

Evolution of anosognosia in Alzheimer's disease and its relationship to amyloid

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ABSTRACT

Objective: Unawareness, or *anosognosia*, of memory deficits is a challenging manifestation of Alzheimer's disease (AD) that adversely affects a patient's safety and decision-making.

However, there is a lack of consensus regarding the presence, as well as the evolution of altered awareness of memory function across the preclinical and prodromal stages of AD. Here, we aimed to characterize change in awareness of memory abilities and its relationship to beta-amyloid (A β) burden in a large cohort (N=1,070) of individuals across the disease spectrum.

Methods: Memory awareness was longitudinally assessed (average number of visits=4.3) and operationalized using the discrepancy between mean participant and partner report on the Everyday Cognition scale (ECog; memory domain). A β deposition was measured at baseline using [18F]Florbetapir positron emission tomography imaging.

Results: A β predicted longitudinal changes in memory awareness, such that awareness decreased faster in participants with increased A β burden. A β and clinical group interacted to predict change in memory awareness, demonstrating the strongest effect in dementia participants, but could also be found in the CN participants. In a subset of CN participants who progressed to MCI, heightened memory awareness was observed up to 1.6 years before MCI diagnosis, with memory awareness declining until the time of progression to MCI (-0.08discrepant-points/year). In a subset of MCI participants who progressed to dementia, awareness was low initially and continued to decline (-0.23discrepant-points/year), reaching anosognosia 3.2 years before dementia onset.

Interpretation: A β burden is associated with a progressive decrease in self-awareness of memory deficits, reaching anosognosia approximately three years before dementia diagnosis.

INTRODUCTION

The capability to accurately assess our cognitive abilities is crucial to function effectively. This is particularly important in the setting of Alzheimer's disease (AD), when the deterioration of mental capacity can threaten even the most basic functions of everyday living. Unawareness of memory deficits, or *anosognosia*, is a challenging manifestation of AD that has been associated with increased hours of informal care, greater use of support services, and increased total family care costs^{1, 2}. Despite the impact of anosognosia on patients and their caregivers, there is a lack of consensus regarding the presence, as well as the evolution of altered awareness of memory function across the preclinical and prodromal stages of AD.

Anosognosia is a common symptom in patients with AD dementia, with a prevalence estimated to range between 21%³ to 81%⁴, and the disorder has been shown to correlate with overall disease severity⁵⁻⁹. Previous studies, conducted primarily in AD dementia, have reported that awareness decreases over time¹⁰⁻¹², whereas other studies have reported mixed results^{6, 13} or no change¹⁴⁻¹⁹. One longitudinal study examining 239 older adults with incident dementia showed that, on average, awareness of memory functioning declines 2-3 years before dementia onset²⁰. In contrast, awareness of cognitive dysfunction shown by individuals with mild cognitive impairment (MCI) is highly variable, ranging from heightened awareness with marked concerns²¹ to complete unawareness about their cognitive difficulties^{22, 23}.

A recent publication using Alzheimer's Disease Neuroimaging Initiative (ADNI) data has demonstrated that amnesic MCI individuals with impaired awareness were harboring increased

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beta-amyloid (A β) burden, one of the hallmark pathologies of AD, as measured *in vivo* using [18F]Florbetapir (FBP) positron emission tomography (PET)²⁴. These findings have also been extended to cognitively normal (CN) older adults taking part of the INSIGHT-PreAD study in which participants exhibiting low awareness showed increased cortical A β burden, as compared to CN participants with heightened awareness²⁵. In contrast, using cross-sectional data Vannini and colleagues observed that heightened memory awareness was related to increased A β burden in CN participants from the Harvard Aging Brain Study²⁶. On the whole, the evolution of altered self-awareness of memory function across the preclinical and prodromal stages of AD is not fully understood. Specifically, it remains unclear as to which stage in the AD continuum anosognosia occurs and if an individual's self-judgment of his/her own cognitive abilities changes over the course of the disease as pathology increases.

The present study aimed to characterize change in awareness of memory abilities and its relationship to A β burden in a large cohort (N=1,070) of individuals across the disease spectrum (CN, MCI and dementia). Specifically, we aimed to 1) examine the change in memory self-awareness by baseline amyloid burden and clinical stage, 2) determine the onset of unawareness of memory deficits over the course of AD progression, and 3) determine predictive capabilities of low and/or high awareness for clinical progression. Overall, we hypothesized that altered memory self-awareness would be associated with baseline A β burden and that these initial pathophysiological changes would be associated with decreased memory self-awareness after longitudinal follow-up.

