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## Cognitive Correlates of Metamemory in Alzheimer's Disease

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### Abstract

**Objective**—Metamemory, or knowledge of one's memory abilities, is often impaired in individuals with Alzheimer's disease (AD), although the basis of this metacognitive deficit has not been fully articulated. Behavioral and imaging studies have produced conflicting evidence regarding the extent to which specific cognitive domains (i.e., executive functioning (EF), memory) and brain regions contribute to memory awareness. The primary aim of this study was to disentangle the cognitive correlates of metamemory in AD by examining the relatedness of objective metamemory performance to cognitive tasks grouped by domain (EF or memory) as well as by preferential hemispheric reliance defined by task modality (verbal or nonverbal).

**Method**—89 participants with mild AD recruited at Columbia University Medical Center and the University of Pennsylvania underwent objective metamemory and cognitive testing. Partial correlations were used to assess the relationship between metamemory and four cognitive variables, adjusted for recruitment site.

**Results**—The significant correlates of metamemory included nonverbal fluency ( $r = .27$ ,  $p = .02$ ) and nonverbal memory ( $r = .24$ ,  $p = .04$ ).

**Conclusions**—Our findings suggest that objectively measured metamemory in a large sample of individuals with mild AD is selectively related to a set of inter-domain nonverbal tasks. The association between metamemory and the nonverbal tasks may implicate a shared reliance on a right-sided cognitive network that spans frontal and temporal regions.

### Keywords

metamemory; cognition; Alzheimer's disease; anosognosia; awareness

Episodic memory loss is typically the most salient symptom of Alzheimer's disease (AD) and is nearly ubiquitous among individuals with early AD. In contrast, memory awareness (metamemory), measured either subjectively (i.e., via clinician's rating or patient/caregiver self-report) or with objective testing, is highly variable, with some individuals being keenly aware of their deficit and others demonstrating an ostensible lack of knowledge of any change (Cosentino & Stern, 2005; Neary et al., 1986; Reed, Jagust, & Coulter, 1993; Smith, Henderson, McCleary, Murdock, & Buckwalter, 2000). Lack of awareness regarding memory impairment can have significant consequences for health outcomes, such as the likelihood of seeking treatment, accepting at-home assistance, maintaining capacity to make healthcare decisions (Karlawish, Casarett, James, Xie, & Kim, 2005) or effectively managing medications (Arlt, Lindner, Rosler, & von Renteln-Kruse, 2008; Cosentino, Metcalfe, Cary, De Leon, & Karlawish, 2011; Koltai, Welsh-Bohmer, & Schmechel, 2001).

The basis of impaired metamemory in AD is not fully understood. Behavioral and imaging studies have produced conflicting evidence regarding the role of specific cognitive domains, particular brain regions, and hemispheric specialization in supporting memory awareness. Although metamemory awareness appears to have a specifically self-evaluative component that is dissociable from primary cognitive abilities (Cosentino, Metcalfe, Holmes, Steffener, & Stern, 2011), existing work and models of metacognition also point to a potentially important role for executive function (EF) and/or episodic memory in supporting metamemory. Several studies of metamemory in healthy older adults as well as in patients with prefrontal compromise have shown a relationship between metamemory and EF (Perrotin, Belleville, & Isingrini, 2007; Perrotin, Isingrini, Souchay, Clarys, & Tacconnat, 2006; Perrotin, Tournelle, & Isingrini, 2008; Souchay, Isingrini, & Espagnet, 2000; Souchay, Isingrini, Pillon, & Gil, 2003). Moreover, subjectively assessed deficits in memory awareness have been tied to executive dysfunction in AD (Dalla Barba, Parlato, Lavarone, & Boller, 1995; Fernandez-Duque, Baird, & Posner, 2000; Lopez, Becker, Somsak, Dew, & DeKosky, 1994; Michon, Deweer, Pillon, Agid, & Dubois, 1994; Ott et al., 1996; Reed et al., 1993; Starkstein et al., 1995).

These behavioral associations are consistent with cognitive models that portray metacognition as closely related to executive functioning (Fernandez-Duque et al., 2000) and models of metamemory such as the *Cognitive Awareness Model* (CAM), which point to a critical role of EF in the operation of a functional metamemory system (Agnew & Morris, 1998; Morris & Hannesdottir, 2004). Despite the conceptual similarities between metamemory and EF, and its frequently reported relationship in healthy older adults, however, objective studies of metamemory in AD have not found an association between EF and metamemory (Souchay, Isingrini, & Gil, 2002; Souchay et al., 2003).

The CAM also points to a critical role for memory in a functional metamemory system, and a host of studies have also examined the extent to which the memory deficits themselves contribute to impaired memory awareness in AD. Memory performance and objectively measured metamemory have been shown to be related in young adults (T. Nelson & Narens, 1990) but not older adults (Cosentino, Metcalfe, Holmes, et al., 2011; Souchay et al., 2000). However, several studies in AD and Mild Cognitive Impairment (MCI) have shown a relationship between memory deficits and metamemory (Perrotin et al., 2007; Souchay et

al., 2003) as well as awareness measured subjectively (Agnew & Morris, 1998; Brookes, Hannesdottir, Markus, & Morris, 2013; Gallo, Chen, Wiseman, Schacter, & Budson, 2007; Gallo, Cramer, Wong, & Bennett, 2012; Hannesdottir & Morris, 2007; Migliorelli et al., 1995; Mograbi, Brown, & Morris, 2009; Reed et al., 1993) such that those with better memories are also better at monitoring their memory ability. However, at least two studies have failed to find an association between memory and metamemory while strictly looking at individuals with AD (Cosentino, Metcalfe, Butterfield, & Stern, 2007; Souchay et al., 2002). Indeed, individuals grouped by disease stage (mild versus moderate) with significantly different memory abilities have been shown to be comparable in terms of subjectively rated levels of memory awareness (Michon et al., 1994).

