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The right insula contributes to memory awareness in cognitively diverse older adults

Stephanie Cosentino, Ph.D.^{1,2,3}, Adam M. Brickman, Ph.D.^{1,2,3}, Erica Griffith, B.S.², Christian Habeck, Ph.D.^{1,2,3}, Sarah Cines, B.A.², Meagan Farrell, Ph.D.², Danielle Shaked, B.S.², Edward D. Huey, M.D.^{2,3,4}, Tamara Briner, R.N.², and Yaakov Stern, Ph.D.^{1,2,3}

¹Cognitive Neuroscience Division of the Gertrude H. Sergievsky Center, Columbia University Medical Center, NY, NY

²Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Medical Center, NY, NY

³Department of Neurology, Columbia University Medical Center, NY, NY

⁴Department of Psychiatry, Columbia University Medical Center, NY, NY

Abstract

Unawareness of memory loss is a challenging characteristic of Alzheimer's disease (AD) and other age-related neurodegenerative conditions at their earliest stages, adversely affecting important outcomes such as patient decision making and safety. The basis of this metacognitive disturbance has been elusive; however it is almost certainly determined in part by compromise to brain regions critical for self-assessment. The subjectivity of traditional measurements of self-awareness in dementia has likely limited the rigor with which its neuroanatomic correlates can be established. Here we objectively measure memory awareness (metamemory) using a Feeling of Knowing (FOK) task in a group of cognitively diverse older adults, including 14 with mild AD and 20 cognitively healthy older adults. Performance on the metamemory task was examined in relation to the structural integrity of 14 bilateral neuroanatomic regions hypothesized to support self-awareness. Less accurate metamemory was associated only with reduced right insular volume ($r = .41$, $p = .019$). Implications of the current findings for models of metacognitive aging are discussed, with attention to the role of the insula in the conscious detection of errors.

Keywords

Awareness; Anosognosia; Metacognition; Alzheimer's disease; Insula

Corresponding author: Stephanie Cosentino, Columbia University Medical Center, 630 West 168th Street, P&S Mailbox 16, NY NY 10032, sc2460@cumc.columbia.edu.

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1. Introduction

Disordered awareness of cognitive changes in the context of pathological aging challenges patient safety, caregiver quality of life, and decision making capacity.¹⁻³ Indeed, it can be argued that metacognitive deficits have greater implications for functional disability in older adults than do cognitive deficits. Investigation into the basis of metacognitive disturbance in AD, by far the most common cause of pathological cognitive aging, is therefore of critical importance. Existing imaging studies in AD have linked impaired memory awareness to a range of regions in the prefrontal cortex (PFC) spanning inferior, medial, lateral, and dorsal areas, as well as anterior and posterior cortical midline structures including the cingulate and precuneus.⁴⁻⁶ Variability in previous results may stem from the imprecision of subjective measurement tools to measure memory awareness such as clinical rating scales or measures of the discrepancy between patient and informant report. While valuable for characterizing general, day to day levels of self-awareness, these are imperfect gold standards, limited by their lack of objectivity. Clinical ratings, generally scored on an ordinal scale and based on an individual's spontaneous description of their memory, can be difficult to quantify, requiring the rater to make distinctions between somewhat arbitrary levels of awareness (e.g., Full, Moderate, Shallow, None). Moreover, the extent to which participants are willing to openly discuss information about their memory loss is likely influenced by a range of factors such as personality style, cultural variables, and mood, to name a few. Discrepancy scores, in which awareness is generally defined based on answers to discrete closed-ended questions about memory, may be less confounded by these issues. However, in this case, awareness is considered to be impaired to the extent that participants' responses regarding their memory abilities differ from the ratings of an informant, whose perspective may also be influenced by a variety of psychological and motivational factors, as well as the nature of their relationship with the patient.^{7,8} Finally, both types of subjective awareness ratings are relatively less useful for understanding memory awareness in cognitively healthy older adults who by definition have no frank memory impairment of which to be aware or unaware.

