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Comparison of self- and informant-reported change in memory, attention, and spatial navigation in predicting preclinical Alzheimer disease

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Comparison of Self- and Informant-Reported Change in Memory, Attention, and Spatial Navigation in Predicting Preclinical Alzheimer Disease

by
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Dedicated to Miles who made finishing this project a little more difficult and a lot more fun.

ABSTRACT OF THE DISSERTATION

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Professor Denise Head, Chair

Preclinical Alzheimer disease (AD) is characterized as the point at which a person is clinically normal but exhibits AD-related neuropathological change and is associated with developing AD-related dementia in the future (Jack et al., 2018). As such, there has been a focus on identifying procedures sensitive to the preclinical stage. However, the current methods used to detect biomarker abnormalities associated with preclinical AD (e.g., lumbar puncture, PET scan, and MRI) are invasive and/or expensive, which limits feasibility for widescale screening. This leaves the need to develop a non-invasive, time-efficient, and cost-effective screening measure to identify those who are at greater risk of preclinical AD. Such a measure could be used to inform decisions regarding when to use more invasive and/or expensive methods.

Preclinical AD has been associated with subtle, but observable, changes in performance on neuropsychological and experimental measures of memory, attention, and spatial navigation (Allison et al., 2016; Balota et al., 2020; Hedden et al., 2013; Langbaum et al., 2014; Levine et al., 2020; Millar et al., 2017). Unfortunately, these tasks can be time-consuming, which limits their feasibility in clinical settings. The goal of this study is to examine self- and informant-

reported questionnaires assessing changes in these cognitive domains to identify a questionnaire-based screening measure for preclinical AD that could be easily administered in clinical settings.

This dissertation comprised three independent samples, two recruited from Washington University using the Volunteer for Health (VFH) program and Alzheimer Disease Research Center (ADRC) and one including of preexisting data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The project had four specific aims to examine the diagnostic abilities of self- and informant-reported measures of memory, attention, and spatial navigation in preclinical AD. The first aim was to assess the reliability (internal consistency) and validity (confirmatory factor analysis) of the six questionnaires (VFH and ADNI samples). The second aim was to compare the diagnostic accuracy of the six questionnaires using receiver operating characteristic analyses (ADRC and ADNI samples). The third aim was to assess the predictive ability of the questionnaires when controlling for other factors associated with preclinical AD (personality, depressive symptoms, and anxiety symptoms in the ADRC sample and depressive symptoms in the ADNI sample). The final aim was to compare the diagnostic accuracy of the six questionnaires with a previously established measures of cognition (e.g., a self and informant measure of early dementia in the ADRC sample or with neuropsychological composites in the ADNI sample).

All questionnaires demonstrated appropriate reliability and validity. In both samples, self-reported questionnaires were significant predictors of preclinical AD, whereas informant-reported questionnaires were not. Additionally, self-reported attention remained a significant predictor of preclinical AD when controlling for depressive symptoms in the ADNI sample. Of note, the ADRC sample was underpowered based on a priori power analysis. In addition, although significant, the self-reported ADNI questionnaires demonstrated weak diagnostic

accuracy in predicting preclinical AD (area under the curve=.564-.592). Given these limitations, it is unclear whether these questionnaires would be appropriate for widespread clinical use.

Although this study was unable to identify a questionnaire that was both diagnostically accurate and highly sensitive to preclinical AD, the results serve to inform the future development of screening tools for early AD pathological change. These results provide an important foundation for the future development of cognitive screening tools in the preclinical stage.

Chapter 1: Introduction

Alzheimer disease (AD) is the most common neurodegenerative disease and is characterized by the deposition of amyloid plaques and neurofibrillary tangles in the brain (Jack et al., 2018). Although AD can only be formally diagnosed upon autopsy, proxy measures for AD-related neuropathology and neurodegeneration may be detected *in vivo* using Positron Emission Tomography (PET), cerebrospinal fluid (CSF), and magnetic resonance imaging (MRI) (Dubois et al., 2016; Jack et al., 2018; Sperling et al., 2011). Amyloid burden at autopsy has been associated with elevated levels of uptake of the radiotracer Pittsburgh Compound B (PIB) and reduced levels of CSF amyloid-beta ($A\beta_{42}$) *in vivo* (Formaglio et al., 2011; Ikonomovic et al., 2008). Tau burden at autopsy has been associated with elevated levels of uptake of radiotracer on tau PET scans and elevated levels of CSF total-tau (t-tau) and phosphorylated tau (p-tau) *in vivo* (Finehout et al., 2006; Okamura et al., 2014). Beyond these cardinal neuropathological markers, AD has been consistently associated with volumetric decline of several brain regions including the hippocampus, entorhinal cortex, parietal cortex, and prefrontal cortex (for review see Frisoni et al., 2010).

AD-related neuropathologic change may be detected decades before the onset of clinical symptoms (e.g., cognitive decline; Dubois et al., 2016). The stage at which a person is clinically normal but exhibits AD-related pathological change is referred to as preclinical AD (Dubois et al., 2016; Jack et al., 2018; Sperling et al., 2011). Individuals in the preclinical stage are at increased risk of developing symptomatic AD in the future (Davatzikos et al., 2011; Dumurgier et al., 2017).

It has been suggested that although people with preclinical AD are clinically normal, they evidence subtle cognitive changes (Jack et al., 2018; Sperling et al., 2011). The cognitive

changes associated with the preclinical phase have been heterogeneous. Neuropsychological research suggests that memory measures may be sensitive to the earliest stages of AD (Backman et al., 2005; Baker et al., 2017; Hedden et al., 2013), whereas cognitive psychological research has demonstrated that attentional control measures may also be sensitive to the earliest stages of AD (Aschenbrenner et al., 2015; Balota et al., 2010; Hutchison et al., 2010). In addition, deficits in spatial navigation ability have been observed in the preclinical stage of AD (Allison et al., 2016; Allison et al., 2019; Levine et al., 2020).

Due to the increasing prevalence of AD, there is a need for a widely distributable screening measure for the preclinical stage. Current methods (lumbar puncture, PET, and MRI) used to assess pathological changes associated with disease progression are invasive and/or expensive (Jack et al., 2018). As a result, these methods may not be accessible to people with limited finances or in rural clinics with limited resources. Although neuropsychological and experimental tasks are not invasive, they may not represent time- and cost-effective measures for screening. For example, computerized spatial navigations tasks previously employed by our research group took approximately 30 minutes to complete (Allison et al., 2016), which may not be feasible in most clinical settings. An easily distributed, time- and cost-effective screening tool could be used to identify individuals at the highest risk of AD and streamline the use of more conclusive diagnostic methods. To address these limitations and further develop clinical screening methods, the overall goal of this study is to identify self- and/or informant-reported questionnaires that have clinical utility to screen for preclinical AD as identified by CSF measures and hippocampal neurodegeneration.

This study will focus on questionnaire-based measures of memory, attentional control, and spatial navigation, as the literature suggests that subtle changes in these domains are

observable in preclinical AD. First, I will provide a brief overview of the conceptualization of AD and its stages. Then, I will review the literature examining subtle changes in memory, attention, and spatial navigation in preclinical AD to support this focus. Next, I will discuss the potential utility of questionnaires in detecting early clinical change. Lastly, I will review the other factors that may influence self- and informant-reported cognition, specifically personality traits and current affect.

1.1 Alzheimer disease continuum

Clifford Jack and colleagues (2018) proposed a conceptual framework for AD based on a pathophysiological process wherein amyloid and tau accumulate in the brain and may result in clinical symptoms of dementia. More advanced biomarker changes are associated with an increased likelihood of cognitive decline and more rapid progression, however, not all people exhibiting AD pathology develop clinical symptoms of dementia (Jack et al., 2018). Though there are no clear boundaries between clinical stages using this framework, the disease process can be broken down into conceptual stages to better operationalize the disease process: symptomatic AD, mild cognitive impairment (MCI), and preclinical AD (Aisen et al., 2017; Jack et al., 2018).

1.1.1 Symptomatic Alzheimer disease

Symptomatic AD refers to the point at which a person exhibits both AD-related neuropathological change and dementia thought to be a result of this neuropathology (Jack et al., 2018). At this stage, cognitive impairment is severe enough to impact activities of daily living (Jalbert et al., 2008).

1.1.2 Mild cognitive impairment due to Alzheimer disease

MCI is defined as greater cognitive decline than expected given an individual's age and education, but that does not significantly interfere with activities of daily living (Fisher et al.,

2007; Morris et al., 2001). This stage is associated with increased risk of developing AD in the future, with reported annual progression to AD rates between 15-28% (Fischer et al., 2007; Landau et al., 2010; Schmidtke et al., 2008). MCI is often regarded as very mild AD or a transitional stage between normal aging and AD due to this increased rate of progression to symptomatic AD (Morris et al., 2001). MCI is often attributed to the same neuropathologic process as AD with one study reporting that 84% of participants with MCI at baseline were confirmed to meet criteria for AD upon autopsy (Morris et al., 2001). MCI is extremely heterogenous, and as a result different subtypes have been identified (Petersen, 2001). Amnestic MCI (aMCI) refers to individuals with impairment exclusively in the memory domain, whereas non-amnestic MCI (naMCI) refers to individuals with impairment in one or more non-memory cognitive domains (Fisher, 2007). aMCI has a greater reported progression rate to AD than naMCI (Fisher, 2007). Additionally, multi-domain aMCI refers to individuals who exhibit impairments in memory and in at least one other cognitive domain (Fisher, 2007).

1.1.3 Preclinical Alzheimer disease

Preclinical AD is the point at which a person is clinically normal but exhibits AD-related pathological changes, evinced by biomarkers of amyloid and tau and/or neurodegeneration of medial temporal regions such as the hippocampus (Dubois et al., 2016; Jack et al., 2018; Sperling et al., 2011). AD-related pathological changes can begin over a decade before the onset of clinically observable cognitive impairment (Jack et al., 2018; Sperling et al., 2011). Research suggests that amyloidosis in the brain is the first neuropathological change developed on the AD continuum (Jack et al., 2018). Deposition of amyloid may be associated with downstream pathological changes such as tauopathy and neurodegeneration, which ultimately result in cognitive decline (Jack et al., 2018).

The current literature has focused primarily on proxy measures of amyloid in identifying preclinical AD because amyloid changes occur first on the AD continuum (Buchhave et al., 2012; Jack et al., 2018). Preclinical AD can be measured *in vivo* using CSF measures of amyloid ($A\beta_{42}$ and $A\beta_{40}$), total-tau (t-tau), and phosphorylated-tau_{181} ($ptau_{181}$). CSF ratios of $A\beta_{42}/A\beta_{40}$ and $ptau_{181}/A\beta_{42}$ have been found to be strongly associated with PET amyloid (Alcolea et al., 2019; Schindler et al., 2018). Neurodegeneration of medial temporal structures can be measured with structural MRI (Frisoni et al., 2010).

1.2 Preclinical Alzheimer disease and cognition

Studies suggest that, although people with preclinical AD perform within expected limits (e.g., within 1.5 standard deviations of the age-corrected mean) on cognitive tasks, there are subtle observable cognitive changes associated with this stage (Sperling et al., 2011). Identifying the specific cognitive domain(s) most associated with early AD-related pathological change would be of great clinical and research benefit so that preclinical AD-specific measures may be developed. Previous work suggests that subtle changes in memory, attentional control, and spatial navigation are associated with concurrent preclinical status and with risk of clinical progression (Allison et al., 2016; Balota et al., 2010; Hedden et al., 2013; Hutchison et al., 2010; Langbaum et al., 2014; Levine et al., 2020).

1.2.1 Memory

Severe memory impairment is one of the cardinal clinical symptoms associated with symptomatic AD. Subtle changes in hippocampally-based episodic memory have been identified in preclinical AD cross-sectionally and as a predictor of clinical progression longitudinally (for review, see Collie & Maruff, 2000). A meta-analysis of PET studies reported that episodic memory was significantly associated with amyloid burden in clinically normal older adults (Hedden et al., 2013). The association between cross-sectional amyloid burden and performance

on episodic memory tasks was also observed in a meta-analysis combining across PET and CSF methodologies to define preclinical status (Baker et al., 2017). Additionally, this meta-analysis reported that amyloid burden predicts longitudinal decline in both episodic and semantic memory (Baker et al., 2017).

1.2.2 Attentional control

Attentional control refers to the ability to direct attention toward relevant information, while ignoring irrelevant information in the environment. Attentional control is thought to play an important role in the formation and retrieval of memory. It has been postulated that a break down in the attentional control network is directly associated with decline in memory ability (Balota & Duchek, 2015). Longitudinally, error rate on incongruent Stroop trials significantly predicted conversion to AD from clinical normality (Balota et al., 2010). Notably, in this study traditional measures of episodic memory did not predict conversion to AD (Balota et al., 2010). Reduced CSF $A\beta_{42}$ has been associated with poorer performance on a task highly dependent on attentional control and with longitudinal decline in task performance in clinically normal older adults (Millar et al., 2017). Another study of clinically normal older adults found that a composite score composed of three attentional control tasks was associated with concurrent CSF $A\beta_{42}$ level and that higher CSF t-tau level at baseline was associated with longitudinal decline in composite score (Aschenbrenner et al., 2015).

1.2.3 Spatial navigation

Spatial navigation represents a complex multi-componential process that is essential for everyday functioning and refers to the ability to locate specific goal locations within an environment (for reviews see Lester et al., 2017 and Moffat, 2009). Research suggests that there are two different strategies that can be implemented to navigate an environment: cognitive mapping and route learning. These strategies differ in the environmental information used to find

the goal location. Cognitive mapping refers to the process of creating a flexible internal representation of an environment based on the relative locations of landmarks within the environment. By contrast, route learning involves creating a fixed, action-based representation of an environment that is dependent on the navigator's perspective. Cognitive mapping is associated with the hippocampus, whereas route learning is associated with the caudate nucleus (Head & Isom, 2010; Iaria et al., 2003; O'Keefe & Dostrovsky, 1971; for review see Vlček & Laczó, 2014). Successful navigation often requires switching between these two navigation strategies by virtue of available cues or task demands.

Although there is a body of literature examining changes in both navigation strategies in symptomatic AD and mild cognitive impairment (Cushman et al., 2015; Hort et al., 2007; Weniger et al., 2011), there is less information available on navigation changes in preclinical AD. Work from our group demonstrated that performance on a cognitive mapping task was significantly associated with CSF $A\beta_{42}$, whereas performance on a route learning task was not (Allison et al., 2016). Another study from our group demonstrated that performance on the learning phase of a cognitive mapping task was associated with both CSF $A\beta_{42}$ and $ptau_{181}$; the retrieval phase of the cognitive mapping task was associated with CSF $A\beta_{42}$ and showed a trend toward association with CSF $ptau_{181}$ (Allison et al., 2019). Longitudinally, the learning phase of a cognitive mapping task was a significant predictor of clinical progression in clinically normal older adults (Levine et al., 2020). Additionally, Allison et al. (2016) found that cognitive mapping performance was more sensitive to concurrent preclinical status than route learning performance and traditional measures of episodic memory. This result was also observed longitudinally, as cognitive mapping performance was more sensitive to clinical progression in clinically normal older adults than traditional measure of episodic memory, whereas route

learning was not (Levine et al., 2020). The difference in sensitivity between the two navigation strategies may be attributable to the integral role of the hippocampus in cognitive mapping. Cognitive mapping ability may be particularly at risk in early AD due to the risk of hippocampal neurodegeneration at this stage (Apostolva et al., 2006; Jack et al., 1997; Mu & Gage, 2011).

1.2.4 Considerations

Many individual studies have provided evidence that neuropsychological and experimental measures of memory, attentional control, and spatial navigation are sensitive to preclinical AD. However, no study to date has directly compared these three domains in detecting concurrent preclinical status. Identifying the domain most sensitive to the earliest cognitive changes on the AD continuum will inform development of a preclinical AD-specific cognitive screening measure.

1.3 Self- and informant-reported cognitive impairment

Although neuropsychological and experimental tasks are non-invasive and less expensive than MRI, PET, and CSF measures, they can still be relatively time intensive. Questionnaires are potentially less time consuming (5-10 minutes) and can require fewer materials to administer than neuropsychological and experimental tasks. Additionally, questionnaires can be adjusted to ask both about current deficits and changes over time, whereas neuropsychological and experimental tasks would need to be administered multiple times to assess longitudinal change. Further, spatial navigation questionnaires did not exhibit learning effects, whereas experimental navigation measures displayed significant learning effects, which could impact longitudinal assessment (Allison et al., 2019). As such, questionnaires assessing difficulties and/or change in the domains sensitive to preclinical AD represent a potential screening tool for AD pathology.

Questionnaires have been developed and validated to detect symptomatic AD. The AD8 is one commonly used self- and informant-reported questionnaire to detect dementia that consists

of eight questions assessing a variety of cognitive functions including memory, orientation, and judgment (Galvin et al., 2005; Galvin et al., 2006; Galvin et al., 2007). However, less work has been done to develop questionnaires specific to preclinical AD. Developing an optimal screening method for preclinical AD that could be promulgated broadly would facilitate more efficient use of biologically based AD screening. Early identification of AD pathology may provide clinicians a better opportunity to offer therapeutic interventions targeting potential clinical progression.

It is currently unclear whether self- or informant-reported cognitive decline is more predictive of concurrent preclinical status and risk of clinical progression, as study results in clinically normal older adult populations have been inconsistent (Jessen et al., 2014). To provide the most comprehensive examination of subjective cognitive decline, I will examine both self- and informant-reported cognitive change in all three domains.

1.3.1 Memory

Self-reported memory complaints in clinically normal older adults with evidence of amyloid burden have been associated with episodic memory change and clinical progression (Buckley et al., 2016; Pietrzak et al., 2015). Self-reported memory complaints have also been linked to CSF $A\beta_{42}$ cross-sectionally (Cantero et al., 2016). In addition, clinically normal older adults with self-reported memory complaints tend to display reduced hippocampal volume compared to clinically normal older adults without memory complaints (Cantero et al., 2016; van der Flier et al., 2004).

Informant-reported memory complaints have also been associated with future dementia, suggesting that informant feedback may provide predictive information (Ronnlund et al., 2015). In one study, the combination of self- and informant-report significantly improved diagnostic accuracy for mild cognitive impairment, again suggesting that informant-report provides complimentary information to self-report methods (Yim et al., 2017).

Of note, methods for assessing subjective memory change have varied greatly across studies, ranging from brief screening questionnaires to semi-structured interviews. A standardized method of assessing subjective memory change would be of benefit to facilitate comparison across research and clinical samples. Specifically, this would allow for better ability to share data across research sites and assist clinicians in discussing longitudinal memory changes if the patient were to switch providers.

1.3.2 Attentional control

Several different self-reported measures of attentional control have been developed and validated (Buchanan et al., 2010; Derryberry & Reed, 2002; Wilson et al., 1996). These questionnaires have been used in a variety of dysexecutive syndromes such as attention-deficit hyperactive disorder. Notably, in one study self-reported attention differentiated between participants with symptomatic AD and older adult controls (Canali et al., 2007). However, to my knowledge, there is no published work on questionnaire measures of attentional control in the preclinical population.

1.3.3 Spatial navigation

In a study by Cerman and colleagues (2018), self-reported current spatial navigation ability significantly differentiated between healthy older adult controls and cognitively impaired groups (subjective-cognitive complaints, MCI, and AD). However, this questionnaire was unable to distinguish between cognitively impaired groups. Current self-reported spatial navigation ability has been associated with CSF $A\beta_{42}$ (Allison et al., 2018). However, baseline AD-biomarkers did not predict change in self-reported spatial navigation ability over time in clinically normal older adults (Levine et al., 2022). Questionnaires evaluating sense of direction, anxiety surrounding navigation, and confidence in spatial abilities were highly correlated with objective measures of route learning ability and memory of object location (Mitolo et al., 2015).

In addition, ability to learn a map was significantly correlated with confidence in spatial ability (Mitolo et al., 2015).

Our group previously developed reliable and valid self- and informant-report questionnaires assessing change in navigation ability (Allison et al., 2019). The self-reported questionnaire was significantly associated with concurrent CSF $A\beta_{42}$, whereas the informant-report was not. Additionally, the questionnaires did not show practice effects, whereas the learning phase of an objective cognitive mapping task did.

1.4 Factors that may influence self- and informant-reported cognition

While there is support for the reliability and validity of questionnaire-based measures of cognitive function, there are also data demonstrating that subjective cognitive ability is not always related to objective measures of cognitive ability. Self-reported memory measures have produced equivocal results in their association with objective measures (for review see Roberts et al., 2009 and for meta-analysis see Crumley et al., 2014). A meta-analysis observed a small, but significant, association between self-reported and objective memory in older adults (r=.062; Crumley et al., 2014). Self-report measures of attentional control, including the Attentional Control Scale (ACS) and the Webexec, have been inconsistently associated with objective attentional control measures (Buchanan et al., 2010; Buchanan, 2016; Judah et al., 2014; Williams et al., 2017). The spatial navigation questionnaires developed in our lab were not significantly associated with objective measures of spatial navigation ability (Allison et al., 2019). The authors hypothesized that this could be due to differences in constructs assessed by the questionnaires and the tasks: the questionnaires focused on subjective change over time, whereas the objective measures were cross-sectional assessments (Allison et al., 2019). Given the mixed association between questionnaire-based cognition and objective cognitive

performance, it is unclear if these methods are measuring the same aspects of cognitive functioning. Additionally, there may be heterogeneity in individuals' capability to accurately report cognitive ability. There is a body of literature suggesting that other factors such as personality and affective state may influence how individuals and their informants report cognitive ability.

1.4.1 Personality

Personality traits have been observed to predict self-reported cognitive complaints in both younger and older adult populations (Pearman, 2009; Snitz et al., 2015). Specifically, research has consistently demonstrated that neuroticism predicts increased cognitive complaints and conscientiousness predicts decreased cognitive complaints (Jessen et al., 2014; Pearman, 2009). These associations have been observed in the specific cognitive domains examined in this study. For example, self-reported memory complaints have been positively correlated with neuroticism and negatively correlated with conscientiousness (Merema et al., 2013; Steinberg et al., 2013). This pattern was also seen across three different self-report measures of attentional control (Attentional Control Scale, Webexec, and Dysexecutive Functioning Questionnaire), with more attentional control problems being positively correlated with neuroticism and negatively correlated with conscientiousness (Buchanan, 2016; Williams et al., 2017). The relationship between self-reported spatial navigation ability and personality has yet to be explored.

Additionally, neuroticism has been associated with objective memory, attention, and spatial navigation ability. In older adults, high neuroticism has been associated with both worse objective memory performance cross-sectionally and with longitudinal memory decline (Meier et al., 2010; Stephan et al., 2019). High neuroticism has also been associated with worse performance on attentional control tasks (Robinson et al., 2016; Szameitat et al., 2016). Lastly,

one study found that neuroticism was correlated with individual differences in time taken to develop a cognitive map (Burles et al., 2014).

Importantly, both high neuroticism and low conscientiousness have been consistently associated with early AD, AD-related biomarkers, and neurodegeneration. Cross-sectionally, self- and informant-reported higher neuroticism and lower consciousness has been associated with very mild AD (Duchek et al., 2007). Notably, informant-report of these personality factors added unique variance explained to the model beyond performance on a neuropsychological battery (Duchek et al., 2007). Longitudinally, lower conscientiousness predicted conversion from clinical normality to symptomatic AD as strongly as CSF $A\beta_{42}$ and tau (Duchek et al., 2019). Higher neuroticism has been associated with greater tauopathy as measured by tau-PET in clinically normal older adults (Schultz et al., 2019). Additionally, higher neuroticism has been associated with both smaller hippocampus and prefrontal cortex volumes (Jackson et al., 2011; Zufferey et al., 2017). Taken together, these results indicate that it is relevant to consider whether associations between self- or informant-reported cognitive change and preclinical AD is independent of personality.

Although self-reported cognitive decline has been consistently associated with personality traits, personality is not currently used to screen for preclinical AD (Jessen et al., 2014). Interestingly, one study reported that neuroticism moderated the association between self-reported memory functioning and amyloid burden in that participants with high neuroticism demonstrated a significant association between poor self-reported memory and greater amyloid pathology (Snitz et al., 2015). Thus, neuroticism in conjunction with self-reported cognitive decline may be particularly predictive of preclinical AD. In contrast, high conscientiousness may be protective against associations of perceived cognitive change and AD biomarkers. This

suggests that the personality traits of neuroticism and conscientiousness may contribute interactive information with cognitive screening measures in identifying preclinical AD.

