	<.001	.21	34.12	<.001	.21
Attentional control composite	67.53	<.001	.23	57.68	<.001	.17
Episodic memory composite	142.14	<.001	.45	21.16	<.001	.06
MMSE	91.60	<.001	.30	56.00	<.001	.16
Familiarity	20.01	<.001	.07	95.36	<.001	.31
PDP task neutral accuracy	94.49	<.001	.31	39.52	<.001	.11

Table 3a. Logistic regression analyses of recollection predicting CDR status (0 vs. 0.5), controlling for psychometric tests.

15 measures produced a significant improvement to the model and 4 measures produced a non-significant improvement (see Table 3b).

We then compared the unique classification utility of recollection estimates to that of the psychometric measures by comparing model improvement measures, i.e., $\Delta\chi^2$s, in step 2, across the two models, i.e., the recollection-second model in Table 3a vs. the psychometric-second

	For age, education, and recollection			For X, after partialling out age, education, and recollection		
Variable	$\chi^2(3)$	p	R^2	$\Delta\chi^2(1)$	p	ΔR^2
WMS Logical Memory immediate	93.89	<.001	.35	26.82	<.001	.09
WMS Logical Memory delayed	93.89	<.001	.35	41.30	<.001	.13
WMS Digit forward	91.15	<.001	.35	0.32	.57	.001
WMS Digit backward	91.15	<.001	.35	4.76	.03	.02
WMS Associate Memory	94.65	<.001	.36	18.34	<.001	.06
FCSR free recall	102.93	<.001	.35	48.98	<.001	.15
FCSR total	102.93	<.001	.35	33.38	<.001	.10
WMS Mental Control	93.89	<.001	.35	0.81	.37	.003
WAIS Letter Number Sequencing	77.70	<.001	.41	2.11	.15	.01
WAIS-R Digit Symbol	85.01	<.001	.33	12.95	<.001	.05
Animal Naming	113.53	<.001	.37	12.10	<.001	.04
Boston Naming	93.89	<.001	.35	5.69	.02	.02
Word Fluency S-P	93.89	<.001	.35	1.91	.17	.006
Trail Making A	113.53	<.001	.37	9.02	.003	.03
Trail Making B	113.32	<.001	.37	6.79	.01	.02
Reading span	55.67	<.001	.37	9.14	.002	.06
Attentional control composite	110.40	<.001	.36	14.81	<.001	.04
Episodic memory composite	112.48	<.001	.36	50.83	<.001	.15
MMSE	113.53	<.001	.37	34.08	<.001	.10
Familiarity	113.02	<.001	.37	2.35	.12	.007
PDP task neutral accuracy	112.48	<.001	.36	21.53	<.001	.06

Table 3b. Logistic regression analyses of psychometric tests predicting CDR status (0 vs. 0.5), controlling for recollection.

model in Table 3b. The model improvements for recollection after partialling psychometric X (see Table 3a) were greater than the corresponding improvements for psychometric X after partialling recollection (see Table 3b) for all but three psychometric measures: Logical Memory delayed recall, FCSR free recall, and the episodic memory composite, composed of those two measures along with Associate Memory. A non-parametric sign test revealed that the

classification improvement for recollection over the psychometric measures was reliably greater than the classification improvement for psychometric measures over recollection, $n+ = 16$, $n- = 3$, $p = .004$. Thus, a recollection estimate from this 10-minute, computerized task was a relatively useful discriminator of healthy aging from very mild symptomatic AD, and at the very least comparable to the well-established psychometric memory measures.

Additionally, we tested whether the recollection estimates were a more accurate discriminator of very mild symptomatic AD than other indices of performance on the same PDP task. For this test, we performed the same stepwise binomial logistic regression analyses described above, substituting the familiarity estimate and neutral trial accuracy for the psychometric measures. Familiarity was selected for this analysis as it is a process hypothesized to contribute to task performance independently of recollection. Neutral trial accuracy was selected as a simple index of cued recall, without the influence of congruent or incongruent primes. As shown in Table 3a, adding recollection, after controlling for these other task measures, reliably increased classification accuracy in step 2, $\Delta \chi^2$s(1) > 39, ps < .001, Δ Nagelkerke's R^2s ≥ .11. In the reverse-ordered model, familiarity did not significantly improve classification accuracy, after controlling for recollection, $\Delta \chi^2(1) = 2.35$, $p = .12$, Δ Nagelkerke's $R^2 = .007$. Neutral trial accuracy did significantly improve classification accuracy, $\Delta \chi^2(1) = 21.53$, $p < .001$, Δ Nagelkerke's $R^2 = .06$, but this improvement was small in comparison to the recollection-second model, i.e., $\Delta \chi^2(1) = 39.52$, $p < .001$, Δ Nagelkerke's $R^2 = .11$. Thus, the recollection process estimate provided better discrimination between healthy aging and very mild symptomatic AD than another memory process or a simpler measure of performance derived from the same task.