In order to more precisely measure memory awareness in cognitively diverse older adults, we previously developed a metamemory task that objectively assesses the accuracy of individuals' expectations for their memory.⁹ This 20-item task, based on a Feeling of Knowing (FOK) framework, challenges individuals to learn five new pieces of information over four trials and to make judgments regarding their ability to recognize the correct answer for each (e.g., Will you know which one is right – yes, maybe, or no?). The total metamemory score, measured as a gamma value from -1.0 to 1.0, reflects the relative accuracy of judgments across all trials;¹⁰ specifically, the extent to which judgments for performance are concordant with actual performance. Performance on this task has been shown to engage a specifically self-evaluative ability that is independent of primary cognitive functions such as attention, executive abilities, or memory in cognitively healthy older adults.¹¹ Additionally, performance on this task accounts for significant variance in clinically rated awareness levels in individuals with AD, suggesting that this task may be used to understand the basis of disordered memory awareness in AD.⁹

With regard to the anatomic substrates of metamemory, previous studies in healthy adults have pointed most consistently to the PFC as a primary component of a metamemory network. In particular, activity in the ventromedial PFC^{12,13} has been most frequently associated with the accuracy of prospective memory judgments; however, more posterior regions including the medial temporal and parietal cortex as well as the hippocampus have also been implicated.¹⁴ Both the anterior (ACC) and posterior cingulate cortex (PCC) have also been linked to the integrity of self-appraisal in individuals with memory disorders,^{15,16,17} as well as to error detection in healthy adults,^{18,19} although it has been suggested that the role of the ACC in particular may be primarily one of resolving conflicts between potential responses.^{13,20}

With regard to laterality, memory and other types of self-awareness appear to rely preferentially on right hemisphere regions. Indeed, the role of right versus homologous left sided structures in contributing to symptom awareness has historically been recognized across patients with stroke and traumatic brain injury.^{21,22} The functional inequality of the two hemispheres can also be seen in the lateralized presentations of frontotemporal dementia (FTD), with the behavioral variant patients (right PFC predominant) frequently displaying reduced symptom awareness as compared with the non-fluent, agrammatic aphasia patients (left PFC predominant) in whom symptom awareness is more frequently intact.²³ Studies of individuals with AD have been somewhat inconsistent, with approximately half implicating greater right hemisphere involvement²⁴ and the remaining evidencing largely bilateral contributions.^{5,25} However, it is important to note that most of these studies have implemented subjective measures of self-awareness that may be influenced by a range of factors as mentioned above. Interestingly, a recent behavioral study from our lab using the objective metamemory task demonstrated an association between memory awareness in AD and performance on nonverbal cognitive tasks spanning executive and memory domains.²⁶ Such results are consistent with the idea that memory awareness in AD relies in part upon a right lateralized network, spanning prefrontal and temporal regions, that is critical for the online monitoring of information stored in memory.

Taking together findings in healthy adults as well as various clinical populations, we hypothesized that metamemory in this group of cognitively diverse older adults would be correlated with the integrity of a network likely involving the ventromedial PFC, but spanning more posterior regions critical for memory as well, including the medial temporal cortex and hippocampus. We also anticipated the possibility that midline structures including the insula, cingulate, or precuneus may play a role given their previously reported role in supporting a variety of aspects of self-awareness more broadly. Finally, we expected to find a stronger association between metamemory and right hemisphere structures than left sided regions.

2. Methods

2.1. Participants

Fourteen individuals with mild to moderate Probable AD defined as a score of 19 or greater on the Mini-Mental State Examination (MMSE)²⁷ were recruited through the Columbia University Medical Center (CUMC) Department of Neurology Memory Disorders Clinic.

Diagnoses were made according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria. Individuals with a history of neurologic illness or injury, or ongoing psychiatric illness were excluded. All participants provided informed consent and were given monetary compensation (reimbursed \$30.00 per visit).

Twenty non-demented elders were recruited through the Alzheimer's Disease Research Center at CUMC, local senior centers, and market mailing procedures that target a diverse group of elders in New York City. Controls were thoroughly screened by interview to exclude individuals with neurologic, psychiatric, or severe medical disorders, and were eligible for the study if they were age 55 or above, and scored at least 27 on the MMSE.