Taken together, results from existing studies examining the cognitive correlates of metamemory suggest that the compromise of general executive and/or memory abilities may detrimentally affect metamemory. Further, specific cognitive deficits are more or less influential in different populations. Thus, it may be that memory awareness becomes impaired secondary to damage within a broad metacognitive network that is specialized for processing self-relevant information in several different stages, and that is anatomically and functionally coupled with regions engaged during memory or executive tasks. Indeed, the potential importance of a fronto-temporal route for memory awareness has been highlighted in earlier work (Conway, 2005; Moulin, Conway, Thompson, James, & Jones, 2005; Souchay, Moulin, Clarys, Taconnat, & Isingrini, 2007). This network has been theorized to support awareness by processing memory failures, comparing them to one's own personal knowledge, and then storing these occurrences in a personal knowledge base. In fact, using a subjective assessment of awareness, Salmon and colleagues (2006) and more recently Zamboni and colleagues (2013) demonstrated a role for bilateral prefrontal and temporal regions in supporting awareness in AD (E. Salmon et al., 2006; Zamboni et al., 2013).

Examination of the cognitive correlates of metamemory in AD must also consider the wealth of studies that have documented a relatively greater role for right hemisphere functioning in supporting aspects of symptom awareness across a range of disorders. A host of imaging studies have demonstrated that regions in the right prefrontal cortex (PFC), including the right anterior PFC, as well as the right inferior, superior, and middle frontal gyrus, are particularly important for aspects of self-awareness (Fleming, Weil, Nagy, Dolan, & Rees, 2010; Kikyo, Ohki, & Miyashita, 2002; Platek, Keenan, Gallup, & Mohamed, 2004; Schnyer et al., 2004). For example, Fleming and colleagues (2010) demonstrated that metacognitive ability related to decision making was most highly correlated with the integrity of Brodmann area 10 in the right anterior PFC (Fleming et al., 2010). Similarly, damage to the right ventro-medial PFC has been associated with predictions of memory performance (Schnyer et al., 2004). Moreover, more traditional conceptualizations of anosognosia, or disordered symptom awareness, have been described in the context of right hemisphere dysfunction extensively over the past century. The term anosognosia was coined by Babinski to describe unawareness of hemiplegia (Babinski, 1914), and is now used more loosely to describe a broad spectrum of unawareness regarding a range of symptoms across various diseases. Compromise to the right parietal lobe has repeatedly been shown to contribute to presentations of anosognosia, including a disordered body schema (Critchley, 1953; Head & Holmes, 1911) and a severe disturbance in attention to the left side of the

body (Mark, Kooistra, & Heilman, 1988). Importantly, anosognosia has frequently been shown to result from damage to regions spanning both the right parietal and frontal lobes (Venneri & Shanks, 2004).

A series of case studies described by Feinberg (2001) highlights the manner in which damage to different regions within the right hemisphere may produce divergent disorders of self-awareness. For instance, the majority of patients who have hemiplegia and neglect a paralyzed arm have damage to the right frontal and parietal lobes. Capgras syndrome, a disorder in which a person perceives a family member or friend as an imposter, occurs with damage to the right frontal and temporal lobes (Feinberg, 2001). This syndrome has been conceptualized as a distortion of both the self and others. Right hemisphere importance has been shown in AD as well; using single-photon emission, Starkstein and colleagues found that unaware AD patients showed significant blood flow deficit in the right frontal inferior and superior cortices (Starkstein et al., 1995). Furthermore, the preferential role of right hemisphere regions in supporting self-awareness has been detailed for decades in individuals with stroke (Vossel, Weiss, Eschenbeck, & Fink, 2012), traumatic brain injury (Prigatano & Schacter, 1991; Ranssen, Bohaska, & Schmitt, 1990; Schmitz, Rowley, Kawahara, & Johnson, 2006) frontotemporal dementia (FTD) (Mendez & Shapira, 2005), schizophrenia (Shad, Muddasani, Prasad, Sweeney, & Keshavan, 2004; Shad, Tamminga, Cullum, Haas, & Keshavan, 2006), and healthy adults (Fink et al., 1996; Keenan et al., 1999; Platek et al., 2004). Consideration of these examples reinforces the idea that the right hemisphere may be particularly influential in maintaining self-identity.

How might the role of specific right hemisphere regions influence the cognitive correlates of metamemory in AD? One might predict that task modality (i.e., nonverbal versus verbal) would be an important feature to examine because of the preferential roles of the left and right hemispheres in supporting verbal and nonverbal abilities, respectively (Benton & Tranel, 1993; Gallo et al., 2012; Glosser & Goodglass, 1990). In fact, previous work has reported selective associations between nonverbal rather than verbal episodic memory and awareness (Cosentino et al., 2007; Mangone et al., 1991). Examination of memory and executive measures as a function of task modality may increase our ability to identify and understand the cognitive correlates of metamemory in AD.