1.4.2 Affective state

Depression and anxiety have been associated with self-reported and objective measures of cognitive ability across domains. Additionally, informant depression and anxiety has been found to impact informant-reported dementia screening (Jorm, 2004). Of the cognitive domains of interest, self-reported memory has been the most examined and has been consistently associated with depression and anxiety (for review, see Reid & Maclullich, 2006). One study reported that self-reported memory was correlated with both objective memory performance and self-reported depressive symptoms, with older adults with self-reported memory complaints reporting more depressive symptoms than older adults without self-reported memory complaints (Zandi et al., 2004). Balash et al. (2012) found that both depression and anxiety were significantly correlated with self-reported memory complaints. Notably, one study found that self-reported prospective memory and objective prospective memory were highly correlated in participants with low levels of memory complaints, whereas participants with high levels of complaints did not show this correlation (Zeintl et al., 2006). Instead in the high complaint group, self-reported prospective memory was associated with depressive symptomatology (Zeintl et al., 2006). A similar pattern has been seen in attentional control, with both depression and anxiety being significant predictors of the ACS in both younger and older adult samples (DeVito et al., 2019; Olafsson et al., 2011; Quigley et al., 2017). Regarding spatial navigation, one study found that depressed patients performed more poorly on a cognitive mapping task compared to healthy controls (Gould et al., 2007). Another study found that anxiety, but not depression, was a significant predictor of self-reported spatial navigation complaints (Sheardova et al., 2015).

There is also evidence to support a relationship between depression and hippocampal volume, suggesting that depression may be a risk factor for cognitive decline (Dotson et al., 2009; Sawyer et al., 2011). Additionally, preclinical AD has been associated with increased risk of developing depression (Harrington et al., 2016). Anxiety has been associated with neurodegeneration and functional impairment of the hippocampus and prefrontal cortex, suggesting that anxiety may also be a risk factor for dementia (for review see Mah et al., 2016). Anxiety has been found to moderate the relationship between $A\beta_{42}$ and cognitive decline, such that high anxiety in preclinical AD is associated with more rapid clinical progression (Peitrzak et al., 2014; Pietrzak et al., 2015). Given the association between affect and AD-related pathology and neurodegeneration, it is relevant to consider whether associations between self- or informant-reported cognitive change and preclinical AD is independent of affective state.

1.5 Rationale and specific aims

In 2021 an estimated 6.2 million people in the United States had Alzheimer disease (AD) and the number is expected to rise to 12.7 million by 2050 (Alzheimer's Disease Facts and Figures, 2021). As such, there is a need to develop a widely accessible screening measure that is sensitive to the earliest signs of AD. Several different cognitive domains have been identified as particularly sensitive to detecting the earliest cognitive changes in preclinical AD. Specifically, neuropsychological measures of memory and experimental measures of attentional control and spatial navigation have been sensitive to both current preclinical status and longitudinal clinical progression (Allison et al., 2016; Balota et al. 2010; Hedden et al., 2013; Hutchison et al., 2010; Langbaum et al., 2014; Levine et al., 2020). However, it is currently unclear which domain is most sensitive to preclinical AD, as screening measures of these three cognitive constructs have not been directly compared in the preclinical population. The overall goal of the dissertation was

to directly compare self- and informant-report questionnaires of these three cognitive domains to identify which is most sensitive to preclinical AD.

Two independent samples were used to address the originally proposed, primary, aims of this study. Participants from the Washington University Volunteer for Health (VFH) program were recruited to assess the internal consistency and factor structure of the questionnaires used in this study. Participants from the Washington University Knight Alzheimer's Disease Research Center (ADRC) were recruited to assess the diagnostic accuracy of these questionnaires in predicting preclinical AD. Preexisting CSF $A\beta_{42}$ and $A\beta_{40}$, hippocampal volume, and relevant clinical data were obtained through the ADRC database. All participants completed the questionnaires remotely using RedCap. Participants were asked to identify someone who knew them well and interacted with them regularly to act as an "informant." Participants and informants were instructed to complete the questionnaires independently from each other.

Due to limited recruitment from the ADRC for the originally proposed study, the desired sample size could not be reached during the allotted recruitment time. Preliminary results from the ADRC sample will be presented. However, these analyses should be interpreted with caution as they are severely underpowered based on a priori power analyses (N=136 necessary for power of .80). As a result, I proposed an addendum to the dissertation wherein archival data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database was used to answer research questions similar to the originally proposed dissertation using the memory, divided attention, and visuospatial subsections from the Everyday Cognition Scale (ECog). Data used to address the addendum aims were obtained from the ADNI database (adni.loni.use.edu). The ADNI was established in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner. The primary goal of ADNI is to test whether serial MRI, PET, other biological markers,

and clinical and neuropsychological assessment can be combined to measure the progression of AD. For further information, see www.adni-info.org.

Primary and addendum aim 1: Refine self and informant questionnaires of memory, attentional control, and spatial navigation change and assess psychometric properties of the refined questionnaires

Primary aim 1.1: Refine memory and attentional control measures

First, existing self-report questionnaires with established reliability and validity were adapted to assess change in the cognitive domain over the past several years, with the goal of measuring subtle change that may be associated with preclinical AD (MAC-Q: Crook et al., 1992; and ACS: Derryberry & Reed, 2002). Additional items were added to the MAC-Q to more broadly measure change in memory. A reliable and valid shortened version of the Attentional Control Scale (ACS-Short) was used to ensure the measure was time-efficient to administer (DeVito et al., 2019; Judah et al., 2014). In addition, the memory and attentional control questionnaires were adjusted to also have informant-report versions.

Primary aim 1.2: Refine spatial navigation measure

The spatial navigation self- and informant-report questionnaires previously developed in our lab displayed good reliability (Allison et al., 2019). However, both questionnaires had high Cronbach's alphas, suggesting potential redundancy in the questions (Self-report Cronbach's alpha=.965; Informant-report Cronbach's alpha=.957). In addition, the questionnaires were longer than the memory and attention questionnaires (20 questions versus 6 and 13 questions, respectively). As such, the number of items on the questionnaires was reduced to make them more efficient.

Primary aim 1.3 and addendum aim 1: Assess the reliability and validity of refined questionnaires using the VFH sample and ECog subsections using the ADNI sample

Refined versions of the questionnaires were administered to older adults and their informants recruited through VFH. ECog subsection data was obtained from the ADNI database. Internal consistency of each questionnaire was assessed. The factor structure of the self- and informant-report questionnaires was examined using confirmatory factor analyses. In the ADNI cohort, validity was further examined using correlations of self-reported subsections with performance on neuropsychological measures of the same or similar domain (e.g., episodic memory, executive function, and visuospatial abilities).

Hypothesis. I hypothesize that both the self and informant factor models will support a three-factor structure in that each questionnaire will represent a separate factor. This would suggest that the questionnaires are measuring three separable cognitive functions.

Primary and addendum aim 2: Compare the diagnostic accuracy of self- and informant-reported memory, attentional control, and spatial navigation in predicting preclinical AD

Receiver operating characteristic (ROC) analyses were used to assess and compare the diagnostic accuracy of all six questionnaires in the ADRC sample and ECog subsections in the ADNI sample.

Hypotheses. Based on previous studies of objective ability, I expect that the navigation and attention questionnaires will be more sensitive to preclinical status than the memory questionnaire (Allison et al., 2016; Allison et al., 2019; Levine et al., 2020; Balota et al., 2010; Aschenbrenner et al., 2015). Our work suggests that spatial navigation measures are more sensitive to concurrent preclinical status and clinical progression than traditional measures of episodic memory (Allison et al., 2016; Levine et al., 2020). Additionally, Balota and colleagues

(2010) reported that incongruent Stroop errors predicted conversion to AD from cognitive normality, whereas traditional measures of episodic memory did not. Cross-sectionally, PET amyloid was associated with baseline attentional control, but not baseline episodic memory (Aschenbrenner et al., 2015). To my knowledge, there have been no studies directly comparing the predictive ability of spatial navigation and attentional control in predicting preclinical AD or conversion to AD. Therefore, there is insufficient data to formulate a hypothesis regarding the comparative performance of spatial navigation and attentional control.

I hypothesize that self-report measures will provide greater diagnostic accuracy than informant-report measures. Secondarily, I anticipate that the inclusion of both self- and informant-report measures will be significantly more sensitive than self-report alone. Previous work has found a significant disparity between self- and informant-report in regard to cognitive change or ability is observed between dementia patients and their informants, but not between patients with mild cognitive impairment and their informants (Galvin et al., 2007; Farias et al., 2005). Thus, the clinically normal population may be at low risk of under-reporting symptomatology. However, one limitation of informant-report is that some of these behaviors may be unlikely to be observed by informants. Previous work in the lab found that the self-reported navigation questionnaire outperformed the informant questionnaire, potentially due to difficulty observing some navigation behaviors (Allison et al., 2019). We hope that we can develop items that address observable behaviors while completing study aim 1. However, I still expect that self-report will be more sensitive because informants do not have the opportunity to observe the participant's behavior constantly and individuals in the preclinical AD stage may have sufficient insight/awareness to accurately report symptoms. Research suggests that informant reports provide additional, unique informant to that provided by self-report (Yim et al.,

2017). For this reason, I also hypothesize that including both forms of information will better predict preclinical status than either individually.

Primary and addendum aim 3: Examine the ability of questionnaires to predict preclinical AD when controlling for personality traits or current affective state

Aim 3.1: Examine the ability of questionnaires to predict preclinical AD controlling for neuroticism or conscientiousness

Hierarchical linear regression was used to examine whether the refined questionnaires continued to predict preclinical AD when controlling for either neuroticism or conscientiousness in the ADRC sample. Neuroticism and conscientiousness were considered in separate models due to the limited sample available to avoid overfitting the models.

Hypotheses. I hypothesize that higher neuroticism and lower conscientiousness will predict preclinical AD status, consistent with previous literature. Additionally, I hypothesize that higher neuroticism and lower conscientiousness will be associated with increased self-reported complaints regardless of domain. I also hypothesize that all questionnaires will continue to predict preclinical AD status when controlling for neuroticism or conscientiousness.

Previous literature suggests that there is an interaction between neuroticism and subjective memory when predicting preclinical AD status (Snitz et al., 2015). This may be attributable to associations of neuroticism with memory and hippocampal atrophy (Zufferey et al., 2017; Collie & Maruff, 2000). I hypothesize that I will observe an interaction between neuroticism and all three cognitive domains when predicting preclinical status. Cognitive mapping and memory are in part dependent on the hippocampus and attentional control is related to prefrontal circuitry, and both of these regions have been associated with neuroticism (Head & Isom, 2010; Jackson et al., 2011; Zufferey et al., 2017).

Aim 3.2: Examine the ability of questionnaires to predict preclinical AD controlling for depression or anxiety symptoms of the participant or informant

Hierarchical linear regression was used to examine whether the refined questionnaires in the ADRC sample continued to predict preclinical AD when controlling for participant or informant depression or anxiety symptoms. Depressive and anxiety symptoms were considered in separate models due to the limited sample available to avoid overfitting the models. In the ADNI sample, hierarchical linear regression was used to examine whether the ECog subsections continued to predict preclinical AD when controlling for participant depressive symptoms.

Hypotheses. I hypothesize that all questionnaires will continue to predict preclinical AD status when controlling for depression or anxiety symptoms. However, I predict that the spatial navigation and attentional control questionnaires will provide more additional information than the MAC-Q, as the MAC-Q has been found to be highly associated with both depression and anxiety (Reid et al., 2012).

Primary and addendum aim 4: Compare the refined questionnaires to an established screening questionnaire for early-stage dementia or performance on neuropsychological measure of the same or similar cognitive domain in predicting preclinical AD

In the ADRC sample, ROC analyses were used to compare the diagnostic accuracy of the refined questionnaires with an established screening measure for very mild symptomatic AD (AD8; Galvin et al., 2005; Galvin et al., 2007). In the ADNI sample, ROC analyses were used to compare the diagnostic accuracy of self-reported cognitive change and objective performance within the same or similar cognitive domain (memory, executive function, and visuospatial) in predicting preclinical AD.

Hypothesis. I hypothesize that the spatial navigation questionnaires will be more sensitive to preclinical AD than the AD8 because the AD8 was developed to detect early dementia rather than the subtler cognitive deficits associated with the preclinical AD. Although neither the MAC-Q nor the ACS-Short were developed specifically for preclinical AD, I hypothesize that both of these measures will outperform the AD8 in detecting preclinical status because these questionnaires target specific cognitive functions at risk in the preclinical stage.

Chapter 2: Method

2.1 Recruitment and screening procedures

2.1.1 Primary aims (VFH and ADRC samples)

Participants were recruited from VFH and the ADRC at Washington University (Table 1). All VFH participants were not demented and free of neurodegenerative conditions (e.g., Parkinson's disease, Huntington's disease, and multiple sclerosis) based on self-report. All ADRC participants were clinically normal at baseline (CDR=0; Morris, 1991), were screened for major neurological conditions (e.g., Parkinson's, Huntington's, stroke, and seizures), and had CSF data collected within four years of completing the questionnaires. All participants identified someone who knew them well and interacted with them regularly to act as an "informant." All participants and informants were compensated with a $10 Amazon gift card for their participation. Additionally, participants and informants were entered into separate raffles to win an additional $100 Amazon gift card.

Table 1. VFH and ADRC samples

	VFH Participants	*VFH Informants*	*ADRC Participants*	*ADRC Informants*
N	125	104	32	23
Gender (m/f)	41/84	35/69	13/19	8/15
Age (years) (mean (SD))	68 (6.20)	59.93 (14.56)	73.19 (7.48)	69.78 (8.07)
Age range (years)	60-83	22-82	61-89	44-81
Education (years) (mean (SD))	16.31 (2.53)	16.01 (2.36)	16.59 (2.58)	16.44 (2.02)
Education range (years)	12-22	12-20	12-20	12-20
Informant Characteristics				
Length known participant (years) (mean (SD)		42.68 (15.40)		46.30 (13.89)
Length known participant (years) (range)		4-77		21-73
Witnesses participant navigating (N)				
Once a year or less		2		0
More than yearly, but less than monthly		12		1
Monthly		11		1
More than monthly, but less than weekly		10		2
Weekly		9		0
More than weekly, but less than daily		20		3
Daily		39		15

Note. One informant in the VFH sample and one informant in the ADRC sample did not provide information regarding number of times they witnessed the participant navigate.

Table 2. ADRC sample by biomarker status

	CSF $A\beta_{42}$ /$A\beta_{40}$ Normal	*Preclinical CSF $A\beta_{42}$ /$A\beta_{40}$*	*Hippocampal Normal*	*Preclinical Hippocampus*
N	22	10	16	9
Gender (m/f)	8/14	5/5	7/9	3/6
Age (years) (mean (SD))	71.64 (7.31) #	76.60 (7.01) #	69.94 (7.29)*	78.67 (5.50)*
Age range (years)	61-85	68-89	61-89	69-85
Education (years) (mean (SD))	17.14 (2.46) #	15.40 (2.55) #	16.13 (2.28)	16.67 (3.28)
Education range (years)	12-20	12-20	12-20	12-20
CSF $A\beta_{42}$ /$A\beta_{40}$ ratio (mean (SD))	.09 (.01)*	.05 (.01)*		
Hippocampus (cm^3) (mean (SD))			8174.76 (623.21)*	6982.24 (482.43)*

* indicates a significant difference between groups (p<.05); # indicates a trend toward a significant difference between groups (p<.1)

2.1.2 Addendum aims (ADNI sample)

ADNI participants included in this study were clinically normal (CDR=0; Morris, 1991), completed the Everyday Cognition Scale (ECog), and had CSF data collected within two years of completing the ECog. This provided a sample of 371 participants (Table 2). Majority of participants (n=366) also had a study partner complete the ECog on their behalf; however, information about the informant and their relationship to the participant was unavailable.

Table 3. ADNI sample

	Total Sample	*Biomarker Normal*	*Preclinical*
N	371	211	160
Gender (m/f)	154/217	94/117	60/100
Age (years) (mean (SD))*	73.03 (6.76)	71.34 (6.28)	75.25 (6.75)
Age range (years)	56-93	56-93	56-92
Education (years) (mean (SD))#	16.67 (2.39)	16.86 (2.37)	16.43 (2.40)
Education range (years)	10-20	10-20	6-20

Preclinical/biomarker normal distinction made with CSF $ptau_{181}/A\beta_{42}$ ratio; * indicates a significant difference between groups (p<.05); # indicates a trend toward a significant difference between groups (p<.1)

2.2 Biomarker collection and processing

2.2.1 CSF

CSF was collected by the ADRC as previously described (Fagan et al., 2006). Originally, we had proposed to use CSF samples collected within two years of questionnaire completion; however, due to recruitment limitations within the ADRC, this was extended to within four years of questionnaire completion to maximize our sample size. CSF samples were analyzed using chemiluminescent enzyme immunoassay using a fully automated platform (LUMIPULSE

G1200, Fujirebio, Malvern, PA) according to manufacturer's specifications for $A\beta_{40}$ and $A\beta_{42}$. Values for CSF $A\beta_{42}$ above 1700 pg/mL have not been validated and were not used for clinical decision making. The ratio between $A\beta_{42}/A\beta_{40}$ was used to determine preclinical status because it has been found to best correspond with PET amyloid imaging in LUMIPULSE samples (Alcolea et al., 2019).

CSF collected by ADNI were analyzed using Elecsys immunoassays, following the Roche Study Protocol at the UPenn/ADNI Biomarker Laboratory as previously described (Bittner et al., 2016). CSF data was included if collected within two years of completing the ECog. Values for CSF $A\beta_{42}$ above 1700 pg/mL and $ptau_{181}$ below 200 pg/mL have not been validated and were not used for clinical decision making. CSF $ptau_{181}/A\beta_{42}$ ratio was used to define preclinical AD because this measure has been found to be highly associated with PET amyloid in Elecsys samples (Schindler et al., 2018).

2.2.2 Structural MRI

MRI scans were acquired by the ADRC using Siemens 3T scanners (TIM Trio: TE=3ms, TR=2400ms, TI=1000ms, FA=8°, 256x256 mm acquisition matrix, 1x1x1mm voxels; BioGraph scanner: TE=2.95ms, TR=2300ms, TI=900ms, FA=9°, 240x256 mm acquisition matrix, 1x1x1.2mm voxels). ADRC MRI data was used if collected within four years of completing the questionnaires. ADNI 3T MRI acquisition and pre-processing methods have been previously described (http://adni-info.org). ADNI MRI data was used if collected within two years of completing the questionnaires.

The hippocampus was the region-of-interest for the current study. The FreeSurfer image analysis suite was used for image processing and delineation of the hippocampus (Fischl et al., 2002). FreeSurfer implements an automated probabilistic labeling procedure where individual voxels in an image are assigned to a neuroanatomical label based on data from a manually

labeled training set. Volumetric data obtained through this procedure are highly correlated with manually generated volumes (Desikan et al., 2006; Fischl et al., 2002). Volumes were summed across hemispheres and estimated intracranial volume was used to adjust volumes for body size differences using an analysis of covariance approach (Buckner et al., 2004).

2.3 Cognitive questionnaires

2.3.1 Memory questionnaire: MAC-Q (ADRC)

The MAC-Q is a six-item self-report questionnaire that assesses different aspects of episodic memory (Appendix I.V; Crook et al., 1992). This questionnaire asks about change in memory ability since high school or college and each item is rated on a five-point Likert scale (much better than now, somewhat better than now, about the same, somewhat poorer now, much poorer than now). The MAC-Q has demonstrated strong concurrent validity through strong associations with an independent self-report measure of memory complaints and objective memory performance (Crook et al., 1992). Additionally, the MAC-Q has demonstrated satisfactory internal consistency and test-retest reliability (Crook et al., 1992). The MAC-Q was administered to all participants and informants. Items were averaged to create a total score to include participants who skipped individual items and maximize sample size.

2.3.2 Attentional control questionnaire: Attention Control Scale-Short Form (ADRC)

The Attentional Control Scale (ACS) is a 20-item self-report questionnaire assessing current difficulty with attentional control abilities (Appendix I.VIII, Derryberry & Reed, 2002). Each item is rated on a 4-point Likert scale indicating frequency of events (almost never, sometimes, often, and always); notably, a specific timeframe is not specified. The ACS has displayed good internal consistency and validity assessed through factor analytic frameworks (Derryberry & Reed, 2002; DeVito et al., 2019). A shortened (ACS-Short) 13-item version has demonstrated similar reliability and validity, including in older adult populations (Judah at al.,

2013; DeVito et al., 2019). As a result, the more time-efficient ACS-Short was used. The ACS-Short was administered to all participants and informants. Items were averaged to create a total score to include participants who skipped individual items and maximize sample size.

2.3.3 Spatial navigation questionnaire (ADRC)

The self- and informant-reported questionnaires were previously developed in our lab and assess change in spatial navigation ability over the past several years using a seven-point Likert scale ranging from strongly disagree to strongly agree with higher scores representing greater change (Appendix I.I and I.III, Allison et al., 2019). The questionnaires demonstrated good internal consistency and test-retest reliability, as well as good convergent and divergent validity examined using a factor analytic framework. Importantly, the self-reported version was a significant predictor of CSF biomarker burden.

2.3.4 Everyday Cognition Scale (ADNI)

The Everyday Cognition (ECog) scale is a self- or informant-reported assessment of multiple cognitive domains that focuses on changes in aspects of cognition important for daily functioning (Appendix I.XI and I.XIII, Farias et al., 2008). The ECog assesses change in cognitive ability over the past ten years on a four-point Likert scale with higher scores representing greater change. The ECog has demonstrated good test-retest reliability (Farias et al., 2008). Additionally, the ECog has been associated with other independent measures of everyday function and global cognition (convergent validity; Farias et al., 2008). Domain-specific items from the memory (eight items), divided attention (four items), and visuospatial (seven items), which assesses spatial navigation, subsections were used for the purposes of this study. Items were averaged within each domain to maximize the number of participants included in the sample.

2.4 Personality questionnaire: Mini International Personality Item Pool (ADRC)

The Mini International Personality Item Pool – Five Factor Model (Mini-IPIP) assesses the Big Five personality factors of neuroticism, extraversion, openness, agreeableness, and conscientiousness (John & Srivastava, 1999). The Mini-IPIP has demonstrated good psychometric properties, specifically convergent, discriminant, and criterion validity with other measures of personality (Donnellan et al., 2006). Participants answered only items assessing neuroticism and conscientiousness from Mini-IPIP because the literature suggests that these traits are related to AD, whereas there is not consistent research to support associations between and AD and extraversion, openness, and agreeableness (for review, see Robins Wahlin & Byrne, 2010; for meta-analysis, see Low et al., 2013).

2.5 Affective measures

2.5.1 Center for Epidemiologic Studies Depression Scale Short Form (ADRC)

The short form of the Center for Epidemiologic Studies Depression scale (CES-D) is a 10-item self-report questionnaire used to assess depressive symptomatology in older adults (Andresen et al., 1994). The CES-D has demonstrated good test-retest reliability and strong inter-item correlations (Andresen et al., 1994). Additionally, the CES-D demonstrated strong diagnostic accuracy in identifying major depression diagnosed with a semi-structured interview (Beekman et al., 1997). The CES-D was collected in the ADRC sample at the same time as the memory, attention, and spatial navigation questionnaires for both participants and informants.

2.5.2 Geriatric Anxiety Scale Short Form (ADRC)

The Geriatric Anxiety Scale Short Form (GAS) is a 10-item self-report questionnaire used to assess anxiety symptoms in older adults (Mueller et al., 2015). The GAS has demonstrated good internal consistency and diagnostic accuracy in identifying older adults with generalized anxiety disorder (Carlucci et al., 2021). The GAS was collected in the ADRC sample

at the same time as the memory, attention, and spatial navigation questionnaires for both participants and informants.

2.5.3 Geriatric Depression Scale Short Form (ADNI)

The Geriatric Depression Scale short form (GDS) is a 15-item self-report questionnaire used to assess depressive symptomatology in older adults. The GDS has demonstrated good internal consistency and has been correlated with other self-reported Depression scales (Sheikh & Yesavage, 1986; Herrmann et al., 1996; Lesher & Berryhill, 1994). Importantly, the GDS has been found to be sensitive to depression in older adults with dementia (Sheikh & Yesavage, 1986). The GDS was collected in the ADNI participant sample and included in analyses if collected within thirty days of the ECog (n=197, m=18.95 days, sd=10.13 days, range=0-29 days).

2.6 Self- and informant-report dementia screening: AD8 (ADRC)

The AD8 is a commonly used questionnaire to assess cognitive change across several domains (memory, orientation, and judgment) and has self- and informant-report versions. The AD8 has been established as a non-invasive, cost-effective, and time efficient measure of very early symptomatic AD. Both versions have demonstrated strong internal consistency and appropriate diagnostic accuracy in identifying cognitive impairment (Galvin et al., 2005; Galvin et al., 2007). The two versions have been found to be highly correlated (Galvin et al., 2007). The AD8 was collected in both participant and informant samples.

2.7 Neuropsychological assessment (ADNI)

In the ADNI sample, memory, executive function, and visuospatial composite scores were previously derived and validated (Gibbons et al., 2012; Crane et al., 2012; Choi et al., 2020). The memory composite comprised Rey Auditory Verbal Learning Test, AD Assessment

Schedule-Cognition list learning task, Mini-Mental State Examination word recall, and Logical Memory test (Crane et al., 2012). The executive function composite comprised WAIS-R Digit Symbol Substitution, Digit Span Backwards, Trails A and B, Category Fluency, and Clock Drawing (Gibbons et al., 2012). Executive function and attentional control have been highly correlated and for the purposes of this study, executive function will be used as a proxy of attentional control and the terms will be used interchangeably (McCabe et al., 2010). The visuospatial composite comprised a five-point clock copy, MMSE interlocking pentagon copy, and ADAS-Cog constructional praxis (Choi et al., 2020).