2.2. Procedures

All participants completed the metamemory test prior to any cognitive testing to ensure that experience with cognitive tests did not alter their expectations for performance in the context of the metamemory test. Several cognitive tests were administered to characterize differences in primary cognition across the AD and HE groups. The majority of participants underwent structural magnetic resonance imaging (MRI) of the brain within two months of their cognitive assessment, with an average duration of 0.77 (2.46) months. Three participants with AD were scanned outside the two month window at 3.2, 3.9, and 4.7 month intervals, and two healthy controls had intervals of 4.1 and 9.4 months. Analyses were conducted with and without the individual with the 9.4 month interval to be sure that exclusion of this individual did not affect the results. This study was approved by the CUMC Institutional Review Board and all individuals provided informed consent prior to participation.

2.3. Measures

2.3.1. Objective Metamemory Test—The metamemory test was a modified episodic Feeling of Knowing (FOK) task²⁸ consisting of four trials with five items in each trial, yielding a total of 20 metamemory items. Stimuli were selected after several rounds of piloting aimed at eliminating floor or ceiling effects in both AD and HE groups. The final stimuli for the AD participants consisted of five pieces of “pseudo trivia” regarding an individual from history and fake information about his background. Such stimuli performed better than actual facts, or than entirely fictional names and information. A potential risk of using these stimuli is that they are falsifiable; however, they are not easily falsifiable. That is, one would have to be very knowledgeable about these particular individuals to know that the stimuli were untrue (i.e., even someone who is an expert in Cole Porter's music is likely to be unsure of his past educational experience). We assume that if it were to occur, the overall effect on the metamemory score would be relatively small. More difficult items consisting of entirely fictional names and background information were used in the non-demented elders to prevent ceiling effects. As the current HE sample partook in a larger study regarding the cognitive basis of metamemory deficits in AD, healthy controls received one of three versions of the FOK task (i.e., standard, query, or feedback) as described below. Previous work has established that there are no differences in performance across these three

conditions in healthy adults; different conditions were originally administered in this group solely for the purpose of collecting normative data.²⁹

Standard Condition: 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”. After the first learning trial was presented (e.g., Cole Porter attended law school in Chicago; Edward Jenner traveled to Asia to study philosophy, etc.), participants were asked to make prospective judgments for each item in response to written questions (e.g., Who attended law school in Chicago?) and the following prompt read aloud by the examiner: “Please don’t answer aloud. There are eight possible answers on the next page. Will you know which one is right – Yes, Maybe, or No?” Once judgments 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 4 stimuli (to control for basic familiarity effects), and 3 new distractors. In the standard condition, the tester moved onto the next item. This process was repeated for learning trials 2–4 resulting in a total of 20 item-specific judgments. Stimuli were presented in the same order across each of the four learning trials; questions and answer choices were presented in a pseudorandom order.

Query Condition: This condition is identical to the standard condition, with the additional component of a retrospective evaluation after each item, in which the examiner asks the participant, “Do you think that was the correct answer – Yes, Maybe, or No?” The score derived from this condition also examines the relative accuracy of the predictions (not the retrospective judgments).

Feedback Condition: This condition is identical to the standard condition except that the examiner provides feedback regarding memory performance after each item (e.g., “That is correct or That is incorrect”). There are no retrospective ratings included in this condition.

The dependent variable for all conditions of the metamemory task is the relative accuracy of judgments (i.e., resolution), reflecting the extent to which memory accuracy is high when predictions for memory performance are high, and accuracy is low when predictions are low. The nonparametric Goodman-Kruskal gamma statistic, a rank order correlation,¹⁰ was used to measure resolution. Gamma compares the relative number of concordant and discordant judgment/accuracy pairs, discarding “ties”, or instances in which either the rating or accuracy in one pair is equal to that in another pair. A score of 1 indicates perfect concordance between all of the 20 judgment/accuracy pairs within the test. Given the limitations of gamma, including a tendency to be pulled to an extreme value on the basis of only one concordance or discordance, or a possibility that a score is undefined in the event of all ties, gamma scores were corrected in line with previous suggestions.³⁰ This correction has been applied in the context of signal detection theory to address instances in which hit rates are equal to one or false alarm rates are equal to zero, resulting in undefined signal detection measures.³¹ When applied to the calculation of gamma, this correction entails adding 1 to the overall number of concordances as well as the overall number of discordances. This adjustment draws scores slightly away from extreme values and assigns a

score of zero when a score would otherwise be undefined in the case of all ties. For example, if an individual made judgments of “Yes” for every item, regardless of performance, each item would be tied with every other item and a score would thus be incalculable. By adjusting the calculation, this person’s performance is considered equal to 0, representing a random association between predictions and performance. The correlation between calculable gamma scores and the adjusted scores in this sample was 0.99 ($p < .01$).