The goal of the current study was thus to disentangle the cognitive correlates of metamemory in AD by applying a novel task framework in a large sample of individuals (n=89) to examine the relatedness of cognitive domains (EF or memory) and task modality (verbal or nonverbal) to objective metamemory scores. Based on previous results from our lab (Cosentino et al., 2007) demonstrating an association between nonverbal memory and metamemory, as well as extensive literature implicating a critical role for right frontal functioning in supporting aspects of self-awareness, we expected metamemory in AD to be related most strongly to nonverbal tasks of fluency and memory.

## Method

### Participants

Given the cognitive demands of the metamemory task only patients with mild to moderate AD, defined as a score of 18 or greater on the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), were recruited. A total of 109 participants with AD, ages 57 to 99, were enrolled at two separate centers, Columbia University Medical Center and the University of Pennsylvania. Other brain disorders were ruled out through standard diagnostic tests; only individuals with probable AD were included. Subject demographics are presented in the results section below.

Fifty-four individuals with mild AD were recruited through the Memory Disorders Clinic in the Department of Neurology at Columbia University Medical Center (CUMC) or the Alzheimer's Disease Research Center (ADRC). Individuals recruited through the ADRC received comprehensive neurologic and neuropsychological evaluations that were reviewed in a diagnostic consensus conference attended by neurologists and neuropsychologists. Diagnoses of probable AD for all participants were made according to the Neurologic Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria (McKhann et al., 1984). Other brain disorders were ruled out through standard diagnostic tests. Eligible patients and their families at CUMC were first approached by their physicians, and individuals who were interested in participation were then contacted by research staff who explained the study in more detail. All participants provided informed consent and were reimbursed \$30.00 for participation.

Fifty-five individuals with mild AD were recruited through the University of Pennsylvania PENN Memory Center; subjects were diagnosed with AD based on the above criteria. Eligible patients and their family members who were enrolled at the Center and agreed to be contacted for research studies were sent a letter describing the study. A research assistant then called the contact person, and explained the study in more detail. All participants provided informed consent and were reimbursed \$40.00 for participation.

The precise neuropsychological battery used to diagnose dementia at each center varied to some extent based on the manner in which the individual was recruited. In all cases, however, measures in the research battery were non-overlapping with those used for diagnosis except for the MMSE which was used as a screening measure at the start of the study. Duration of time between date of diagnosis and research participation was not recorded. Disease severity was assessed with the MMSE at the time of research testing to ensure that all participants were in the mild to moderate stage of AD. All testers at both sites were trained by a single neuropsychologist and there were several standardization meetings during the course of the study to ensure administration procedures were comparable. In one instance, it was discovered that there was a slight difference in the administration of the Graphic Pattern Generation test across sites. As such, site was used as a covariate in all analyses of this task. Healthy Controls: Fifty healthy controls were also recruited from the healthy control database through the ADRC at CUMC, local senior centers, and market mailing procedures that target a diverse group of elders in New York City with a range of ethnic and educational backgrounds. Controls were screened by interview to exclude

individuals with neurologic, psychiatric, or severe medical disorders. Participants were considered eligible for the study if they were age 55 or above and scored at least 27 on the MMSE.

## Procedures

Participants were seen for up to three two-hour test sessions which included metamemory testing, mood questionnaires, and tests of global cognition, premorbid IQ, memory, and executive functioning described below as part of a larger neuropsychological battery. This study was approved by the Institutional Review Board at both medical centers and all individuals provided informed consent prior to participation.

## Measures

### Metamemory Test

**Task Instructions and Format:** The metamemory task consisted of four trials with five items in each trial, yielding a total of 20 metamemory items. The stimuli consisted of five pieces of “pseudo trivia” regarding a fictitious individual and information about their background. Each trial required global metamemory judgments prior to and following the presentation of the individual items, as well as judgments for each individual item. Specifically, the examiner read the following instructions, “During this task, I am going to tell you about five people. I will tell you their name and something about their background. Your task is to try to remember this information as best you can. Please listen carefully.” Immediately after the first learning trial (e.g., Cole Porter attended law school in Chicago; Wiley Post was employed as a hotel servant in Denver, etc.), predictions for memory performance were acquired one at a time for each item by providing written questions on 8.5” × 11” paper (e.g., *Who was employed as a hotel servant in Denver?*) and the following prompt read aloud by the examiner: “There are eight possible answers on the next page. Will you know which one is right – Yes, Maybe, or No?” Once predictions were recorded, participants were provided with eight answer choices and asked to select the correct answer. The answer choices included the correct response, the correct answers for the remaining four stimuli (to control for basic familiarity effects), and three new distracters (to reduce the possibility that participants selected the correct answer by chance, an event that would have obscured the association between predictions and true accuracy). The tester did not give feedback and moved on to the next item. While eight answer choices may have been particularly challenging for this AD group, we are interested in the relative accuracy of predictions as the primary outcome. As such, those individuals who appreciate the difficulty of the task are those that will adjust their predictions for performance and achieve higher gamma scores regardless of having potentially low memory accuracy.