3.5 Sensitivity of Recollection to Preclinical AD Biomarkers

If recollection estimates are sensitive to the earliest detectable stage of symptomatic AD, then they 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 using hierarchical linear regression 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 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, in order 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.

3.5.1 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 non-normality 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 intra-class 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 inter-individual differences, leaving 45% driven by intra-individual 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. There was considerable variability between individual slopes over time, $\tau_1 = .09$, 95% C.I. = [.04, .19]. 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 between 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 each other two-way interaction 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 over-fitting the data (as conducted by Aschenbrenner, Balota, Fagan, et al., 2015).

The final parameter estimates are displayed in Table 4. In this model, time had a significant, positive relationship with recollection, $\beta = .06$, $p = .02$. As predicted, 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 genotype was not related to recollection, $\beta = .02$, $p = .87$. Sex was positively related to initial recollection, $\beta = .49$, $p < .001$, indicating that females had higher initial recollection 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, $\beta = .14$, $p = .02$ (see Figure 4). To clarify, low levels of $A\beta_{42}$ in the CSF are associated with accumulation of amyloid plaques in the brain (Fagan et al., 2006). Thus, lower recollection estimates were associated with markers of more progressed AD pathology. In contrast, baseline level of tau was not related to initial recollection estimate, $\beta = -.06$, $p = .36$, nor was the interaction between baseline tau and $A\beta_{42}$, $\beta = -.09$, $p = .11$.

Variable	Estimate (*SE*)	df	*t*	*p*
Intercept	-0.33 (0.09)	321	-3.72	<.001
Time	0.06 (0.02)	228	2.33	.02
Age	-0.21 (0.05)	321	-4.21	<.001
Education	0.06 (0.02)	321	3.33	.001
APOE	0.02 (0.10)	321	0.16	.87
Sex	0.49 (0.11)	228	4.64	<.001
$A\beta_{42}$	0.14 (0.06)	321	2.41	.02
Tau	-0.06 (0.06)	321	-0.93	.36
Time * Sex	-0.06 (0.03)	228	-1.99	.048
$A\beta_{42}$ * Tau	-0.09 (0.06)	321	-1.60	.11
Time * $A\beta_{42}$	-0.01 (0.02)	228	-0.47	.64
Time * Tau	0.00 (0.02)	228	0.01	.99
Time * $A\beta_{42}$ * Tau	0.06 (0.02)	228	3.23	.001

Table 4. Hierarchical linear regression analyses of CSF biomarkers and recollection. 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 genotype 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 non-normality using a natural log transform. Baseline age and CSF biomarkers were standardized within the sample.

Turning to longitudinal change in recollection, the model revealed a significant interaction between time, $A\beta_{42}$, and tau, $\beta = .06$, $p < .001$. This interaction is depicted in Figure 5, in which predictions are plotted in separate panels for individuals with abnormal (lower) baseline CSF $A\beta_{42}$, as defined using the Youden index by Vos et al. (2014) as values less than 459 pg/mL, and for individuals within the normal (higher) range. When $A\beta_{42}$ was abnormal, as CSF tau increased, recollection was less likely to increase over time. However, when $A\beta_{42}$ was normal, the relationship between CSF tau and recollection slope was weaker. Improvement over time in the recollection estimate likely reflects a practice effect, which has been noted in similar samples for 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

