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Cross Domain Self-Monitoring in Anosognosia for Memory Loss in Alzheimer's disease

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Abstract

Anosognosia for memory loss is a common feature of Alzheimer's disease (AD). Recent theories have proposed that anosognosia, a disruption in awareness at a *global* level, may reflect specific deficits in self-monitoring, or *local* awareness. Though anosognosia for memory loss has been shown to relate to memory self-monitoring, it is not clear if it relates to self-monitoring deficits in other domains (i.e., motor). The current study examined this question by analyzing the relationship between anosognosia for memory loss, memory monitoring, and motor monitoring in 35 individuals with mild to moderate AD. Anosognosia was assessed via clinical interview before participants completed a metamemory task to measure memory monitoring, and a computerized agency task to measure motor monitoring. Cognitive and psychological measures included memory, executive functions, and mood. Memory monitoring was associated with motor monitoring; however, anosognosia was associated only with memory monitoring, and not motor monitoring. Cognition and mood related differently to each measure of self-awareness. Results are interpreted within a hierarchical model of awareness in which local self-monitoring processes are associated across domain, but appear to only contribute to a global level awareness in a domain-specific fashion.

Key words. Metacognition, anosognosia, agency, cognition, Alzheimer's disease.

Highlights

- Hierarchical models of awareness for memory loss are assessed in Alzheimer's disease
- Self-monitoring in motor and memory domains are associated in Alzheimer' disease.
- Self-monitoring processes dissociate in anosognosia for memory loss.

1. INTRODUCTION

Individuals with Alzheimer's disease (AD) are often unaware of their deficits (see Agnew & Morris, 1998; Cosentino & Stern, 2005; Rosen, 2011). This disordered higher level self-awareness, or anosognosia, has been linked to a variety of negative personal and societal consequences, with "unaware" individuals engaging in and benefiting less from clinical management, demonstrating reduced capacity to make treatment decisions (Clare, Wilson, Carter, Roth, & Hodges, 2004; Cosentino, Metcalfe, Cary, De Leon, & Karlawish, 2011; Koltai, Welsh-Bohmer, & Schmechel, 2001), and engaging in more risky behaviors than those who are aware of their deficits (Cotrell & Wild, 1999; Wild & Cotrell, 2003). Moreover, those responsible for the care of unaware patients report higher degrees of stress and burden (Prigatano, 2005; Rymer et al., 2002; Seltzer, Vasterling, Yoder, & Thompson, 1997), even in the context of Mild Cognitive Impairment (MCI) (Kelleher, Tolea, & Galvin, 2016). As efforts to diagnose AD move toward a preclinical stage during which individuals have the capacity to be highly functional, if aware of their cognitive deficits, understanding the specific metacognitive impairments leading to anosognosia in AD may be critical for enabling individuals to maintain their autonomy.

There is a growing yet incomplete understanding of the ways in which self-awareness breaks down in AD, as well as other conditions such as stroke. Existing models of anosognosia, or *global* awareness, have outlined the ways in which dysfunctional memory and executive systems can give rise to disordered awareness in AD (see Agnew & Morris, 1998; Ansell & Bucks, 2006; Morris & Mograbi, 2013). However, given that disruptions to memory (Derouesne et al., 1999; Reed, Jagust, & Coulter, 1993; Starkstein et al., 1995) and executive functions (Lopez, Becker, Somsak, Dew, & DeKosky, 1994; Michon, Deweer, Pillon, Agid, & Dubois, 1994; Reed et al.,

1993; Starkstein, Sabe, Chemerinski, Jason, & Leiguarda, 1996) do not fully explain anosognosia in AD, it is clear that other mechanisms are at play in the deterioration of higher levels of self-awareness. Currently, there is a drive in both the cognitive and motor literatures towards a dynamic and multifaceted notion of self-awareness wherein factors specific to metacognition, not simply cognition, give rise to this fascinating disorder (Clare, Markova, Roth, & Morris, 2011; Davies, Davies, & Coltheart, 2005; Fotopoulou, 2014; Levine, 1990; Rosen, 2011).

In this vein, research has begun to examine processes that may be uniquely self-evaluative, (i.e., processes that, although potentially dependent on primary cognitive abilities such as memory or executive functions, have a unique variance that cannot be simply explained by these primary cognitive abilities). One such process is self-monitoring or *local* awareness—the process by which one evaluates aspects of one's own individual thoughts, intentions and actions compared to those of others or those arising from the external world (Agnew & Morris, 1998; Fotopoulou, 2014; Jenkinson & Fotopoulou, 2010; McGlynn & Schacter, 1989; Rosen, 2011; Saj, Vocat, & Vuilleumier, 2014; Venneri & Shanks, 2004). Leading theorists in anosognosia for memory loss have conceptualized awareness within a hierarchical structure in their models, with monitoring processes, or local awareness, considered to be underlying anosognosia, or higher order global awareness (Agnew & Morris, 1998; Clare et al., 2011; Mograbi & Morris, 2013). Previous work in AD has linked traditional clinical ratings of anosognosia, understood as a higher level of awareness (i.e., *global* awareness), with performance on memory monitoring or metamemory measures, understood as lower levels of awareness (i.e., *local* awareness) (Clare et al., 2011). However, relatively little work has examined the extent to which anosognosia in AD, stroke, or other conditions is characterized by broad deficits in self-monitoring or domain specific deficits in self-monitoring.