### Dependent Variable

**Resolution:** Resolution, or the relative accuracy of self-judgments, reflects the extent to which accuracy is high when predictions for performance are high, and accuracy is low when predictions are low. The nonparametric Goodman-Kruskal gamma statistic, a rank order correlation, (T. O. Nelson & Narens, 1984) was used to measure resolution. Gamma compares the relative number of concordant and discordant prediction/accuracy pairs,

discarding “ties,” or instances in which either the rating or accuracy in one pair is equal to that in another pair. Limitations of gamma include a tendency to be pulled to an extreme value on the basis of only one concordance or discordance, and a possibility that no score can be calculated in the event of all ties. Although there are many potential metamemory metrics, gamma has been shown to correlate highly with other measures such as the Hamman coefficient (Souhay et al., 2002) and was used in the current study based on its selective association with clinical ratings of memory awareness in AD in two previous studies (Cosentino et al., 2007; Cosentino, Metcalfe, Holmes, et al., 2011).

**Global Cognition and Premorbid IQ**—Global cognition was assessed using the MMSE (Folstein et al., 1975) and premorbid intellectual functioning was assessed using the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001).

### Memory

**Philadelphia Repeatable Verbal Learning Test (PVLТ) (Price et al., 2009):** The PVLТ is a list-learning task modeled after the nine-word California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987; Libon, et al., 1996) in which participants are required to learn nine words (comprising three different categories: fruit, tools, and furniture) over the course of five trials. The primary dependent variable was delayed recall presented after 20-40 minutes.

**Biber Figure Learning Test (Glosser, Goodglass, & Biber, 1989):** This nonverbal list learning task consists of nine black and white geometric designs presented over five trials. Designs were presented one at a time in a fixed order, for three seconds each. During the test phase, participants were asked to draw as many designs as they could remember. After a 20 to 40 minute delay, participants were again asked to recall as many designs as possible, and subsequently to copy each of the stimuli to ensure that constructional abilities required for intact performance did not affect memory performance. Each drawing was scored according to strict guidelines on a scale of zero to three. The dependent variable was delayed recall presented after 20-40 minutes.

### Executive tests

**Verbal Fluency (Stuss & Benson, 1986):** Participants were given 60 seconds to generate words beginning with the letter ‘F’. Total score represented the number of words generated during the 60 seconds, excluding proper nouns and grammatical variations of the same word (i.e., *eat, eating*). Four additional verbal fluency measures were calculated to reflect a broader variety of executive abilities: relating to maintenance of mental set (rule violations), perseverative behavior (number of perseverations and preservative distance), and organization of information (clustering). Instances of rule violations included proper nouns and generating the same word with a different ending (i.e. *run, runs*), as well as words that did not begin with the target letter. Instances of perseverations included any repetition of the exact same word and preservative distance was defined as the number of words between a perseveration and the most proximal last occurrence of that same word. The distances of all perseverations were summed, and divided by the total perseveration score. We also computed the extent to which participants used a clustering strategy to facilitate word

generation. Both phonemic and semantic clusters were generated by participants. Phonemic clusters were defined as groups of at least two successively generated words that begin or end with the same two or more letters (i.e. *fool, fowl* or *foil, fail*) or differ by only one vowel sound (i.e. *fun, fan*). Verbal fluency tests also offer the opportunity to examine semantic clustering (Troyer, Moscovitch, & Winocur, 1997). In our study we defined semantic clusters as groups of at least two successively generated words belonging to the same semantic categories. Common semantic categories included body parts (i.e. *finger, foot*), food (i.e. *food, fruit*), and relationships (i.e. *family, friend, foe*). If an erroneous word fell into a cluster, it was not included in the clustered word count, but did not break up the cluster. For example, if a repetition fell in the middle of a three word cluster (i.e. *fill, fill\*, fin*), the total number of clustered words in that instance would be two. We then summed the total number of clustered words generated during the 60 second interval and calculated the proportion of clustered words out of the total output. The cluster variable was the proportion of words occurring in clusters out of the total words generated.

**Graphic Pattern Generation (GPG) (Glosser, Goodglass, & Biber, 1989):** The GPG test requires participants to generate multiple unique designs among arrays of dots. The test is characterized by a row of stimuli, consisting of 20 identical 5-dot arrays. The test requires participants to generate as many novel designs as they can. They are required to do so using exactly four lines to join the dots in each array. During a practice trial, the examiner demonstrates five different approaches to drawing a design and asks the participant to complete the remaining five practice designs without repeating any, including the ones provided by the examiner. All errors are corrected during practice. The examiner then administers the row of stimuli, reminding the participant to try to draw a new design each time and to use four lines to connect the dots. The first instance of a perseveration and the first instance of a rule violation are corrected. Slightly different scoring procedures were used across site, such that University of Pennsylvania's participants were allowed to correct the first error of each type, in which case it was not scored as an error. Due to this discrepancy, site was entered as a covariate in partial correlations examining the association between metamemory and the cognitive variables. In addition to total number of novel designs generated, we calculated four additional subscores including: time to completion, rule violations, perseverations, and preservative distance. Instances of rule violations include using more or less than four lines, drawing lines that are not connected to dots, or connecting dots from adjacent arrays. Instances of perseverations include any repetition of the exact same design and perseverative distance is defined as the number of items between a perseveration and the most proximal last occurrence of that same design. The distances of all perseverations are summed, and divided by the total perseveration score.