2.8 Planned analyses

2.8.1 Preclinical Alzheimer disease classification

Biomarkers of neuropathologic change and neurodegeneration were used to define preclinical AD. Preclinical AD in the ADRC sample was defined using $A\beta_{42}/A\beta_{40}$ ratio with a cutoff of <.0673 to identify biomarker positivity (Table 2). Preclinical AD in the ADNI sample was defined using a CSF $ptau_{181}/A\beta_{42}$ ratio with a >0.0198 cutoff to identify preclinical status (Table 3). Different CSF ratios were used to measure biomarker burden because the ADRC and ADNI used different CSF assays (LUMIPULSE and Elecsys, respectively). The literature recommends the use of different CSF ratios based on the assay used (Alcolea et al., 2019; Schindler et al., 2018). When using hierarchical regression analyses, CSF ratio was used as a continuous variable. Using the ratio as a continuous variable provides more power to detect interaction effects than if the dichotomous variable indicating preclinical status was used. Because there is not an established cutoff volume to indicate preclinical status, when using hippocampal volume as a dichotomous marker of preclinical status, the participants with hippocampal volumes in the lowest tertile of the total sample were considered to be biomarker positive. In the ADNI sample, the highest tertile of the total sample was considered to be

biomarker negative. To maximize the ADRC sample, the higher two tertiles was considered to be biomarker negative; nine participants were identified as being in the preclinical stage.

2.8.2 Primary aim 1.2: Refine spatial navigation questionnaire

The original spatial navigation questionnaires had high Cronbach's alphas, suggesting potential redundancy in the questions (Self-report Cronbach's alpha=.965; Informant-report Cronbach's alpha=.957). As such, previously collected data from these questionnaires was used to determine which items would be appropriate to omit for the purposes of this study (Allison et al., 2019).

Data previously collected for questionnaire development (self-report n=91; informant-report n=81) were used to make decisions regarding adapting the questionnaires for this study (Allison et al., 2019). Participants were recruited from the Washington University VFH program and ADRC. VFH participants were screened for dementia using a cut-off score of <5 on the Short Blessed Test (Katzman et al., 1983). All ADRC participants were clinically normal based on the CDR (CDR=0; Morris, 1991). All participants completed the self-report navigation questionnaire in the lab and then completed five objective measures of spatial navigation. CSF data within the last two and half years and MRI data within the last three years were available for all ADRC participants (n=30). VFH and ADRC participants provided a person who knew them well and interacted with them regularly to complete the informant-reported spatial navigation questionnaire.

A factor analytic framework was used to assess which items may be appropriate to omit in the revised questionnaire using the Mplus program (Muthén & Muthén, 1998-2017). The self-report and informant-report questionnaires were examined independently, wherein questionnaire items, objective navigation measures, and CSF $ptau_{181}/A\beta_{42}$ ratio were assumed to belong to the same factor. Then, the factor loadings were considered; if an item had a low loading and did not

have theoretical justification (e.g., is not related to cognitive mapping ability) for inclusion, it was removed from the questionnaire. However, secondary analyses (linear regression, Cronbach's alpha, item-scale correlation, inter-item correlation, and content analysis) were planned in the situation where these models were unable to be interpreted or provided limited information due to weak correlations between the measures.

2.8.3 Primary aim 1.3 and addendum aim 1: Assess reliability and validity of questionnaires

Internal consistency of each questionnaire was assessed using Cronbach's alpha. Confirmatory factor analyses assuming three-factor and one-factor models separately for the self- and informant-report questionnaires were used to examine validity. Model fit was evaluated using the comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Using previously published criteria, good fit was defined by CFI>.95, RMSEA<.06, and SRMR<.06 (Hu & Bentler, 1999). Acceptable fit was defined by CFI>.90, RMSEA<.08, and SRMR<.08 (Brown, 2006; Brown & Cudeck, 1993).

Power: Using a Monte Carlo simulation in the Mplus program (Muthén & Muthén, 1998-2017), we estimated that a sample of 122 participants would yield 80% power for detecting the hypothesized three-factor structure. Output was interpreted following parameters put forth by Muthén and Muthén (2002). The simulation was constructed using previously reported factor loadings from the MAC-Q and ACS-Short and factor loadings calculated from previously collected spatial navigation questionnaire data (Russell & Pachana, 2004; DeVito et al., 2019; Allison et al., 2019). I was unable to estimate power for informant-report questionnaires because factor loadings were unavailable for the informant-reported MAC-Q and ACS-Short. Additionally, factors loadings for self- and informant-report ECog subsections were unavailable, so a separate power analysis for these questionnaires was unable to be conducted.

2.8.4 Primary and addendum aim 2: Compare diagnostic accuracy of questionnaires

ROC analyses were conducted to assess and compare the diagnostic accuracy in identifying concurrent preclinical AD across all of the refined questionnaires or ECog subsections. The goal of these analyses was to identify if a particular measure outperforms the others. Using previously published criteria, AUC values .70-.80 were considered to provide acceptable diagnostic accuracy, .80-.90 excellent diagnostic accuracy, and >.90 outstanding diagnostic accuracy (Mandrekar, 2010). The DeLong, DeLong, and Clark-Pearson (1998) method was used to compare areas under the curve and to identify significant differences.

Power: Estimated samples sizes to obtain 80% power were obtained by using power calculations put forth by Hajian-Tilaki (2014) and previously reported area under the curve (AUC) data for each questionnaire. Based on the AUC value for the self-reported spatial navigation questionnaire predicting current preclinical status and the AUC value for the self-reported MAC-Q predicting clinical progression from clinical normality, an estimated sample size of 136 participants (68 preclinical) will be used to compare their diagnostic accuracy (Allison et al., 2019; Glodzik-Sobanska et al., 2007). Using the same methodology, approximately the same sample size was identified to be needed to compare the self- and informant-report navigation questionnaires (Allison et al., 2019). AUC information was unavailable for the ACS-Short; therefore, no power estimation could be made. The MAC-Q and ACS-Short have not previously been adapted for informant-report; therefore, no power estimation could be made. AUC information for the ECogs subsections were not available; therefore, no power estimation could be made.

2.8.5 Primary and addendum aim 3: Examine impact of personality and affective factors on the association of questionnaires and preclinical AD in the ADRC sample and the impact of depressive symptoms on the association of questionnaires and preclinical AD in the ADNI sample

In the ADRC sample, a three-step hierarchical linear regression was used to examine the unique predictive information provided by the questionnaires when controlling for other predictors of preclinical AD (neuroticism, conscientiousness, depressive symptoms, or anxiety symptoms). There were separate models for memory, attention, and spatial navigation. The dependent variable in the models was biomarker burden (e.g., CSF $A\beta_{42}/A\beta_{40}$ ratio or hippocampal volume). In step one, demographic variables of age, gender, and education were entered as covariates. In step two, the questionnaire of interest was added to the model. In step three, the personality or affect variable was added to the model.

In the ADNI sample, a four-step hierarchical linear regression was used to examine the unique predictive information provided by the ECog subsections when controlling for depressive symptoms. There were separate models for memory, attention, and spatial navigation. The dependent variable in the models was biomarker burden (e.g., CSF $ptau_{181}/A\beta_{42}$ ratio or hippocampal volume). In step one, demographic variables of age, gender, and education were entered as covariates. In step two, the questionnaire of interest was added to the model. In step three, depressive symptoms were added to the model. Finally, the interaction between the questionnaire and depressive symptoms was added to the model in step 4.

In both samples, hierarchical linear regression was also used to compare the predictive ability of memory, attention, and spatial navigation questionnaires when controlling for personality or affect. In step one, demographic variables of age, gender, and education were entered as covariates. In step two, all self- or informant-report questionnaires were added to the model, and in step 3 the personality or affective variable of interest was added to the model.

Variables were z-scored increase the ease of interpretation and comparison of beta values. Standardized beta coefficients and incremental R^2 were used to compare nested models.

Power: Allison et al. (2019) did not examine the effect of depressive symptoms on self- and informant-report. Using the same statistical model as Allison et al. (2019) to examine the association between CSF $ptau_{181}/A\beta_{42}$ ratio and self-reported spatial navigation, the GDS score closest to the time of study completion (within two years) was added as a covariate if available through the ADRC database. A bootstrapped power analysis randomly sampling with replacement from the dataset 1000 times, indicated that 136 participants would provide 80% power. Anxiety and personality data were unavailable, therefore power for these analyses could not be completed.

2.8.6 Primary and addendum aim 4: Compare diagnostic accuracy of questionnaires to previously established measures of cognition

In the ADRC sample, ROC analyses were conducted to compare the diagnostic accuracy of the refined questionnaires and the AD8, a previously established self- and informant-questionnaire for very early dementia. In the ADNI sample, ROC analyses were conducted to compare the diagnostic accuracy of the ECog subsections and their corresponding neuropsychological composite score. Using previously published criteria, AUC values .70-.80 were considered to provide acceptable diagnostic accuracy, .80-.90 excellent diagnostic accuracy, and >.90 outstanding diagnostic accuracy (Mandrekar, 2010). The DeLong, DeLong, and Clark-Pearson (1998) method will be used to compare areas under the curve and to identify significant differences.

Power: The AD8 was created to identify people with dementia and has not been examined in the preclinical population. AUC values previously published for the AD8 are in reference to their ability to identify dementia from non-dementia. Therefore, it would not be

appropriate to use these AUC values in a power analysis to estimate the needed size of a preclinical AD sample. Additionally, AUC values for the ADNI neuropsychological composite scores were unavailable and therefore a power analysis was unable to be conducted.

2.8.7 Outliers

Variables greater than three standard deviations from the group mean were identified as outliers. Results were the same with and without outliers, unless otherwise specified.

Chapter 3: Results

3.1 Aim 1.1: Refine memory and attention measure

Both the MAC-Q and ACS-Short response scales were changed to a seven-point Likert scale ranging from strongly disagree to strongly agree with higher scores representing greater change to be consistent with the spatial navigation questionnaires. The phrasing of Likert items was changed to fit this rating scale. Additionally, the instructions were adjusted to ask about change in memory or attention abilities over the past several years to be consistent with the spatial navigation questionnaire (Appendix I.VI and I.IX). The informant-report was the same as the self-report except that the word "I" was replaced by the word "they" (e.g., They have greater difficulty remembering the name of a person just introduced to them; Appendix I.VII and I.X).

The MAC-Q originally focused entirely on episodic memory, but the literature suggests that semantic memory is also at risk in preclinical AD (Baker et al., 2017). The following items were added to the MAC-Q to measure episodic and semantic memory more completely: "I have greater difficulty recalling the content of conversations I have recently had" and "I have greater difficulty coming up with the right words even when I know what I am trying to say."

3.2 Aim 1.2: Refine spatial navigation measure using preexisting data from Allison et al., 2019

The original spatial navigation questionnaire demonstrated high Cronbach's alphas, suggesting potential redundancy in the questions (Self-report Cronbach's alpha=.965; Informant-report Cronbach's alpha=.957). Using data previously collected by Allison and colleagues (2019), items were examined to determine whether they should be omitted from the questionnaire for the purposes of this study (Table 4).

First, confirmatory factor analyses were conducted independently for self- and informant-reported questionnaires, wherein questionnaire items, objective navigation measures, and CSF $ptau_{181}/A\beta_{42}$ ratio were assumed to belong to a single factor. In the self-report model, all questionnaire items significantly loaded onto the single factor and the $ptau_{181}/A\beta_{42}$ ratio trended toward significance; however, none of the objective navigation tasks significantly loaded onto the factor (Appendix II, Table 17). Notably, item 9 of the self-report questionnaire had a relatively low factor loading (.545), suggesting that this item may be appropriate to eliminate from the questionnaire. In the informant-report model, all questionnaire items and the $ptau_{181}/A\beta_{42}$ ratio significantly loaded onto a single factor; again, none of the objective navigation tasks significantly loaded onto the factor (Appendix II, Table 18). Consistent with the self-report model, item 9 had a relatively low factor loading (.534), suggesting that this item may be appropriate to eliminate from the informant-report questionnaire as well.

Due to the limited information garnered from these models, secondary analyses of linear regression, Cronbach's alpha, item-scale correlations, and inter-item correlations were used to determine which items could be omitted from the original measure (Table 4).

Lastly, content of the items was considered. In their original form, the questionnaires assessed spatial navigation in terms of both cognitive mapping and route learning strategies.

However, the literature suggests that cognitive mapping may be more sensitive to preclinical AD than route learning. Navigation using a cognitive mapping strategy has been consistently associated with the hippocampus (Head & Isom, 2010; Iaria et al., 2003; O'Keefe 1971; Morris, 1982). Our group has demonstrated that cognitive mapping is associated with both concurrent preclinical status and risk of clinical progression (Allison et al., 2016; Levine et al., 2020). In addition, cognitive mapping demonstrated greater diagnostic accuracy both in detecting preclinical AD cross-sectionally and in detecting clinical progression than route learning (Allison et al., 2016; Levine et al., 2020). Consequently, keeping items the clearly referenced a cognitive mapping strategy was prioritized.

In addition, the content of the informant questionnaire was adjusted to consistently contain items referencing navigation behaviors likely to be observed by the informant. The original informant-report questionnaire was not correlated with preclinical status (Allison et al., 2016). The authors hypothesized that this could be because informants did not observe the behaviors queried in some of the items frequently enough to accurately identify subtle changes in navigation ability.

The steps above suggested that ten self-report items could be omitted (items 3, 5, 7, 9, 10, 12, 13, 17, 19, and 20; see Appendix II, Table 21 for details) and eleven informant-report items could be omitted (items 3, 4, 5, 7, 9, 10, 12, 13, 17, 19, and 20; see Appendix II, Table 22 for details). Thus, the final self-report questionnaire consisted of 10 items and the final informant-report questionnaire consisted of 9 items (Appendix I.II and I.IV).

Table 4: Item inclusion and exclusion criteria

Method	Inclusion	Exclusion
Linear Regression predicting either CSF $ptau_{181}$ or $A\beta_{42}$	F-statistic > 1sd from the mean of F-statistic across all items	R^2<.001
Cronbach's alpha with individual items omitted		Neutral or positive effect on full-scale alpha
Item-scale correlations		Below average item-scale correlation based on item-scale correlations across all items
Inter-item correlation		Below average inter-item correlation based on inter-item correlations across all items
Test-retest reliability		Below average test-retest reliability based on test-retest reliability across all items
Content analysis	Reference a cognitive mapping strategy; for informant, reference observable behaviors	

3.3 Primary aim 1.3 and addendum aim 1: Assess internal consistency and factor structure of refined questionnaires and ECog Subsections

3.3.1 Primary aim 1.3: Reliability and validity in the ADRC cohort

All refined questionnaires demonstrated good internal consistency using Cronbach's alpha (Table 5). Self and informant version of the questionnaires were moderately correlated (MAC-Q r=.403, df=102, p<.001; ACS-Short r=.393, df=102, p<.001; spatial navigation r=.446, df=102, p<.001).

Table 5. Internal consistency of refined questionnaires.

	α (95% CI)
Self-Reported Memory	.91(.89-.94)
Self-Reported Attention	.95(.94-.96)
Self-Reported Spatial Navigation	.95(.94-.96)
Informant-Reported Memory	.94(.93-.96)
Informant-Reported Attention	.97(.96-.97)
Informant-Reported Spatial Navigation	.96(.95-.97)

Note. α=Cronbach's Alpha

A CFA was conducted to assess whether self-reported memory, attentional control, and spatial navigation loaded on to three independent factors (Figure 1). Model fit was good overall for the hypothesized latent structure (CFI=.973, RMSEA=.066, SRMR=.05), but the chi squared

(χ^2) test indicated potential model misspecification ($\chi^2(431)=663.760$, $p<.001$). Additionally, a one-factor model was considered, assuming that all self-reported questionnaires converged on to a single factor; however, model fit was poor (CFI=.885, RMSEA=.135, SRMR=.107, $\chi^2(434)=1415.511$, $p<.001$). Chi square difference testing indicated the self-report one- and three-factor models were significantly different from each other ($\chi^2(3)=109.138$, $p<.001$).

The same pattern was observed in the informant-report models, with the three-factor model (Figure 2) indicating good fit overall, but with potential model misspecification (CFI=.984, RMSEA=.068, SRMR=.045, $\chi^2(402)=594.483$, $p<.001$) and the one-factor model indicating poor fit overall (CFI=.931, RMSEA=.142, SRMR=.091, $\chi^2(405)=1249.487$, $p<.001$). Chi square statistics are highly sensitive to sample size; due to our relatively small sample size, the chi square results may overemphasize a lack of model fit (Bollen, 1989). The informant-report one and three-factor models were significantly different from each other ($\chi^2(3)=111.481$, $p<.001$).

Figure 1. CFA for three-factor model of refined self-report questionnaires

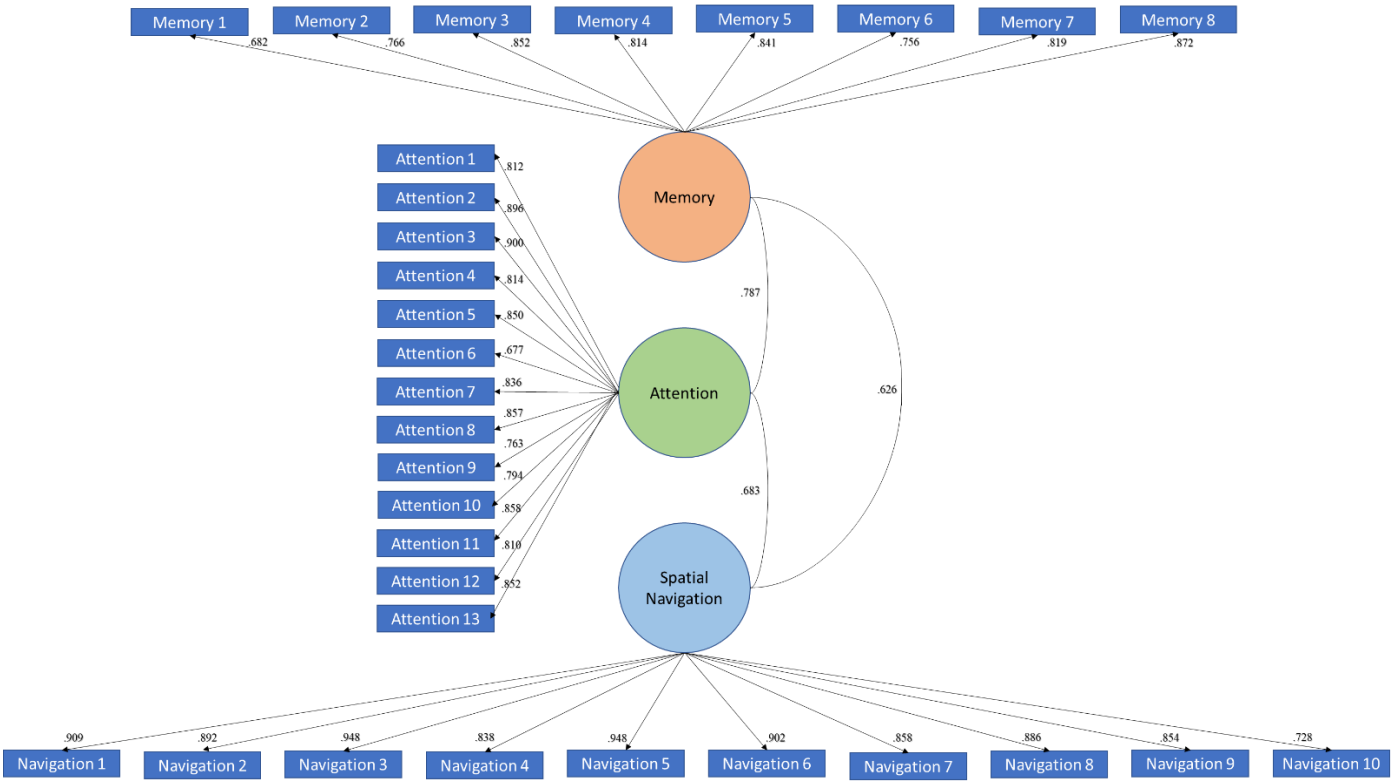
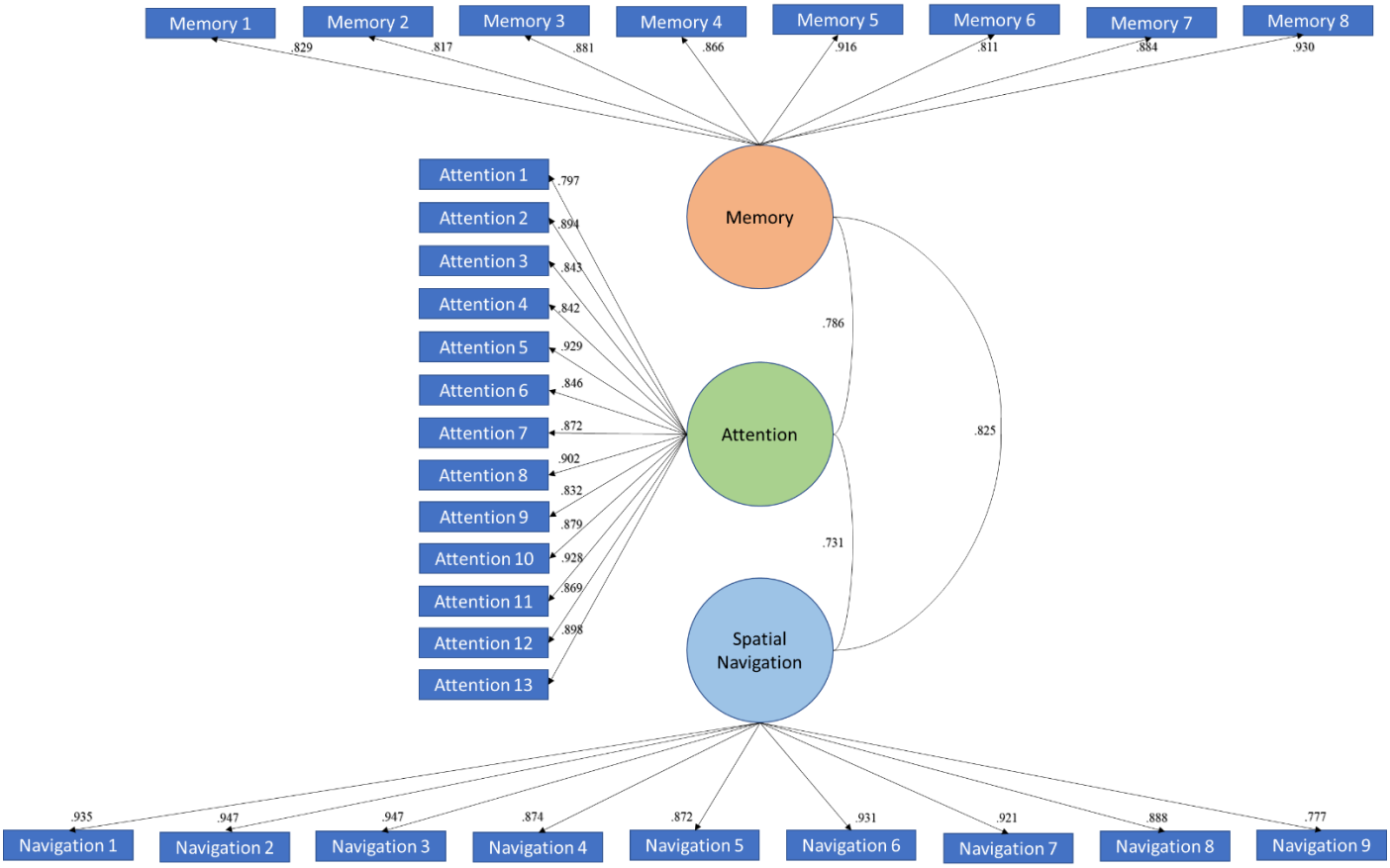


Figure 2. CFA for three-factor model of refined informant-report questionnaires



Post-hoc analyses

Previous work found that self-reported spatial navigation was associated with preclinical AD, whereas informant-reported spatial navigation was not (Allison et al. 2019). The authors hypothesized that informants may not observe participants navigating often enough to reliably report subtle changes in navigation behavior. To explore this, a two-tailed t-test was conducted to examine whether total score on the navigation questionnaire differed between the informants who observed participants navigating more often than once a week and informants who observed participants navigating once a week or less. There were not significant differences in informant-report total scores between the two groups (p=.433).

3.3.2 Addendum aim 1: Reliability and validity in the ADNI cohort

The self- and informant-reported memory and attention ECog subsections demonstrated good internal consistency using Cronbach's alpha, whereas the self- and informant-report spatial navigation subsections demonstrated fair internal consistency (Table 6). Self and informant ECog memory and attention subsections were moderately correlated (memory r=.372, df=364, p<.001; attention r=.369, df=-362, p<.001). The self and informant ECog spatial navigation subsections were weakly correlated (r=.104, df=363, p=.047).