In the current study, we examined the association between anosognosia for memory loss in AD, memory monitoring, and motor monitoring (i.e., agency judgments, or the extent to which individuals perceive themselves to be the agent of a determined outcome or action) (Gallagher, 2000). There is an inherent necessity of accessing self-specific information when making a judgment of agency related to an action or thought, and agency tasks have been used to understand unawareness of hemiplegia or other motor deficits following stroke (Fotopoulou et al., 2008), providing an ideal framework to examine self-referential monitoring in a non-memory domain. Indeed, much of the work dedicated to modeling anosognosia and examining the role of monitoring difficulties has occurred in the context of impaired motor functioning, specifically in individuals

who are unaware of hemiplegia following stroke (Jenkinson, Edelstyn, Drakeford, & Ellis, 2009; Saj et al., 2014; Venneri & Shanks, 2004; Vocat, Saj, & Vuilleumier, 2013). Conceptually, it has been proposed that discrepancies in monitoring between one's intentions (i.e., motor plan) and one's actual motor performance may result in unawareness of hemiplegia (Berti, Spinazzola, Pia, & Rabuffetti, 2007; Cocchini, Beschin, Fotopoulou, & Della Sala, 2010; Fotopoulou et al., 2008; Moro, Pernigo, Zapparoli, Cordioli, & Aglioti, 2011). The *Comparator Model* of motor control posits that for each produced movement, an individual *implicitly* monitors their intentions and predicted outcome in relation to sensory and perceptual feedback about the actual outcome (Blakemore, Wolpert, & Frith, 2002). The comparison between these two processes allows the detection of a mismatch that would occur in the context of a movement error, and therefore allows correction of the error. The comparison also provides a neural basis for the perception of a distinction between internally driven movements (where the match between the two processes is high) and those movements caused by an external source (I. Feinberg, 1978; Frith, 2005).

Another explanatory model of judgments of agency or judgments of motor monitoring is the *Theory of Mental Causation* (Wegner, 2002; Wegner & Wheatley, 1999). This theory proposes that individuals *consciously* assess the relationship between intentions and actions, and infer causal judgments of agency. This conceptualization moves away from the underlying process of motor monitoring, arguing that such processes are unconscious, and proposes that individuals utilize conscious processes such as the intention associated with the action and contextual cues of the outcome itself, to derive an inferential judgment of agency or judgments of motor monitoring (Haggard & Tsakiris, 2009; Metcalfe, Eich, & Castel, 2010; Moore, 2016; Synofzik, Vosgerau, & Newen, 2008; Wegner, 2002; Wegner & Wheatley, 1999).

Several studies have supported the association of motor monitoring and anosognosia for hemiplegia (e.g., Jenkinson & Fotopoulou, 2010; Vocat et al., 2013). Interestingly, monitoring deficits in patients unaware of their motor deficits seem to relate to monitoring deficits in other cognitive domains (T. E. Feinberg, Roane, Kwan, Schindler, & Haber, 1994; Jenkinson et al., 2009; Venneri & Shanks, 2004). These cross-domain associations suggest that at least in the case of anosognosia for motor deficits, its underlying mechanisms may not be domain specific and that a combination of different processes may be key to the emergence of impaired awareness (e.g., deficient error prediction, encoding, monitoring and premorbid factors) (Cocchini, Beschin, & Sala, 2002; Davies et al., 2005; Fotopoulou, 2014; Levine, 1990; Marcel, Tegnér, & Nimmo-Smith, 2004; McGlynn & Schacter, 1989; Vuilleumier, 2004). The association of self-monitoring

abilities across different task domains has also been demonstrated in non-demented cohorts in which the integrity of memory monitoring and motor monitoring (i.e., *agency*) judgments have been linked (Cosentino, Metcalfe, Holmes, Steffener, & Stern, 2011).

To our knowledge, there are no previous studies examining judgments of agency in AD. Given the cross-domain monitoring deficits seen in individuals with anosognosia for hemiplegia, and the link between memory monitoring and agency monitoring in older adults, one might hypothesize that anosognosia in AD may be associated with compromised agency in AD. However, there is also reason to believe that these processes may be dissociated. While they are both self-referential, the substrates that contribute to each judgment are seemingly very different. For example, memory monitoring has been hypothesized to rely on memory abilities, executive functioning, and underlying implicit internal monitoring of mnemonic processes such as familiarity and partial access to information (Cosentino, Metcalfe, Holmes, et al., 2011; Koriat, 1993; Koriat & Levy-Sadot, 2001; Metcalfe, Schwartz, & Joaquim, 1993; Reder & Ritter, 1992; Schnyer et al., 2004; Schwartz & Metcalfe, 1992). In contrast, judgments of agency have been hypothesized to rely on the monitoring of sensory and perceptual stimuli of the action, and the integration of different contextual cues such as; perceived success, temporal delay between intention, and outcome and reward (Blakemore et al., 2002; Frith, Blakemore, & Wolpert, 2000; Kirkpatrick, Metcalfe, Greene, & Hart, 2008; Metcalfe, Van Snellenberg, DeRosse, Balsam, & Malhotra, 2014; Michotte, 1963; Moore, 2016; Schlottman & Shanks, 1992).

The purpose of this study is to clarify the association between different domains and levels of awareness in AD by examining the relationship between anosognosia for memory loss, memory monitoring, and agency. For this purpose, we ran regression models examining the associations among these three self-evaluative measures including covariates such as memory, executive functions, and mood (Ansell & Bucks, 2006; Bertrand et al., 2016; Cines et al., 2015; Clare et al., 2012; Conde-Sala et al., 2014; Cosentino, Metcalfe, Holmes, et al., 2011; Mograbi & Morris, 2013; Perrotin, Isingrini, Souchay, Clarys, & Taconnat, 2006; Reed et al., 1993). In doing so, this study will refine and build upon current models of self-awareness with the goal of improving their ultimate utility for guiding the management of anosognosia in AD.

2. METHODS

2.1. Participants

As part of a larger study, 51 participants with mild to moderate AD were recruited through the Department of Neurology at the Columbia University Medical Center. Participants had a diagnosis of Alzheimer's following the criteria of the Neurologic Disorders and Stroke - Alzheimer's disease and Related Disorders Association (NINDS-ADRDA). Participants were excluded from the study if there was evidence of moderate to severe psychiatric illness, history of acquired brain injury (traumatic and vascular), or any other neurological conditions that may have had an impact on cognition. Participants were also excluded if they scored under 20 in the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975) to ensure comprehension of the tasks. Participants with atypical presentations of AD that were not characterized primarily by memory loss (i.e., language or frontal variant AD) were excluded. All participants provided informed consent and all procedures were approved by the Institutional Review Board at Columbia University Medical Center.