**Data Analysis:** We first ran a series of partial correlations to investigate the relationship between cognitive variables and metamemory, adjusting for site. Following the correlations, we conducted linear regressions to further investigate the extent to which associations were retained after accounting for any shared variance with other cognitive correlates.



## Results

### Descriptive Statistics

Metamemory (gamma) scores were calculable for 89 of 109 individuals with AD. The 20 participants without a gamma score demonstrated either no variability in their predictions (Yes, Maybe, No), or in their accuracy, preventing the calculation of gamma. As such, these individuals were excluded from all analyses. To confirm that these participants did not differ systematically from those included in analyses, one-way ANOVAs were conducted to compare the two groups on global cognition, premorbid IQ, and demographics (MMSE, age, gender, education, and WTAR IQ). There were no differences between the two groups on any measure.

The mean age and educational level of participants was 78.32 (SD = 8.55) and 15.33 (SD = 2.91), respectively. Fifty-eight of 89 (65%) participants were female, and 99% indicated Non-Hispanic as their ethnicity, with the following breakdown across race: 91% Caucasian and 9% African American.

There were no associations between metamemory and demographic variables, including gender, age, education, or race. Metamemory was also unrelated to global cognition and premorbid IQ. Furthermore, in order to ensure there was no systematic difference across any of the measures between the two sites, we ran ANOVAs comparing the two sites and found no significant differences on any of the measures. Mean metamemory and cognitive scores for our tested sample as well as for a group of healthy elders are presented in Table 1. ANOVAs were run to compare the difference between the two groups, and scores were significantly different on all tests except for WTAR IQ.

Table 2 details the distribution of performance across the four primary cognitive tasks. Standardized scores were normalized against performance in a group of healthy elders.

### Partial Correlations

We conducted four primary partial correlations, controlling for site, to investigate the relationship between cognitive variables and metamemory; reported in full in Table 3. Some participants were missing certain cognitive tests, and the exact numbers of each comparison are also reported in Table 3. The only significant correlates of metamemory included GPG total unique designs ( $r = .27$ ,  $p = .02$ ) and Biber long delay ( $r = .24$ ,  $p = .04$ ).

After checking for skewness and kurtosis and determining that the distribution was in fact skewed, we ran nonparametric correlations. The verbal and non-verbal fluency subscores remained unrelated to metamemory. Mean, standard deviation, and ranges for all the fluency subscores are presented in Table 4. Moreover, while 'F' fluency was highly correlated with performance on the full 'FAS' task in a smaller subset ( $n = 39$ ) who completed the entire task ( $r = .69$ ,  $p < .01$ ), we also examined the association between gamma and performance on the full verbal fluency measure. The association was strengthened but remained non-significant ( $r = .23$ ,  $p = .16$ ).

## Regression Analyses

A linear regression was conducted to determine if either of the two nonverbal cognitive scores was predominantly accounting for the relationship with metamemory. After entering the nonverbal scores as predictors of metamemory in a single block, the overall model was significant at  $F=3.747$ ,  $df=2$ ,  $p=.029$ . However, neither of the two variables retained independent predictive utility. Regression results are reported in Table 5, Model 1.

Two additional individual regression analyses were run to determine the extent to which lack of independent associations in the above model reflected a lack of power by comparison of beta values. The first model included GPG as an independent variable and the second included Biber long delay; both models were significant at  $F=4.738$ ,  $df=1$ ,  $p=.033$  and  $F=4.549$ ,  $df=1$ ,  $p=.036$ , respectively. Additionally, the beta values were comparable to those seen in the model including both variables. Individual regression results are reported in Table 5, Models 2 and 3.

## Discussion

The cognitive correlates of metamemory in AD have yet to be fully articulated. Existing studies and models of awareness have pointed to both executive functioning and memory as potentially important components of memory awareness. Imaging, lesion, and neuropathologic studies in various clinical populations have also pointed to a critical role for a range of brain regions including prefrontal and temporal regions, as well as a preferential role for the right hemisphere in supporting aspects of self-awareness. In the current study, we examined patterns of correlations across four cognitive tasks grouped by domain and modality to better understand the cognitive correlates of metamemory. Our findings suggest that objectively measured metamemory in a large sample of individuals with mild AD is preferentially related to a set of inter-domain nonverbal tasks that span executive and memory domains.

Specifically, partial correlations revealed that metamemory was associated with both nonverbal fluency as well as nonverbal memory. To determine whether one cognitive task primarily accounted for the association with metamemory, both tasks were entered simultaneously into a regression. The overall model was significant; however, neither score retained independent predictive utility. It is possible that removing the shared variance between the two tasks by entering them simultaneously eliminated the aspect of the tasks that is most related to metamemory. For example, it may be that their shared reliance on nonverbal processing rather than the more specific elements of each task is what drives the association between those cognitive tasks and metamemory. It is also possible that a lack of statistical power accounted for this result, as effect sizes were largely comparable across regression models examining the predictors as a pair (Model 1) and in isolation (Models 2 and 3; see Table 5).