MATERIAL AND METHODS

Study participants

This prospective study analyzed data from 1,070 participants enrolled in Alzheimer's Disease Neuroimaging Initiative (ADNI) (adni.loni.usc.edu). ADNI is an ongoing, longitudinal, multicenter study conducted in 59 sites across North America, enrolling CN, amnesic MCI, and

AD participants age 55-94. ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early Alzheimer's disease. For up-to-date information, see www.adni-info.org. Exclusion criteria included a history of alcoholism, drug abuse, head trauma, as well as serious medical or psychiatric conditions. Cholinesterase inhibitors and memantine are only allowed in patients if they are stable for three months before screening. Moreover, antidepressants are allowed if participants are not significantly depressed at the time of screening and do not have a history of major depressive disorder within the past year. Institutional Review Board approvals and informed consents were obtained prior to all procedures. The global Clinical Dementia Rating (CDR) obtained at the clinical assessment closest to each individual's baseline PET was used as a diagnostic criterion for CN (CDR=0), MCI (CDR=0.5), and dementia (CDR $\geq$ 1) clinical groupings. Clinical progression of CN to MCI was defined as a global CDR increase from 0 at baseline to 0.5 at final follow-up, and progression from MCI to dementia was defined as a global CDR increase from 0.5 at baseline to greater than or equal to 1 at final follow-up. Baseline MMSE (Mini-Mental State Examination) in CN and MCI participants was greater than or equal to 24.

Estimation of awareness of memory performance

The memory functioning subtest of the Everyday Cognition (ECog) scale was used to estimate self-awareness of memory performance²⁷. ECog is a 39-item measure that was specifically developed to assess subjective cognitive decline and daily functioning abilities in older adults. The study partner and self-rated versions of the ECog are composed of identical questions, framed in the context of current performance compared to ten years ago and scored on a Likert scale. Specifically, the discrepancy between the mean study partner-rated and the mean self-rated Everyday Memory 8-item subtest was used to assess memory self-awareness, as previously implemented in other ADNI studies^{23, 28}. Using this approach, a negative score indicates an over-

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estimation of memory functioning or low memory awareness, meaning that these individuals believe they are functioning at a higher level than their partners have rated. In contrast, a positive score indicates under-estimation of memory functioning or heightened memory awareness, meaning that these individuals believe they are functioning worse than their partners have rated. An awareness score of 0 indicates that the participant and the study partner judge memory similarly, suggesting that the participant has insight into his/her memory functioning. Additionally, we defined a threshold for anosognosia using the mean discrepancy score when participants are reporting *significantly* fewer difficulties than their study partners (see statistical analyses). Conversely, a threshold for heightened awareness was defined using the mean discrepancy score when participants are reporting *significantly* more difficulties than their study partner. Note that in the CN participants we are using the term low awareness instead of anosognosia as these individuals are still performing within normal limits on cognitive tests.

PET Imaging

A β burden was assessed for each participant at baseline using FBP-PET. FBP data were expressed as standard uptake volume ratios (SUVr; 50-70 minutes) in a large neocortical region scaled to cerebellar gray, including large areas of the frontal, lateral temporal, and parietal lobes. FBP SUVr was used as a continuous variable in all statistical analyses. Albeit, a threshold set at SUVr=1.11²⁹⁻³¹ was used both for visualization purposes and for breaking down the interaction between baseline A β and baseline clinical stage.

Statistical Analyses

Participants were divided into six subgroups based on clinical stage (CN, MCI, or dementia) and A β status (high or low FBP binding). Two sample t-tests and chi-squared tests were used to examine differences in demographics and baseline ECog data for each group as compared to the low A β CN participants. Additional *post hoc* tests, using linear regression, examined awareness at baseline amongst clinical and A β groups. A linear mixed-effect model with time by participants as random factors was used to evaluate the association between baseline continuous

measures of FBP binding, baseline clinical stages, and longitudinal changes in awareness, while adjusting for baseline age, sex, education, and Apolipoprotein E4 (*APOE* ϵ 4) genotype. To evaluate whether the A β effect on longitudinal change in awareness increased over the disease spectrum, we computed the interactive effect of baseline A β , baseline diagnosis, and time on longitudinal awareness. The effects of baseline age and time were added as covariates, as well as time by subject as random factors. To further explore this three-way interaction, the effect of baseline diagnosis and time were estimated in both high and low A β participants. Additionally, we computed the baseline A β by time effect within each diagnostic group (CN, MCI, and dementia).