As part of the larger study, participants were asked to complete three structured sessions, with the main measures of interest for this study administered across the three sessions. Of the original sample size of 51 participants, 11 (22%) cases dropped out of the study and failed to complete the three visits and 5 cases had missing data on the agency task specifically. Out of these, 4 (8%) had missing trials because of technical difficulties (e.g., task quitting unexpectedly) and 1 (2%) case could not follow the instructions. This resulted in a final sample size of 35 participants (69% female). The overall mean age of these 35 participants was 77.72 (*SD* = 9.40; range = 57-99), and over 91% of the participants were Caucasians; the remaining 9% were African American. All participants were assessed across three visits.

2.2. Measures

2.2.1. Anosognosia

Anosognosia was evaluated via a brief interview at the beginning of each of the three study visits, generating a Clinical Rating of Awareness (CRA) of memory functioning. We used a modified version of Reed et al.'s (1993) clinical awareness scoring categories. Participants were asked an open-ended question about their memory (i.e., "how is your memory?"). Based on

participants' responses, the examiner rated their awareness with the following scoring system: 1.00 = Full Awareness (Patient spontaneously complains of significant memory loss and may discuss memory loss as consequential of the disease); 2.00 = "Moderate Awareness" (Patient spontaneously admits significant memory loss but attributes it to normal aging); 3.00 = "Shallow Awareness" (Patient is inconsistent or uncertain about memory loss); 4.00 = "No Awareness" (Patient denies memory loss). Repeated measures examined if there were significant differences of awareness across the three visits before averaging these into one score. For the purposes of this study, the scoring ratings were then collapsed into two categories (1-2 = "Aware"; >2- 4 = "Unaware") in line with previous publications (Cosentino et al., 2016).

2.2.2. Cognitive Measures

Participants underwent neuropsychological examination, which included measures of global cognition, memory, executive functions, and attention. Memory measures consisted of the Philadelphia Verbal Learning Task (PVLT - Price et al., 2009) for verbal memory and the Biber Figure Learning Test (Glosser, Goodglass, & Biber, 1989) as a nonverbal memory measure. Executive function measures included a design fluency task (Glosser & Goodglass, 1990), a verbal fluency task (i.e., FAS - Stuss & Benson, 1986), and the Digit and Spatial backward spans from the Wechsler Memory Scale - Revised (WMS-R - Wechsler, 1997). Attention was assessed with a visual scanning task. Cognitive index scores were obtained from these measures to represent three main cognitive domains: memory, executive functions, and attention. A memory index score was obtained by averaging z scores of the total immediate recall and long delayed recall of both the PVLT and the Biber Figure learning memory tests. An executive index score was derived from an average of the Digit and Spatial spans backward, FAS, and Design fluency z scores. Finally, an attention score was derived from the z scores of the visual scanning task (Cosentino, Metcalfe, Holmes, et al., 2011).

2.2.3. Mood

Mood was assessed with the 30 item Geriatric Depression Scale (GDS). This measure includes a variety of items targeting symptoms of depression such as sadness, hopelessness, dissatisfaction with life, and worthlessness. Higher scores represent higher endorsement of depressive items, with a cut off of 10 as indicative of probable depression. This measure has been

shown to have high validity and reliability in measuring the construct of depression (Yesavage et al., 1982).

2.2.4. Self-Monitoring Measures

Memory Monitoring Task. A modified Feeling of Knowing or FOK task was used in this study. As part of this task, participants underwent three different task conditions (standard, query, and feedback; described below) counterbalanced across three visits. Task condition and trivia set were compared and analyzed to determine that performance was not affected by condition before collapsing the scores. Each condition of the FOK task was comprised of four trials with five items per trial. Prior to commencing all trials, participants were instructed: (i.e., "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 hearing the information read aloud, participants were asked to give a global Judgment of Learning (JOL) (i.e., "Now I am going to test your memory for those names, giving you answer choices. Of the five names, how many do you think you will get right?"). Then, for each of the five items, participants were shown the individual question and asked to estimate the likelihood of knowing the right answer (FOK judgment) (i.e., "There are eight possible answers on the next page. Will you know which one is right – Yes, Maybe, or No?"). After each FOK judgment, participants were shown eight answer choices that included the correct answer as well as seven distractors. These seven distractors included the other four names that had been presented in the learning trials, and three unrelated distractors. This procedure was the same for each condition (standard, query and feedback) except that for the query and feedback conditions, in which one more element was included. In the query condition, participants were also asked to make a judgment, after each item, regarding the accuracy of their answer. In the feedback condition, the examiner provided participants with verbal feedback on the accuracy of their response after each item. Each of the four global JOLs provided before each trial ranged from 0 to 5. Item level prediction judgments were given ordinal values of 0 = No, 0.5 = Maybe, and 1 = Yes. Performance (i.e., memory) accuracy had values of 0 = incorrect and 1 = correct to enable the calculation of the measures below.

Resolution (Gamma). Resolution reflects the extent to which participants are able to adjust their predictions for performance on each item in line with actual memory performance on that item.

Resolution was measured with the Goodman-Kruskal gamma statistic; a rank order correlation that is based on the total amount of ***concordances*** across the test (*C*; predictions for performance on an item are heightened when performance on that item is high, and vice versa) and the total number of ***discordances*** (*D;* predictions for performance on an item are lowered when performance on that item is high, and vice versa). Gamma is calculated as (C-D)/(C+D). Following this formula, more concordances will result in a value of gamma closer to 1 (perfect resolution), whilst the opposite will result in a value of gamma closer to -1. This calculation does not take in account the number of "ties" where predictions and accuracy are equal in two pairs. Therefore, if someone "ties" across all pairs, gamma cannot be calculated. To avoid losing data in these cases, a formula was developed so that a value of 0 was assigned to gamma, representing the randomness or no association between predictions and actual accuracy (see Cosentino et al., 2015).