The associations between the nonverbal cognitive tasks and the metamemory task are quite striking given the lack of superficial task similarities. At the behavioral level, the relationship between metamemory and design fluency might stem from similar cognitive demands shared by the two tasks, most notably, performance monitoring. Earlier work has

suggested that accurate metamemory in part relies on the monitoring of memory performance earlier in the task as measured with the Memory for Past Test (MPT) heuristic (Finn & Metcalfe, 2007). The MPT heuristic examines the extent to which predictions for performance on Trial N are based on accuracy for that item on trial N-1. Healthy older adults as well as individuals with AD who had high metamemory appeared to implement the MPT heuristic whereas individuals with poor metamemory did not (Cosentino et al., 2007). That is, those individuals who make more accurate metamemory predictions are those that appear to be monitoring previous performance on the task. Those that monitor previous performance are also likely to do well on the design fluency task, during which participants have sustained access to the designs they produce. It is plausible that those participants that actively monitor their previous responses are less likely to repeat previous designs or produce rule violations. The opportunity to actively monitor performance is a characteristic particular to design fluency, as verbal fluency does not allow the individual to easily evaluate their past responses without holding the words in short-term memory. The non-timed nature of design fluency is also likely to facilitate performance monitoring.

The association between design fluency and metamemory may also reflect shared neuroanatomic substrates. As discussed earlier, both imaging and neuropsychological evidence has indicated the involvement of right prefrontal regions in both metamemory and nonverbal executive tasks. The right PFC has been shown to be critical for multiple aspects of self-awareness (Fleming et al.; Kikyo et al., 2002; Platek et al., 2004; Schnyer et al., 2004). Executive visual/spatial type tasks have also been shown to rely differentially on the right PFC relative to left sided structures (Benton & Tranel, 1993). For example, in a study comparing patients with right-hemisphere and left-hemisphere lesions, patients with right hemisphere damage, especially those with frontal-lobe lesions, were shown to have greater impairments on design fluency than those with left-hemisphere damage, even though patients with both types of lesions were impaired in relation to healthy adults (Glosser & Goodglass, 1990).

While performance on the metamemory and design fluency tasks may have been expected due to similar monitoring demands and/or shared reliance on right prefrontal regions, the association between metamemory and delayed nonverbal memory is perhaps more surprising. The dissimilarity between the cognitive demands of these two tasks begs a neuroanatomical explanation for their shared variance, although we lack direct anatomical data in the current paper. Nonverbal learning has been repeatedly shown to involve right-sided medial temporal lobe structures (de Toledo-Morrell et al., 2000; Dickerson et al., 2004; Gallo et al., 2012). For example, Glosser and colleagues demonstrated that while both Right Temporal Lobe Epilepsy (RTLE) patients and Left Temporal Lobe Epilepsy (LTLE) patients performed worse than healthy subjects on the free-recall measures on the Biber Figure Learning test, the task used in the current study, the RTLE patients performed significantly worse than both LTLE patients and healthy subjects on a free-recall long-term memory measure, (Glosser, Cole, Khatri, DellaPietra, & Kaplan, 2002) the delayed recall measure used in our study. These results show that while these visuo-spatial tasks recruit bilateral brain activity, they seem to be more reliant on right-hemisphere functioning. Interestingly, the only neuropathological study of anosognosia in AD found that cell counts in the subiculum region of the right hippocampus were lower in unaware patients than

aware patients (Marshall et al., 2004). Moreover, the current findings are consistent with earlier cognitive findings from our lab demonstrating a selective relationship between metamemory and performance on a different nonverbal learning task (Cosentino et al., 2007), as well as an early study pointing to an association between subjectively measured insight in AD and a third nonverbal learning task (Mangone et al., 1991). The current study supports these earlier findings and extends them to implicate an association between metamemory and a nonverbal aspect of nonverbal executive functioning as well.

While speculative, it is plausible to consider that both metamemory and nonverbal memory have a shared reliance on right hemisphere functioning. The potential importance of right temporal lobe functioning in supporting memory awareness would be consistent with the idea that the specific distortion of self-awareness will be related to the particular brain region involved (Feinberg, 2001; Prigatano, 1991). In this framework, altered perceptions of one's body in space (i.e., unilateral neglect) involve damage to the right parietal lobe while altered awareness of oneself with regard to social interactions (i.e., behavioral variant FTD) involves damage to the right ventromedial PFC (E. Salmon et al., 2003). In the case of AD, it may be that compromise to the right medial temporal lobe contributes to impaired memory monitoring. However, it also appears evident from the current study as well as studies in other clinical populations (Feinberg, 2001; Prigatano, 1991) that concomitant damage to right frontal lobe functions may be a prerequisite for impaired self-awareness. This is consistent with the idea that limited insight is a core feature across individuals with behavioral variant FTD (Rascovsky et al., 2011), a presentation of FTD that involves damage to the right PFC (Broe et al., 2003; Seeley, Zhou, & Kim, 2013).

The association between metamemory and nonverbal tasks has another interpretation. It is possible that greater variability in the nonverbal task scores enabled a more significant association with metamemory than could be seen with the verbal tasks. This may particularly be the case for the memory tasks, as delayed recall on verbal list learning tasks is often at floor in mild to moderate AD. Consistent with this idea, a higher percentage of subjects in the current study performed at floor on the verbal memory task as compared to the nonverbal memory task (see Table 3). However, significant correlations were seen between verbal and nonverbal memory, suggesting that there was sufficient variability to determine an association between verbal memory and another cognitive measure.