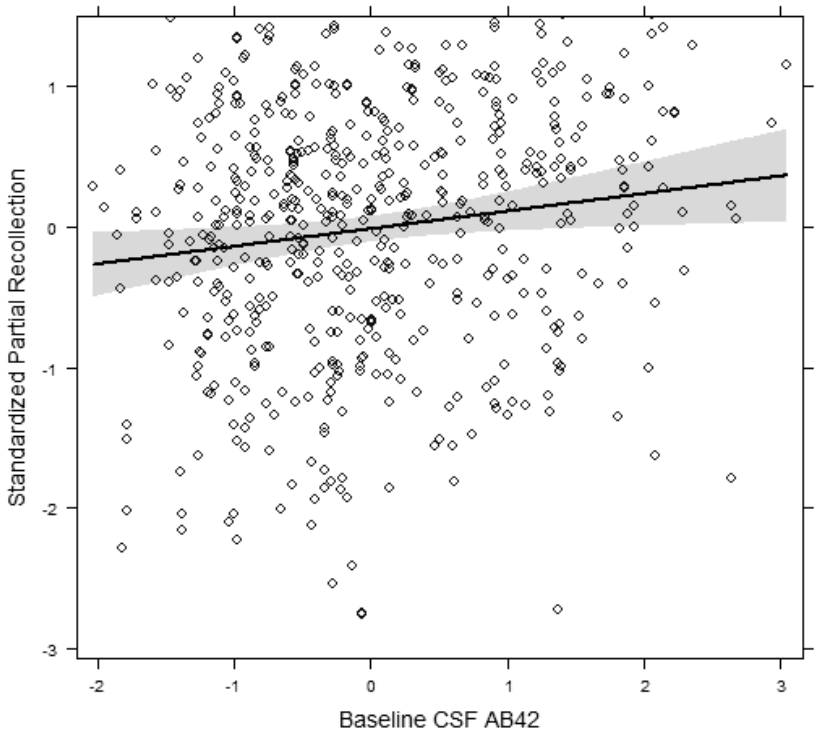

Figure 4. Relationship between recollection and CSF $A\beta_{42}$. Points are residual observations. Line is the model prediction. Shaded area is the 95% confidence region.

(Hassenstab et al., 2015). Thus, CSF $A\beta_{42}$ and tau, both indicative of progressed AD pathology, had an interactive effect on the practice effect for recollection.

3.5.2 Sensitivity of Recollection to PIB-PET

We then tested whether recollection was related to presence of amyloid plaques as observed by PIB-PET. 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

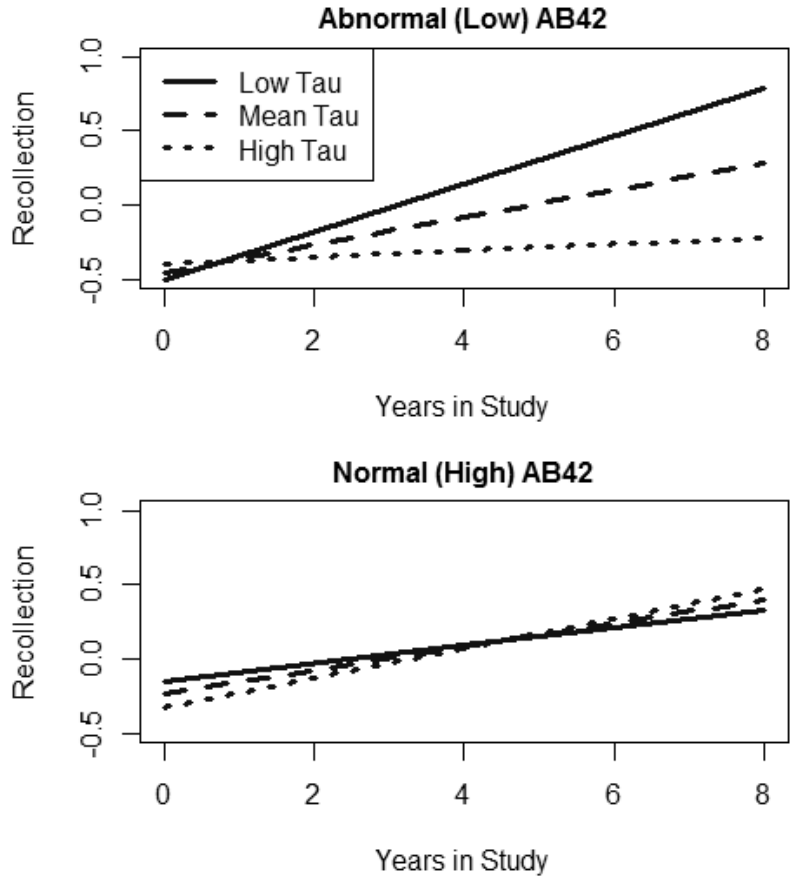

Figure 5. Interaction between $A\beta_{42}$, tau, and time on recollection. Regression lines of recollection, predicted by time, are plotted separately for mean levels of tau, as well as 1 standard deviation above and below the mean, for individuals with abnormal levels of $A\beta_{42}$ (<459 pg/mL, upper panel) and those with normal levels (≥459 pg/mL, lower panel).

positivity in a similar cohort using the Youden index (as performed by Vos et al., 2014). 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 = .10, as well as a significant random effect of time, 95% C.I. = [-.09, .14]. The final model parameters are presented in Table 5. Crucially, PIB positivity was not related to baseline recollection, β = .00, p

= .99, but it significantly interacted with time to predict change in recollection, β = -.10, p = .02. As shown in Figure 6, in individuals who were PIB- at baseline, recollection tended to slightly increase over time, while in individuals who were PIB+, recollection decreased over time.