Calibration. Calibration scores reflect the extent to which individuals are generally over or under confident in their predictions. For this study, two measures of calibration were obtained, global calibration judgments and item level calibration.

Global calibration judgments reflect the overall level of predictive confidence participants had in their upcoming performance for each 5-item learning trial. These scores were calculated for each of the four trials by subtracting predictions of accuracy (ranging from 0-5) from total accuracy (ranging from 0-5) and dividing by 5 (the total number of items in the trial). The global calibration judgments represent the average score across all four trials. Values closer to 0 represent accurate judgments. Positive values indicate overconfidence, and negative values indicate under-confidence.

Item level calibration indicates the extent to which participants are under- or over confident in their performance at the item by item level (i.e., "Will you know whether this item is right? Yes? Maybe? No?"). Predictions were given a score of 0 if the participant stated they would not recognize the correct choice, 0.5 if they were not sure and stated "maybe", and a score of 1 if they were sure they would recognize the right answer. Memory recognition accuracy was scored as 0 if they chose the wrong answer, and 1 if they chose the correct answer. Item level calibration was calculated by summing all predictions for performance within all trials, subtracting the sum of accuracy scores, and dividing by the total number of items (e.g., ($\sum$ prediction – $\sum$ accuracy)/ total items). The resulting measure reflects the extent to which a patient is overconfident (positive

values), or under confident (negative values) in their item-level predictions compared to their actual performance. Item level calibration was calculated across each of the four trials and averaged to create a single score. A final average score was computed across conditions (i.e., standard, query and feedback).

Agency Task. A computer task was used to measure patients' ability to monitor when they were or were not in control of motor outcomes whilst playing a simple computerized game. A modified version of Metcalfe and Greene's (2007) task was used (see Cosentino, Metcalfe, Holmes, et al., 2011). In this task, participants were required to move the cursor of a computer horizontally across the bottom of the screen to try to "catch" as many "X"s as possible whilst avoiding the "O"s, both of which were falling vertically in the screen. In the modified version of Metcalfe and Greene's task, on some of the trials, participants were in complete control of the computer mouse, and so they should have said that they were 'in control.'; on other trials, the computer interfered with the position of the cursor, and so on these trials, to the extent that they correctly recognized their own lack of control over the cursor, they should have said that the computer was 'in control'. Participants were given 1 practice trial, 8 trials in which they were in complete control of the cursor, 8 trials in which the computer controlled the cursor, and 8 mixed trials in which they were in control half of the time and the computer took over the other half. These mixed trials were introduced to enhance uncertainty. In computer controlled trials, the cursor on the screen moved directly towards the proximal target in a linear fashion without actively attempting to avoid O's. The person's own mouse movements had no effect on this trajectory. The trials were presented in random order and each had a duration 10 seconds.

To begin each trial, the participant had to move the cursor. If they failed to do so, a message would inform them that the game would not begin if they did not perform a movement. This avoided the strategy of waiting to see if the computer moved the cursor. At the end of each trial participants were required to make a judgment of agency (i.e., "who was in control") between two dichotomous choices of themselves or the computer as being in control.

Agency judgments, or motor monitoring, was measured as the total accuracy of all judgments on self-and computer-based trials. A combined score of both trial types ranged from 0 to 16. Accuracy for each trial was also derived which ranged from 0 to 8 in each. Mixed trials

were excluded from analysis. The inclusion of trials in the analysis followed that of Cosentino et al., (2011) to allow comparison of our results with those of healthy ageing individuals.

2.2.5. Computer Experience Questionnaire

Three questions regarding computer experience were presented to participants about how often and how comfortable they felt using a mouse: (i) "How often did you use a mouse before the study?", responses were recorded in a Likert scale from 0 = Never, 1 = A few times, and 2 = Many times; (ii) "How comfortable are you using a mouse ?", responses were recorded in a Likert scale from 0 = Not comfortable, 1 = Somewhat comfortable, and 2 = Very comfortable; (iii) "How often did you use a mouse last year?", responses were recorded in a Likert scale from 0 = Never, 1 = A few times, 2 = Several times a month, 3 = Several times a week, and 4 = Daily. A composite score, used as a measure of overall computer experience, was developed by averaging the results of the three questions.

2.3. Statistical analysis

GLM and non-parametric Friedman tests for repeated measures were used to explore differences between metacognitive and CRA scores administered across the three visits before averaging these into one score. Two-tailed independent t-tests and Mann-Whitney U tests were used to explore differences in cognitive and other self-evaluative measures (memory monitoring and judgments of agency) between participants aware and unaware of their memory deficits as defined by the CRA. Bivariate one and two-tailed Pearson's and Spearman correlations were then used to examine the relationship between the self and computer trials of the agency test, between agency and computer experience, and between agency and memory monitoring measures. Finally, linear and logistic regression analyses were conducted to examine the correlates of CRA, memory monitoring and agency.

3. RESULTS

3.1. Descriptive Results

3.1.1. Anosognosia

Anosognosia was examined through CRA at each visit. A non-parametric Friedman test for repeated measures revealed no significant difference of awareness ratings across the three sessions (χ^2 (2) = .95, p = .62). The scores of the three visits were averaged to provide a composite score, and the scores were then collapsed into two categories described in the methods (aware and unaware). 57% of our sample was classified as unaware (shallow or no awareness) and 43% as aware of their memory deficits (full or moderate awareness). The awareness groups did not differ significantly in demographic variables (see Table 1).

With regard to cognitive tasks, unaware participants appeared to perform somewhat worse on memory tasks, though this qualitative difference was not significant (t (33) = -1.69, p = .10). No differences were found in executive functions (t (29) = .11, p =.90), or attention (t (32) = 1.61, p = .11). Depressive symptoms were comparable across groups (U = 94, z = -1.87, p = .06).