Self-reported ability and objective performance were not strongly correlated across any of the domains (memory r=-.133, df=369, p=.010; attention/executive function r=-.097, df=369, p=.063; and spatial navigation/visuospatial r=-.009, df=368, p=.864).

Table 6. Internal consistency of ECog subsections

	α (95% CI)
Self-Reported Memory	.85(.83-.88)
Self-Reported Attention	.85(.83-.88)
Self-Reported Spatial Navigation	.74(.71-.78)
Informant-Reported Memory	.87(.84-.89)
Informant-Reported Attention	.89(.87-.91)
Informant-Reported Spatial Navigation	.71(.67-.75)

Note. α=Cronbach's Alpha

A CFA was conducted to assess whether the ECog memory, attention, and spatial navigation subsections loaded on to three independent factors. Model fit indices were good (CFI=.956, RMSEA=.059) or acceptable (SRMR=.083) for the hypothesized latent structure, but the chi squared test indicated potential model misspecification ($\chi^2(149)=340.246$, p<.001). Additionally, a one-factor model was considered, assuming that all self-reported questionnaires converged on to a single factor; however, model fit was poor (CFI=.876, RMSEA=.098, SRMR=.108, $\chi^2(152)=695.991$, p<.001). Chi square difference testing indicated the self-report one- and three-factor models were significantly different from each other ($\chi^2(3)=129.511$, p<.001)

The same pattern was observed in the informant-report models, with the three-factor model providing better fit than the one-factor model, but not without indications of model misspecification. The informant three-factor model provided some indication of good or acceptable fit (CFI=.951 and RMSEA=.072, respectively), but also showed indications of poor fit (SRMR=.120 and $\chi^2(149)=433.994$, $p<.001$). Of note, one of the informant-reported spatial navigation items had a factor loading greater than 1, which suggests that this item was highly correlated with other items on the questionnaire (Jöreskog, 1999). This in conjunction with the high Cronbach's alpha highlights the possibility of further shortening the questionnaire. The one-factor model demonstrated poor fit overall (CFI=.901, RMSEA=.102, SRMR=.160, $\chi^2(152)=730.337$, $p<.001$). Chi square difference testing indicated the informant-report one- and three-factors models were significant different from each other ($\chi^2(3)=145.347$, $p<.001$).

Figure 3. CFA for three-factor model of self-reported ECog subsections

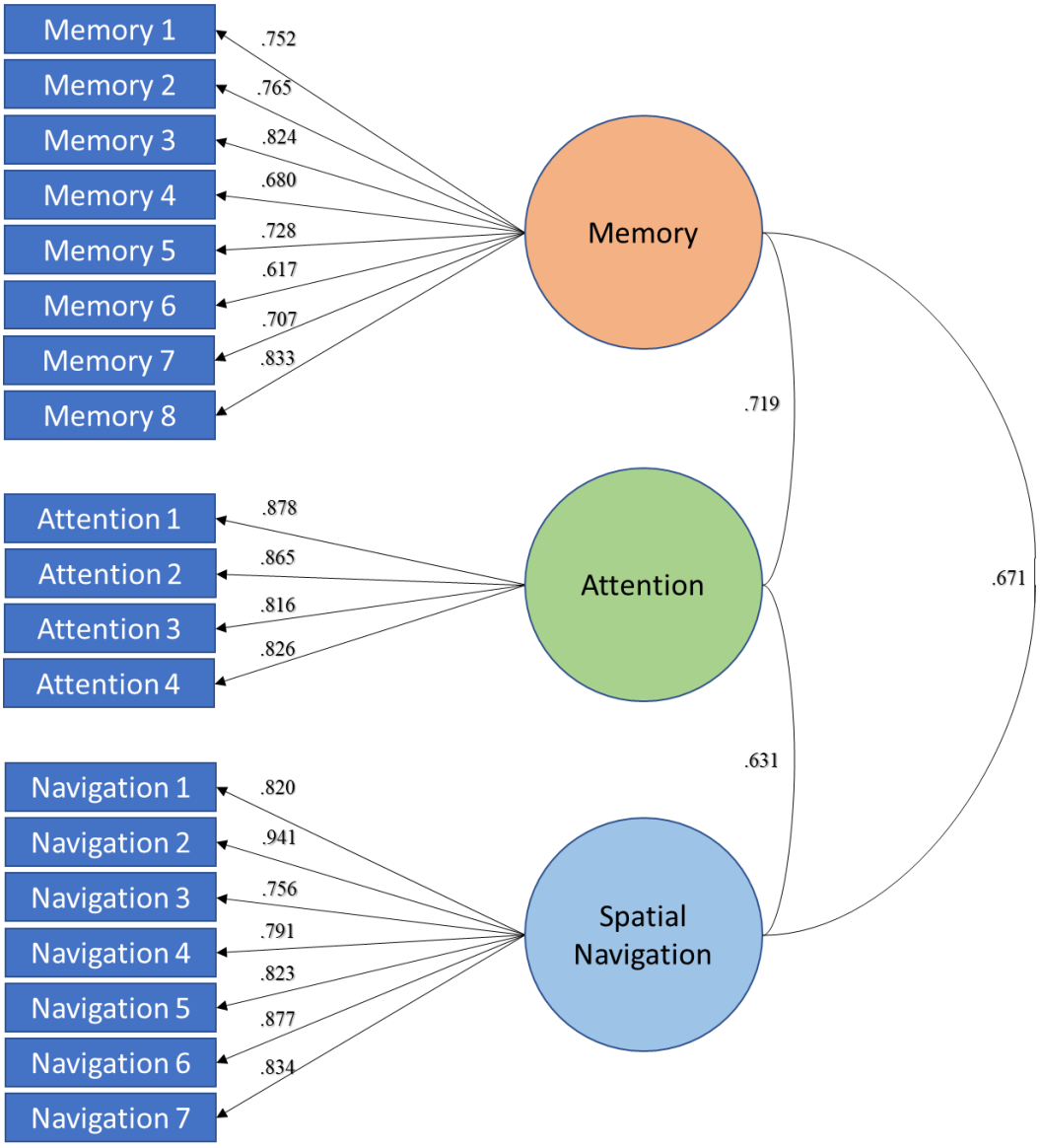
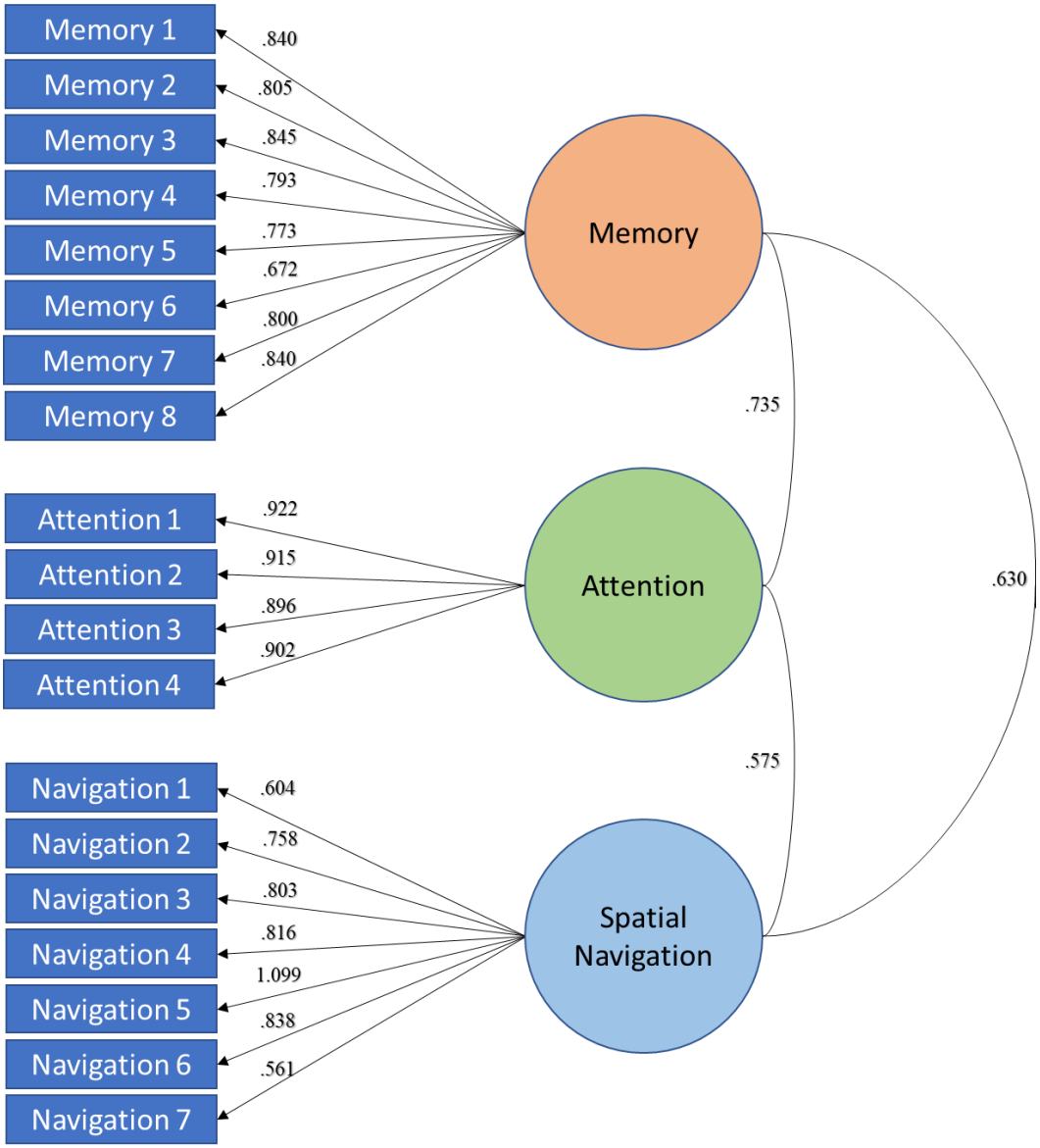


Figure 4. CFA for three-factor model of informant-reported ECog subsections



3.3.3 Summary

All refined questionnaires and ECog subsections demonstrated acceptable internal consistency. Both the self- and informant-report refined questionnaires and ECog subsections exhibited good fit overall in a three-factor model, with the exception of chi square tests which may reflect sample size issues. Although the latent constructs were strongly correlated, considering all items as measuring a single latent factor significantly reduced the fit statistics.

This suggests that these measures assess different domains of cognitive function. As such, analyses in subsequent aims considered all refined questionnaires and ECog subsections as separate variables.

3.4 Primary and addendum aim 2: Compare the diagnostic accuracy of self- and informant-reported questionnaires

3.4.1 ADRC sample

Predicting preclinical AD defined by CSF $A\beta_{42}/A\beta_{40}$ ratio

The AUCs for self-reported memory, attention, and spatial navigation were significant (Table 7). There were no significant differences between the AUCs across cognitive domain (memory/attention n=32, z=.103 p=.918; memory/spatial navigation n=32, z=.785 p=.433; attention/spatial navigation n=32, z=.840, p=.401).

The AUCs for informant-reported memory, attention, and spatial navigation were not significant (Table 7). None of the informant-report AUCs significantly differed from each other (memory/attention n=23, z=1.057, p=.291; memory/spatial navigation n=23, z=.195, p=.846; attention/spatial navigation n=23, z=.500, p=.617).

Self-report questionnaires did not outperform informant-report questionnaires (memory n=23, z=1.398, p=.162; attention n=23, z=.282, p=.777; spatial navigation n=23, z=1.232, p=.218). Combining self- and informant-reported memory, attention, and spatial navigation did not produce significant AUCs (Table 7).

Figure 5. ROC curves predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

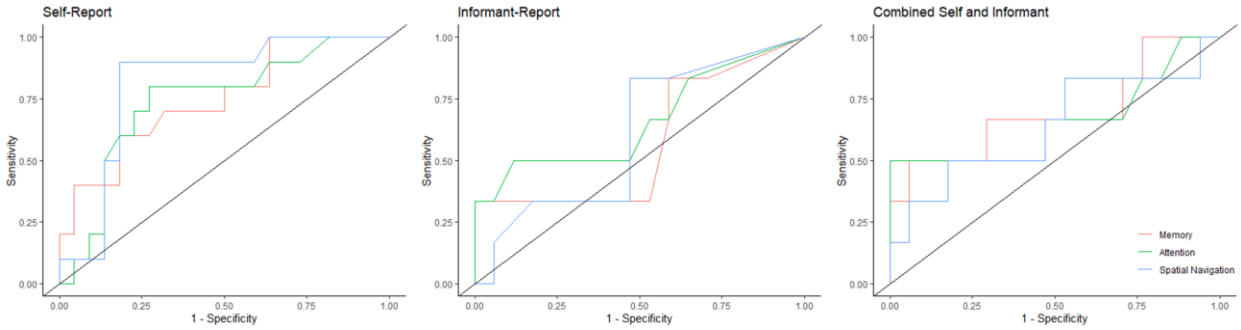


Table 7. ROC analyses predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Sensitivity	Specificity	Youden Index	AUC	95% CI	SE	p
Self-Reported Memory	.600	.818	.418	.748	.565-.931	.093	.027*
Self-Reported Attention	.800	.727	.337	.741	.554-.928	.095	.031*
Self-Reported Navigation	.900	.818	.718	.811	.653-970	.081	.005*
Informant-Reported Memory	.333	1.00	.333	.574	.282-.865	.149	.600
Informant-Reported Attention	.500	.824	.324	.662	.377-.947	.145	.248
Informant-Reported Navigation	.833	.529	.362	.603	.344-.862	.132	.462
Combined Memory	.500	.941	.441	.696	.417-.975	.142	.161
Combined Attention	.500	1.00	.500	.657	.352-.962	.156	.263
Combined Navigation	.500	.824	.324	.637	.350-.924	.146	.327

Notes. AUC=Area Under the Curve; CI=Confidence Interval; SE=Standard Error; * indicates p<.05

Preclinical Alzheimer disease defined by hippocampal volume

The AUCs for self-reported memory, attention, and spatial navigation were not significant (Table 8). There were no significant differences between the AUCs across cognitive domain (memory/attention n=25, z=0.000, p=1.00; memory/spatial navigation n= 25, z=.644, p=.519; attention/spatial navigation n=25, z=.660, p=.510).

The AUCs for informant-reported memory, attention, and spatial navigation were not significant (Table 8). None of the informant-report AUCs significantly differed from each other (memory/attention n=18, z=.46 p=.642; memory/spatial navigation n=18, z=.987, p=.324; attention/spatial navigation n=18, z=.813, p=.416).

Self-reports did not outperform informant report (memory n=18, z=.254, p=.800; attention n=18, z=.365, p=.716; spatial navigation n=18, z=.541, p=.589). Combining self- and informant report memory, attention, and spatial navigation did not produce significant AUCs (Table 8).

Figure 6. ROC curves predicting hippocampal volume in the ADRC sample

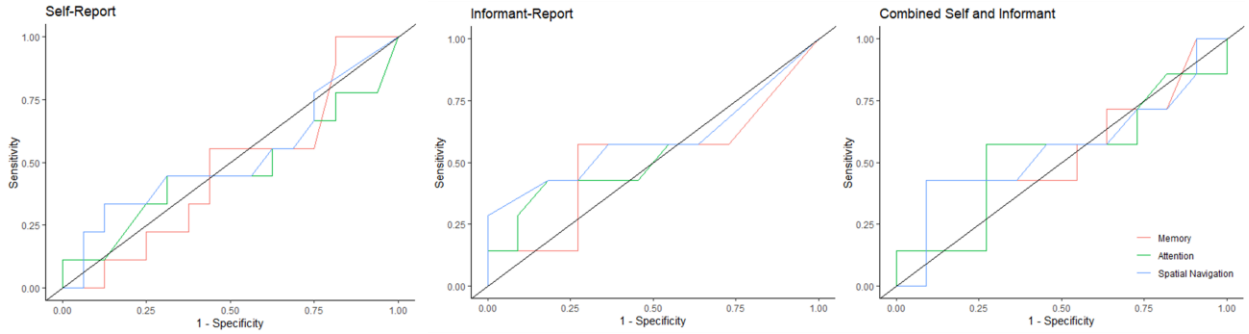


Table 8. ROC analyses predicting hippocampal volume in the ADRC sample

	Sensitivity	Specificity	Youden Index	AUC	95% CI	SE	p
Self-Reported Memory	1.00	.187	.187	.469	.234-.704	.120	.799
Self-Reported Attention	.444	.687	.131	.469	.212-.725	.131	.799
Self-Reported Navigation	.333	.875	.208	.517	.264-.771	.129	.887
Informant-Reported Memory	.571	.727	.298	.513	.213-.813	.153	.928
Informant-Reported Attention	.429	.818	.247	.545	.247-.844	.152	.751
Informant-Reported Navigation	.282	1.00	.282	.529	.288-.894	.155	.526
Combined Memory	.429	.727	.156	.506	.220-.793	.146	.964
Combined Attention	.571	.727	.298	.526	.229-.822	.151	.856
Combined Navigation	.429	.909	.338	.552	.254-.850	.152	.717

Notes. AUC=Area Under the Curve; CI=Confidence Interval; SE=Standard Error

Post-hoc analyses

Although it is recommended that the CSF $A\beta_{42}/A\beta_{40}$ ratio be used to determine preclinical AD with the LUMIPULSE CSF assays used in the ADRC sample (Alcolea et al., 2019), I wanted to also examine the CSF $ptau_{181}/A\beta_{42}$ ratio as the determiner for preclinical AD because that was what was available in the ADNI sample. This change resulted in self-reported memory (.691 (SE=.100), p=.098; Youden index=.348; sensitivity=1.00, specificity=.348) and attention (.696 (SE=.101), p=.090; Youden index=.474; sensitivity=.778, specificity=.696) demonstrating a nonsignificant trend toward predicting preclinical AD. All other results remained the same, see Appendix IV for full results.

3.4.2 ADNI sample

Predicting preclinical AD defined by CSF $ptau_{181}/A\beta_{42}$ ratio

The AUCs for self-reported memory and attention were significant, whereas the AUC for self-reported spatial navigation was not (Table 9). There was a nonsignificant trend for the self-

reported memory AUC to be significantly higher than the self-reported spatial navigation AUC (n=371, z=1.799 p=.072). There was not a significant difference between the self-reported memory AUC and the self-reported attention AUC (z=371, z=.687, p=.492) and between self-reported attention and self-reported spatial navigation (n=371, z=1.097, p=.273).

The AUCs for informant-reported memory, attention, and spatial navigation were not significant (Table 9). None of the informant-report AUCs significantly differed from each other (memory/attention n=364, z=1.131, p=.258; memory/spatial navigation n=366, z=1.354, p=.176; attention/spatial navigation n=364, z=.215, p=.830).

Self-reported memory outperformed informant-reported memory (n=366, z=1.696, p=.002). There was a nonsignificant trend for the self-reported attention AUC to be higher than the informant-reported attention AUC (n=364, z=1.696, p=.090), but this trend was not seen with outliers removed (n=353, z=1.598, p=.110). The self- and informant-reported spatial navigation AUCs did not significantly differ (n=366, z=.565, p=.571). Combining self- and informant-reported memory and spatial navigation did not produce significant AUCs, whereas the AUC for combined self- and informant-report attention demonstrated a nonsignificant trend toward significance (Table 9).

Figure 7. ROC curves predicting CSF ptau$_{181}$/Aβ$_{42}$ ratio in the ADNI sample

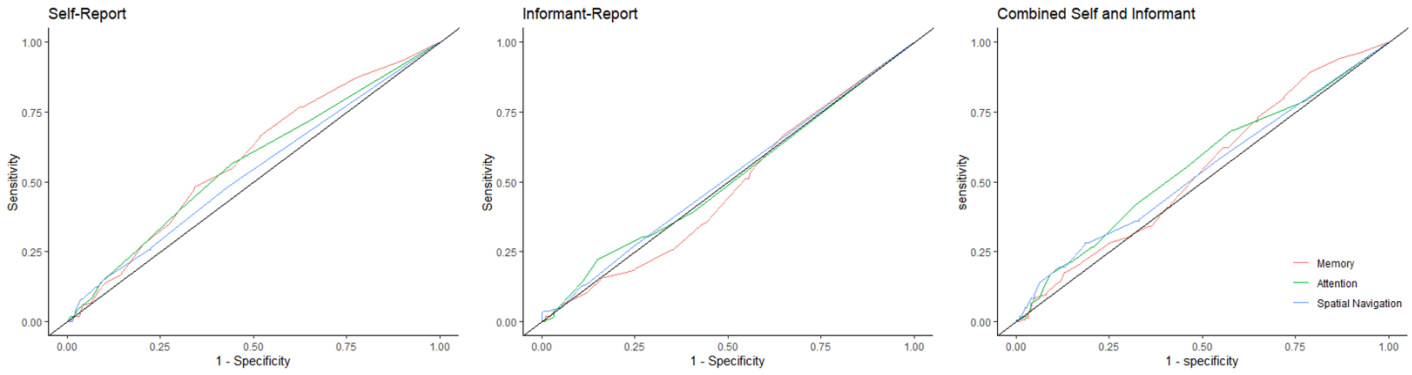


Table 9. ROC analyses predicting CSF ptau$_{181}$/Aβ$_{42}$ ratio in the ADNI sample

	Sensitivity	Specificity	Youden Index	AUC	95% CI	SE	p
Self-Reported Memory	.663	.483	.146	.582	.524-.640	.030	.007*
Self-Reported Attention	.563	.559	.122	.564	.505-.623	.030	.036*
Self-Reported Navigation	.163	.890	.053	.533	.473-.592	.030	.278
Informant-Reported Memory	.667	.353	.020	.476	.417-.536	.030	.433
Informant-Reported Attention	.146	.888	.033	.505	.445-.566	.031	.861
Informant-Reported Navigation	.038	.995	.033	.513	.453-.573	.031	.675
Combined Memory	.805	.280	.085	.541	.482-.600	.030	.179
Combined Attention	.684	.422	.106	.557	.497-.617	.031	.063#
Combined Navigation	.283	.816	.099	.536	.476-.596	.031	.234

Notes. AUC=Area Under the Curve; CI=Confidence Interval; SE=Standard Error; * indicates p<.05

Preclinical Alzheimer disease defined by hippocampal volume

The AUC for self-reported spatial navigation was significant (Table 10). The AUC for self-reported memory demonstrated a nonsignificant trend, but this trend was not observed with outliers removed (Table 10). The AUC for self-reported attention was not significant (Table 10). There was a nonsignificant trend for the self-reported spatial navigation AUC to be larger than the self-reported attention AUC (n=209, z=1.856, p=.063). There was not a significant difference between the self-reported memory AUC and the self-reported attention AUC (n=209, z=1.460, p=.144) or the self-reported spatial navigation AUC (n=209, z=.575, p=.565).

The AUC for informant-reported memory demonstrated a trend toward significance and was marginal with outliers removed (Table 10). The AUCs for informant-reported attention and spatial navigation were not significant (Table 10). There was not a significant difference between any of the informant reported AUCs (memory/attention n=204, z=1.159, p=.247; memory/spatial navigation n=206, z=.617, p=.538; attention/spatial navigation n=204, z=.591, p=.555).

There was not a significant difference between any of the self- and informant-report AUCs (memory n=206, z=.076, p=.939; attention n=204, z=.207, p=.836; spatial navigation n=206, z=.990, p=.322). Combining self- and informant-reported memory and spatial navigation produced significant AUCs (Table 10). However, there were not significant differences between

the AUCs for combined and self-report measures (memory n=206, z=.512, p=.609 and spatial navigation n=206, z=.205, p=.837). The AUC for combined self- and informant-report attention was not significant (Table 10).

Figure 8. ROC curves predicting hippocampal volume in the ADNI sample

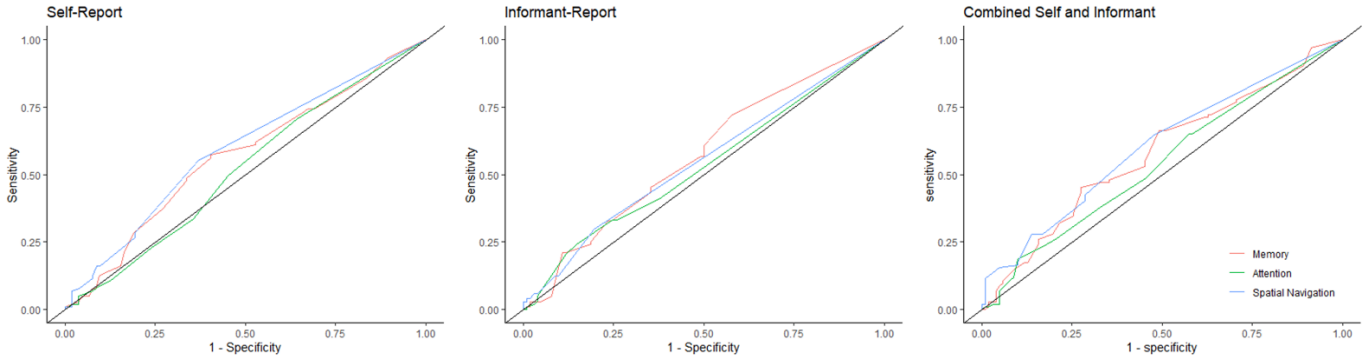


Table 10. ROC analyses predicting hippocampal volume in the ADNI sample

	Sensitivity	Specificity	Youden Index	AUC	95% CI	SE	p
Self-Reported Memory	.10 /.567	.663/.596	.139/.163	.566/.562	.488-.644/ .484-.640	.040/.040	.099#/.123
Self-Reported Attention	.705	.356	.061	.517	.439-.596	.040	.669
Self-Reported Navigation	.552	.631	.183	.592	.515-.699	.039	.022*
Informant-Reported Memory	.721/.718	.422/.430	.142/.148	.572/.579	.494-.650 .501-.658	.040/.040	.074#/.050*
Informant-Reported Attention	.243	.851	.094	.532	.452-.611	.040	.434
Informant-Reported Navigation	.298	.804	.102	.550	.471-.629	.040	.216
Combined Memory	.453	.725	.178	.579	.501-.657	.040	.050*
Combined Attention	.184	.901	.085	.542	.463-.621	.040	.299
Combined Navigation	.644	.525	.169	.603	.526-.680	.039	.011*

Notes. AUC=Area Under the Curve; CI=Confidence Interval; SE=Standard Error; * indicates p<.05; # indicates p<.1; Results presented with/without outliers.