2.3.2 Immediate Auditory

Attention Forward Digit Span: This subtest from the Wechsler Memory Scales - Third edition WMS-III,³² required participants to repeat a series of digits, beginning with only two and increasing until the participant failed two consecutive items at a given series length. The dependent variable was the total raw score.

2.3.3. Memory

Philadelphia Repeatable Verbal Learning Test (PVLТ)³³: The PVLТ is a list learning task in which participants are required to learn 9 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:³⁴ This nonverbal list learning task consists of 9 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 30 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.

2.3.4. Executive Functioning

Graphic Pattern Generation (GPG)³⁵: The GPG test requires participants to generate multiple unique designs among arrays of dots. The short form of the test is characterized by a row of stimuli, consisting of 20 identical 5-dot arrays.³⁶ The test requires participants to generate as many novel designs as they can using exactly four lines to join the dots in each array. The first instance of a perseveration and the first instance of a rule violation were corrected. The dependent variable was total number of perseverations.

2.3.5. Structural Neuroimaging—Using each individual’s T1-weighted MPRAGE image, measures of global and regional brain volume were derived using the automated volume-based stream in the Freesurfer software package (<http://surfer.nmr.mgh.harvard.edu/>).^{37,38} The FreeSurfer volumetric processing stream involves affine transformation of each subject’s T1 weighted image into Talairach space, probabilistic segmentation of grey and white matter structures using values from both a subject-independent atlas (derived from a training set) and subject-specific values, bias field intensity normalization, and automatic labeling of anatomical regions of interest in both cerebral hemispheres. The procedures have been described in full detail previously.^{37,38} All

labeled images were inspected visually and corrected manually by an expert operator. Freesurfer is widely considered a gold-standard approach for morphological analysis of MRI data in older adults, evidenced by its use as a primary analytic tool in the Alzheimer's Disease Neuroimaging Initiative. Freesurfer avoids many of the registration, atrial volume, and segmentation errors commonly observed with other techniques, such as voxel-based morphometry.³⁹

To limit the number of analyses, fourteen bilateral ROIs previously implicated in studies of awareness were derived, including right and left sided: 1) Prefrontal: medial orbital, superior frontal and frontal pole; 2) Temporal: entorhinal, parahippocampal, temporal pole; 3) Parietal: superior parietal, precuneus; 4) Anterior Cingulate Cortex (ACC): caudal and rostral ACC; 5) Posterior Cingulate Cortex (PCC); 6) Hippocampus; and 7) Insula.

3. Data Analysis

ANOVAs were used to compare the HE and AD groups on demographic, cognitive, and metacognitive variables. A general linear model adjusted for total intracranial volume was used to compare ROI volume across HE and AD groups. For the primary correlational analyses, partial correlations were conducted in all participants to examine the association between the 14 ROIs and metamemory performance. Given the relatively small size of the HE and AD samples, correlations were conducted in the entire sample, adjusting for diagnostic group. The results of such analyses therefore are interpreted to reflect the regions of the brain related to metamemory in both groups. Correlations were also adjusted for total intracranial volume (TCV), and metamemory test condition (in healthy elders). As the regions examined were all hypothesis-driven, and the sample size was relatively small, corrections for multiple comparisons were not applied.

Results

We evaluated 34 participants including 14 individuals with mild to moderate AD (mean age = 77.81 + 11.56 years) and 20 cognitively healthy elders (mean age = 68.26 + 9.04 years). See Table 1 for cognitive and metamemory scores across diagnostic group. Global cognition, ($F(1, 32) = 84.76, p < .001$), verbal memory ($F(1, 32) = 221.85, p < .001$), nonverbal memory ($F(1, 32) = 89.82, p < .001$), and design fluency scores ($F(1, 32) = 8.47, p = .007$) were lower in the AD group as compared to the healthy older adults. See Table 2 for ROI volume by diagnostic group. Adjusting for multiple comparisons, the AD group had significantly smaller volume in the following left sided ROIs: 1) temporal, $F(1, 31) = 4.47, p = .043$, parietal, $F(1, 31) = 10.99, p = .002$, ACC, $F(1, 31) = 4.62, p = .04$, PCC, $F(1, 31) = 6.93, p = .013$ and hippocampus, $F(1, 31) = 9.57, p = .004$; and the following right sided regions: parietal, $F(1, 31) = 7.92, p = .008$, PCC, $F(1, 31) = 14.41, p = .001$, and hippocampus, $F(1, 31) = 13.90, p = .001$.