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3.1.2. Memory Monitoring Task

As noted in the methods section, the data presented in this paper are part of a larger study, and participants were exposed to three different FOK conditions (standard, query and feedback). GLM Repeated measures corrected for Green House Geisser showed no difference in memory monitoring as measured by gamma across the conditions (F (1.62, 50.24) = 1.72, p = .19). Similarly, GLM repeated measures for prospective global calibration judgments revealed no differences across conditions for either the global or item level predictions (F (2, 56) = .64, p = .53; F (2, 62) = 1.26, p = .28). These metacognitive metrics were therefore averaged across visits to create composite scores for comparison with agency and anosognosia for memory loss. Within the memory monitoring scores, resolution (i.e., gamma) was not significantly correlated with item calibration (r = .28, p = .11) or global calibration judgments (r = -.11, p = .55).

3.1.3. Agency Task

Bivariate Pearson's correlation revealed no association between accuracy of agency judgments in self trials and computer trials (r = - .10, p = .54). Therefore, agency was broken down into two scores reflecting each trial type and examined separately in subsequent analyses. Overall, both unaware and aware participants performed significantly better on self trials (M = 6.02, SD = 1.69) as compared to computer trials (M = 2.40, SD = 2.38) (t (34) = 7.02, p < .001; d = 1.75).

3.1.4. Computer Experience Questionnaire

Computer mouse experience data were available for 25 participants. Out of these, 44% reported using a mouse before the study many times, whilst 24% had used it a few times, and 32% had never used one. More specifically, 64% of participants reported using the mouse at least once within the last year. Finally, participants were asked how comfortable they felt using a mouse, and 36% reported being very comfortable, 24% somewhat comfortable and 40% not comfortable. The relationship between computer experience and agency was not significant for self (r = 0.00, p = .99) or computer trials (r = .33, p = .11).

3.2. Bivariate Relationships between Awareness Measures

Comparison of the three memory monitoring metrics (gamma, global, and item level calibrations) between unaware and aware participants showed a significant difference only for the gamma score (t (33) = -3.02, p =.005; d = 1.06; see Table 2) such that participants who were unaware of their deficits tended to have lower resolution scores—that is, unaware participants showed greater difficulties in predicting their memory performance. This difference remained significant after Bonferroni correction for multiple comparisons. There were no differences between anosognosic and aware participants in the accuracy of their agency judgments for self trials (t (33) = -.51, p = .61) or computer trials (t (33) = 0.00, p = 1.00). Total judgments of agency showed a qualitative but not significant association with gamma (r = .28, p = .0501; d =.57). Although the correlation between the accuracy of the agency judgments on the computer trials and the resolution gamma correlations was not significant (r = .11, p = .25), an association was found between the accuracy of agency judgments for self trials and the resolution gamma correlations (r = .30, p = .04).

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3.3. Regression analyses

Because our interest was in exploring the relation between the three measures of self-evaluation (i.e., memory monitoring as measured by gamma, CRA, and agency), these three variables were included in all models as dependent variables and/or predictors, adjusting for potential covariates. Covariates were selected on theoretical bases as well based on previously shown associations. The first linear regression was conducted to examine the extent to which gamma could be predicted by scores on agency self trials, CRA, mood, memory, and executive function indexes, entered in a single block. Results indicated that the overall model was significant and explained 50 % of the variance (R^2 = .50, F (5, 28) = 5.77, p = .001). It was found that higher memory (B = .25, p = .002), greater accuracy for agency self trials (B = .08, p = .008), and higher clinical rated awareness (B = .23, p = .03) significantly predicted higher gamma. When controlling for demographics, including age, sex and education, the model remained significant, as did the three predictors.

Two additional linear regressions were conducted to examine the predictors of accurate judgments of agency in the self trials and in the computer trials. Predictors included the executive function index, gamma, CRA, and computer experience. The overall model, however, was not significant for either the self (R^2 = .30, F (5, 19) = 1.68, p =.19) or the computer trials (R^2 = .21, F (4, 20) = 1.31, p =.30).

Finally, a logistic regression was conducted to explore the extent to which CRA could be predicted by gamma, agency accuracy for self trials, mood, memory, and executive function, entered in one block. Results indicated that the overall model was significant (χ^2 (5) = 13.37, p =.02) and explained 44 % of the variance (Nagelkerke R^2) in clinically rated awareness. Increasing accuracy in gamma was associated with increased likelihood of being aware of their memory deficits (B = 3.77, Wald χ^2 (1) = 4.42, p = .03) as was endorsing more depression in the Geriatric Depression scale (B = .21, Wald χ^2 (1) = 4.10, p = .04). No other predictors were significant. When controlling for demographics, only gamma remained a significant predictor of clinically rated awareness. All predictors, for each model, are summarized in Table 3.

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4. DISCUSSION

This paper examined the extent to which anosognosia (i.e., a global marker of awareness) in AD is characterized by deficits in specific aspects of online self-monitoring (i.e., lower level of awareness) across domains. Moreover, we explored whether these specific forms of self-monitoring deteriorate in tandem or are dissociable processes. By exploring different measures of self-awareness, this study seeks to understand how different aspects of self-evaluation operate in the context of AD.

The conceptualization of the association between local awareness (monitoring) and global awareness (anosognosia) —previously described as different levels of awareness—is represented in two of the most influential models of awareness, *the Conscious Awareness Model (CAM)* and Clare and colleagues' Hierarchical Model – (Agnew & Morris, 1998; Clare et al., 2011). In the CAM, domain specific monitoring processes are located at a lower level (i.e., *cognitive comparator mechanisms (CCMs)* (see Figure 1). Supervising each of these domain-specific mechanisms is a central supervisory process, described to function under executive control. The CCMs are specified as those in charge of comparing recent errors in given domains with previous experiences, giving rise to global, higher order self-evaluation of one's abilities. Based on this formulation, dissociation between anosognosia (global awareness) across different domains would be due to a domain-specific comparator (Cm) impairment. On the other hand, a dysfunctional central supervisory system would lead to anosognosia across domains (i.e., *executive anosognosia)* (Agnew & Morris, 1998; McGlynn & Schacter, 1989; Morris & Hannesdottir, 2004; Morris & Mograbi, 2013). That said, this conceptualization has not been experimentally assessed.