Variable	Estimate (*SE*)	df	*t*	*p*
Intercept	-0.16 (0.10)	280	-1.62	.11
Time	0.02 (0.02)	212	0.94	.35
Age	-0.24 (0.05)	280	-4.56	<.001
Education	0.06 (0.02)	280	3.29	.001
APOE	-0.24 (0.12)	280	-1.96	.051
Sex	0.29 (0.11)	280	2.78	.006
PIB	0.00 (0.15)	280	-0.01	.99
Time * APOE	0.06 (0.03)	212	1.65	.10
Time * PIB	-0.10 (0.04)	212	-2.33	.02

Table 5. Hierarchical linear regression analyses of PIB positivity and recollection. 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 genotype 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. Baseline age was standardized within the sample.

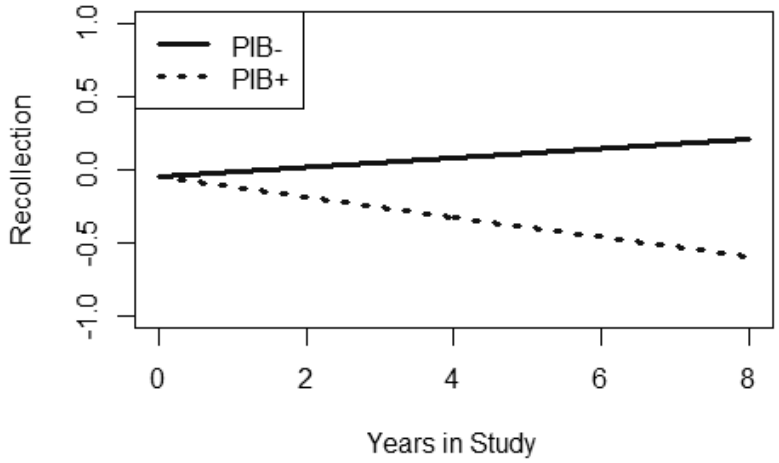

Figure 6. Interaction between PIB positivity and time on recollection. Regression lines of recollection, predicted by time, are plotted separately for individuals who were PIB+ (MCBP >.23) and those who were PIB- (MCBP ≤ .23).

Consistent with the CSF model, age, β = -.24, p < .001, education, β = .06, p = .001, and sex, β = .29, p = .006, were significantly related to recollection estimates. Unlike the CSF model, however, APOE was marginally related to baseline recollection, β = -.24, p = .051, as well as longitudinal change in recollection, β = .06, p = .10. Note that the APOE * Time interaction is opposite to the hypothesized direction. The difference in slope between ε4+ and ε4- groups may be driven in part by the difference in baseline recollection. Moreover, because neither the baseline effect of APOE nor its interaction with time was significant in the CSF analyses, and APOE relations to cognition in healthy non-demented individuals has been inconsistent in the literature (for meta-analysis, see Wisdom, Callahan, & Hawkins, 2011), we believe that one should interpret the current APOE effects with caution.

Chapter 4: General Discussion

The results from the present study yielded a number of noteworthy results. Specifically, using a short 10-minute procedure that affords PDP analyses in a large cohort, we find that an estimate of recollection, but not familiarity, is (a) sensitive to healthy aging, (b) particularly sensitive to early stage symptomatic AD, compared to 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 important role of attention in memory, and the potential applied utility of recollection estimates.

4.1 Memory Processes in Healthy Aging and Early Stage Symptomatic AD

The current results indicate that healthy aging is associated with a large deficit in recollection, but no change in familiarity. This finding 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. 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) to older adult samples (typically recruited from the community; mean sample age = 71.14, range = 60.61 – 77.00). By contrast, the present study compares three groups of older adults (45-59 years, 60-74, and 75-95), recruited from the community, grouped by 15- to 20-year age intervals. Furthermore, in both the present hierarchical linear models for CSF and PIB biomarkers, we demonstrate continuous effects of age on recollection, controlling for AD biomarkers. To our knowledge, no other study has examined age effects on process estimates, without including younger adult samples. 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, *S.D.* = 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- or multiple-domain aMCI reported in the meta-analysis, recollection reliably decreased in aMCI, compared to healthy controls, in every study, while familiarity had only a marginal deficit. Of those studies, only the

ones with 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). In terms of power, 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 substantial power to detect a familiarity deficit, and yet no evidence of such a deficit was found. Moreover, to our knowledge, no other study has tested the effect of symptomatic AD on memory process estimates using a cued stem 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). Together, these observations solidify the proposal that in contrast to the automatic familiarity process, the attention-demanding recollection process exhibits a more robust deficit in the earliest stages of symptomatic AD.