To determine how much time before or after clinical progression anosognosia becomes evident in the AD course, we characterized longitudinal awareness in participants who clinically progressed. In CN-to-MCI and in MCI-to-dementia progressors, we computed linear mixed-effect models predicting awareness over time, with the time vector anchored on clinical progression (i.e., time=0 when progression occurs). We evaluated the significance of the intercept at different times (spotlight analysis) and computed a 5000-trial bootstrap to provide 95% confidence intervals (CI95) around the time at which awareness was significantly non-zero (floodlight analysis). A threshold for low memory awareness/anosognosia was determined as the memory awareness index at that time (the Johnson-Neyman point), i.e., the time when participants are reporting significantly less difficulties than their study partners do³². Similarly, a threshold for heightened awareness was determined as the awareness index (the Johnson-Neyman point) when participants are reporting significantly more difficulties than their partners do. To validate these thresholds, we reported the proportion of participants with low awareness/anosognosia or heightened awareness at baseline in CN and MCI, and used age-adjusted logistic regression to evaluate whether low awareness/anosognosia or heightened awareness was associated with clinical progression. We illustrate these results by computing survival curves displaying the predictive power of these awareness thresholds to clinical

progression. Statistics were performed in MATLAB R2018a (MathWorks, Inc., Natick, MA) and are reported with two-tailed p -values ($\alpha=0.05$).

RESULTS

Cohort characteristics and baseline awareness measures

Table 1 shows participant characteristics and highlights the differences between clinical (CN, MCI, or dementia) and A β subgroups (low or high FBP). All groups are compared at baseline to low FBP CN participants. APOE ϵ 4 carriage was more frequent in high FBP CN than in low FBP CN participants ($X^2 = 22.89$, $p < .001$) and the proportion of APOE ϵ 4 carriers was higher in high FBP MCI and high FBP dementia ($X^2 = 130.36$, $p < .001$; $X^2 = 94.63$, $p < .001$). However, no APOE ϵ 4 carriers were found amongst low FBP dementia, preventing us from disentangling the contributions of APOE ϵ 4 carriage and FBP binding in dementia participants. Compared to low FBP CN, high FBP CN ($t(358)=3.34$, $p < 0.001$) and low FBP AD ($t(254)=3.52$, $p < .001$) were older, while low FBP MCI were younger ($t(481)=-3.99$, $p < .001$). Sex was well balanced amongst groups, with high FBP CN being the only group having a larger percentage of females ($X^2 = 9.06$, $p = 0.003$). As expected, MMSE decreased with increasing CDR.

Average ECog follow-up duration was 3.1 years in low FBP CN and 3.0 years in high FBP CN. Comparatively, low FBP MCI had longer follow-up (3.4 years; $t(481)=-2.45$, $p = 0.01$), while high FBP MCI (2.8 years; $t(589)=1.99$, $p = 0.05$), low FBP dementia (1.7 years; $t(254)=3.87$, $p < .001$) and high FBP dementia (1.1 years; $t(334)=12.62$, $p < .001$) participants had shorter follow-up ranges. From baseline to final clinical assessment, 68 participants progressed from CN to MCI and 135 participants progressed from MCI to dementia.

Using linear regression, the effects of FBP group and clinical status interacted at baseline ($t(1066)=-4.05$, $\beta=-1.90$, $p < .001$). In *post hoc* analyses looking within clinical groups, baseline awareness did not significantly differ by FBP group within CN as well as dementia participants

($t(358)=0.87, p=0.38$; $t(112)=-0.35, p=0.72$), yet differed significantly within MCI participants ($t(594)=-4.61, p<.001$). In comparison to low FBP CN participants, baseline awareness was not significantly different in low FBP MCI participants ($t(481)=0.42, p=0.67$), but was significantly lower in high FBP MCI ($t(589)=-5.61, p<.001$) as well as in both low and high FBP dementia participants ($t(254)=-9.50, p<.001$; $t(334)=-18.05, p<.001$).

-- **TABLE 1** HERE—

Change in awareness by baseline Florbetapir binding and clinical group

Baseline FBP binding was the most significant predictor of longitudinal changes in awareness (**Table 2**; $\beta = -0.22, p<0.001$), such that awareness decreased faster in participants with high FBP SUVR. Baseline clinical group, age, and APOE ϵ 4 carriage were also significant, such that awareness decreased faster in participants with advanced clinical status (i.e., higher global CDR; $\beta = -0.07, p=0.03$), older ages ($\beta = -0.003, p=0.005$), and in APOE ϵ 4 carriers ($\beta = -0.05, p=0.007$). Adjusting for the Geriatric Depression Scale (GDS) score did not alter the results.

-- **TABLE 2** HERE--

Baseline FBP and baseline clinical group interacted to predict longitudinal awareness (**Table 3A** and **Figure 1**), such that the effect of FBP on decreasing awareness increased with advanced clinical status. When breaking down the interaction, we observed that baseline clinical status only had an effect in high FBP participants yet no effect in low FBP participants (**Table 3B**). Although FBP binding had the most significant effect on awareness changes in the dementia group (**Table 4**; $\beta = -0.57, p=0.002$), followed by MCI ($\beta = -0.30, p<0.001$), it also had a significant effect in CN ($\beta = -0.12, p=0.02$), suggesting that awareness starts to decrease in the preclinical stage of the disease.