In Clare et al.'s (2011) hierarchical model of awareness, ongoing monitoring processes during a task, in which current errors can be detected, are defined as *performance monitoring*. Superior to this level lies the *evaluative judgment* and the *meta-representation* levels, where awareness can be reached though informant interview and in depth clinical interview with the

patient. These superior levels of awareness can also be described as global levels of awareness, as they rely on lower levels to produce a stable representation of one self, one that provides the continuity of an individual through time.

---------INSERT FIGURE 1---------

The representation of a lower level or local level of awareness, as measured through memory monitoring judgments (i.e., gamma), and its association to a more global level of awareness, as measured through clinical interview (i.e., CRA) is supported in the current and previous studies (Cosentino et al., 2015; Cosentino, Metcalfe, Butterfield, & Stern, 2007; Cosentino, Metcalfe, Cary, et al., 2011; Morris et al., 2016). Similarly, there was a link between local levels of awareness across domains, as measured by gamma and the accuracy of the agency judgments for self trials.

The main question that we attempted to answer in this paper was the extent to which individuals with anosognosia for memory loss in AD demonstrated deficits at the lower level of awareness (or metacognitive output) in self-monitoring mechanisms beyond memory. This was explored by assessing agency judgments in relation to anosognosia. If monitoring deficits underlying anosognosia are not domain specific, agency should be distorted in anosognosic patients. The lack of an observed association between anosognosia and judgments of agency in our study suggests that the mechanisms of awareness in AD are modular, at least to some extent, across the domains of memory and motor functioning. The pattern of performance on the agency task was very similar in both aware and unaware patients, with a clear trend for higher performance on self trials than computer trials. In computer trials, both aware and unaware participants performed below chance. A similar pattern of findings has been previously observed in controls (i.e., healthy ageing adults), who completed the same agency task, performing worse on computer trials than self trials (Cosentino et al., 2011). Interestingly, previous literature has supported that agency changes with age, specifically that, as people age, they tend to disregard or become more resistant to external cues when making judgments of agency (Cioffi, Cocchini, Banissy, & Moore,

2017; Metcalfe et al., 2010). Our participants were indeed older than the healthy ageing participants studied in the previous study, and thus they might be showing an exacerbated inability to appropriately weigh external cues when making these judgments. Further, due to drop out and technical difficulties, some participants did not complete the motor monitoring task. This might have included some bias in our results as it is not clear if those not considered in the final analyses might have performed differently than those completing the full study. As both memory and motor monitoring measures were related, we explored this possibility by comparing our main memory monitoring measure (i.e., gamma) in those participants included in the study (N=35) against the 16 participants who did not complete the motor monitoring task. We did not observe any significant difference in their abilities to monitor their memory performance as measured in the first visit (e.g., FOK task, first visit ($t(49) = 1.04$, $p = .31$).

Taken together, the current results support the notion that within-domain awareness such as memory, may be associated across levels (i.e., CRA and gamma), but cross-domain monitoring (e.g., motor and memory monitoring) may be associated only within a given level of awareness (i.e., gamma and agency). Though Morris & Mograbi's (2013) CAM parallels Clare and colleagues' (2011) in terms of its hierarchical progress from 'unimodal to heteromodal processes', the CAM does not explicitly address the potential for different levels of metacognitive output (e.g., local contextual judgments of memory and motor performance versus global offline memory awareness). While the CAM does include conscious perception of error through the *Metacognitive Awareness System (MAS)*, which also serves as an 'emergent' process that can represent metacognitive judgments in general, we suggest that it may be useful to conceptualize different levels of metacognitive output separately as the processes and factors associated with each level of output can differ (Clare et al., 2011; Perrotin, Belleville, & Isingrini, 2007). Figure 2 provides an attempt to incorporate our pattern of results into existing models of awareness. As shown in that figure, we propose a simplified model of the different levels of metacognitive output focused on the two domains explored in this paper.

---------INSERT FIGURE 2---------

Based on the CAM model and our findings, monitoring of performance depends on domain specific monitors (i.e., CCMs), identified as unconscious processes that can lead to a local metacognitive output of performance (e.g., context local judgment of motor or memory monitoring). At the same time, these monitors are part of the evaluative process by which an individual makes more global and stable judgments of their own abilities. Specific deficits to each CCM would contribute to a domain specific anosognosia. Following the CAM and the motor literature of anosognosia, some individuals may have a more generalized impairment in executive control, leading to a generalized impairment of monitoring across domains. In our sample of individuals suffering from AD, we found support for a domain specific CCM deficit (i.e., Cm) contributing to a specific global awareness deficit. The relationship between Cm (memory) and Cn (motor), however, speaks to a shared variance at a local level of awareness.

Finally, our examination of the cognitive and mood correlates of each self-evaluation measure revealed different predictive factors associated with different levels of memory awareness. Specifically, within the cognitive factors, poorer memory performance was a significant predictor of deficits in memory monitoring (i.e., gamma). People who were less able to monitor their memory functioning were also more likely to have lower memory scores. This relationship between memory and awareness went in the same direction for CRA, but was not significant. Memory has been proposed to be a predictive factor for both levels of awareness (e.g., local memory monitoring and global memory awareness). This association between memory impairment and anosognosia provides support for the *mnemonic model of anosognosia* as described by the CAM. Individuals suffering from mnemonic anosognosia are theorized to fail to encode and or recall information about their memory deficits. Consequentially, their global representation of memory abilities remains 'petrified' in time (Mograbi, Brown, & Morris, 2009). Similarly, associations between memory and monitoring have been interpreted through the *memory-constraint hypothesis* for example which assumes that memory monitoring relies on an inferential process by which one derives a judgment based on different cues such as familiarity or accessibility of target. These cues are, themselves, hypothesized to be byproducts of the retrieval process (Koriat, 2000; Metcalfe, 2000; Metcalfe et al., 1993). The quality of the cues retrieved by people with memory difficulties would be hampered, resulting in a blurring of the distinctiveness between what is known and what is not. Thus, the memory-constraint hypothesis also predicts that poor memory would lead to poor memory monitoring (Hertzog, Dunlosky, & Sinclair, 2010).