4.2 Cognitive Correlates of Preclinical AD Biomarkers

In the present analysis of preclinical AD biomarkers, we found 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. One reason for this sensitivity might stem from the utility of extracting a recollection process estimate from memory task

performance. Since the recollection process is highly dependent on attention, it might amplify sensitivity to the attentional component of memory performance. 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. The interaction between executive/attentional processes and memory, as well as its relevance to recollection, are discussed in more detail below.

4.3 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, preclinical AD-related memory changes may be in part driven by changes in executive and/or attentional processes. 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 task, 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, while the relative strength of the competing pathways may vary.

4.4 Clinical Utility of Recollection

The results from the binomial 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 minutes, is entirely computer-based, and may be automatically scored. Thus, it would be very easy to administer in a clinical setting.

It is worth noting that the Free and Cued Selective Reminding test (FCSR) free recall portion (Grober et al., 1988), WMS Logical Memory (WMS-LM) delayed recall units (WMS-LM; Wechsler, 1997), as well as the episodic memory composite of those two measures along with WMS Associate Memory (Wechsler, 1987), outperformed the recollection estimate. Unlike the recollection estimate, these tasks currently lack computer implementation and instead must be manually administered and scored. Furthermore, the current PDP task is comparable in duration to FCSRT (12-15 minutes; National Institute on Aging) and is much shorter than the retention interval of 30 to 40 minutes required for 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 to 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]) and episodic memory composite (ICC = .74, 95% C.I. = [.69, .79]).

Interestingly, the FCSR free recall, WMS-LM delayed recall, and the episodic composite, like recollection, all involve strong components of controlled recall. It is possible that

recollection estimates, FCSR, WMS-LM, and the composite are tapping similar processes, particularly memory 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, WMS-LM, and the cognitive composite are likely not tapping *identical* processes to recollection. Indeed, recollection is only modestly correlated with FCSR free recall (r = .53), WMS-LM delayed recall (r = .46), and the episodic memory composite (r = .55) in the current sample. Furthermore, in the logistic regression models, the addition of recollection significantly improves CDR classification accuracy *controlling for FCSR, WMS-LM, or the composite*, and vice versa (see Tables 4a & b), suggesting that each measure is capturing a significant portion of unique variance within the sample. Therefore, recollection estimates, FCSR, WMS-LM, and the episodic memory composite might each be indicative of *similar, but different*, processes or combinations of processes.

4.5 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.

References

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., … Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia*, (7), 270–279. http://doi.org/10.1016/j.jalz.2011.03.008

Ally, B. A., Gold, C. A., & Budson, A. E. (2009). An evaluation of recollection and familiarity in Alzheimer's disease and mild cognitive impairment using receiver operating characteristics. *Brain and Cognition*, *69*(3), 504–513. http://doi.org/10.1016/j.bandc.2008.11.003

Anderson, N. D., Ebert, P. L., Jennings, J. M., Grady, C. L., Cabeza, R., & Graham, S. J. (2008). Recollection- and familiarity-based memory in healthy aging and amnestic mild cognitive impairment. *Neuropsychology*, *22*(2), 177–87. http://doi.org/10.1037/0894-4105.22.2.177

Armitage, S. G. (1946). An Analysis of Certain Psychological Tests Use for the Evaluation of Brain Injury. *Psychological Monographs*, *60*(1).

Aschenbrenner, A. J., Balota, D. A., Fagan, A. M., Duchek, J. M., Benzinger, T. L. S., & Morris, J. C. (2015). Alzheimer Disease Cerebrospinal Fluid Biomarkers Moderate Baseline Differences and Predict Longitudinal Change in Attentional Control and Episodic Memory Composites in the Adult Children Study. *Journal of the International Neuropsychological Society*, *21*(8), 573–583. http://doi.org/10.1017/S1355617715000776

Aschenbrenner, A. J., Balota, D. A., Tse, C.-S., Fagan, A. M., Holtzman, D. M., Benzinger, T. L. S., & Morris, J. C. (2015). Alzheimer Disease Biomarkers, Attentional Control, and Semantic Memory Retrieval: Synergistic and Mediational Effects of Biomarkers on a Sensitive Cognitive Measure in Non-Demented Older Adults. *Neuropsychology*, *29*, 368–381. http://doi.org/10.1037/neu0000133

Balota, D. A., Burgess, G. C., Cortese, M. J., & Adams, D. R. (2002). The Word-Frequency Mirror Effect in Young, Old, and Early-Stage Alzheimer's Disease: Evidence for Two Processes in Episodic Recognition Performance. *Journal of Memory and Language*, *46*(1), 199–226. http://doi.org/10.1006/jmla.2001.2803

Balota, D. A., & Duchek, J. M. (2015). Attention, Variability, and Biomarkers in Alzheimer's Disease. In *Remembering: Attributions, Processes, and Control in Human Memory* (pp. 285–303). New York: Psychology Press.