The current study failed to find a significant association between metamemory and letter fluency, a verbally based executive task. To ensure that this lack of relationship was not due to the total score being too multidimensional to capture the association, we also calculated a number of more specific executive subscores to assess organization, maintenance of mental set, and perseverative behavior, none of which were related to metamemory. Moreover, examination of the full fluency task (FAS) in a subset of our sample also revealed a non-significant association with metamemory, though it should be noted that the association was strengthened. The lack of a significant association between metamemory and the verbal fluency task was somewhat surprising given previous reports of such associations. However, close examination of previous studies reveals important nuances. First, while Souchay and Isingrini found an association between metacognition and EF (WCST and verbal fluency) in AD, their study examined metacognitive control, the process by which individuals adapt

their behavior or strategy based on information from the monitoring system (Souchay & Isingrini, 2004). This aspect of metamemory differs from the monitoring component evaluated in the current study, the latter being a measure of self-awareness and the former representing a person's reaction to his or her self-assessment. Second, although Mantyla and colleagues report a link between metamemory and EF in healthy adults, they defined metamemory similarly to subjective memory – that is, the extent to which the person *reported* memory problems, but not whether their report was accurate (Mantyla, Ronnlund, & Kliegel, 2010). Finally, the remaining papers investigating the relationship between EF and metamemory found a relationship between EF and metamemory in healthy elders only (Perrotin et al., 2007; Perrotin et al., 2006; Perrotin et al., 2008; Souchay et al., 2000), which may suggest that the factors that influence metamemory in healthy elders may be at least partially different than those that influence disordered metamemory in AD. In fact, in AD verbal memory has been reported to be related to objectively measured metamemory more frequently than EF (Souchay et al., 2002; Souchay et al., 2003). However, the association between memory and metamemory in AD has primarily been demonstrated by examining memory as a mediating variable when examining between-group differences in metamemory across healthy elders and individuals with AD. In these studies (Souchay et al., 2002; Souchay et al., 2003) and in the current study, no association was found when directly examining the correlation between verbal memory and metamemory within individuals with AD. Moreover, several studies demonstrate a dissociation between verbal memory and memory awareness measured subjectively (Cosentino et al., 2007; Michon et al., 1994), a discrepancy that is frequently seen clinically.

Consideration of existing findings in combination with current results has the potential to inform models of anosognosia in AD. According to the CAM, successful executive processes allow information about a memory failure to be processed through a comparator mechanism that detects the failure and compares it to information held in one's personal knowledge base. Failure of the comparator mechanism to detect a memory error results in what has been referred to as *executive anosognosia* (Agnew & Morris, 1998). In contrast, deficits in memory can give rise to *mnemonic anosognosia*, also conceptualized as a petrified sense of self (Mograbi et al., 2009; Souchay et al., 2007). Essentially, patients forget that they forget, and therefore cannot accurately reflect on their memory abilities. Mnemonic anosognosia is the product of a faulty personal knowledge base that results in the inability to consolidate memory failures over time (Agnew & Morris, 1998; Hannesdottir & Morris, 2007) and has been proposed to be the major basis of disordered awareness in early AD (Ansell & Bucks, 2006; Mograbi et al., 2009). However, there has not been compelling evidence for either a primarily mnemonic or executive based anosognosia in AD when measured using verbally based tasks of memory or executive abilities. This may reflect the fact that critical variability in a right hemisphere network that spans executive and mnemonic abilities, and presumably frontal and temporal regions, contributes to memory awareness in AD. In this conceptualization, anosognosia is driven not just by impairment within a specific domain per se (EF or memory) but by compromise to a network that spans these abilities and is specialized for self-assessment of memory. We should emphasize that the associations between metamemory and nonverbal tasks, while selectively significant, were not dramatically stronger than those between metamemory and the verbal tasks

(particularly when the full FAS fluency score was considered). As such, it is likely that there is a role for verbally mediated memory or executive abilities, and presumably left hemisphere networks, in supporting metamemory. Indeed several imaging studies have shown bilateral involvement of frontal and temporal regions in supporting memory awareness (E. Salmon et al., 2006; Zamboni et al., 2013). Based on the current results and earlier cognitive studies (Cosentino et al., 2007; Mangone et al., 1991) and imaging studies (Fleming et al., 2010; Kikyo et al., 2002; Platak et al., 2004; Schnyer et al., 2004), however, it appears to be that the degree of compromise to critical right hemisphere structures accounts for important variability in awareness in AD.

Our first regression model revealed that the two non-verbal tasks account for about ten percent of the total variance in metamemory. Our lab has previously shown that metamemory seems to have a distinctive self-evaluative component that is dissociable from primary cognitive abilities (Cosentino et al., 2011); therefore, while the current non-verbal cognitive tasks may account for a significant amount of the variance based on some common underlying anatomic networks, it is likely that metamemory has distinct cognitive and neuroanatomic components that may be specific to the process of self-evaluation that are not engaged by primary cognitive tasks. For example, the insula and anterior and posterior cingulate have been shown to be critically involved with metacognitive performance both in AD patients (Hanyu et al., 2008) and in healthy adults (Chua, Schacter, & Sperling, 2009; Moritz, Glascher, Sommer, Buchel, & Braus, 2006) and the functionality of these areas are not measured in this study. The integrity of these areas likely account for some of the variance in performance in metamemory. Finally, it is plausible that other factors such as personality also account for some of the reliable variance.