-- **TABLE 3** HERE--

-- TABLE 4 HERE--

Figure 1 middle and right panels separately illustrate the participant-rated and partner-rated versions of the ECog. It shows that low FBP dementia participants reported more difficulties over time (top row, middle plot; $\beta=0.19$, $p=0.001$), together with their partners ($\beta=0.17$, $p=0.001$), resulting in stable awareness (left plot; $\beta=0.02$, $p=0.85$). High FBP dementia participants reported less difficulties over time (bottom row, middle) while their study partners reported more difficulties over time (right plot), resulting in decreasing memory awareness that is specific of high FBP participants. These observations are however limited by the short follow-up of participants with dementia. Noteworthy, high FBP MCI participants did not change their assessments over time (middle plot) while their partners progressively reported increased memory difficulties (right plot). Although high FBP CN participants did increase their reports of memory difficulties over the course of the study, they did so to a lesser extent than their partners.

--FIGURE 1 HERE—

Evaluating the change of memory self-awareness across the AD spectrum

To investigate how self-awareness of memory functioning changes across the AD spectrum, we conducted a sub-analysis on participants who clinically progressed over the course of the study. Clinical progression of CN to MCI was defined as a global CDR increase from 0 at baseline to 0.5 at follow-up, and progression from MCI to dementia was defined as a global CDR increase from 0.5 at baseline to greater than or equal to 1 at follow-up. For this analysis, we modified our time vector to defined time=0 as the year when participants progressed (rather than defining time=0 as the time of PET imaging). By doing so, we anchored all changes to clinical progression (**Figure 2**).

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In the 68 CN participants who progressed to MCI, the discrepancy score was close to zero (i.e., normal insight) at the time of MCI progression, as the reports of memory difficulties did not significantly differ between the participant and their partners (**Table 5**, $p=0.64$). In general, CN participants reported more memory difficulties than their study partners up to 1.6 years before progression to MCI (CI95 around the Johnson-Neyman-point: -0.5 to 4.3 years), indicating a state of heightened awareness. This is equivalent to an awareness index of +0.20, i.e., a one-point difference on at least two of the eight items of the ECog memory-scale. However, memory awareness decreased over time (-0.08 discrepant-points/year, $p=0.002$), reaching an awareness index close to 0 approximately at the time of MCI diagnosis.

--TABLE 5 HERE--

In the 135 MCI participants who progressed to dementia, reports of memory difficulties were different between participants and partners at the time of dementia progression (**Table 5**, $p<0.001$), with awareness decreasing over time (-0.23 discrepant-points/year, $p<0.001$), indicating a progressively lower awareness. Low awareness, i.e., a significantly lower participant-rated than partner-rated ECog score, was observed in MCI participants 3.2 years (CI95: 2.8 to 4.4 years) before progression to dementia. This was equivalent to an awareness index of -0.26, i.e., a one-point difference on at least three of the eight items of the ECog memory-scale.

Evaluating whether low or high baseline awareness predicts clinical progression

Figure 3 (top row) illustrates density plots of the awareness measures at baseline for CN and MCI participants who progressed and who did not progress over the course of the study. Using the thresholds for low awareness/anosognosia and heightened awareness derived in our flood light analyses presented above, we calculated the prevalence of these two states in our CN and MCI participants at baseline. We found that 46 CN (14%) and 214 MCI (36%) participants could be defined as exhibiting low awareness/anosognosia, while 207 CN (58%) and 260 MCI (44%) participants could be defined as exhibiting heightened awareness. In CN, both the continuous

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awareness index ($\beta = +2.6$, $p=0.01$) and the binary low awareness category ($\beta = +2.1$, $p=0.038$) predicted progression to MCI. In contrast, heightened awareness was not predictive ($\beta = -1.46$, $p=0.14$). In MCI, both continuous ($\beta = +5.7$, $p<0.001$) and binary ($\beta = +7.4$, $p<0.001$) measures of low awareness strongly predicted progression to dementia (**Figure 3**, bottom row). MCI participants with heightened awareness had a lower risk of progression compared to the MCI who had normal awareness ($\beta = -5.5$, $p<0.001$).

--FIGURE 3 HERE--

Adjusting for FBP SUVR, MMSE, or memory (logical memory test, delayed story recall) at baseline did not modify the results, such that anosognosia predicted a greater risk of subsequent progression to dementia in MCI participants with equal amyloid burden and memory performance. Similar, albeit weaker, results were observed in CN participants.