The association between memory and metamemory in AD has been inconsistent throughout the literature and our previous work. Our impression is that the presence or absence of this association depends to a large extent on the disease severity of the sample. While memory awareness and disease severity are not linked in a one to one fashion (awareness is highly variable in the early stage of AD), disease progression is generally associated with decreasing awareness as individuals move along the dementia spectrum as the increased overall cognitive difficulties complicate available processes for accurate realization of one deficits. As such, it is possible that the association between memory impairment and awareness emerges more strongly when individuals with various levels of memory loss are included in a given sample.

By way of contrast with memory performance, the executive function index was not associated with either memory monitoring (i.e., gamma) or anosognosia (i.e., CRA) in our data. In contrast to the findings presented here, executive functions have been hypothesized to be associated with both CRA and memory monitoring (Agnew & Morris, 1998; Schacter, 1990; Shimamura, 1995). Such a relation between executive functions and global level of awareness would support the *executive model of anosognosia*, where due to an executive failure, the ongoing experience of making a memory error is neither monitored nor detected. As noted earlier, this definition establishes that monitoring is supported by executive supervisory processes. Similarly, monitoring of memory has been proposed to be reliant on underlying executive processes, and similarities between these two processes have been highlighted (Fernandez-Duque, Baird, & Posner, 2000; Shimamura, 2000). Of note, although such an association between memory monitoring and executive functions has been supported in healthy ageing individuals, the relationship is not so clear with AD and other dementias (Perrotin et al., 2006; Souchay, Isingrini, & Espagnet, 2000; Souchay, Isingrini, Pillon, & Gil, 2003), and was not observed in our study.

The association of both levels of awareness, memory and executive function, has not been consistent across studies (Correa, Graves, & Costa, 1996; Cosentino et al., 2007; Dalla Barba, Parlato, Iavarone, & Boller, 1995; DeBettignies, Mahurin, & Pirozzolo, 1990; Michon et al., 1994; Reed et al., 1993; Shaked et al., 2014; Starkstein et al., 1996). As mentioned earlier, these contradictory results can be partially explained through the differences between sampling methods and measures used (Clare, 2004; Cosentino & Stern, 2005). Another possibility is that impairment in memory or executive function alone is not sufficient to cause anosognosia or memory monitoring deficits, as other process likely contribute to self-reflection. It has also been suggested that cognitive and metacognitive processes may simply be concomitant deficits effected in the

neurodegenerative process. For example, previous work by Shaked et al. (2014), showed that an index of non-verbal memory and non-verbal executive functions was more closely related to memory monitoring (i.e., gamma) than was a verbal index of these cognitive domains. These results were interpreted within a neuroanatomic framework as potentially pointing to differential disruption in right hemisphere networks critical for processing nonverbal information as well as for supporting self-reflective processes (Cosentino, 2014).

Lastly, in regards to mood, our results showed different relations between depression and our three measures of self-evaluation. Specifically, we found that endorsing higher levels of depression was associated with being globally more aware of one's memory deficits, consistent with a number of previous studies (Bertrand et al., 2016; Cines et al., 2015; Conde-Sala et al., 2014), but not with memory monitoring. These findings support a previously shown dissociation of the correlates found between these measures of self-evaluation. For example, Cosentino, Metcalfe, Cary, et al. (2011) found that decision making capacity pertaining to medication management was related to global memory awareness but not local (gamma). The authors suggested that global awareness likely reflects a general, context independent higher level of awareness. On the other hand, memory monitoring, as measured by gamma, is a specific and local, context dependent lower level of awareness. This argument might explain the observed dissociation in our study between mood and the two measures of self-awareness. As suggested by Clare and colleagues, and consistent with the Hierarchical model, global measures of awareness may in part reflect beliefs, premorbid factors, or psychological functioning, as they are not constrained by the same type of specific contextual details that constrain self-evaluative judgments in the context of local awareness measures (Clare et al., 2012). As such, local metacognitive evaluations might reflect a more 'objective' or 'pure' measure of someone's self-evaluative ability.

To conclude, while global unawareness in AD (i.e., anosognosia) seems to break down in tandem with deficits in mnemonic self-monitoring (i.e., gamma), anosognosia for memory loss was not associated with local self-monitoring processes in the motor domain as measured by metacognition of agency in the data presented here. However, the local or online forms of self-evaluation that are at play during agency judgments appear to relate to those used to make judgments about mnemonic self-monitoring. That is, it seems that within-domain awareness may be associated across levels, but cross-domain monitoring may be associated only within their level of awareness (i.e., local awareness). Future research should examine other types of monitoring processes as well as anosognosia for other deficits, to evaluate the extent and qualitative

differences of self-monitoring at different levels of awareness for memory and other deficits. Due to the important clinical implications of deficits in awareness among individuals suffering from AD, it is essential that we continue to refine our current theoretical models of self-awareness. Doing so will open the door to shaping specific rehabilitation programs in order to minimize the negative consequences of unawareness.