3.1. Correlates of Metamemory

Performance on the metamemory test was not significantly associated with education ($r = .27, p = .12$), verbal memory ($r = .28, p = .11$), or global cognition ($r = .26, p = .13$). Although performance was related to age ($r = -.35, p = .04$), age was related to diagnostic

group ($F(1, 32) = 7.31, p = .01$) and the association between age and metamemory became non-significant when controlling for group. The primary correlational analyses examining metamemory performance in relation to the volumetric ROIs were adjusted for diagnostic group, total intracranial volume, and metamemory task condition (as there were three conditions to which healthy elders were randomly assigned). Results of the final adjusted correlation revealed that metamemory performance was associated selectively with right insular volume ($r = .41, p = .019$). See Figure 1. Correlational results remained the same when excluding the healthy control with a 9.4 month interval between cognitive assessment and MRI. Results also remained the same when entering education, verbal memory, or global cognition as covariates. Although not significantly related to metamemory, the left insula has also been implicated in supporting aspects of self-awareness and we sought to determine the robustness of the apparent right lateralization. The association between the right insula and metamemory persisted ($r = .43, p = .017$) when entering left insular volume as a covariate. See Table 3 for all correlational results.

4. Discussion

The current study used objective metamemory testing to examine the neuroanatomic substrates of memory awareness in a group of cognitively diverse older adults including individuals with normal cognition as well as individuals with AD. To our knowledge, this is the first study to demonstrate a specific role for the insula in supporting memory awareness in cognitive aging. This finding maps onto the expectation that a right sided network functionally linked with prefrontal and temporal regions would be important for supporting metamemory in this group. While novel in this specific context, our finding is in concert with conceptualizations of the insula as a critical contributor to a range of self-evaluative processes.⁴⁰ Indeed, the right insula in particular has been linked to awareness deficits related to limb ownership and limb functioning in the context of anosognosia for hemiplegia⁴¹ as well as degree of insight in patients with schizophrenia.⁴² Craig (2009) has argued that this brain region provides a central resource for processing and representing subjective states across time, and that a spatial gradient exists such that the posterior insular cortex is specialized for re-representing primary interoceptive experiences (e.g., heart rate, breathing, temperature) while the anterior insula is engaged in relation to awareness of higher order cognitive and emotional experiences.⁴³

The mechanism by which the insula enacts this metacognitive function may relate to its role in the conscious detection of errors, a process that seems to preferentially engage the right rather than left insula.^{44,45} Indeed, a meta-analysis of 55 functional magnetic resonance imaging studies examining performance monitoring revealed that the insula is consistently activated⁴⁰. Ullsperger and colleagues (2010) pursued these findings by examining four task conditions during which performance should be expected to be under adjustment including pre-response conflict, decision uncertainty, error production, and negative feedback.⁴⁶ Interestingly, while the anterior insula was active for all conditions, the post response conditions including error production and negative feedback were characterized by greater activity in the right versus left insula. Importantly, it is also the case that the insula is activated only when individuals are consciously aware of their errors, and it is in part this characteristic that has led to the hypothesis that insular activity is indirectly involved in the

generation of the fronto-parietal Pe response on EEG, a response that is only present when individuals are aware of their errors.⁴⁴ The apparent role for the insula in performance monitoring is bolstered by its consistent association with autonomic nervous system (ANS) activity including heart rate deceleration, pupil dilation, and elevated skin conductance responses, all of which appear in the context of conscious error perception.^{47,48} The extent to which the insular activity leads to this type of orienting response, or is a reaction to such ANS activity remains unclear, however.