Benjamin, A. S. (2001). On the Dual Effects of Repetition on False Recognition. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *27*(4), 941–947.

Berg, L., McKeel, D. W., Miller, J. P., Storandt, M., Rubin, E. H., Morris, J. C., … Saunders, A. M. (1998). Clinicopathologic Studies in Cognitively Healthy Aging and Alzheimer Disease. *Archives of Neurology*, *55*(3), 326. http://doi.org/10.1001/archneur.55.3.326

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., … Mintun,

M. a. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *25*(34), 7709–17. http://doi.org/10.1523/JNEUROSCI.2177-05.2005

Carlesimo, G. a., & Oscar-Berman, M. (1992). Memory deficits in Alzheimer's patients: A comprehensive review. *Neuropsychology Review*, *3*(2), 119–170. http://doi.org/10.1007/BF01108841

Castel, A. D., Balota, D. A., Hutchison, K. A., Logan, J. M., & Yap, M. J. (2007). Spatial attention and response control in healthy younger and older adults and individuals with Alzheimer's disease: Evidence for disproportionate selection impairments in the simon task. *Neuropsychology*, *21*(2), 170–182. http://doi.org/10.1037/0894-4105.21.2.170

Castel, A. D., & Craik, F. I. M. (2003). The effects of aging and divided attention on memory for item and associative information. *Psychology and Aging*, *18*(4), 873–885. http://doi.org/10.1037/0882-7974.18.4.873

Craik, F. I. M. (1983). On the transfer of information from temporary to permanent memory. *Philosophical Transactions of the Royal Society of London: Series B*, (302), 341–359.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. *Journal of Verbal Learning and Verbal Behavior*, *11*(6), 671–684. http://doi.org/10.1016/S0022-5371(72)80001-X

Engle, R. W., Tuholski, S. W., Laughlin, J. E., & Conway, A. R. (1999). Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. *Journal of Experimental Psychology: General1*, *128*(3), 309.

Fagan, A. M., Mintun, M. A., Mach, R. H., Lee, S. Y., Dence, C. S., Shah, A. R., … Holtzman, D. M. (2006). Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta;42 in humans. *Annals of Neurology*, *59*(3), 512–519. http://doi.org/10.1002/ana.20730

Fagan, A. M., Roe, C. M., Xiong, C., Mintun, M. a, Morris, J. C., & Holtzman, D. M. (2007). Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Archives of Neurology*, *64*(3), 343–349. http://doi.org/10.1001/archneur.64.3.noc60123

Faust, M. E., & Balota, D. A. (2007). Inhibition, Facilitation, and Attention Control in Dementia of the Alzheimer Type: The role of unifying principles in cognitive theory development. In D. S. Gorfein & C. McLeod (Eds.), *The place of inhibition in Cognition.* (pp. 213–238).

Fischl, B. (2012). FreeSurfer. *Neuroimage2*, *62*(2), 774–781. http://doi.org/10.1016/j.neuroimage.2012.01.021.FreeSurfer

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. http://doi.org/10.1016/0022-3956(75)90026-6

Galvin, J. E., Powlishta, K. K., Wilkins, K., McKeel, D. W., Xiong, C., Grant, E., … Morris, J. C. (2005). Predictors of preclinical Alzheimer disease and dementia: a clinicopathologic study. *Archives of Neurology*, *62*(5), 758–765. http://doi.org/10.1001/archneur.62.5.758

Goodglass, H., & Kaplan, E. (1983). Boston Diagnostic Aphasia Examination Booklet. Lea & Febiger.

Gordon, B. a., Zacks, J. M., Blazey, T., Benzinger, T. L. S., Morris, J. C., Fagan, A. M., … Balota, D. A. (2015). Task-evoked fMRI changes in attention networks are associated with preclinical Alzheimer's disease biomarkers. *Neurobiology of Aging*. http://doi.org/10.1016/j.neurobiolaging.2015.01.019

Grober, E., Buschke, H., Crystal, H., Bang, S., & Dresner, R. (1988). Screening for dementia by memory testing. *Neurology*, *38*(June), 900–903. http://doi.org/10.1212/WNL.38.6.900

Hasher, L., & Zacks, R. T. (1979). Automatic and Effortful Processes in Memory. *Journal of Experimental Psychology: General*, *108*(3), 356–388.