Post-hoc analyses

Traditional ROC analyses do not allow for inclusion of covariates, such as demographic variables of age, education, and sex. In a linear regression model including these three covariates, age was a significant predictor of CSF ratio and hippocampal volume, whereas education and gender were not. The literature suggests that older age is associated with increased self-reported cognitive change (Medonca et al., 2016; Gallassi et al., 2010), whereas the literature regarding the impact of education and gender on self-reported cognition is mixed and

limited (Holmen et al., 2013; Giacomucci et al., 2021; Rami et al., 2014; Jonker et al., 2000). As such, post-hoc analyses were designed to examine whether ECog subsections demonstrated differential predictive ability across age groups. The sample was divided into the "young-old" (<74 years old) and "old-old" (≥74 years old; Martin et al., 2015). AUCs for each ECog subsection in these age groups were compared. None of the ECog subsections demonstrated differing diagnostic accuracy in predicting CSF $ptau_{181}/A\beta_{42}$ or hippocampal volume by age group. See Appendix IV for results.

3.4.3 Summary

In the ADRC sample, self-reported memory, attention, and spatial navigation were significant predictors of preclinical AD defined by CSF biomarker burden. In the ADNI sample, self-reported memory and attention were significant predictors of preclinical AD defined by CSF biomarker burden, but not hippocampal volume. Self-reported spatial navigation was a significant predictor of preclinical AD defined by hippocampal volume, but not CSF biomarker burden. Informant-reported cognitive change was not significant in either sample in predicting preclinical AD defined by CSF biomarker burden or hippocampal volume.

It is important to highlight that the results from the ADRC sample represent underpowered preliminary analyses and conclusions cannot be drawn from then. Additionally, although some of the self-reported ECog subsections demonstrated significant AUCs in well-powered analyses, these AUCs were small (all AUCs<.60) and therefore do not provide a level of diagnostic accuracy appropriate for clinical use (Mandrekar, 2010). As such, none of the questionnaires used in this study can be recommended to be used to identify preclinical AD.

3.5 Aim 3: Ability of questionnaires to predict preclinical AD when controlling for personality traits or current affective state

3.5.1 ADRC sample

Preclinical AD defined by CSF $A\beta_{42}/A\beta_{40}$ ratio

The step 1 model, including only covariates of age, gender, and education, was not significant in predicting CSF $A\beta_{42}/A\beta_{40}$ ratio.

Self-report. Self-reported attention demonstrated a nonsignificant trend toward predicting CSF $A\beta_{42}/A\beta_{40}$ ratio (Table 11). This trend persisted when anxiety symptomatology or neuroticism was added to the model (Table 11). However, this trend dissipated when depressive symptomatology or conscientiousness was added to the model (Table 11). Self-reported memory and spatial navigation were not significant predictors of CSF $A\beta_{42}/A\beta_{40}$ ratio. This remained true when depression symptomatology, anxiety symptomatology, neuroticism, or conscientiousness was added to the model. When all three self-reported questionnaires were added to the model, none of the measures were significant predictors of CSF $A\beta_{42}/A\beta_{40}$ ratio. This remained true when controlling for depressive symptomatology, anxiety symptomology, neuroticism, or conscientiousness. For full results see Appendix V.

Informant-report. Informant-reported memory, attention, and spatial navigation were not significant predictors of CSF $A\beta_{42}/A\beta_{40}$ ratio. This remained true when informant depressive or anxiety symptomatology was added to the model. When all three informant-reported questionnaires were added to the model, none of the measures were significant predictors of CSF $A\beta_{42}/A\beta_{40}$ ratio. This remained true when controlling for depressive or anxiety symptomology. For full results see Appendix V.

Table 11: Self-reported attention hierarchical linear regression predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.089	.135		
Step 2 Model				.158	.070#	.069	.069
Self-Reported Attention	-.307	-1.817	.080#				
Step 3 Model: Depression							
Self-Reported Attention	-.250	-1.175	.251	.133	.120	-.025	.044
Depressive Symptoms	-.983	-.460	.650				
Step 3 Model: Anxiety				.130	.124	-.028	.041
Self-Reported Attention	-.320	-1.821	.080#				
Anxiety Symptoms	-.062	.350	.729				
Step 3 Model: Neuroticism				.188	.062#	.030	.099
Self-Reported Attention	-.332	-1.989	.057#				
Neuroticism	-.237	-1.407	.171				
Step 3 Model: Conscientiousness				.146	.103	-.012	.057
Self-Reported Attention	-.269	-1.512	.143				
Conscientiousness	.139	.780	.442				

# indicates p<.1

Preclinical AD defined by hippocampal volume

The step 1 model, including only covariates of age, gender, and education, was significant in predicting hippocampal volume.

Self-report. Self-reported memory, attention, and spatial navigation were not significant predictors of hippocampal volume. This remained true with depression symptomatology, anxiety symptomatology, neuroticism, or conscientiousness was added to the model. When all three self-reported questionnaires were added to the model, none of the measures were significant predictors of hippocampal volume. This remained true when controlling for depressive symptomatology, anxiety symptomology, neuroticism, or conscientiousness. For full results see Appendix V.

Informant-report. Informant-reported memory, attention, and spatial navigation were not significant predictors of hippocampal volume. This remained true with depression symptomatology, anxiety symptomatology, neuroticism, or conscientiousness was added to the model. When all three informant-reported questionnaires were added to the model, none of the

measures were significant predictors of hippocampal volume. This remained true when controlling for depressive or anxiety symptomology. For full results see Appendix V.

3.5.2 ADNI sample

Preclinical AD defined by CSF ptau$_{181}$/Aβ$_{42}$

The step 1 model, including only covariates of age, gender, and education, was significant in predicting CSF ptau$_{181}$/Aβ$_{42}$ ratio.

Self-reported attention was a significant predictor of CSF ptau$_{181}$/Aβ$_{42}$ ratio and remained significant when depressive symptomatology and the interaction between self-reported attention and depressive symptomatology was added to the model (Table 12). Self-reported memory and spatial navigation were not significant predictors of CSF ptau$_{181}$/Aβ$_{42}$ ratio. This was consistent in models controlling for depressive symptomatology and the interaction between self-reported memory and depressive symptomatology. When all three self-reported questionnaires were added to the model, only attention was a significant predictor of CSF ptau$_{181}$/Aβ$_{42}$. This remained true when controlling for depressive symptomatology (Table 13). For full results see Appendix V.

Table 12: Self-reported attention hierarchical linear regression predicting CSF ptau$_{181}$/Aβ$_{42}$ ratio in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.037	.016*		
Step 2 Model				.094	<.001*	.057	.057
Self-Reported Attention	.250	3.632	<.001*				
Step 3 Model				.095	<.001*	.001	.058
Self-Reported Attention	.267	3.784	<.001*				
Depressive Symptoms	-.076	-1.081	.281				
Step 4 Model				.091	<.001*	-.004	.054
Self-Reported Attention	.265	3.658	<.001*				
Depressive Symptoms	-.081	-1.054	.293				
Self-Reported Attention X Depressive Symptoms	.013	.163	.871				

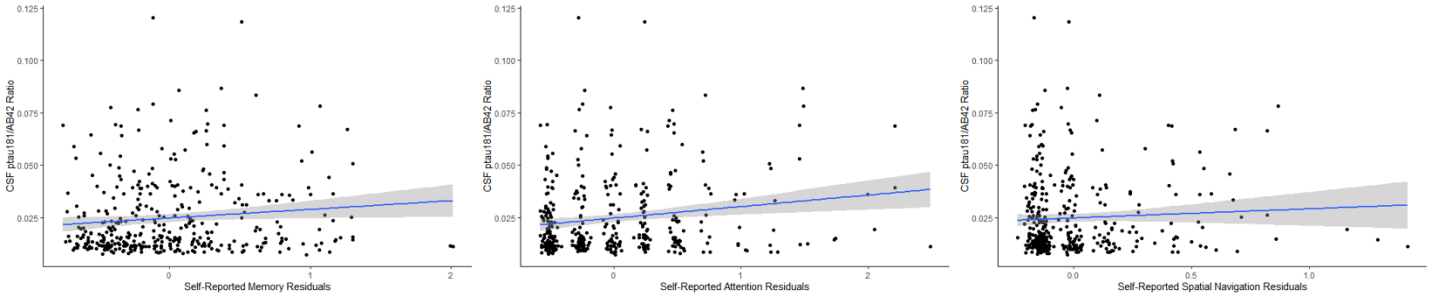
* indicates p<.05

Table 13: All self-reported questionnaires hierarchical linear regression predicting CSF ptau$_{181}$/Aβ$_{42}$ ratio in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.037	.016*		
Step 2 Model				.092	<.001*	.055	.055
Self-Reported Memory	-.007	-.740	.461				
Self-Reported Attention	.031	3.629	<.001*				
Self-Reported Navigation	-.005	-.624	.533				
Step 3 Model				.092	<.001*	.000	.055
Self-Reported Memory	-.006	-.623	.534				
Self-Reported Attention	.324	3.729	<.001*				
Self-Reported Navigation	-.006	-.653	.515				
Depressive Symptoms	-.007	-.989	.324				

* indicates p<.05

Figure 9. Self-reported ECog subsections predicting CSF ptau$_{181}$/Aβ$_{42}$ ratio after controlling for demographic variables in the ADNI sample



Preclinical AD defined by hippocampal volume

The step 1 model, including only covariates of age, gender, and education, was significant in predicting hippocampal volume.

Self-reported memory was a significant predictor of hippocampal volume and remained significant when depressive symptomatology and the interaction between self-reported memory and depressive symptomatology were added to the model (Table 14). However, when outliers were removed, self-reported memory only demonstrated a nonsignificant trend toward predicting hippocampal volume when depressive symptomatology was added to the model and did not significantly predict hippocampal volume when the interaction between self-reported memory and depressive symptomatology was added to the model (Table 14). Self-reported attention and spatial navigation were not significant predictors of hippocampal volume. This was consistent

when depressive symptomatology and the interaction between self-reported cognitive ability and depressive symptomatology were added to the models. When all three self-reported questionnaires were added to the model, only memory was a significant predictor of hippocampal volume. This remained true when controlling for depressive symptomatology (Table 15). For full results see Appendix V.

Table 14: Self-reported memory hierarchical linear regression predicting hippocampal volume in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.233	<.001*		
Step 2 Model				.252/ .249	<.001*/ <.001*	.019/ .016	.019
Self-Reported Memory	-.153/ -.142	-2.272/ -2.092	.024*/ .038*				
Step 3 Model				.248/ .245	<.001*/ <.001*	-.004/ -.004	.015
Self-Reported Memory	-.159/ -.137	-2.272/ -1.926	.024*/ .056#				
Depressive Symptoms	.024	.345	.731				
Step 4 Model				.246/ .241	<.001*/ <.001*	-.002/ -.004	.013
Self-Reported Memory	-.145/ -.171	-2.014/ -1.608	.046*/ .110				
Depressive Symptoms	.055	.697	.487				
Self-Reported Memory X Depressive Symptoms	-.052	-.868	.387				

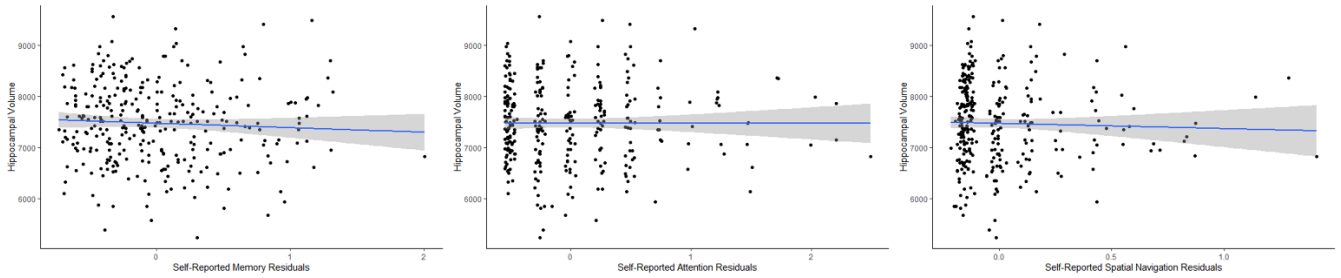
Results presented with/without outliers; * indicates p<.05; # indicates p<.1

Table 15: All self-reported questionnaires hierarchical linear regression predicting hippocampal volume in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.233	<.001*		
Step 2 Model				.252	<.001*	.019	.019
Self-Reported Memory	-.202	-2.172	.031*				
Self-Reported Attention	-.122	1.371	.172				
Self-Reported Navigation	-.049	-.592	.555				
Step 3 Model				.247	<.001*	-.005	.014
Self-Reported Memory	-.204	-2.166	.032*				
Self-Reported Attention	.120	1.337	.183				
Self-Reported Navigation	-.048	-.580	.563				
Depressive Symptoms	.013	.181	.857				

* indicates p<.05

Figure 10. Self-reported ECog subsections predicting hippocampal volume after controlling for demographic variables in the ADNI sample



Post-hoc analyses

ECog data was skewed toward participants and informants reporting very little cognitive change (Appendix III). As such, ECog subsections were dichotomized for post-hoc hierarchical linear regression analyses. Self-reported memory was divided into participants who on average reported no cognitive change (average item score<2; n=284) and participants who on average reported worse cognition (average item score ≥2; n=87). Self-reported attention and spatial navigation were divided into participants who reported no cognitive change (all items rated 1; attention n=119 and spatial navigation n=203) and participants who reported cognitive change on at least one item (attention n=252 and spatial navigation n=167).

Results from models predicting CSF $ptau_{181}/A\beta_{42}$ ratio remained consistent with the primary results (Appendix V). Self-reported memory and attention model results remained consistent with the primary results in predicting hippocampal volume (Appendix V).

Dichotomized self-reported spatial navigation was a significant predictor of hippocampal volume. This remained significant when depressive symptoms and the interaction between self-reported spatial navigation and depressive symptomatology were added to the model (Table 16). When all self-reported ECog subsections were added to the model, none of the subsections were significant predictors of hippocampal volume. For full results see Appendix V.

Table 16: Self-reported dichotomous spatial navigation hierarchical linear regression predicting hippocampal volume in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.233	<.001*		
Step 2 Model				.249	<.001*	.016	,016
Self-Reported Navigation	-.294	-2.151	.033*				
Step 3 Model				.245	<.001*	-.004	.012
Self-Reported Navigation	-.293	-2.130	.035*				
Depressive Symptoms	-.011	-.155	.877				
Step 4 Model				.242	<.001*	-.003	.009
Self-Reported Navigation	-.294	-2.133	.034*				
Depressive Symptoms	.051	.441	.660				
Self-Reported Navigation X Depressive Symptoms	-.094	-.655	.513				

* indicates p<.05

3.5.3 Summary

In preliminary analyses, the refined questionnaires were not significant predictors of AD biomarkers in the ADRC sample, and this remained true with personality or affective factors were added to the models.

The self-reported attention ECog subsection was a significant predictor of CSF biomarker burden even when controlling for depressive symptomatology in the ADNI sample. The self-reported memory ECog subsection was a significant predictor of hippocampal volume even when controlling for depressive symptomatology; however, the predictive ability weakened when outliers were removed. The self-reported spatial navigation ECog subsection was a significant predictor of hippocampal volume if the measure was considered dichotomous and this remained true when depressive symptomatology was added to the model. These results suggest that participants are able to report change in cognitive ability regardless of depressive symptoms.

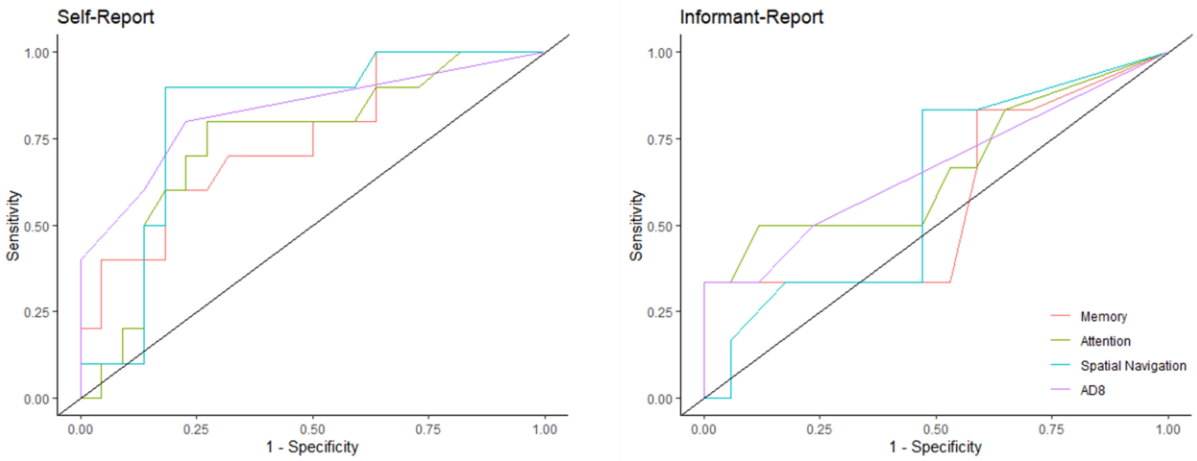
3.6 Aim 4: Compare diagnostic accuracy of questionnaires with an established questionnaire for early dementia and neuropsychological assessment

3.6.1 ADRC sample

Predicting preclinical AD defined by CSF $A\beta_{42}/A\beta_{40}$ ratio

The AUC for self-reported AD8 was significant (.827 (SE=.088), p=.003; Youden Index=573; sensitivity=.800, specificity=.773), whereas the AUC for informant-report AD8 was not significant (.662 (SE=.145), p=.248; Youden Index=.33; sensitivity=.333, specificity=1.00). There were no significant differences between the domain-specific self-report questionnaires and self-reported AD8 (memory n=32, z=1.403, p=.161; attention n=32, z=1.597, p=.110; spatial navigation n=32, z=.180, p=.857) and between informant-report questionnaires and informant-reported AD8 (memory n=23, z=.895, p=.371; attention n=23, z=0, p=1.00; spatial navigation n=23, z=.381, p=.704).

Figure 11: ROC curves comparing refined questionnaires and AD8 in predicting preclinical AD defined by CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

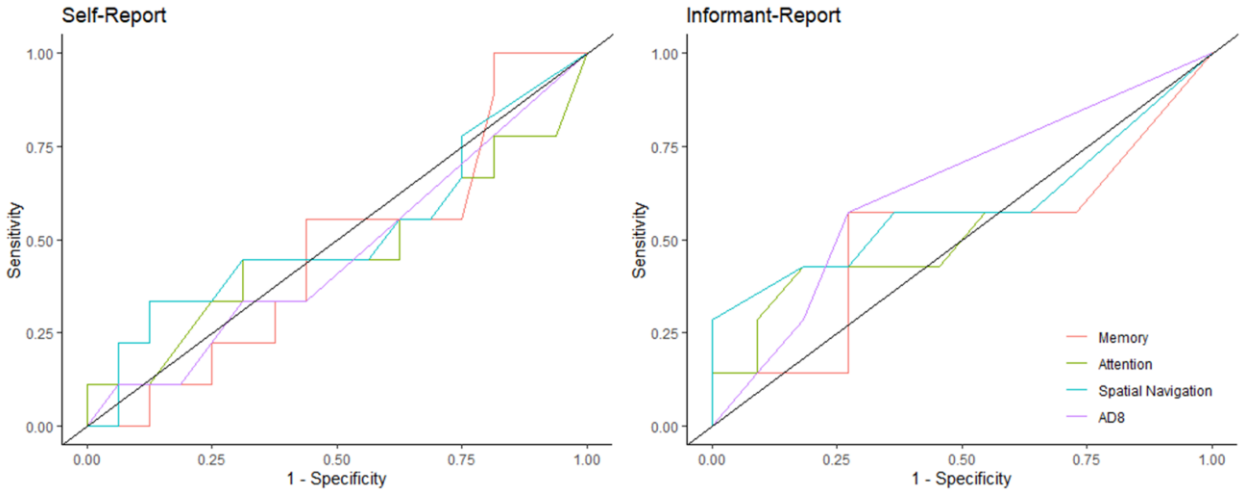


Preclinical AD defined by hippocampal volume

The AUCs for both self (.462 (SE=.123), p=.756; Youden Index=.048; sensitivity=.111, specificity=.937) and informant (.636 (SE=.139), p=.342; Youden Index=.298; sensitivity=.571, specificity=.727) report AD8 were not significant. There were no significant differences between the domain-specific self-reported questionnaires and self-reported AD8 (memory n=25, z=.089, p=.929; attention n=25, z=.089, p=.929; spatial navigation n=25, z=.535, p=.593) and between

informant-report questionnaires and informant-reported AD8 (memory n=18, z=1.603, p=.109; attention n=18, z=.963, p=.336; spatial navigation n=18, z=.408, p=.684).

Figure 12: ROC curves comparing refined questionnaires and AD8 in predicting preclinical AD defined by hippocampal volume in the ADRC sample



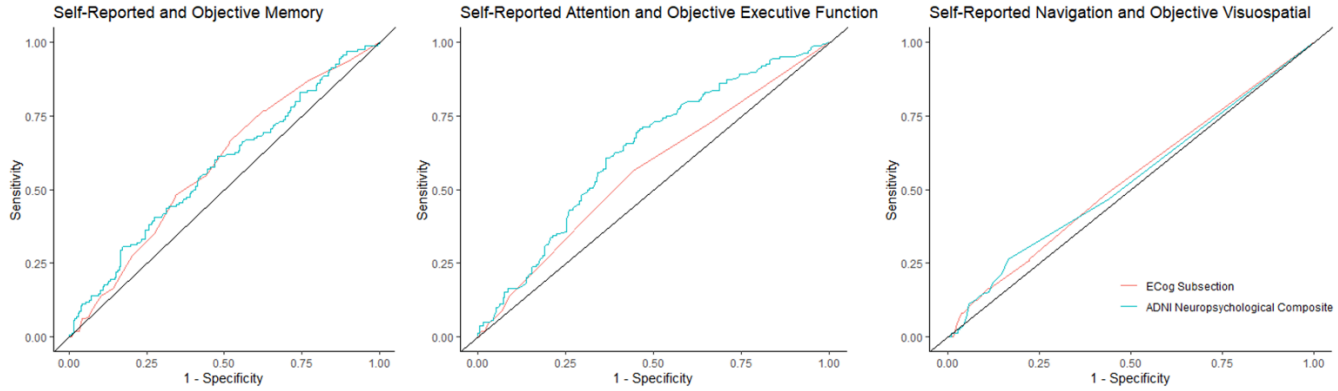
3.6.2 ADNI sample

Predicting preclinical AD defined by CSF ptau$_{181}$/Aβ$_{42}$ ratio

The AUCs for the objective memory (.576 (SE=.030), p=.012; Youden index=.134; sensitivity=.613, specificity=.521) and executive function composites (.633 (SE=.029), p<.001; Youden index=.246; sensitivity=.706, specificity=.540) were significant. The AUC for the objective visuospatial composite was not significant (.531 (SE=.031), p=.303; Youden index=-.096; sensitivity=.262, specificity=.834).

There was a nonsignificant trend for the objective executive function composite AUC to be higher than self-reported attention (n=371, z=1.738, p=.084). Self-reported memory and the objective memory composite AUCs and self-reported spatial navigation and the objective visuospatial composite AUCs did not significantly differ from each other (n=371, z=.154, p=.878 and n=371, z=.069, p=.945, respectively).