It should also be noted that recent research has begun examining implicit levels of awareness as measured through facial expressions and mood report after experience with task failure (Mograb, Brown, Salas, & Morris, 2012). Interestingly, despite poor explicit awareness, individuals with AD showed preserved emotional reactivity in the context of memory failures. Moreover, implicit and explicit levels of awareness were uncorrelated in healthy adults, suggesting that these two pathways are dissociable. Continued examination of the manner in which implicit and explicit awareness interact in AD will further advance our understanding of the cognitive and neural underpinnings of impaired metamemory in AD.

Limitations of the current study include a relatively limited battery of neuropsychological testing, particularly in the domain of executive functioning. However, deconstruction of the verbal fluency measure into several different scores representing various components of executive functioning allowed more nuanced examination of the association between metamemory and EF. We are currently completing structural and functional imaging in this sample of individuals to follow up this examination of the cognitive correlates of metamemory with a detailed examination of the neuroanatomic correlates. Understanding both the cognitive and neural correlates of metamemory will inform the treatment and care of individuals with awareness deficits.

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**Table 1**

## Metamemory and Cognition

	Scores	Alzheimer's Disease			Healthy Elders		
		Mean	SD	N	Mean	SD	N
<b>Metamemory Test</b>	Gamma (-1 to 1)	.24	.71	89	.64	.56	40
<b>Global Cognition</b>	MMSE (0-30)	24.32	2.65	87	29.45	.90	50
<b>Premorbid IQ</b>	WTAR IQ	108.62	10.76	78	110.00	11.12	48
<b>Memory</b>	PVLT LD (0-9)	1.14	1.83	80	7.14	1.84	50
	Biber LD (0-27)	3.74	4.71	74	21.49	6.27	47
<b>Executive</b>	VF Total Words	11.95	4.44	65	16.66	4.74	47
	GPG Total Unique Designs (0-20)	11.99	4.23	73	16.59	2.28	46

Note. MMSE = Mini Mental State Exam; WTAR = Wechsler Test of Adult Reading; PVLT = Philadelphia Repeatable Verbal Learning Test; LD = Long Delay; VF = Verbal Fluency; GPG = Graphic Pattern Generation.

**Table 2**

Distribution of Z-Scores for Cognitive Tests

	VF	PVLT LD	Biber LD	GPG
<b>Minimum</b>	-2.94	-3.33	-3.01	-6.96
<b>25<sup>th</sup> %ile</b>	-1.64	-3.33	-3.01	-3.06
<b>50<sup>th</sup> %ile</b>	-.99	-3.33	-2.72	-1.61
<b>75<sup>th</sup> %ile</b>	-.23	-2.38	-2.14	-.71
<b>Maximum</b>	1.17	.95	.02	1.07

Note. Z-scores were derived by standardization against scores in a group of healthy elders.

**Table 3**

Executive Function and Memory correlates of Metamemory Score (Gamma)

	<b>VF</b>	<b>PVLT LD</b>	<b>Biber LD</b>	<b>GPG</b>
<b>Gamma</b>	.13	.18	.24*	.27*
	N=65	N=80	N=74	N=73
<b>VF</b>		.04	.10	.03
		N=63	N=62	N=59
<b>PVLT LD</b>			.67**	.10
			N=74	N=73
<b>Biber LD</b>				.18
				N=70

Note.

\*  
p < .05\*\*  
p < .01. Values reported are r values from partial correlations.

**Table 4**

## Fluency Subscores in AD Group

	<b>Mean</b>	<b>SD</b>	<b>Minimum</b>	<b>Maximum</b>
VF Perseverations	1.25	1.70	0	8
VF Perseverative Distance	5.43	4.40	1	14
VF Rule Violations	.52	.97	0	4
VF Proportion Clustered Words (0-1)	.39	.25	0	1
DF Time to Completion (sec)	394.40	197.33	104	994
DF Rule Violations	3.16	4.28	0	18
DF Perseverations	4.94	3.40	0	17
DF Perseverative Distance	2.16	3.05	1	10

Note. VF = Verbal Fluency; DF = Design Fluency.

**Table 5**

## Predictors of Metamemory Score (Gamma)

	<b>B</b>	<b>SE(B)</b>	<b>Beta</b>	<b>t</b>	<b>Sig. (p)</b>
<b>Model 1</b>					
GPG	.03	.02	.20	1.75	.085
Biber LD	.03	.02	.25	1.74	.089
<b>Model 2</b>					
GPG	.04	.02	.26	2.27	.026*
<b>Model 3</b>					
Biber LD	.04	.02	.24	2.04	.046*

Note. Model 1 includes both variables as predictors,  $r^2 = .10$ ; Model 2 includes GPG total as a predictor,  $r^2 = .06$ ; Model 3 includes Biber LD as a predictor,  $r^2 = .06$ ;

\*  $p < .05$ .