Taken together, the numerous studies highlighting the insula in performance monitoring, and the right insula in particular in relation to post response error information, provide a meaningful context in which to consider the neuroanatomic basis of impaired metamemory in AD and the potential role for deficient error detection in compromising metamemory. A model of impaired metamemory based on insular dysfunction would therefore entail impaired conscious detection of individual memory failures. Indeed, recent data from our lab have shown that the relative accuracy of metamemory judgments in individuals with AD who are unaware of their memory loss does not significantly improve from pre-test to post-test.²⁹ In other words, experience with memory failures does not alter judgments of performance, suggesting that error detection is compromised. Deficient conscious detection of errors was also reported in a recent study demonstrating preserved implicit awareness for memory failures, evidenced through emotional reactivity and physiological measures, despite an absence of explicit error awareness in AD.⁴⁹ Additionally, ERP studies of error awareness in patients with AD have implicated slow and somewhat impaired ERN (error-related negativity) as compared with healthy older adults.^{50,51} Interestingly, in these studies, the Pe (error positivity) is preserved, implicating awareness of errors despite slower processing of such errors. It should be noted, however, that these studies both used language tasks to elicit errors, whereby participants were required to identify either a mismatch between a picture and its verbal label, or to distinguish between words and non-words. It may be that awareness for language related errors differs from memory errors, and in fact recent work from our lab suggests that AD patients are more frequently aware of language deficits than memory deficits.⁵²

The evidence pointing to a role for the insula, and potentially error detection, in memory awareness could be consistent either with a “primary” model of anosognosia in AD, or an “executive” model, two of several potential forms of anosognosia outlined in the Cognitive Awareness Model.^{53,54} In primary anosognosia, there is a failure to experience the error at a conscious level despite implicit processing of the error. This is in contrast to an “executive” anosognosia in which errors are not explicitly compared to one’s expected performance either due to impairment at the level of the comparator mechanism, or as a result of deficient emotional motivation necessary for perceiving errors.⁵⁵ Finally, in “mnemonic” anosognosia, awareness deficits are the product of “forgetting that one forgets”.^{56,57} To date, the few studies examining the nature of memory awareness deficits in AD have generally pointed to the latter model as the most likely scenario.

Recently, the right insula has been identified as one of a number of structures that support self-awareness in a heterogeneous group of individuals with and without dementia.⁶ Specifically, in the first large scale structural imaging study of awareness deficits in

dementia, Shany-Ur and colleagues reported an association between broad aspects of self-awareness related to cognition, everyday behavior, emotional control and interpersonal behavior (measured using a discrepancy score between patient and informant report) and wide-spread prefrontal and subcortical regions, right greater than left, including dorsal superior and middle frontal gyri, lateral and medial orbitofrontal gyri, orbital regions of the inferior and superior frontal gyri, right anterior insula, putamen, thalamus, caudate, pons, and midbrain in a mixed group of patients with FTD and AD, as well as healthy older adults. Such results provide a context in which to interpret findings from the current study, which by comparison, is a targeted examination of memory awareness along a more typical spectrum of cognitive aging. Whereas a broad network of structures is certain to be implicated in supporting many different aspects of self-awareness, as would be the case when considering awareness related to a range of symptoms in multiple degenerative diseases, it is likely the case that a more discrete network mediates online memory monitoring.

Nonetheless, it should be noted that the correlation between the insula and metamemory in the current study was only moderate, suggesting that other neuroanatomic regions, and likely other person-specific factors contribute to performance on the metamemory test. In the current study, the left ACC and right PCC had correlations of .29 and .26 respectively, associations that may have been significant with a larger sample size. The ACC has been implicated in previous studies of memory awareness in AD^{17,58} as well as error detection^{18,19} and the PCC has also been implicated in aspects of self-reflection in AD. Indeed, evidence across fMRI, ERP and lesion studies suggest that the ERN is generated in the ACC.^{59,60} In addition to the neuroanatomic contributors to memory awareness, characteristics of the individual related to personality, culture, and mood are also likely contribute to metamemory performance.

Understanding the basis of metamemory deficits in cognitive aging will provide a foundation upon which appropriate interventions can be developed to preserve or even improve specific aspects of self-awareness across the spectrum of cognitive aging; in the interest of enhancing decision making and maintaining individual autonomy to the greatest extent possible. The inability to appreciate memory loss is not universal in AD, but when present, is often a debilitating feature of the disease. Whereas individuals who are aware of their memory loss usually evidence sound decision making regarding a range of issues related to treatment and everyday affairs (e.g., choosing to implement an assistive strategy for managing medications), those with reduced awareness of memory loss often make suboptimal choices.^{1,2}