Figure 13: ROC curves comparing self-report and objective performance in predicting preclinical AD defined by CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADNI sample

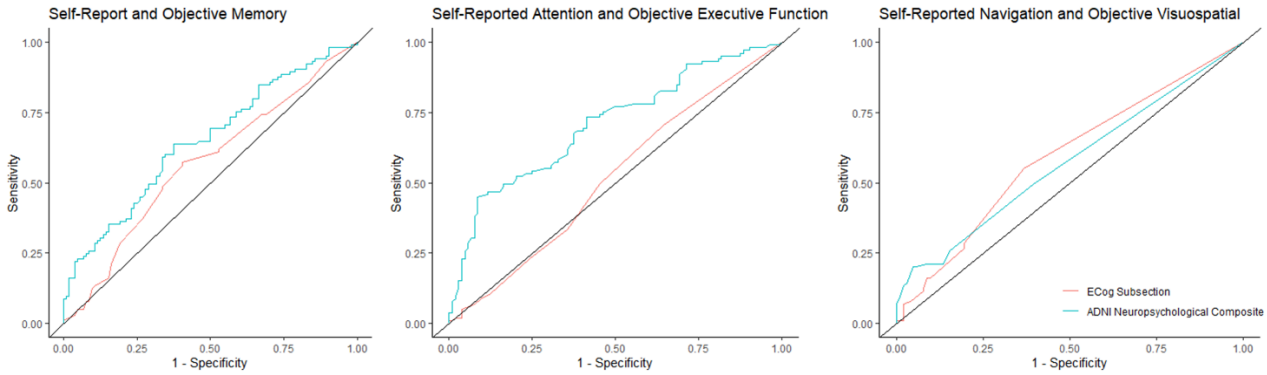


Preclinical AD defined by hippocampal volume

The AUCs for objective memory (.647 (SE=.038), p<.001; Youden index=.263; sensitivity=.638, specificity=.625) and objective executive function (.708 (SE=.036), p<.001; Youden index=.361; sensitivity=.448, specificity=.913) composites were significant. The objective visuospatial composite (.572 (SE=.040), p=.071; Youden index=.152; sensitivity=.200, specificity=.952) demonstrated a nonsignificant trend toward significance.

The objective executive function composite AUC was significantly higher than the self-reported attention AUC (n=209, z=3.880, p<.001). The AUCs between the objective memory composite and self-reported memory and between the objective visuospatial composite and self-reported spatial navigation were not significantly different (n=209, z=1.519, p=.129 and n=209, z=.439, p=.660, respectively).

Figure 14: ROC curves comparing self-report and objective performance in predicting preclinical AD defined by hippocampal volume in the ADNI sample



3.6.3 Summary

The self-reported AD8 was a significant predictor of preclinical AD defined by CSF biomarker burden but not hippocampal volume. Informant-reported AD8 was not a significant predictor of preclinical AD regardless of the biomarker used to define it. The refined questionnaires did not outperform the AD8 in predicting preclinical AD.

The objective memory and executive function composites were significant predictors of preclinical AD defined by both CSF biomarker burden and hippocampal volume. The objective visuospatial composite demonstrated a nonsignificant trend toward predicting preclinical AD defined by hippocampal volume but not CSF biomarker burden. The objective executive function composite outperformed self-reported attention in predicting preclinical AD as defined by hippocampal volume and demonstrated a nonsignificant trend when defined by CSF biomarker burden. The differences between objective memory composite and self-reported memory and between objective visuospatial composite and self-reported spatial navigation were not significant.

Taken together, the questionnaires included in the study were not more sensitive to preclinical AD than existing measures of cognition.

Chapter 4: Discussion

The current study provides preliminary evidence to support the hypothesis that self-reported cognitive change can contribute to effective screening for preclinical AD. Both the refined questionnaires and the ECog subsections demonstrated appropriate reliability and validity. In the ADRC sample, although the self-reported memory, attention, and spatial navigation questionnaires demonstrated high diagnostic accuracy, conclusions regarding clinical utility cannot be drawn given the underpowered nature of the analyses. In the ADNI sample, although the self-reported memory and attention ECog subsections were significant predictors of preclinical AD defined by CSF biomarker burden and the self-reported spatial navigation ECog subsection was significant predictor of preclinical AD defined by hippocampal volume, they demonstrated inadequate diagnostic accuracy suggesting limited clinical utility. The current study did not successfully identify an appropriate questionnaire measure to screen for preclinical AD.

4.1 Reliability and validity

All refined self and informant questionnaires demonstrated excellent internal consistency in the ADRC sample (all α>.90; DeVellis, 2012). This suggests there is potential redundancy in the questionnaires and there may be further opportunity to shorten them. Notably, the refined self-reported MAC-Q in the current study demonstrated higher internal consistency than previously reported in the literature (α=.91 and .57-.88, respectively; Crook et al., 1992; Truong et al., 2021). It is possible this difference is attributable to how the questionnaire assessed the period of change, with the original version asking about change "since high school or college" and the refined version asking about change "over the past several years." Participants and informants may be able to more reliably report more recent change. The refined self-reported

ACS-Short in the current study demonstrated similar internal consistency with previously published data (Derryberry & Reed, 2002; DeVito et al., 2018). Despite decreasing the number of items on the spatial navigation questionnaire from 20 to 10 items on the self-reported version and to 9 on the informant-report version, internal consistency remained in the excellent range. The current focus on cognitive mapping functions may continue to contribute to redundancy of items. Further shortening these questionnaires will make them extremely time-efficient and increase clinical utility.

All ECog subsections were within the fair to good range for internal consistency using Cronbach's alpha (DeVallis, 2012). This is consistent with previous literature demonstrating that the total ECog score has excellent internal consistency (.96; Farias et al., 2011). Internal consistency of subsections may be lower than the total ECog because Cronbach's alpha is impacted by number of items. Despite fewer items, each ECog subsection demonstrated acceptable internal consistency. It is unclear why the spatial navigation subsection had relatively lower internal consistency compared with the memory and attention subsections. One possibility is that participants and their informants have a more difficult time assessing behaviors related to spatial navigation that were queried in the ECog subsection. Specifically, the ECog subsection asked about navigation behaviors that may not be experienced often or require the combination of familiar and novel environments (e.g., "reading a map and helping with directions when someone else is driving"). Similarly, informants may not frequently observe participants engaging in these navigation behaviors (e.g., "finding his/her car in a parking lot"). In the ADRC sample, we confirmed that informants witnessed participants navigating regularly, but no informant information was available through ADNI. As such, it is possible the ADRC and ADNI sample informants differed in their relationship and interactions with the participants, which

could have affected internal consistency. Additionally, the refined questionnaire used in the ADRC sample was developed to specifically include behaviors thought to be engaged in often by participants and thought to be observable by informants.

Confirmatory factor analyses supported the hypothesis that each domain-specific measure represented a unique aspect of cognition using both the refined questionnaires and ECog subsections. Importantly, this suggests that both participants and informants were able to differentially report changes across cognitive domains and were not simply reporting general cognitive change. Broadly, these results support the proposed concept for the development of a domain-specific questionnaire for preclinical AD.

4.2 Diagnostic accuracy

Given the overall strong reliability and validity of the questionnaires, we further examined the diagnostic accuracy of each questionnaire in predicting preclinical AD. Broadly, self-reported cognitive change demonstrated potential in screening for preclinical AD, whereas informant-reported change did not. In the ADRC sample, all self-report questionnaires were significant predictors of preclinical AD defined by CSF biomarker burden but not hippocampal volume. In the ADNI sample, self-reported memory and attention were significant predictors of preclinical AD defined by CSF biomarker burden, but not hippocampal volume and spatial navigation was a significant predictor of preclinical AD defined by hippocampal volume but not CSF biomarker burden. However, these promising results come with important caveats: 1) the results from the ADRC sample are based on underpowered preliminary analyses, and 2) although significant, the AUCs in the ADNI sample did not provide adequate diagnostic accuracy for clinical use (all AUCs<.7; Mandrekar, 2010).

Self-reported memory and attention were significant predictors of preclinical AD defined by CSF biomarker burden in both samples. This observation is consistent with the substantial

body of literature associating objective performance on memory and attention neuropsychological and experimental tasks with AD biomarkers and progression along the AD continuum (Baker et al., 2017; Hedden et al., 2013; Balota et al., 2010; Millar et al., 2017). Additionally, in the ADNI sample, self-reported memory was significantly correlated with performance on objective memory tasks and self-reported attention demonstrated a marginal correlation with performance on objective executive function tasks. Thus, these data support the notion that self-reported cognitive change in these domains may be capturing aspects of objective performance in a more time-efficient way.

Although both objective spatial navigation performance and self-reported spatial navigation abilities were previously found to predict CSF biomarker burden (Allison et al., 2016; Allison et al., 2019), in the current study self-reported spatial navigation was a predictor of preclinical AD defined by CSF biomarker burden in the ADRC sample, but not in the ADNI sample. Notably, 55% of ADNI participants reported no change on all the spatial navigation items on the ECog subsection, whereas only 25% of the ADRC participants reported no change on all the spatial navigation items on the refined measure. This skew in the data may limit the ability of the spatial navigation subsection to detect preclinical AD in the ADNI sample. Additionally, item content varied between the ECog subsection and refined questionnaire. The ECog subsection primarily focused on reading maps (two items) and navigating familiar environments (three items). Conversely, the refined spatial navigation questionnaire focused on navigation of new environments (8/10 items). Navigating novel environments is more difficult than navigating familiar environments for individuals with AD, and therefore changes in the former may be more noticeable earlier in the disease process (Jheng & Pai, 2009). The

significant results observed in the ADRC sample suggests that spatial navigation has potential to detect CSF biomarker burden but may require probing of specific abilities.

Despite potential limitations in detecting CSF biomarker burden, self-reported spatial navigation was a significant predictor of preclinical AD defined by hippocampal volume in the ADNI sample. Of note, when preclinical AD was defined by hippocampal volume in the ADNI sample, only two-thirds of the sample was used (top and bottom tertile based on hippocampal volume). This potentially biased our results toward finding a significant result despite the skew in data because the independent variable was purposefully different between groups.

Interestingly, none of the self-reports were significant predictors of preclinical AD defined by hippocampal volume in the ADRC sample. Generally, this was consistent with the ADNI data where self-reported spatial navigation was the only questionnaire associated with preclinical AD defined by hippocampal volume. This could be due to the limited sample size in the ADRC cohort or to the methods used to establish a cutoff for preclinical AD defined by hippocampal volume in both samples. The full ADRC sample (n=32) had CSF data available, whereas only 25 participants had MRI data available. This may have impacted the precision of ROC analyses evidenced by wider confidence intervals when preclinical AD was defined by hippocampal volume compared to CSF $A\beta_{42}/A\beta_{40}$ ratio. Previous literature supports a specific cutoff for CSF biomarker burden, whereas a hippocampal volume cutoff for preclinical AD has yet to be established. As a result, a sample-specific cutoff was calculated using the bottom tertile of the sample's hippocampal volume. Another potential factor is that amyloidosis in the brain is thought to be the first neuropathological change that occurs on the AD continuum with hippocampal volume change occurring later in the disease process (Jack et al., 2018). The current samples consisted entirely of clinically normal participants, and it is possible that the

participants in the sample did not exhibit hippocampal volume change that would be reliably associated with cognitive change.

Although significant AUCs were produced by many of the self-reported questionnaires, none of the AUCs were significantly different from each other. Consequently, no single domain could be identified as being more appropriate for use as a screening measure of preclinical AD. Qualitatively, the self-reported spatial navigation AUC was greater than the self-reported memory and attention AUCs when preclinical AD was defined by CSF biomarker burden (spatial navigation AUC=.811, memory AUC=.748, attention AUC=.741) and hippocampal volume (spatial navigation AUC=.517, memory and attention AUCs=.469). In the future, a larger sample with appropriate power could be used to examine whether this qualitative difference becomes significant and whether a domain-specific screening measure may be recommended.

Informant-report measures were limited in their ability to identify preclinical status, suggesting that informant-reported cognitive change may have limitations in screening for the earliest signs of cognitive change. Only informant-reported memory in the ADNI sample demonstrated a trend toward significance (and was significant with outliers removed) in discriminating preclinical AD based on hippocampal volume. All other informant-report AUCs were not significant. In the ADNI sample, self-reported memory had a significantly higher AUC than informant-reported memory; all other self- and informant-report AUCs did not significantly differ in both samples. AUCs in the ADRC sample had very wide confidence intervals due to the very small sample size which limits our ability to interpret the results with certainty. In the ADNI sample, the lack of differences between the significant self-report AUCs and the nonsignificant informant-report AUCs highlight the limited clinical utility of the self-reported ECog subsections. Taken together, informant-reported cognitive complaints must be interpreted

with caution and may not be reflective of preclinical AD-related pathology. Future research should focus on potential ways to improve informants' ability to report cognitive change such has querying behaviors that may more often observed.

4.3 Predictive ability in the context of other factors

Although the current ROC analyses provided information regarding diagnostic accuracy, they had limitations: 1) required the use of a dichotomous outcome variable and 2) did not allow for covariates to be included in the model. As such, hierarchical linear regression was used to 1) examine the association between questionnaires and biomarker burden measured as a continuous variable and 2) examine how this association is impacted when controlling for factors associated with subjective cognition (e.g., personality or affect).

In the ADRC sample, neither self-reported nor informant-reported questionnaires were significant predictors of AD biomarkers controlling for covariates. Additionally, the observed lack of association between questionnaires and AD biomarkers was not impacted by participant or informant depressive or anxiety symptomatology, nor participant personality traits of neuroticism or conscientiousness.

In the ADNI sample, self-reported attention significantly predicted CSF biomarker burden, and this remained true when controlling for depressive symptoms and the interaction between self-reported attention and depressive symptoms and in a model controlling for the other two self-reported ECog subsections. This finding in combination with the significant AUCs for predicting preclinical AD defined by CSF biomarker burden, provide evidence for self-reported attention being particularly sensitive to CSF biomarker burden. However, this needs to be further explored to see if an attention questionnaire can demonstrate significantly better diagnostic accuracy than questionnaires assessing other domains.

Additionally, in the ADNI sample, the self-reported memory subsection significantly predicted hippocampal volume, and this remained true when controlling for depressive symptoms. This effect, however, became a nonsignificant trend when depressive symptoms was added to the model and outliers were removed. Furthermore, the effect became nonsignificant when the interaction between self-reported memory abilities and depressive symptoms was added to the model.

In post-hoc analyses considering the self-reported measures as dichotomous (e.g., change vs. no change), self-reported spatial navigation was a significant predictor of hippocampal volume even when controlling for depressive symptoms. The lack of significant results when using the full response range of the spatial navigation questionnaire could be due to the skew toward participants reporting no or very little change in spatial navigation abilities.

Taken together, these results suggest that participants and informants are able to report cognitive change without significant interference from personality or affective factors. This supports the idea that subjective reports could be used to assess cognitive change in the population broadly without having to consider individual differences related to personality or affect.

Notably, adding these personality or affective variables often decreased the adjusted R^2. This may be attributable to significant or marginally significant correlations between the cognitive questionnaires and personality and affective variables added to the model, as collinearity may impact variance explained (Appendix VI). Of note, all self-reported refined questionnaires and ECog subsections were significantly or marginally correlated with depressive symptoms (Appendix VI, Tables 52 and 56). Additionally, in the ADRC sample, due to the small

sample size, increasing the number of independent variables may be contributing to overfitting the model.

Interestingly, results from the linear regression analyses were not entirely consistent with ROC results. Specifically, self-reported memory was associated with hippocampal volume in the linear regression analysis but not the ROC analysis and self-reported spatial navigation was associated with the hippocampal volume in the ROC analysis but not the linear regression analysis when the full response range was considered. This inconsistency may be due to differences in the sample used; ROC analyses examined only the participants in the top and bottom hippocampal volume tertiles, whereas linear regression analyses examined only participants with self-reported depressive symptomatology available within one month of the ECog. In addition, this sample comprised of only ADNI participants who had depressive data available within a month of completing the ECog, and therefore the sample size was about half the size of the sample used in ROC analyses. Lastly, a large number of models were run as a part of this aim by nature of using hierarchical linear regression. This introduces the increased possibility of type one error. Given the consistency of association between self-reported attention ECog subsection and CSF biomarker burden, this result seems robust. However, the association between self-reported memory and spatial navigation subsections and hippocampal volume depended on how the sample was analyzed and as a result must be interpreted with caution.

4.4 Questionnaires compared to established measures of cognitive ability

Many other subjective and objective measures of cognition have been developed to try to detect cognitive change, including the AD8 and neuropsychological composites. As such, I wanted to compare the diagnostic accuracy of the questionnaires used in my study to the diagnostic accuracy of other measures of cognition in the same samples.

Neuropsychological assessment is considered the gold-standard for assessing cognitive ability. ADNI participants completed a comprehensive neuropsychological battery and cognitive composites for memory, executive function, and visuospatial abilities have been developed and validated to assess these domain-specific abilities. ADNI neuropsychological composites of memory and executive function significantly discriminated between biomarker normal and preclinical individuals defined by both CSF biomarker burden and hippocampal volume. However, only the executive function composite when predicting preclinical AD defined by hippocampal volume produced adequate diagnostic accuracy for clinical use (AUC=.708; Mandrekar, 2010). The visuospatial composite demonstrated a trend toward significance when preclinical AD was defined by hippocampal volume but was not significant when preclinical status was determined by the CSF biomarker burden. The visuospatial composite may have demonstrated limited discriminative ability because the visuospatial skills assessed were limited to construction ability (e.g., copying a clock and interlocking pentagons) and did not include other visuospatial skills highly associated with AD, such as topographical tasks (Salimi et al., 2018). Broadly, these results are consistent with previous literature that has found that neuropsychological assessments of memory and executive functioning are associated with preclinical AD, whereas neuropsychological assessments of visuospatial abilities are variably related to preclinical AD (for meta-analyses see Hedden et al., 2013 and Backman et al., 2005; for review see Salimi et al., 2018).

The AUC for executive function composite was significantly greater than the AUC for self-reported attention abilities when defining preclinical AD by hippocampal neurodegeneration and trended toward significance when defining preclinical AD by CSF biomarker burden. The AUC for executive function composite predicting preclinical AD defined by hippocampal

volume was the only measure to provide clinically appropriate diagnostic accuracy in the ADNI study (AUC=.708). The executive function composite contained measures of both attentional control (e.g., digit span) and executive planning (e.g., category fluency), making this a more comprehensive measure of executive abilities than the four item self-report attention subsection. Given the disparity in amount of information gathered, it is unclear whether the differences between the objective composite and self-report are due to better domain coverage of the composite or the superiority of objective measurement.

Notably, self-reported memory and objective memory composite yielded similar AUCs, which, while significant, produced inadequate diagnostic accuracy. This suggests that self-reported memory has the potential to provide as much diagnostic information as a lengthier neuropsychological assessment, thus providing support for using survey-based measures of memory abilities as a clinical screening method if a questionnaire with higher diagnostic accuracy could be developed. Additionally, AUCs did not differ between self-reported spatial navigation abilities and the objective visuospatial composite. These results did not support the hypothesis that a measure targeting spatial navigation abilities would outperform a measure of visuospatial ability unrelated to spatial navigation. The inability to detect a difference between self-reported visuospatial abilities and objective performance could be a limitation resulting from the ECog spatial navigation subsection not being developed to specifically detect subtle changes associated with the preclinical stage of AD.

It has long been recognized that neuropsychological assessment is too time intensive to be conducted widely in clinical settings as a screening measure and consequently there is a great need for time-efficient, valid and accurate screening measure for cognitive impairment (Cullen et al., 2007). Although there are a multitude of existing screening measures, due to the

heterogeneity of cognitive impairment resulting from neurodegenerative conditions. It is critical to identify a screening measure that is accurate in detecting preclinical AD-related cognitive change specifically. In the ADRC sample, the AD8, a commonly used self- and informant-reported measure of cognitive change in early symptomatic AD, performed similarly in predicting preclinical AD as the refined questionnaires of memory, attention, and spatial navigation. The self-reported AD8 was a significant predictor of CSF biomarker burden, whereas the informant-report AD8 was not. Although the self-reported AD8 and self-reported cognitive questionnaires were all significant predictors of preclinical AD defined by CSF biomarker burden, no one questionnaire outperformed any of the others. Qualitatively the self-reported AD8 had a slightly higher AUC than the self-report questionnaires when preclinical AD was defined by CSF biomarker burden (AD8 AUC=.827). This was inconsistent with the hypothesis that domain-specific cognitive change would outperform the AD8 in identifying preclinical AD because the AD8 was developed to assess broad cognitive change across several domains rather than preclinical-related cognitive change specifically. A larger sample will be required to examine this effect further. Neither version of the AD8 was significant in predicting preclinical AD defined by hippocampal volume. This discrepancy could be due to using a sample specific volumetric cutoff to defined preclinical AD because of the the lack of an established cutoff. Although the AD8 was developed to detect symptomatic AD, these preliminary results suggest the self-reported AD8 may also have clinical utility in preclinical samples. The informant-reported AD8 may have more limited utility in detecting preclinical AD-related change for the same reasons as domain-specific informant reports: informants may not be able to readily observe the subtle change associated with this stage of the disease.

4.5 Limitations

It is critical to address the limitations of the current work. Primarily, the ADRC sample was severely underpowered to detect the effects examined based on a priori power analyses. To maximize the ADRC sample available, we extended the timeframe for which biomarker data could be included from within two years of self-report questionnaires to within four years. As such, some participants may have entered the preclinical stage since their last lumbar puncture or MRI and been already in the preclinical stage when completing the surveys. Additionally, the purpose of refining previously existing measures was to make them increasingly more sensitive to cognitive change specifically related to preclinical AD (e.g., instructing participants and informants to reflect on change over the past several years). This refinement was impossible to complete using previously collected ADNI ECog data. Although the analyses using the ECog subsections were properly powered, appropriating a measure developed to assesses more basic functioning (e.g., "Remembering the current date or day of the week) over a ten year period for preclinical AD-related cognitive change may have contributed to the limited diagnostic accuracy and sensitivity observed.

4.6 Conclusion

Taken together, this study suggests that self-reported cognitive change represents a promising screening tool for preclinical AD; however, continued work needs to be done to establish an effective self-report screening measure. Notably, none of the significant AUCs in the ADNI sample provided robust diagnostic accuracy in identifying preclinical AD. This highlights the need for continued refinement of self-report questionnaire measures in the preclinical phase. To address this gap in the literature, we are continuing to collect data within the ADRC to examine whether refined questionnaires continue to provide acceptable diagnostic accuracy in clinically normal samples. These analyses, when properly powered, can inform

whether self- and/or informant-reported cognitive change could be used as a screening measure for preclinical AD and which cognitive domain is most appropriate for such a measure. Additionally, we plan to examine the ADRC sample longitudinally to determine whether these questionnaires predict clinical progression to symptomatic AD.

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Appendix I: Self- and informant-reported questionnaires

Appendix I.I: Original Self-report spatial navigation

This questionnaire asks about changes in your ability to travel to new places over the past several years. Please base your responses on changes related to thinking or memory difficulties. New places should include any place that you have never been before, such as a new city, new restaurant, new neighborhood, etc. Traveling can include any mode of transportation, such as driving, walking, biking, etc.

You will respond to each item on a scale of 1 to 7. 1 represents that you strongly disagree with the statement. 7 represents that you strongly agree with the statement. You may or may not have experienced any of the changes listed in this questionnaire. Please just respond the best you can to each question.

1. I have greater difficulty finding my way to a new place.
2. It takes me longer to learn a route to a new place.
3. I have greater difficulty following directions to a new place.
4. I have greater difficulty forming a mental map of a new place.
5. I have greater difficulty remembering the direction associated with each landmark along a new route, such as a right turn at the gas station.
6. I have greater difficulty memorizing directions in order to get to a new place.
7. It takes me longer to get to a new place.
8. I have greater difficulty using a directory to find a store in a shopping mall.
9. I am more likely to stop and ask someone for directions when traveling to a new place.
10. I have greater difficulty finding my way in a new building.
11. I have greater difficulty using a map to navigate to a new place.
12. It takes me longer to realize I have made a wrong turn when traveling to a new place.
13. I have greater difficulty using an alternate route when traveling to a familiar place.
14. It takes me longer to get home from a new place.
15. I am more likely to get lost when traveling to a new place.
16. I am more likely to make a wrong turn when traveling to a new place.
17. I have greater difficulty giving directions to other people.
18. I have greater difficulty understanding directions in terms of north, south, east, and west.
19. I have greater difficulty returning home from a new place.
20. I have greater difficulty estimating the number of blocks or miles of a new route that I have traveled once.

Appendix I.II: Refined Self-report spatial navigation

This questionnaire asks about changes in your ability to travel to new places over the past several years. Please base your responses on changes related to thinking or memory difficulties. New places should include any place that you have never been before, such as a new city, new restaurant, new neighborhood, etc. Traveling can include any mode of transportation, such as driving, walking, biking, etc.

You will respond to each item on a scale of 1 to 7. 1 represents that you strongly disagree with the statement. 7 represents that you strongly agree with the statement. You may or may not have experienced any of the changes listed in this questionnaire. Please just respond the best you can to each question.