DISCUSSION

The present study aimed to characterize change in awareness of memory abilities and its relationship to A β burden in a large cohort of individuals across the AD spectrum. We observed that although A β burden was not associated with awareness at baseline in CN participants, A β was associated with decreasing participant awareness after longitudinal follow-up and with increasing levels of clinical impairment. In those CN who progressed clinically to MCI during the course of the study, the participants themselves appeared to be the first to report difficulties with their memory, but as awareness decreased during the preclinical stage, at the time of MCI diagnosis participant and study partner complaints were equivalent. Awareness continued to decrease during the MCI stage; low awareness/anosognosia, i.e., study partners reporting significantly more difficulties than participants, was observed on average three years before progression to dementia. Notably, using the full cohort we found that low awareness/anosognosia

in both CN (13%) and MCI (36%) predicted clinical progression, whereas heightened awareness in CN (58%) and MCI (44%) did not. These results suggest that individuals who are unaware of memory changes may represent a specific group at risk for clinical progression and provide additional support for the usefulness of informant-reported decline.

Although there has been extensive work on the behavioral characterization of anosognosia at the stage of AD dementia (e.g. see overview in Kaszniak and Edmonds³³), our knowledge of the pathological mechanisms underlying anosognosia as well as the evolution of altered awareness of memory function across the earlier AD spectrum is very limited. In fact, our knowledge about unawareness of memory impairment was limited for a long time to cross-sectional studies or longitudinal studies of prevalent dementia, suggesting that anosognosia was a variable feature of the dementia syndrome. However, as more recent studies have started to emerge it has become clear that anosognosia is present in a relevant number of cases of individuals with MCI (see reviews by Roberts³⁴ Starkstein³⁵), and furthermore, the syndrome has been related to an increased rate of progression to AD dementia^{9, 23, 24, 36}. Previous studies also suggest that anosognosia can be linked to AD pathophysiology. For instance, in one of the first post mortem studies, Marshall, Kaufer³⁷ found that anosognosia is associated with medial temporal A β plaque burden in moderate to severe AD dementia. In addition, using fludeoxyglucose ([¹⁸F]-FDG) PET Salmon and colleagues found that anosognosia in AD patients was related to decreased glucose metabolism in the temporoparietal junction³⁸. Moreover, using ADNI data Theriault and colleagues found that MCI individuals with impaired awareness had decreased FDG metabolism as well as increased amyloid burden in the default mode network (e.g., posterior cingulate cortex)²⁴, with brain regions that have been shown to be both vulnerable to early AD pathology and important for self-referential processing^{39, 40}.

In addition, recent studies have extended these findings to preclinical AD^{25, 41, 42}. Specifically, in a cross-sectional study Cacciamani and colleagues reported that CN participants who were unaware of memory deficits in everyday life, as noticed by their study partner, showed greater

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amyloid burden and lower cortical metabolism as compared to CN participants with high levels of awareness, suggesting that low awareness could be a useful marker of preclinical AD¹⁴. In line with these findings, we found that amyloid was associated with decreases in awareness over time, and that awareness was predictive of subsequent clinical progression in individuals who were CN at baseline. *Post hoc* analyses revealed that awareness declined over the clinical stages, reaching the lowest scores at the stage of dementia (**Table 1**). However, at the dementia stage we did not find a significant change between the A β groups, suggesting equal decreases in awareness. Note that at the dementia stage we only had 17 A β - participants, thus limiting conclusions to be drawn from that group. At the stage of MCI, we found a significant group effect such that A β + participants had significantly decreased awareness as compared to the A β - participants, replicating both previous studies using ADNI data to investigate awareness in MCI^{23, 24}, as well as our previous findings from the Harvard Aging Brain Study²⁶. However, we did not find a significant main effect of A β in the CN participants at baseline, indicating that awareness was the same at the start of the study in this cohort. These results are in contrast to previous findings by Cacciamani and colleagues¹⁴ as well as Vannini and colleagues¹⁵, the latter demonstrating that increased amyloid was associated with heightened awareness in CN older participants. These discrepant findings could be due to several reasons. For instance, the method to calculate awareness of memory is a factor to consider. Vannini and colleagues used discrepancy scores between subjective memory concerns and actual memory performance on an objective task, whereas Cacciamani and colleagues used a similar approach to the current study by using the Healthy Aging Brain Care Monitor⁴³ (HABC-M) questionnaire, which was administered to both the participant and their study partner. However, the most important issue is perhaps difference in the time to clinical progression in the different studies. That is, it could be hypothesized that levels of self-awareness vary on a continuum, starting with normal awareness of memory function, followed by a phase of heightened awareness with objectively normal memory performance, and lastly unawareness. The differential results from Cacciamani and colleagues and Vannini and colleagues support this notion, although future longitudinal studies in these cohorts will be necessary to evaluate how the participants' awareness change over time.