Hassenstab, J., Ruvolo, D., Jasielec, M., Xiong, C., Grant, E., & Morris, J. C. (2015). Absence of practice effects in preclinical Alzheimer's disease. *Neuropsychology*, *29*(6), 940–948. http://doi.org/http://dx.doi.org/10.1037/neu0000208

Healy, M. R., Light, L. L., & Chung, C. (2005). Dual-process models of associative recognition in young and older adults: evidence from receiver operating characteristics. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *31*(4), 768–788. http://doi.org/10.1037/0278-7393.31.4.768

Hedden, T., Oh, H., Younger, A. P., & Patel, T. A. (2013). Meta-analysis of amyloid-cognition relations in cognitively normal older adults. *Neurology*, *80*, 1341–1348.

Jacoby, L. L. (1991). A process dissociation framework: Separating automatic from intentional uses of memory. *Journal of Memory and Language*, *30*(5), 513–541. http://doi.org/10.1016/0749-596X(91)90025-F

Jacoby, L. L. (1996). Dissociating Automatic and Consciously Controlled Effects of Study/Test Compatibility. *Journal of Memory and Language*, *35*, 32–52. http://doi.org/10.1006/jmla.1996.0002

Jacoby, L. L. (1998). Invariance in Automatic Influences of Memory : Toward a User 's Guide for the Process-Dissociation Procedure. *Journal of Experimental Psychology: Learning, Memory, and Cognition*.

Jacoby, L. L. (1999a). Deceiving the Elderly: Effects of Accessibility Bias in Cued-Recall Performance. *Cognitive Neuropsychology*, *16*(3–5), 417–436. http://doi.org/10.1080/026432999380861

Jacoby, L. L. (1999b). Ironic effects of repetition: measuring age-related differences in memory. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, *25*(1), 3–22. http://doi.org/10.1037/0278-7393.25.1.3

Jacoby, L. L., Toth, J. P., & Yonelinas, A. P. (1993). Separating Conscious and Unconscious Influences of Memory: Measuring Recollection. *Journal of Experimental Psychology: General*, *112*(2), 139–154.

Kaplan, E., Goodglass, H., & Weintraub, S. (1976). Boston Naming Test Scoring Booklet, Experimental Edition. Boston: Veterans Administration Hospital.

Koen, J. D., & Yonelinas, A. P. (2014). The Effects of Healthy Aging, Amnestic Mild Cognitive Impairment, and Alzheimer's Disease on Recollection and Familiarity: A Meta-Analytic Review. *Neuropsychology Review*, 332–354. http://doi.org/10.1007/s11065-014-9266-5

Mandler, G. (1980). Recognizing: The judgment of previous occurrence. *Psychological Review*, *87*(3), 252–271. http://doi.org/10.1037/0033-295X.87.3.252

McCabe, D. P., Roediger, H. L., McDaniel, M. A., & Balota, D. A. (2009). Aging reduces veridical remembering but increases false remembering: Neuropsychological test correlates of remember-know judgments. *Neuropsychologia*, *47*(11), 2164–2173. http://doi.org/10.1016/j.neuropsychologia.2008.11.025

McCabe, D. P., Roediger, H. L., McDaniel, M. A., Balota, D. A., & Hambrick, D. Z. (2010). The relationship between working memory capacity and executive functioning: evidence for a common executive attention construct. *Neuropsychology*, *24*(2), 222–43. http://doi.org/10.1037/a0017619

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*, *34*, 939–944. http://doi.org/10.1212/WNL.34.7.939

Mintun, M. A., Larossa, G. N., Sheline, Y. I., Dence, C. S., Lee, S. Y., MacH, R. H., … Morris, J. C. (2006). [11C]PIB in a nondemented population: Potential antecedent marker of Alzheimer disease. *Neurology*, *67*(3), 446–452. http://doi.org/10.1212/01.wnl.0000228230.26044.a4

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, *43*(11), 2412–4.

Morris, J. C., Blennow, K., Froelich, L., Nordberg, A., Soininen, H., Waldemar, G., … Dubois, B. (2014). Harmonized diagnostic criteria for Alzheimer's disease: Recommendations. *Journal of Internal Medicine*, *275*(3), 204–213. http://doi.org/10.1111/joim.12199

Morris, R. G., & Kopelamn, M. D. (1986). The memory deficits in Alzheimer-type dementia: A review. *Quarterly Journal of Experimental Psychology*, *38A*(October), 575–602. http://doi.org/10.1080/14640748608401615

Perry, R. J., & Hodges, J. R. (1999). Attention and executive deficits in Alzheimer ' s disease A critical review, 383–404.

Pinheiro, J., Bates, D., DebRoy, S., & Sarkar, D. (2014). R Core Team. nlme: Linear and Nonlinear Mexed Effects Models R package version 3.1-117.