1. I have greater difficulty finding my way to a new place.
2. It takes me longer to learn a route to a new place.
3. I have greater difficulty forming a mental map of a new place.
4. I have greater difficulty memorizing directions in order to get to a new place.
5. I have greater difficulty using a directory to find a store in a shopping mall.
6. I have greater difficulty using a map to navigate to a new place.
7. It takes me longer to get home from a new place.
8. I am more likely to get lost when traveling to a new place.
9. I am more likely to make a wrong turn when traveling to a new place.
10. I have greater difficulty understanding directions in terms of north, south, east, and west.

Appendix I.III: Original Informant-report spatial navigation

This questionnaire asks about changes in your spouse's, partner's, friend's, sibling's, or parent's ability to travel to new places over the past several years. Please base your responses on changes related to thinking or memory difficulties. New places should include any place that they have never been before, such as a new city, new restaurant, new neighborhood, etc. Traveling can include any mode of transportation, such as driving, walking, biking, etc.

You will respond to each item on a scale of 1 to 7. 1 represents that you strongly disagree with the statement. 7 represents that you strongly agree with the statement. They may or may not have experienced any of the changes listed in this questionnaire. Please just respond the best you can to each question.

1. They have greater difficulty finding their way to a new place.
2. It takes them longer to learn a route to a new place.
3. They have greater difficulty following directions to a new place.
4. They have greater difficulty forming a mental map of a new place.
5. They have greater difficulty remembering the direction associated with each landmark along a new route, such as a right turn at the gas station.
6. They have greater difficulty memorizing directions in order to get to a new place.
7. It takes them longer to get to a new place.
8. They have greater difficulty using a directory to find a store in a shopping mall.
9. They are more likely to stop and ask someone for directions when traveling to a new place.
10. They have greater difficulty finding their way in a new building.
11. They have greater difficulty using a map to navigate to a new place.
12. It takes them longer to realize they have made a wrong turn when traveling to a new place.
13. They have greater difficulty using an alternate route when traveling to a familiar place.
14. It takes them longer to get home from a new place.
15. They are more likely to get lost when traveling to a new place.
16. They are more likely to make a wrong turn when traveling to a new place.
17. They have greater difficulty giving directions to other people.
18. They have greater difficulty understanding directions in terms of north, south, east, and west.
19. They have greater difficulty returning home from a new place.
20. They have greater difficulty estimating the number of blocks or miles of a new route that they have traveled once.

Appendix II.IV: Refined Informant-report spatial navigation

This questionnaire asks about changes in your spouse's, partner's, friend's, sibling's, or parent's ability to travel to new places over the past several years. Please base your responses on changes related to thinking or memory difficulties. New places should include any place that they have never been before, such as a new city, new restaurant, new neighborhood, etc. Traveling can include any mode of transportation, such as driving, walking, biking, etc.

You will respond to each item on a scale of 1 to 7. 1 represents that you strongly disagree with the statement. 7 represents that you strongly agree with the statement. They may or may not have experienced any of the changes listed in this questionnaire. Please just respond the best you can to each question.

1. They have greater difficulty finding their way to a new place.
2. It takes them longer to learn a route to a new place.
3. They have greater difficulty memorizing directions in order to get to a new place.
4. They have greater difficulty using a directory to find a store in a shopping mall.
5. They have greater difficulty using a map to navigate to a new place.
6. It takes them longer to get home from a new place.
7. They are more likely to get lost when traveling to a new place.
8. They are more likely to make a wrong turn when traveling to a new place.
9. They have greater difficulty understanding directions in terms of north, south, east, and west.

Appendix I.V: Original MAC-Q

As compared to when you were in high school or college, how would you describe your ability to perform the following tasks involving your memory?

Response Scale: 1 = Much better than now; 2 = Somewhat better than now; 3 = About the same; 4 = Somewhat poorer now; 5 = Much poorer than now

1. Remembering the name of a person just introduced to you.
2. Recalling telephone numbers or zip codes that you use on a daily or weekly basis.
3. Recalling where you put objects (such as keys) in your home or office.
4. Remembering specific facts from a newspaper or magazine article you have just finished reading.
5. Remembering the item(s) you intend to buy when you arrive at the grocery store or pharmacy.
6. In general, how would you describe your memory compared to when you were in high school?

Index Calculations: An overall index of cognitive decline is calculated by summing scores for all 6 items, with double weighting for item f; higher scores indicate greater decline in memory.

Appendix I.VI: Refined Self-Report MAC-Q

This questionnaire asks about changes in your memory over the past several years.

You will respond to each item on a scale of 1 to 7. 1 represents that you strongly disagree with the statement. 7 represents that you strongly agree with the statement. You may or may not have experienced any of the changes listed in this questionnaire. Please just respond the best you can to each question.

1. I have greater difficulty remembering the name of a person just introduced to me.
2. I have greater difficulty recalling telephone numbers that I use on a daily or weekly basis.
3. **I have greater difficulty recalling the content of conversations I have recently had.**
4. I have greater difficulty recalling where I put objects (such as keys) in my home or office.
5. I have greater difficulty remembering specific facts from a newspaper or magazine article I have just finished reading.
6. **I have greater difficulty coming up with the right words even when I know what I am trying to say.**
7. I have greater difficulty remembering the item(s) I intend to buy when I arrive at the grocery store or pharmacy.
8. In general, my memory is worse than it was several years ago.

Appendix I.VII: Refined Informant-Report MAC-Q

This questionnaire asks about changes in your spouse's, partner's, friend's, sibling's or parent's memory over the past several years.

You will respond to each item on a scale of 1 to 7. 1 represents that you strongly disagree with the statement. 7 represents that you strongly agree with the statement. They may or may not have experienced any of the changes listed in this questionnaire. Please just respond the best you can to each question.

1. They have greater difficulty remembering the name of a person just introduced to them.
2. They have greater difficulty recalling telephone numbers that they use on a daily or weekly basis.
3. They have greater difficulty recalling the content of conversations they have recently had.
4. They have greater difficulty recalling where they put objects (such as keys) in their home or office.
5. They have greater difficulty remembering specific facts from a newspaper or magazine article they have just finished reading.
6. They have greater difficulty coming up with the right words even when they know what they are trying to say.
7. They have greater difficulty remembering the item(s) they intend to buy when they arrive at the grocery store or pharmacy.
8. In general, their memory is worse than it was several years ago.

Appendix I.VIII: Original ACS (questions included in short form in bold)

Here are some different ways that people can feel about working and concentrating. Please indicate how strongly each statement applies to you.

Response Scale: 1 = almost never; 2 = sometimes; 3 = often; 4 = always

1. **Hard for me to concentrate on a difficult task when there are noises around.**
2. **When need to concentrate/solve a problem, trouble focusing.**
3. **When working on something, still get distracted by events around me.**
4. Concentration is good, even if there is music in the room around me
5. When concentrating, can focus and become unaware
6. **When reading/studying, get easily distracted if people talking.**
7. **7.When trying to focus, have difficulty blocking out distracting thoughts.**
8. **Have a hard time concentrating when excited about something.**
9. When concentrating, ignore feelings of hunger or thirst.
10. **Can quickly switch from one task to another.**
11. Takes me a while to get really involved in a new task
12. **Difficult to coordinate attention between listening/writing.**
13. **Can become interested in a new topic very quickly when I need to.**
14. **Easy for me to read/write while talking on the phone.**
15. Have trouble carrying on two conversations at once.
16. Have hard time coming up with new ideas quickly.
17. **After being interrupted/distracted, easily shift attention back.**
18. **Distracting thought comes to mind, easy for me to shift my attention away.**
19. **Easy for me to alternate between two different tasks.**
20. Hard to break from one way of thinking to another.

Appendix I.IX: Refined Self-Report ACS-Short

You will respond to each item on a scale of 1 to 7. 1 represents that you strongly disagree with the statement. 7 represents that you strongly agree with the statement. You may or may not have experienced any of the changes listed in this questionnaire. Please just respond the best you can to each question.

1. I have greater difficulty concentrating on a difficult task when there are noises around.
2. I have more trouble focusing when I need to concentrate/solve a difficult problem.
3. I get more distracted by events around me when working on something.
4. I get more distracted if people are talking when I am reading.
5. I have greater difficulty blocking out distracting thoughts when trying to focus.
6. I have difficulty concentrating when I am excited about something.
7. I have greater difficulty switching from one task to another.
8. I have greater difficulty coordinating attention between listening/writing.
9. I have greater difficulty becoming interested in a new topic very quickly when I need to.
10. I have greater difficulty reading/writing while talking on the phone.
11. I have greater difficulty shifting my attention back after being interrupted/distracted.
12. I have greater difficulty shifting my attention away when a distracting thought comes to mind.
13. I have greater difficulty alternating between two different tasks.

Appendix I.X: Refined Informant-Report ACS-Short

This questionnaire asks about changes in your spouse's, partner's, friend's, sibling's or parent's attention over the past several years.

You will respond to each item on a scale of 1 to 7. 1 represents that you strongly disagree with the statement. 7 represents that you strongly agree with the statement. They may or may not have experienced any of the changes listed in this questionnaire. Please just respond the best you can to each question.

1. They have greater difficulty concentrating on a difficult task when there are noises around.
2. They have more trouble focusing when they need to concentrate/solve a difficult problem.
3. They get more distracted by events around them when working on something.
4. They get more distracted if people are talking when they are reading.
5. They have greater difficulty blocking out distracting thoughts when trying to focus.
6. They have difficulty concentrating when they are excited about something.
7. They have greater difficulty switching from one task to another.
8. They have greater difficulty coordinating attention between listening/writing.
9. They have greater difficulty becoming interested in a new topic very quickly when they need to.
10. They have greater difficulty reading/writing while talking on the phone.
11. They have greater difficulty shifting their attention back after being interrupted/distracted.
12. They have greater difficulty shifting their attention away when a distracting thought comes to mind.
13. They have greater difficulty alternating between two different tasks.

Appendix I.XI: Self-Report ECog Subsections

Compared to 10 years ago, has there been any change in…

Response scale: 1=better or no change; 2=questionable/occasional change; 3=consistently a little worse; 4=consistently much worse

Memory

1. Remembering a few shopping items without a list.
2. Remembering things that happened recently (such as recent outings, events in the news).
3. Recalling conversations a few days later.
4. Remembering where I have placed objects.
5. Repeating stories and/or questions.
6. Remembering the current date or day of the week.
7. Remembering I have already told someone something.
8. Remembering appointments, meetings, or engagements.

Spatial Navigation

1. Following a map to find a new location.
2. Reading a map and helping with directions when someone else is driving.
3. Finding my car in a parking lot.
4. Finding the way back to a meeting spot in the shopping mall or other location.
5. Finding my way around a familiar neighborhood.
6. Finding my way around a familiar store.
7. Finding my way around a house visited many times.

Divided Attention

1. The ability to do two things at once.
2. Returning to a task after being interrupted.
3. The ability to concentrate on a task without being distracted by external things in the environment.
4. Cooking or working and talking at the same time.

Appendix I.X11: Informant-Report ECog Subsections

Compared to 10 years ago, has there been any change in…

Response scale: 1=better or no change; 2=questionable/occasional change; 3=consistently a little worse; 4=consistently much worse

Memory

1. Remembering a few shopping items without a list.
2. Remembering things that happened recently (such as recent outings, events in the news).
3. Recalling conversations a few days later.
4. Remembering where she/he has placed objects.
5. Repeating stories and/or questions.
6. Remembering the current date or day of the week.
7. Remembering he/she has already told someone something.
8. Remembering appointments, meetings, or engagements.

Spatial Navigation

1. Following a map to find a new location.
2. Reading a map and helping with directions when someone else is driving.
3. Finding his/her car in a parking lot.
4. Finding the way back to a meeting spot in the shopping mall or other location.
5. Finding his/her way around a familiar neighborhood.
6. Finding his/her way around a familiar store.
7. Finding his/her way around a house visited many times.

Divided Attention

1. The ability to do two things at once.
2. Returning to a task after being interrupted.
3. The ability to concentrate on a task without being distracted by external things in the environment.
4. Cooking or working and talking at the same time.

Appendix II: Aim 1.2 data

This appendix presents the data used to shorten the original spatial navigation questionnaire in primary study aim 1.2

Table 17: Confirmatory factor analysis: Original self-reported spatial navigation questionnaire

Measure	Estimate	Standard Error	p-value
Self-Report Item 1	.830	.047	>.0001
Self-Report Item 2	.825	.049	>.0001
Self-Report Item 3	.747	.075	>.0001
Self-Report Item 4	.873	.038	>.0001
Self-Report Item 5	.924	.029	>.0001
Self-Report Item 6	.913	.030	>.0001
Self-Report Item 7	.897	.037	>.0001
Self-Report Item 8	.870	.041	>.0001
Self-Report Item 9	.545	.081	>.0001
Self-Report Item 10	.950	.016	>.0001
Self-Report Item 11	.766	.061	>.0001
Self-Report Item 12	.944	.019	>.0001
Self-Report Item 13	.751	.063	>.0001
Self-Report Item 14	.901	.039	>.0001
Self-Report Item 15	.914	.030	>.0001
Self-Report Item 16	.827	.043	>.0001
Self-Report Item 17	.946	.019	>.0001
Self-Report Item 18	.870	.035	>.0001
Self-Report Item 19	.869	.032	>.0001
Self-Report Item 20	.938	.023	>.0001
$ptau_{181}/A\beta_{42}$ ratio	.238	.133	.072
CM-Learning	-.004	.104	.961
CM-Retrieval	-.016	.119	.893
Shape-Color Binding	-.092	.122	.451
Shape-Location Binding	-.007	.110	.949
Perspective Taking	.076	.097	.437

Table 18: Confirmatory factor analysis: Original informant-reported spatial navigation questionnaire

Measure	Estimate	Standard Error	p-value
Informant-Report Item 1	.876	.047	>.0001
Informant-Report Item 2	.784	.068	>.0001
Informant-Report Item 3	.787	.067	>.0001
Informant-Report Item 4	.886	.046	>.0001
Informant-Report Item 5	.847	.051	>.0001
Informant-Report Item 6	.922	.032	>.0001
Informant-Report Item 7	.818	.056	>.0001
Informant-Report Item 8	.897	.053	>.0001
Informant-Report Item 9	.534	.106	>.0001
Informant-Report Item 10	.909	.032	>.0001
Informant-Report Item 11	.825	.078	>.0001
Informant-Report Item 12	.950	.019	>.0001
Informant-Report Item 13	.799	.081	>.0001
Informant-Report Item 14	.928	.027	>.0001
Informant-Report Item 15	.884	.045	>.0001
Informant-Report Item 16	.861	.041	>.0001
Informant-Report Item 17	.887	.039	>.0001
Informant-Report Item 18	.905	.031	>.0001
Informant-Report Item 19	.835	.059	>.0001
Informant-Report Item 20	.942	.023	>.0001
$ptau_{181}/A\beta_{42}$ ratio	.630	.197	.001
CM-Learning	-.222	.140	.112
CM-Retrieval	.199	.122	.101
Shape-Color Binding	.061	.129	.638
Shape-Location Binding	.178	.127	.159
Perspective Taking	.004	.119	.971

Table 19: Secondary analyses for self-reported spatial navigation questionnaire items

Measure	$ptau_{181}$ F	$ptau_{181}$ R^2	$A\beta_{42}$ F	$A\beta_{42}$ R^2	Alpha	ISC	ICC	Test-Retest
Self-Report Item 1	.038	.001	**3.299**	.105	.962	.822	.623	.661
Self-Report Item 2	**2.573**	.084	**5.553**	.166	.963	.787	*.593*	*.517*
Self-Report Item 3	.279	.010	1.496	.051	.964	*.649*	*.501*	*.628*
Self-Report Item 4	**2.76**	.090	1.422	.048	.963	.787	.607	*.540*
Self-Report Item 5	.548	019	.276	.010	.962	.859	.657	*.492*
Self-Report Item 6	.519/**3.73**	.018	.381	.013	.962	.837	.68	.679
Self-Report Item 7	.216	.008	.418	.015	.963	.810	.632	*.541*
Self-Report Item 8	.061	.002	.195	.007	.963	*.750*	*.584*	.736
Self-Report Item 9	1.104	.038	.474	.017	*.968*	*.530*	*.362*	*.612*
Self-Report Item 10	.761	.027	.007	*<.001*	.961	.893	.686	.739
Self-Report Item 11	**3.549**	.113	.718	.025	.965	*.653*	*.497*	.684
Self-Report Item 12	.183	.007	.338	.012	.962	.885	.685	.729
Self-Report Item 13	.062	.002	.411	.015	.964	*.667*	*.508*	*.510*
Self-Report Item 14	**2.23**	.074	1.288	.044	.963	.806	.629	*.509*
Self-Report Item 15	.138	.005	**2.958**	.096	.962	.862	.660	*.562*
Self-Report Item 16	.111	.004	**2.977**	.096	.963	*.765*	*.570*	.656
Self-Report Item 17	.005	*<.001*	.891	.031	.962	.881	.671	.652
Self-Report Item 18	.106	.004	1.453	.049	.963	.803	.602	.786
Self-Report Item 19	.013	*<.001*	1.472/**4.50**	.050	.963	.817	.616	.659
Self-Report Item 20	.072	.003	.885	.031	.963	.857	.662	.734

F, linear regression F-statistic; ISC, item-scale correlation; ICC, inter-item correlation. **Bolded** values indicate support for inclusion. *Italicized* values indicate support for exclusion. Results changed with outliers removed presented (all data/without outliers)

Table 20: Secondary analyses for informant-reported spatial navigation questionnaire items

Measure	$ptau_{181}$ F	$ptau_{181}$ R^2	$A\beta_{42}$ F	$A\beta_{42}$ R^2	Alpha	ISC	ICC	Test-Retest
Informant-Report Item 1	.027	.001	.218	.009	.954	.799	.590	*.542*
Informant-Report Item 2	**5.035**	.180	1.515	.062	.956	*.691*	*.500*	*.521*
Informant-Report Item 3	.492	.021	.105	.005	.957	*.601*	*.441*	*.467*
Informant-Report Item 4	**1.358**	.056	.003	*<.001*	.955	*.742*	*.550*	*.517*
Informant-Report Item 5	.974	.041	.493	.021	.954	.780	.571	.595
Informant-Report Item 6	.762	.032	.585	.025	.954	.802	.597	*.459*
Informant-Report Item 7	.510	.022	.265	.011	.955	*.722*	*.530*	*.529*
Informant-Report Item 8	.356	.015	.432	.018	.954	.802	.599	*.488*
Informant-Report Item 9	.003	*<.001*	.259	.011	*.963*	*.549*	*.359*	.575
Informant-Report Item 10	.066	.003	.629	.027	.954	.827	.607	.644
Informant-Report Item 11	.413	.018	.092	.004	.956	*.706*	*.520*	.814
Informant-Report Item 12	.310	.013	.062	.003	.953	.870	.648	*.514*
Informant-Report Item 13	.144	.006	2.051	.082	.955	*.732*	*.542*	.662
Informant-Report Item 14	.762	.032	.585	.025	.955	.798	.599	.612
Informant-Report Item 15	.269	.012	1.961	.079	.954	.780	.582	*.415*
Informant-Report Item 16	.092	.004	**13.480**	.369	.954	.802	.576	.668
Informant-Report Item 17	<.001	*<.001*	2.037	.081	.954	.803	.600	.577
Informant-Report Item 18	.287	.012	.777	.033	.953	.841	.609	.653
Informant-Report Item 19	.002	*<.001*	1.473	.060	.955	*.759*	*.548*	.601
Informant-Report Item 20	.210	.009	.838	.035	.954	.849	.632	*.360*

F, linear regression F-statistic; ISC, item-scale correlation; ICC, inter-item correlation. **Bolded** values indicate support for inclusion. *Italicized* values indicate support for exclusion.

Table 21: Summary of inclusion and exclusion decisions for original self-reported spatial navigation questionnaire items

Item	Decision	Inclusion Support	Exclusion Support
1	Include	Associated with $A\beta_{42}$	
2	Include	Associated with $A\beta_{42}$ Associated with $ptau_{181}$	
3	Exclude		Low IIC Low ISC Low test-retest reliability
4	Include	Associated with $ptau_{181}$ Cognitive mapping content	
5	Exclude		Low test-retest reliability Route learning content
6	Include	Associated with $ptau_{181}$ with outlier removed	
7	Exclude		Low test-retest reliability Content overlaps with item 1
8	Include	Cognitive mapping content	
9	Exclude		Low IIC Low ISC Low test-retest reliability Alpha higher when excluded Low factor loading on CFA
10	Exclude		Low association with $A\beta_{42}$
11	Include	Associated with $ptau_{181}$ Cognitive mapping content	
12	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$
13	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$ Low IIC Low test-retest
14	Include	Associated with $A\beta_{42}$ Cognitive mapping content	
15	Include	Associated with $A\beta_{42}$	
16	Include	Associated with $A\beta_{42}$	
17	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$
18	Include	Associated with $A\beta_{42}$ with outlier removed Cognitive mapping content	
19	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$
20	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$

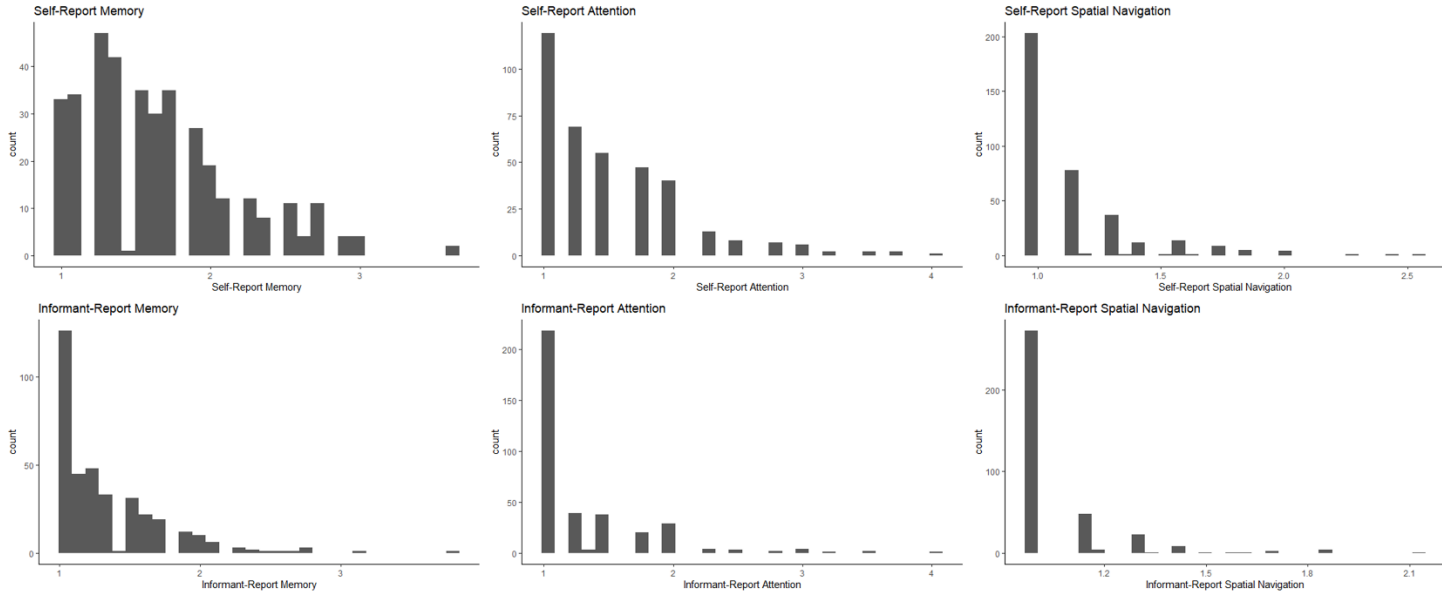
Table 22: Summary of inclusion and exclusion decisions for original self-reported spatial navigation questionnaire items

Item	Decision	Inclusion Support	Exclusion Support
1	Include	No evidence to support omission	
2	Include	Associated with $A\beta_{42}$ Associated with $ptau_{181}$	
3	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$ Low IIC Low ISC Low test-retest reliability
4	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$ Low IIC Low ISC Low test-retest Does not reference observable behavior
5	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$ Route learning content
6	Include	No strong evidence for omission, keep for consistency with self-report	
7	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$ Low IIC Low ISC
8	Include	Keep for consistency with self-report	
9	Exclude		Low IIC Low ISC Low test-retest reliability Alpha higher when excluded Low factor loading on CFA
10	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$
11	Include	Cognitive mapping content	
12	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$
13	Exclude		Low association with $ptau_{181}$ Low IIC Low ISC
14	Include	Keep for consistency with self-report	
15	Include	No evidence to support omission	
16	Include	Associated with $A\beta_{42}$	
17	Exclude		Low association with $ptau_{181}$

18	Include	No evidence to support omission	
19	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$
20	Exclude		Low association with $A\beta_{42}$ Low association with $ptau_{181}$ Low test-retest reliability Behavior may be difficult to observe

Appendix III: Histograms of total ECog scores in ADNI sample

Figure 15. Raw ECog scores in ADNI sample



Appendix IV: Aim 2 post-hoc data

Table 23. ROC analyses predicting CSF $ptau_{181}/A\beta_{42}$ ratio in the ADRC sample