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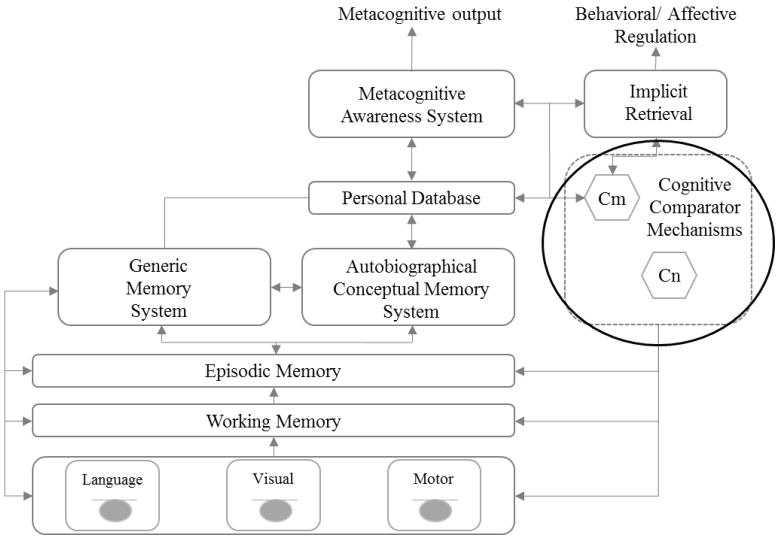

Figure 1. Modified version of the revised CAM model from Morris and Mograbi (2013). Comparator mechanisms proposed to underlie monitoring of different cognitive domains highlighted.

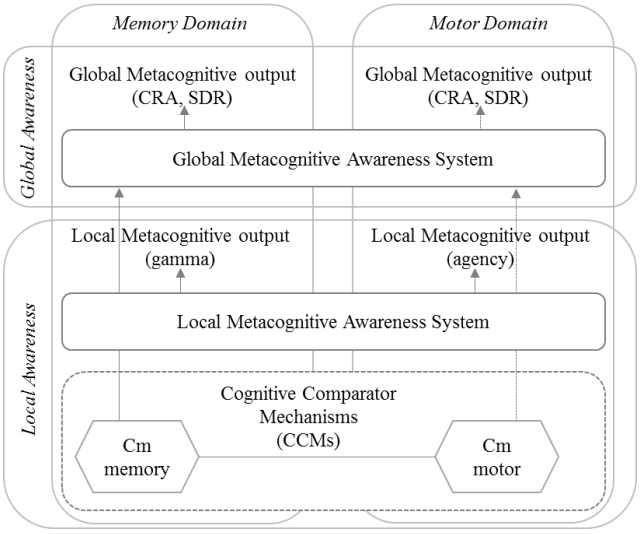

Figure 2. Metacognitive output of global and local levels of awareness in both memory and motor domains. Solid lines represent relationships found in this current study. Dotted arrows represent relationships previously shown in anosognosia for hemiplegia but not assessed in this study (see Jenkinson & Fotopoulou, 2010; Saj et al., 2014; Vocat et al., 2013). CRA – Clinically rated awareness; SRD – Subjective rating discrepancy; Cm – memory comparator; Cn – motor comparator.

Table 1. Mean and standard deviations of demographic and neuropsychological variables in participants unaware and aware of their memory difficulties.

Demographics details, mood and neuropsychological performance	**Unaware (n=20)**	**Aware (n=15)**	**Sig. Two tailed**	**95 % Confidence intervals**
Age	79.94 (8.02)	74.78 (10.54)	.10	- 1.21, 11.54
Education	16.00 (2.73)	16.73 (3.10)	.46	-1.55, 11.87
Gender (female/male)	14/6	10/5	.94	-
Race (Caucasian/African American)	19/1	13/2	.38	-
MMSE (0-30)	25.05 (1.93)	25.07 (2.18)	.98	-1.43, 1.40
Memory index (Z score)	-.20 (.58)	.19 (.79)	.10	-.86, .07
Executive Index (Z score)	.01 (.89)	-.01 (.80)	.69	-.28, .41
Attention Index (Z score)	.11 (1.03)	-.15 (1.02)	.48	-.49, 1.00
Mood (0-30)*	3.00 (6.75)	7.00 (9.00)	.06	-

Higher scores on MSMSE reflect better performance. Higher scores in the Mood variable reflect higher endorsement of depressive items. *Non normal data is reported as median and interquartile ranges.

Table 2. Mean and standard deviations of metacognitive measures for memory and agency in participants unaware and aware of their memory deficits.

Metacognitive measures of memory and motor domains (range)	**Unaware (n=20)**	**Aware (n=15)**	**Sig. Two tailed**	**95% Confidence intervals**
Gamma (-1–1)	.18(.34)	.50(.26)	.005	-.53, -.10
Global calibration (-1–1)	.07(.18)	.09(.18)	.72	-.15, .10
Item level calibration (-1–1)	.01(.12)	.02(.08)	.78	-.08, .06
Agency total (0-16)	8.30(2.61)	8.60(3.04)	.76	-2.25, 1.65
Agency computer trials (0–8)	2.40(2.11)	2.40(2.77)	1.00	-1.67, 1.67
Agency self trials (0–8)	5.90(1.74)	6.20(1.65)	.61	-1.48, .88

Table 3. Regression models of self-awareness measures of memory monitoring (gamma), anosognosia (CRA), and the accuracy of agency judgments in self trials and in computer trials.

Predictors of memory monitoring (gamma), CRA and agency	**Gamma** B (Std. error)	**CRA** B (Std. error)	**Agency self trials** B (Std. error)	**Agency computer trials** B (Std. error)
Gamma	-	**3.77 (1.79)**	1.47 (1.47)	2.10 (1.87)
CRA	**.23 (.10)**	-	.23 (.82)	- .81 (1.05)
Agency self	**.08 (.03)**	-.15 (.32)	-	-
Executive functions	- .02 (.09)	-.14 (.87)	- .01 (.77)	.69 (.97)
Memory	**.25 (.07)**	.12 (.88)	-	-
Mood	- .01 (.01)	**.21 (.10)**	-	-
Computer experience	-	-	- .03 (.13)	.24 (.16)

Unstandardized betas and standard errors of the individual predictors are included. Significant predictors are shown in bold ($p < .05$).