Serra, L., Bozzali, M., Cercignani, M., Perri, R., Fadda, L., Caltagirone, C., & Carlesimo, G. A. (2010). Recollection and familiarity in amnesic mild cognitive impairment. *Neuropsychology*, *24*(3), 316–26. http://doi.org/10.1037/a0017654

Simon, J. R. (1969). Reactions toward the source of stimulation. *Journal of Experimental Psychology*, *81*(1), 174–176. http://doi.org/10.1037/h0027448

Sperling, R. A., Aisen, P. S., Beckett, L. A., Bennett, D. A., Craft, S., Fagan, A. M., … Phelps, C. H. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. *Alzheimer's & Dementia*, *7*(3), 1–13. http://doi.org/10.1016/j.jalz.2011.03.005

Spieler, D. H., Balota, D. A., & Faust, M. E. (1996). Stroop Performance in Healthy Younger and Older Adults and in Individuals With Dementia of the Alzheimer's Type, *22*(2), 461–479.

Storandt, M., Botwinick, J., Danziger, W. L., Berg, L., & Hughes, C. P. (1984). Pyschometric differentiation of mild senile dementia of the Alzheimer type. *Archives of Neurology*, *41*, 497–499.

Storandt, M., Grant, E. A., Miller, J. P., & Morris, J. C. (2006). Longitudinal course and neuropathologic outcomes in original vs revised MCI and in pre-MCI. *Neurology*, *67*(3), 467–473.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. http://doi.org/10.1037/h0054651

Su, Y., D'Angelo, G. M., Vlassenko, A. G., Zhou, G., Snyder, A. Z., Marcus, D. S., … Benzinger, T. L. S. (2013). Quantitative analysis of PiB-PET with FreeSurfer ROIs. *PLoS ONE*, *8*(11). http://doi.org/10.1371/journal.pone.0073377

Thurstone, L. L., & Thurstone, T. G. (1947). SRA Primary Mental Abilities.

Tse, C.-S., Balota, D. a, Yap, M. J., Duchek, J. M., & McCabe, D. P. (2010). Effects of healthy aging and early stage dementia of the Alzheimer's type on components of response time distributions in three attention tasks. *Neuropsychology*, *24*(3), 300–15. http://doi.org/10.1037/a0018274

Vos, S. J. B., Xiong, C., Visser, P. J., Mateusz, S., Hassenstab, J., Grant, E. A., … Fagan, A. M. (2014). Preclinical Alzheimer's disease and it's outcome: a longitudinal cohort study. *Lancet Neurol*, *12*(10), 957–965. http://doi.org/10.1016/S1474-4422(13)70194-7.Preclinical

Wechsler, D. (1981). WAIS-R manual: Wechsler adult intelligence scale-revised. Psychological Corporation.

Wechsler, D. (1987). WMS-R: Wechler Memory Scale-Revised: Manual. Psychological Corporation.

Wechsler, D. (1997). WAIS-III: Administration and Scoring Manual: Wechsler Adult Intelligence Scale. Psychological Corporation.

Wechsler, D., & Stone, C. P. (1973). Manual: Wechsler memory scale. New York: Psychological Corporation.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L.-O., … Petersen, R. C. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *Journal of Internal Medicine*, *256*(3), 240–246. http://doi.org/10.1111/j.1365-2796.2004.01380.x

Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: A meta-analysis. *Neurobiology of Aging*, *32*(1), 63–74. http://doi.org/10.1016/j.neurobiolaging.2009.02.003

Wolak, M. E., Fairbairn, D. J., & Paulsen, Y. R. (2012). Guidelines for estimating repeatability. *Methods in Ecology and Evolution*, *3*(1), 129–137. http://doi.org/10.1111/j.2041-210X.2011.00125.x

Wolk, D. A., Mancuso, L., Kliot, D., Arnold, S. E., & Dickerson, B. C. (2013). Familiarity-based memory as an early cognitive marker of preclinical and prodromal AD. *Neuropsychologia*, *51*(6), 1094–1102. http://doi.org/10.1016/j.neuropsychologia.2013.02.014

Wolk, D. A., Signoff, E. D., & DeKosky, S. T. (2008). Recollection and familiarity in amnestic mild cognitive impairment: A global decline in recognition memory. *Neuropsychologia*, *46*(7), 1965–1978. http://doi.org/10.1016/j.neuropsychologia.2008.01.017

Yonelinas, A. P., & Jacoby, L. L. (2012). The process-dissociation approach two decades later: Convergence, boundary conditions, and new directions. *Memory & Cognition*, *40*(5), 663–680. http://doi.org/10.3758/s13421-012-0205-5