	Sensitivity	Specificity	Youden Index	AUC	95% CI	SE	p
Self-Reported Memory	1.00	.348	.348	.691	.495-.887	.100	.098#
Self-Reported Attention	.778	.696	.474	.696	.497-.894	.101	.090#
Self-Reported Navigation	.889	.739	.628	.756	.580-.932	.090	.026*
Informant-Reported Memory	.400	1.00	.400	.594	.267-.922	.167	.526
Informant-Reported Attention	.400	.500	-.100	.600	.276-.924	.165	.502
Informant-Reported Navigation	.800	.500	.300	.528	.253-.803	.140	.852
Combined Memory	.400	1.00	.400	.633	.316-.950	.162	.371
Combined Attention	.400	1.00	.400	.578	.240-.916	.173	.602
Combined Navigation	.800	.444	.244	.533	.238-.829	.151	.823

Notes. AUC=Area Under the Curve; CI=Confidence Interval; SE=Standard Error; * indicates p<.05; # indicates p<.1

Table 24. Comparing AUCs in young-old and old-old in predicting CSF $ptau_{181}/A\beta_{42}$ ratio in the ADNI sample

	Young-Old	Old-Old	p-value
Self-Reported Memory	.539	.621	.178
Self-Reported Attention	.525	.604	.187
Self-Reported Navigation	.485	.555	.216
Informant-Reported Memory	.477	.477	.997
Informant-Reported Attention	.529	.501	.613
Informant-Reported Navigation	.509	.510	.984

p-value from Delong, Delong, Pearson method for comparing AUCs across young-old and old-old

Table 25. Comparing AUCs in young-old and old-old in predicting Hippocampal volume in the ADNI sample

	Young-Old	Old-Old	p-value
Self-Reported Memory	.579	.519	.547
Self-Reported Attention	.463	.577	.264
Self-Reported Navigation	.523	.636	.204
Informant-Reported Memory	.604	.558	.693
Informant-Reported Attention	.629	.475	.086
Informant-Reported Navigation	.570	.570	.997

p-value from Delong, Delong, Pearson method for comparing AUCs across young-old and old-old

Appendix V: Aim 3 results

Table 26: Self-reported memory hierarchical linear regression predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.089	.135		
Step 2 Model				.115	.121	.026	.026
Self-Reported Memory	-.248	-1.354	.187				
Step 3 Model: Depression				.105	.163	-.010	.016
Self-Reported Memory	-.156	-.729	.473				
Depressive Symptoms	.170	-.833	.412				
Step 3 Model: Anxiety				.082	.209	-.033	-.007
Self-Reported Memory	-.251	-1.334	.194				
Anxiety Symptoms	.022	.124	.902				
Step 3 Model: Neuroticism				.142	.108	.027	.053
Self-Reported Memory	-.280	-1.539	.136				
Neuroticism	-.235	-1.359	.186				
Step 3 Model: Conscientiousness				.104	.165	-.011	.015
Self-Reported Memory	-.193	-.983	.335				
Conscientiousness	.151	.813	.424				

Table 27: Self-reported spatial navigation hierarchical linear regression predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.089	.135		
Step 2 Model				.104	.140	.015	.015
Self-Reported Navigation	-.231	-1.212	.236				
Step 3 Model: Depression				.103	.167	-.001	.014
Self-Reported Navigation	-.145	-.691	.496				
Depressive Symptoms	-.191	-.991	.331				
Step 3 Model: Anxiety				.071	.233	-.033	-.018
Self-Reported Navigation	-.237	-1.206	.239				
Anxiety Symptoms	.036	.195	.847				
Step 3 Model: Neuroticism				.124	.132	.020	.035
Self-Reported Navigation	-.253	-1.338	.193				
Neuroticism	-.222	-1.276	.213				
Step 3 Model: Conscientiousness				.098	.177	-.006	.009
Self-Reported Navigation	-.176	-.878	.388				
Conscientiousness	.165	.898	.377				

Table 28: All self-reported questionnaires hierarchical linear regression predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.089	.135		
Step 2 Model							
Self-Reported Memory	.115	.303	.764	.094	.207	.005	.005
Self-Reported Attention	-.384	-1.125	.271				
Self-Reported Navigation	-.026	-.090	.929				
Step 3 Model: Depression				.064	.290	-.030	-.025
Self-Reported Memory	.119	.309	.760				
Self-Reported Attention	-.328	-.892	.381				
Self-Reported Navigation	-.027	-.090	.929				
Depressive Symptoms	-.100	-.450	.656				
Step 3 Model: Anxiety				.062	.295	-.032	-.027
Self-Reported Memory	.139	.356	.725				
Self-Reported Attention	-.410	-1.159	.258				
Self-Reported Navigation	-.038	-.128	.899				
Anxiety Symptoms	.073	.388	.701				
Step 3 Model: Neuroticism				.122	.180	.028	.131
Self-Reported Memory	.080	.214	.833				
Self-Reported Attention	-.381	-1.134	.268				
Self-Reported Navigation	-.0248	-.087	.931				
Neuroticism	-.234	-1.335	.194				
Step 3 Model: Conscientiousness				.083	.251	-.011	-.006
Self-Reported Memory	.168	.433	.669				
Self-Reported Attention	-.396	-1.151	.261				
Self-Reported Navigation	-005	-.018	.986				
Conscientiousness	.157	.827	.416				

Table 29: Informant-reported memory hierarchical linear regression predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.089	.135		
Step 2 Model				.121	.182	.032	.032
Informant-Reported Memory	-.198	-.975	.342				
Step 3 Model: Depression				.139	.186	.018	.097
Informant-Reported Memory	-.164	-.808	.431				
Depressive Symptoms	-.240	-1.177	.255				
Step 3 Model: Anxiety				.089	.263	-.032	0.000
Informant-Reported Memory	-.144	-.641	.530				
Anxiety Symptoms	-.147	-.617	.546				

Table 30: Informant-reported attention hierarchical linear regression predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.089	.135		
Step 2 Model				.105	.207	.016	.016
Informant-Reported Attention	-.163	-.785	.443				
Step 3 Model: Depression				.130	.199	.025	.041
Informant-Reported Attention	-.140	-.681	.505				
Depressive Symptoms	-.250	-1.231	.235				
Step 3 Model: Anxiety				.080	.280	-.025	-.009
Informant-Reported Attention	-.108	-.481	.637				
Anxiety Symptoms	-.164	-.715	.485				

Table 31: Informant-reported spatial navigation hierarchical linear regression predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.089	.135		
Step 2 Model				.077	.256	-.012	-.012
Informant-Reported Navigation	-.051	-.224	.825				
Step 3 Model: Depression				.111	.227	.034	.022
Informant-Reported Navigation	-.068	-.306	.763				
Depressive Symptoms	-.267	-1.301	.211				
Step 3 Model: Anxiety				.067	.303	-.010	-.022
Informant-Reported Navigation	-.006	-.027	.979				
Anxiety Symptoms	-.200	-.904	.379				

Table 32: All informant-reported questionnaires hierarchical linear regression predicting CSF $A\beta_{42}/A\beta_{40}$ ratio in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.089	.135		
Step 2 Model				.051	.358	-.038	-.038
Self-Reported Memory	-.376	-.822	.423				
Self-Reported Attention	-.048	-.108	.916				
Self-Reported Navigation	.307	.811	.429				
Step 3 Model: Depression				-.013	.492	-.064	-.102
Self-Reported Memory	-.377	-.798	.438				
Self-Reported Attention	-.041	-.084	.934				
Self-Reported Navigation	.303	.768	.454				
Depressive Symptoms	-.006	-.053	.958				
Step 3 Model: Anxiety				.002	.466	-.049	-.087
Self-Reported Memory	-.320	-.663	.518				
Self-Reported Attention	-.036	-.080	.938				
Self-Reported Navigation	.276	.701	.494				
Anxiety Symptoms	-.115	-.463	.650				

Table 33: Self-reported memory hierarchical linear regression predicting hippocampal volume in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.287	.017*		
Step 2 Model				.256	.041*	-.031	-.031
Self-Reported Memory	.062	.316	.756				
Step 3 Model: Depression				.247	.061#		-.040
Self-Reported Memory	-.049	-.209	.836			-.009	
Depressive Symptoms	.203	.881	.390				
Step 3 Model: Anxiety				.284	.041*	.028	-.003
Self-Reported Memory	.064	.334	.742				
Anxiety Symptoms	-.228	-1.34	.196				
Step 3 Model: Neuroticism				.272	.047*	.016	-.015
Self-Reported Memory	.105	.531	.601				
Neuroticism	-.245	-1.20	.245				
Step 3 Model: Conscientiousness				.248	.060#	-.008	-.039
Self-Reported Memory	.137	.640	.530				
Conscientiousness	.169	.899	.380				

* indicates p<.05; # indicates p<.1

Table 34: Self-reported attention hierarchical linear regression predicting hippocampal volume in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.287	.017*		
Step 2 Model				.252	.042*	-.035	-.035
Self-Reported Attention	-.015	-.071	.944				
Step 3 Model: Depression				.267	.049*	.015	-.020
Self-Reported Attention	-.194	-.753	.461				
Depressive Symptoms	.281	1.19	.249				
Step 3 Model: Anxiety				.280	.043*	.028	-.007
Self-Reported Attention	.004	.021	.983				
Anxiety Symptoms	-.227	-1.33	.199				
Step 3 Model: Neuroticism				.264	.051#	.012	-.023
Self-Reported Attention	.060	.274	.787				
Neuroticism	-.243	-1.15	.266				
Step 3 Model: Conscientiousness				.234	.070#	-.018	-.053
Self-Reported Attention	.048	.209	.837				
Conscientiousness	.137	.726	.477				

* indicates p<.05; # indicates p<.1

Table 35: Self-reported spatial navigation hierarchical linear regression predicting hippocampal volume in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.287	.017*		
Step 2 Model				.253	.042*	-.034	-.034
Self-Reported Navigation	.044	.207	.838				
Step 3 Model: Depression				.246	.062#	-.007	-.041
Self-Reported Navigation	-.014	-.062	.951				
Depressive Symptoms	.181	.889	.385				
Step 3 Model: Anxiety				.282	.042*	.029	-.005
Self-Reported Navigation	.053	.251	.804				
Anxiety Symptoms	-.229	-1.34	.195				
Step 3 Model: Neuroticism				.270	.048*	.017	-.017
Self-Reported Navigation	.109	.497	.625				
Neuroticism	-.250	-1.208	.242				
Step 3 Model: Conscientiousness				.240	.066*	-.013	-.047
Self-Reported Navigation	.101	.445	.662				
Conscientiousness	.147	.805	.431				

* indicates p<.05; # indicates p<.1

Table 36: All self-reported questionnaires hierarchical linear regression predicting hippocampal volume in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.287	.017*		
Step 2 Model				.196	.123	-.091	-.091
Self-Reported Memory	.338	.700	.493				
Self-Reported Attention	-.341	-.722	.480				
Self-Reported Navigation	.005	.014	.989				
Step 3 Model: Depression				.210	.130	.014	-.077
Self-Reported Memory	.246	.507	.619				
Self-Reported Attention	-.512	-1.04	.312				
Self-Reported Navigation	.111	.310	.760				
Depressive Symptoms	.292	1.15	.268				
Step 3 Model: Anxiety				.215	.126	.019	-.072
Self-Reported Memory	.274	.569	.577				
Self-Reported Attention	-.268	-.569	.577				
Self-Reported Navigation	.015	.043	.966				
Anxiety Symptoms	-.214	-1.19	.249				
Step 3 Model: Neuroticism				.195	.147	-.001	-.092
Self-Reported Memory	.226	.455	.655				
Self-Reported Attention	-.199	-.404	.691				
Self-Reported Navigation	.055	.156	.878				
Neuroticism	-.223	-.981	.341				
Step 3 Model: Conscientiousness				.181	.162	-.015	-.106
Self-Reported Memory	.383	.781	.446				
Self-Reported Attention	-.313	-.655	.521				
Self-Reported Navigation	.008	.024	.981				
Conscientiousness	.160	.811	.429				

Table 37: Informant-reported memory hierarchical linear regression predicting hippocampal volume in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.287	.017*		
Step 2 Model				.196	.148	-.091	-.091
Informant-Reported Memory	.209	1.305	.215				
Step 3 Model: Depression				.133	.255	-.063	-.154
Informant-Reported Memory	.267	1.052	.314				
Depressive Symptoms	.086	.220	.830				
Step 3 Model: Anxiety				.139	.247	-.066	-.148
Informant-Reported Memory	.238	.878	.397				
Anxiety Symptoms	.128	.371	.717				

* indicates p<.05

Table 38: Informant-reported attention hierarchical linear regression predicting hippocampal volume in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.287	.017*		
Step 2 Model				.254	.099#	-.033	-.033
Informant-Reported Attention	.388	1.685	.116				
Step 3 Model: Depression				.130	.199	-.124	-.157
Informant-Reported Attention	-.003	-.681	.505				
Depressive Symptoms	-.005	-1.231	.235				
Step 3 Model: Anxiety				.080	.280	-.174	-.207
Informant-Reported Attention	-.002	-.481	.637				
Anxiety Symptoms	-.003	-.715	.485				

* indicates p<.05; # indicates p<.1

Table 39: Informant-reported spatial navigation hierarchical linear regression predicting hippocampal volume in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.287	.017*		
Step 2 Model				.077	.256	-.210	.210
Informant-Reported Navigation	<-.001	-.224	.825				
Step 3 Model: Depression				.111	.227	.034	-.176
Informant-Reported Navigation	-.001	-.306	.763				
Depressive Symptoms	-.005	-1.301	.211				
Step 3 Model: Anxiety				.067	.303	-.010	-.220
Informant-Reported Navigation	<-.001	-.027	.979				
Anxiety Symptoms	-.004	-.904	.379				

* indicates p<.05; # indicates p<.1

Table 40: All informant-reported questionnaires hierarchical linear regression predicting hippocampal volume in the ADRC sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.287	.017*		
Step 2 Model				.252	.159	-.035	-.035
Informant-Reported Memory	-.674	-1.037	.322				
Informant-Reported Attention	.564	.841	.418				
Informant-Reported Navigation	.660	1.258	.234				
Step 3 Model: Depression				.250	.190	-.002	-.037
Informant-Reported Memory	-.691	-1.061	.314				
Informant-Reported Attention	.431	.630	.543				
Informant-Reported Navigation	.772	1.437	.181				
Depressive Symptoms	.101	.985	.348				
Step 3 Model: Anxiety				.177	.263	-.075	-.110
Informant-Reported Memory	-.675	-.987	.347				
Informant-Reported Attention	.566	.773	.458				
Informant-Reported Navigation	.600	1.199	.258				
Anxiety Symptoms	-.004	-.012	.991				

* indicates p<.05

Table 41: Self-reported memory hierarchical linear regression predicting CSF $ptau_{181}/A\beta_{42}$ ratio in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.037	.016*		
Step 2 Model				.039	.021*	.002	.002
Self-Reported Memory	.008	1.149	.252				
Step 3 Model				.035	.038*	-.004	-.002
Self-Reported Memory	.009	1.224	.223				
Depressive Symptoms	-.004	-.478	.633				
Step 4 Model				.036	.042*	.001	-.001
Self-Reported Memory	.100	1.373	.171				
Depressive Symptoms	.007	.081	.933				
Self-Reported Memory X Depressive Symptoms	-.072	-1.128	.261				

* indicates p<.05

Table 42: Self-reported spatial navigation hierarchical linear regression predicting CSF $ptau_{181}/A\beta_{42}$ ratio in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.037	.016*		
Step 2 Model				.036	.027*	-.001	-.001
Self-Reported Navigation	.005	.824	.411				
Step 3 Model				.031	.051#	-.005	-.006
Self-Reported Navigation	.006	.854	.394				
Depressive Symptoms	-.002	-.318	.751				
Step 4 Model				.033	.053#	.002	-.004
Self-Reported Navigation	.081	1.107	.270				
Depressive Symptoms	.006	.084	.934				
Self-Reported Navigation X Depressive Symptoms	-.067	-1.192	.235				

* indicates p<.05; # indicates p<.1

Table 43: Self-reported attention hierarchical linear regression predicting hippocampal volume in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.233	<.001*		
Step 2 Model	-.029	-.423	.673	.229	<.001*	-.004	-.004
Self-Reported Attention							
Step 3 Model				.224	<.001*	-.005	-.009
Self-Reported Attention	-.026	-.359	.720				
Depressive Symptoms	-.014	-.192	.848				
Step 4 Model				.229	<.001*	.005	-.004
Self-Reported Attention	.001	.020	.984				
Depressive Symptoms	.030	.385	.701				
Self-Reported Attention X Depressive Symptoms	-.113	-1.427	.155				

* indicates p<.05

Table 44: Self-reported spatial navigation hierarchical linear regression predicting hippocampal volume in the ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.233	<.001*		
Step 2 Model				.239	<.001*	.006	.006
Self-Reported Navigation	-.103	-1.513	.132				
Step 3 Model				.234	<.001*	-.005	.001
Self-Reported Navigation	-.102	-1.483	.140				
Depressive Symptoms	-.007	-.102	.919				
Step 4 Model				.230	<.001*	-.004	-.003
Self-Reported Navigation	-.093	-1.299	.196				
Depressive Symptoms	.004	.054	.957				
Self-Reported Navigation X Depressive Symptoms	-.026	-.481	.631				

* indicates p<.05

Table 45: Self-reported dichotomous memory hierarchical linear regression predicting CSF $ptau_{181}/A\beta_{42}$ ratio in ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.037	.016*		
Step 2 Model				.041	.017*	.004	.004
Self-Reported Memory	.217	1.314	.190				
Step 3 Model				.037	.032*	.000	.000
Self-Reported Memory	.233	1.381	.169				
Depressive Symptoms	-.035	-.486	.628				
Step 4 Model				.033	.052#	-.004	-.004
Self-Reported Memory	.246	1.439	.152				
Depressive Symptoms	-.002	-.020	.984				
Self-Reported Memory X Depressive Symptoms	-.079	-.537	.592				

* indicates p<.05; # indicates p<.1

Table 46: Self-reported dichotomous attention hierarchical linear regression predicting CSF $ptau_{181}/A\beta_{42}$ ratio in ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.037	.016*		
Step 2 Model				.067	.002*	.030	.030
Self-Reported Attention	.408	2.672	.008*				
Step 3 Model				.063	.004*	-.004	.026
Self-Reported Attention	.414	2.695	.008*				
Depressive Symptoms	-.031	-.450	.653				
Step 4 Model				.059	.007*	-.004	.022
Self-Reported Attention	.406	2.611	.010*				
Depressive Symptoms	.021	.122	.903				
Self-Reported Attention X Depressive Symptoms	-.063	-.335	.738				

* indicates p<.05

Table 47: Self-reported dichotomous spatial navigation hierarchical linear regression predicting CSF $ptau_{181}/A\beta_{42}$ ratio in ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.037	.016*		
Step 2 Model				.034	.030*	-.003	-.003
Self-Report Navigation	.096	.677	.500				
Step 3 Model				.030	.056#	-.004	-.007
Self-Report Navigation	.099	.694	.488				
Depressive Symptoms	-.019	-.271	.786				
Step 4 Model				.028	.078#	-.002	-.009
Self-Report Navigation	.098	.681	.497				
Depressive Symptoms	.058	.468	.640				
Self-Report Navigation X Depressive Symptoms	-.115	-.764	.446				

* indicates p<.05; # indicates p<.1

Table 48: All self-reported dichotomous questionnaires hierarchical linear regression predicting CSF $ptau_{181}/A\beta_{42}$ ratio in ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.037	.016*		
Step 2 Model				.059	.007*	.022	.022
Self-Report Memory	.125	.697	.487				
Self-Report Attention	.392	2.404	.017*				
Self-Report Navigation	-.049	-.316	.752				
Step 3 Model				.056	.012*	-.003	.019
Self-Report Memory	.143	.784	.434				
Self-Report Attention	.395	2.417	.017*				
Self-Report Navigation	-.049	-.316	.752				
Depressive Symptoms	-.041	-.572	.568				

* indicates p<.05

Table 49: Self-reported dichotomous memory hierarchical linear regression predicting hippocampal volume in ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.233	<.001*		
Step 2 Model				.253	<.001*	.020	.020
Self-Report Memory	-.364	-2.317	.022*				
Step 3 Model				.248	<.001*	-.005	.015
Self-Report Memory	-.377	-2.314	.022*				
Depressive Symptoms	.023	.322	.748				
Step 4 Model				.247	<.001*	-.001	.014
Self-Report Memory	-.355	-2.138	.034*				
Depressive Symptoms	.075	.800	.425				
Self-Report Memory X Depressive symptoms	-.119	-.842	.401				

* indicates p<.05

Table 50: Self-reported dichotomous attention hierarchical linear regression predicting hippocampal volume in ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.233	<.001*		
Step 2 Model				.234	<.001*	.001	.001
Self-Report Attention	-.174	-1.158	.248				
Step 3 Model				.230	<.001*	-.004	-.003
Self-Report Attention	-.172	-1.133	.259				
Depressive Symptoms	-.013	-.192	.848				
Step 4 Model				.233	<.001*	.003	.000
Self-Report Attention	-.202	-1.319	.189				
Depressive Symptoms	.180	1.085	.280				
Self-Report Attention X Depressive Symptoms	-.233	-1.279	.203				

* indicates p<.05

Table 51: All self-reported dichotomous questionnaires hierarchical linear regression predicting hippocampal volume in ADNI sample

	Standardized β	β T-Value	β p-value	Adjusted R^2	R^2 p-value	Incremental R^2	Step 1 R^2 difference
Step 1 Model				.233	<.001*		
Step 2 Model				.253	<.001*	.020	.020
Self-Report Memory	-.269	-1.560	.121				
Self-Report Attention	-.038	-.239	.812				
Self-Report Navigation	-.199	-1.326	.187				
Step 3 Model				.248	<.001*	-.005	.015
Self-Report Memory	-.281	-1.577	.117				
Self-Report Attention	-.039	-.244	.808				
Self-Report Navigation	-.197	-1.311	.192				
Depressive Symptoms	.020	.280	.780				

* indicates p<.05

Appendix VI: Correlations between questionnaires and personality and affective variables

Table 52. Correlations between refined questionnaires and depressive symptoms.

	r	df	p
Self-Reported Memory	.507	30	.003*
Self-Reported Attention	.598	30	<.001*
Self-Reported Spatial Navigation	.424	30	.016*
Informant-Reported Memory	.169	30	.441
Informant-Reported Attention	.028	30	.901
Informant-Reported Spatial Navigation	-.135	30	.539

*indicates p<.05

Table 53. Correlations between refined questionnaires and anxiety symptoms.

	r	df	p
Self-Reported Memory	.069	30	.707
Self-Reported Attention	.201	30	.269
Self-Reported Spatial Navigation	.128	30	.487
Informant-Reported Memory	.402	30	.057#
Informant-Reported Attention	.250	30	.251
Informant-Reported Spatial Navigation	.061	30	.782

#indicates p<.1

Table 54. Correlations between refined questionnaires and neuroticism.

	r	df	p
Self-Reported Memory	-.126	30	.491
Self-Reported Attention	-.082	30	.654
Self-Reported Spatial Navigation	-.088	30	.634

Table 55. Correlations between refined questionnaires and conscientiousness.

	r	df	p
Self-Reported Memory	-.344	30	.054#
Self-Reported Attention	-.305	30	.090#
Self-Reported Spatial Navigation	-.247	30	.173

#indicates p<.1

Table 56. Correlations between ECog subsections and depressive symptoms.

	r	df	p
Self-Reported Memory	.216	195	.002*
Self-Reported Attention	.226	195	.001*
Self-Reported Spatial Navigation	.123	195	.085#

*indicates p<.05; #indicates p<.1

Appendix VII: Correlations between questionnaires and AD biomarkers

Table 57. Correlations between refined self-reported questionnaires and AD biomarkers

	Memory	Attention	Navigation	CSF Ratio	Hippocampus
Memory	1				
Attention	.840*	1			
Navigation	.746*	.664*	1		
CSF Ratio	-.270	-.338#	-.304#	1	
Hippocampus	-.067	-.067	-.214	.140	1

Table 58. Correlations between refined informant-reported questionnaires and AD biomarkers

	Memory	Attention	Navigation	CSF Ratio	Hippocampus
Memory	1				
Attention	.859*	1			
Navigation	.731*	.783*	1		
CSF Ratio	-.175	-.236	-.132	1	
Hippocampus	.129	.051	.013	-140	1

Table 59. Correlations between self-reported ECog subsections and AD biomarkers

	Memory	Attention	Navigation	CSF Ratio	Hippocampus
Memory	1				
Attention	.600*	1			
Navigation	.523*	.506*	1		
CSF Ratio	.129*	.175*	.084	1	
Hippocampus	-.061	<-.001	-.063	-.151	1

Table 60. Correlations between informant-reported ECog subsections and AD biomarkers

	Memory	Attention	Navigation	CSF Ratio	Hippocampus
Memory	1				
Attention	.600*	1			
Navigation	.396*	.355*	1		
CSF Ratio	-.007	.081	.037	1	
Hippocampus	-.062	.050	-.075	-.151	1