Furthermore, inclusion criteria of the previous studies were different. For instance, in the study by Cacciamani and colleagues, only participants with subjective memory complaints were assessed. This was not the case in the study by Vannini and colleagues, as well as the current study (as ADNI only introduced these criteria in later studies). We acknowledge that it will be important to address the inter-relationships between subjective memory complaints and awareness more thoroughly. Thus, future studies in which CN with and without subjective memory complaints are recruited at baseline would be helpful to address this issue.

As alluded to above, one important issue to keep in mind when discussing previous work investigating anosognosia is that it can be considered a multidimensional concept with no single clear conceptual and theoretical model or definition³⁴. Although a majority of studies have used a discrepancy score between participants and their study partner for assessing a level of awareness, other studies have used clinical judgment or comparison of participants' self-assessment and objective task performance, which are other strategies that have been used to assess anosognosia in AD⁴⁴. To this end, apart from clinical judgment, we also acknowledge that there is a lack of operational criteria in assigning an anosognosia diagnosis. In this study, we propose a new methodological approach to define anosognosia and/or heightened awareness that could be used in research projects that handle discrepancy scores between self versus informant report or self versus objective test performance and would like to define these states empirically. Using this approach, a threshold for low awareness was determined as having a discrepancy score of -0.26, corresponding to approximately 3.2 years (CI95: 2.8 to 4.4 years) before progression to dementia. This would be equivalent to a one-point difference on at least three of the eight items part of the ECog memory scale. This ADNI sample was limited in that few CN participants progressed to dementia, restricting our analyses to CN individuals who progressed to either MCI, as well as MCI who progressed to dementia. Nonetheless, these results are similar to the findings of Wilson and colleagues, who reported that in 2,092 individuals who were cognitively normal at baseline, awareness started to decline approximately 2.6 years before their dementia diagnosis²⁰. Moreover, using our linear mixed effects model to evaluate awareness over time in individuals

who were considered CN at baseline but progressed clinically revealed that they generally reported more difficulties in memory than their study partner, indicating a state of heightened awareness. However, their awareness score decreased over time (-0.08 discrepant points/year), reaching almost equivalent discrepancy scores at the time of MCI diagnosis. Using this approach, a threshold for heightened awareness was determined as having a discrepancy score of +0.20, corresponding to approximately 1.6 years (CI95: -0.5 to 4.3 years) before progression to MCI.

The frequencies of low and heightened awareness we observed in this study are very similar to previous findings involving CN participants. For instance, Cacciamani and colleagues found that within a cohort of 318 cognitively normal older adults, 19 participants (6%) had low awareness and 86 participants (27%) had high awareness²⁵. Similarly, Sánchez-Benavides and colleagues recently found that in a cohort of 2,640 participants from the ALFA cohort, 173 participants (6.6%) had low awareness and 568 participants (21.5%) had high awareness.⁴¹ Of greater significance, we observed that in both CN and MCI participants low awareness predicted clinical progression, whereas MCI participants with heightened awareness had a lower risk of progression. Not only do these MCI results replicate previous ADNI findings showing that low awareness predicts clinical progression²⁴, as well as our previous finding⁹, but they also extend those findings by showing that heightened awareness does not predict clinical progression. We acknowledge that our findings in CN participants may seem contradictory, such that in the floodlight analysis we report that our CN participants displayed more memory difficulties than their study partners, but in our logistic regression analysis we found that low-awareness (not heightened awareness) predicted progression to MCI. We interpret these findings in two ways: 1) We believe that these data must be considered in relation to the proximity to clinical progression. That is, all our data point to the fact that awareness decreases over time from the preclinical AD stage. Thus, the tipping point for showing symptoms of unawareness of memory likely occurs in close proximity to the onset of cognitive symptoms. 2) In addition, as can be observed in **Figure 1** (left panel) and even better in the density plots (**Figure 3**), all CN and MCI

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participants had an overall tendency to show heightened awareness. Notably, all CN participants (both participants who progressed to MCI as well as CN participants who did not progress to MCI) had an overall tendency to complain about their memory. Due to this overlap, i.e. non-progressors participants are also complaining about their memory, heightened awareness became a non-predictive measure of progression to MCI. This again highlights the importance of assessing these measures over time, as self-awareness is likely varying over the course of the disease. Heightened awareness may indeed occur for reasons other than AD pathology, e.g., anxiety or fear of potentially developing dementia (nosophobia), psycho-affective disorders such as neuroticism⁴⁵, depression⁴⁶, and sleep disorders⁴⁷ or normal age-related changes, leading normal older individuals to complain about their memory more than their partners. When adjusting analyses for one such potential contributing factor to heightened awareness, depressive symptoms, we again found more CN and MCI participants with heightened awareness who did not progress as compared to CN and MCI participants who progressed. This suggests that non-AD factors contributing to heightened awareness are likely varied and multifactorial, which will be an important area of future investigation. The limited years of follow-up in our findings warrants longer follow-up in cognitively normal individuals as well.