Certainly, in the context of cognitive impairment, it is prudent for individuals to modify the manner in which they approach cognitively demanding activities such as bill paying, caring for grandchildren, driving, or working, for example. Preliminary work from our lab has shown that even in the context of Mild Cognitive Impairment, the extent to which individuals appreciate their memory loss appears to determine their decisions about such activities, including whether to: 1) ask for assistance in carrying out the activity; 2) modify their approach in some other way; or 3) discontinue the activity altogether.⁶¹ Moreover, it appears that some cognitively normal older adults also modify their everyday activities

based on concerns about cognitive functioning, suggesting that differences in self-assessment and self-awareness may have relevance for decision making and everyday function even in the absence of a cognitive disorder. Precisely characterizing the neuroanatomy of impaired memory awareness in cognitive aging will better direct cognitive and behavioral experiments in which awareness may be manipulated or even remediated in a targeted fashion. Increased attention to the role of the right insula, and the integrity of error detection, may provide valuable insights in this endeavor.

There were several limitations to this study. First, the sample size was relatively small. Ideally, correlations would have been conducted both across and within diagnostic groups to determine differences in the strength or regions of association within each group. It is important to note that the current analyses, adjusted for diagnostic group, speak only to the regions that relate to metamemory in both groups, and it is certainly possible that other regions may be more or less relevant for one group in particular. This study was also limited to a degree by the application of relatively traditional methodologies such as a correlational approach combined with an ROI based measurement of brain integrity, as opposed to a more comprehensive analysis that examines connectivity throughout multiple regions of the brain. However, few if any studies have directly examined the structural correlates of metamemory in individuals with AD, rendering the current findings an appropriate starting point for more in depth, multivariate imaging approaches in the future.

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Highlights

- Disordered awareness of memory loss is a common feature of Alzheimer's disease
- We examined the structural correlates of metamemory in cognitively diverse elders
- Metamemory was associated with right insular volume
- Disordered awareness of memory loss in AD may reflect impaired detection of errors

Figure 1.
Right insula

Table 1

Cognition and Metamemory by Group

Test	Possible Range	HE (n=20)	AD (n = 14)
MMSE	0 – 30	29.25 (1.45)	23.29 (2.34) *
Verbal Memory	0 – 9	7.53 (1.31)	0.79 (1.31) *
Nonverbal Memory	0 – 27	22.32 (5.50)	4.83 (4.06) ***
Auditory Attention	0 – x	11.00 (2.15)	10.46 (2.50)
Design Fluency	0 – 19	3.47 (1.81)	5.73 (2.41) **
Metamemory	–1.0 – 1.0	0.53 (0.47)	0.30 (0.58) *

Note.

*
p < .05.

**
p < .01,

p < .001.

Table 2

ROI Volume

	Left		Right	
	HE	AD	HE	AD
Prefrontal	24348.50 (3582.96)	22454.93 (3651.31)	24192.90 (3482.38)	23103.29 (2161.03)
Temporal	4739.25* (1113.30)	4061.86 (884.54)	4663.65 (951.18)	4109.57 (790.59)
Parietal	20563.90** (2605.16)	18121.79 (2614.99)	20699.05** (2759.97)	18777.71 (2081.93)
Anterior Cingulate	4282.45* (910.81)	3707.00 (943.58)	4009.05 (842.65)	3782.36 (975.86)
Posterior Cingulate	3033.05* (555.41)	2528.07 (694.32)	3025.20** (477.80)	2556.00 (372.38)
Hippocampus	3289.35** (506.01)	2748.57 (527.00)	3491.80** (494.86)	2806.21 (577.97)
Insula	6000.20 (835.95)	5728.64 (916.70)	6087.90 (1043.08)	5914.71 (872.55)

Note.

*
p < .05;

**
p < .01.

Analyses compare TCV adjusted ROI volume across HE versus AD.

Table 3

Correlations between Metamemory and Volumetric ROIs

	Right r	Left r
Prefrontal	.15	-.01
Temporal	.13	.17
Parietal	.14	.19
Anterior Cingulate	.08	.29
Posterior Cingulate	.26	-.03
Hippocampus	.12	.23
Insula	.42*	.06

Note. Bivariate analyses in the entire group were adjusted for total intracranial volume (TCV), diagnostic group, and metamemory test condition;

* $p < .05$.