Several limitations of this study should be noted. As mentioned above, the ADNI cohort has very few CN individuals who, so far, have progressed to dementia, especially given the relatively short duration of follow-up. For those reasons, and in regard to the discussion above about whether or not heightened awareness may predict progression to dementia, we acknowledge that our findings warrants further studies that investigate CN individuals during a longer follow-up period, and perhaps more frequently, to map out the very early changes in memory self-awareness which may occur during the preclinical period of the disease. In addition, and also mentioned above, to date there is no consensus on how to optimally assess anosognosia in AD, but see Starkstein³⁵ for more information. Here, we used a discrepancy score between participant self-assessment and study partner assessment, an approach that has been used in several previous publications investigating anosognosia in AD. We also acknowledge that the

current study only assessed awareness based on memory reports, not taking into account other cognitive domains (e.g., language, executive function, etc.). As patients and their partners often report non-memory complaints, future studies should investigate the specificity of awareness of memory as compared to other cognitive domains, as this may be an important clinical issue. Finally, the current study only considered brain amyloidosis as a central neuropathological event in anosognosia and thus might not fully explain if altered self-awareness is an independent symptom with a unique pathobiology or if it is part of the AD symptom complex. Specifically, studies evaluating the relationships between tau and anosognosia should be conducted in the future. These limitations also underscore the importance of replicating these findings in other large cohorts following CN individuals over long periods of time.

We conclude that altered memory self-awareness is associated with baseline A β burden and these initial pathophysiological changes are associated with decreased self-awareness after longitudinal follow-up. Unawareness of memory change is observed approximately 3 years before clinical progression to dementia. Low awareness, not heightened awareness, predicted clinical progression from CN to MCI, providing both further evidence to the notion that individuals who are unaware of cognitive change may represent a specific risk group as well as additional support for the usefulness of informant-reported decline.

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AUTHOR CONTRIBUTIONS

BJH and PV contributed to the conception and design of the study; BJH, MRS, MJP, and PV contributed to the acquisition and analysis of data; BJH, MRS, PV, GAM, JG, SS, and ES contributed to drafting the text and preparing the figures.

POTENTIAL CONFLICTS OF INTEREST:

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Authors report no competing interests.

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FIGURES LEGEND

Figure 1 – Awareness of memory deficits decreases over time in high-amyloid participants

Left: Longitudinal changes in awareness (discrepant--points between participants and partners) in low- (top row) and high- (bottom row) amyloid participants.

Middle: Longitudinal changes in participants' self-complaints about memory deficits over time. Higher values are indicative of more severe memory difficulty reports.

Right: Longitudinal changes in partners' complaints about memory deficits over time. Higher values are indicative of more severe memory difficulty reports.

In high-amyloid CN, MCI, and AD participants, self-complaints do not increase over time as much as partners' complaints increase, resulting in a progressive decrease in memory awareness. Error bars are 95% confidence intervals. All plots are adjusted for age and sex.

Figure 2 – Significant anosognosia is observed three years before progression to dementia

Longitudinal changes in participants' self-complaints and partners' complaints in CN (n=68) and MCI (n=135) participants who clinically progressed during the study. Slopes were obtained from a linear mixed effect model with random intercept and slope predicting complaints over time, adjusting for age and sex. Dotted lines are located at -1.6 years and +3.2 years.

Figure 3 – Anosognosia in CN and MCI participants predicts future clinical progression

Top row: Kernel density plots of awareness for the CN (left) and MCI (right) participants who clinically progressed or remained stable. The left and right dotted lines are the awareness thresholds for significant anosognosia (-.26) and heightened awareness (+.20), respectively.

Bottom row: Survival curves indicating the probability of remaining stable within a diagnostic group for CN and MCI participants with low awareness/anosognosia versus those with normal or heightened awareness at baseline.

Table 1. Demographic Information

	CN		MCI		Dementia		
	Low A β	High A β	Low A β	High A β	Low A β	High A β	All
Number of subjects	239	121	244	352	17	97	1070
N (% of subsample)							
<i>APOE</i> ϵ 4+	46 (19.3)	52 (43.0) **	56 (23.0)	236 (67.1) **	0 (0.0) **	73 (75.3) **	463 (43.2)
Sex(F)	112 (46.9)	77 (63.6) *	106 (43.4)	150 (42.6)	2 (11.8) *	45 (46.4)	492 (46.0)
N							
Progression to MCI	32	36	--	--	--	--	68
Progression to dementia	2	4	14	121	--	--	141
Mean (SD)							
Baseline age (years)	74.1 (6.7)	76.5 (6.3) **	71.3 (8.3) **	74.1 (7.2)	79.9 (6.3) **	74.9 (8.3)	73.9 (7.5)
Years of education	16.7 (2.5)	16.0 (2.8) *	16.4 (2.5)	16.1 (2.8) *	16.2 (2.1)	15.2 (2.8) **	16.2 (2.7)
Baseline MMSE	29.1 (1.2)	28.9 (1.2)	28.1 (2.7) **	26.8 (2.9) **	21.6 (6.4) **	22.4 (2.7) **	27.4 (3.2)
Baseline Logical Memory	15.4 (4.0)	14.9 (4.1)	9.2 (5.0) **	11.4 (5.5) **	5.7 (5.5) **	4.9 (3.6) **	11.3 (5.9)
Baseline ECog memory score - participant	1.7 (0.5)	1.7 (0.5)	2.2 (0.7) **	2.4 (0.7) **	2.1 (0.7) **	2.3 (0.8) **	2.1 (0.7)
Baseline ECog memory score - partner	1.4 (0.5)	1.4 (0.4)	2.0 (0.7) **	2.5 (0.8) **	3.3 (0.5) **	3.5 (0.5) **	2.1 (0.9)
Baseline awareness index	0.3 (0.6)	0.3 (0.5)	0.3 (0.9)	-0.1 (0.9) **	-1.1 (1.0) **	-1.2 (1.0) **	-0.0006 (0.9)
ECog follow-up duration (years)	3.1 (1.4)	3.0 (1.5)	3.4 (1.6) *	2.8 (1.6) *	1.7 (1.6) **	1.1 (1.0) **	2.9 (1.6)
Number of ECog visits	4.1 (1.2)	4.0 (1.3)	5.0 (1.7) **	4.5 (1.6) *	3.1 (1.6) *	2.6 (1.0) **	4.3 (1.6)

Subject information is presented across six levels of baseline diagnosis (DX) and baseline A β as well as the full sample N=1,070. Missing data: 5 participants did not have information regarding biological sex, 7 did not have *APOE* ϵ 4 status, and 5 did not have information regarding years of education.

Key: * significantly different from CN, low amyloid ($p<.05$); ** significantly different from CN, low amyloid ($p<.001$); CN = clinically normal; MCI = mild cognitive impairment; A β = beta-amyloid; *APOE* ϵ 4 = Apolipoprotein E4 genotype; MMSE = Mini-Mental State Examination; ECog = Everyday Cognition scale.

Table 2. Effects of independent variables on longitudinal awareness

	Estimate	SE	DF	<i>t</i> -value	<i>p</i> -value
(Intercept)	1.82	0.33	4527	5.47	<.001**
Baseline age	-0.02	0.003	4527	-4.42	<.001**
Baseline A β	-0.44	0.13	4527	-3.53	<.001**
Time	0.55	0.10	4527	5.22	<.001**
Sex(F)	0.07	0.05	4527	1.28	0.20
<i>APOE</i> ϵ 4+	-0.008	0.06	4527	-0.14	0.89
Years of education	0.01	0.009	4527	1.33	0.18
Baseline DX	-1.08	0.09	4527	-12.62	<.001**
Baseline age:Time	-0.003	0.001	4527	-2.82	0.005*
Baseline A β :Time	-0.22	0.04	4527	-5.42	<.001**
Time:Sex(F)	-0.007	0.02	4527	-0.42	0.67
Time: <i>APOE</i> ϵ 4+	-0.05	0.02	4527	-2.68	0.007*
Time:Years of education	-0.005	0.003	4527	-1.65	0.10
Time:Baseline DX	-0.07	0.03	4527	-2.21	0.03*

Key: * $p < .05$; ** $p < .001$; SE = standard error; DF = degrees of freedom; A β = beta-amyloid; *APOE* ϵ 4 = Apolipoprotein E4 genotype; DX = diagnosis;

Table 3. Interactive effect of diagnosis and A β on longitudinal awareness

3A.

All subjects					
	Estimate	SE	DF	<i>t</i>-value	<i>p</i>-value
(Intercept)	1.29	0.31	4552	4.13	<.001**
Baseline age	-0.02	0.003	4552	-5.06	<.001**
Baseline A β	0.30	0.19	4552	1.57	0.12
Time	0.27	0.10	4552	2.57	0.01*
Baseline DX	0.89	0.43	4552	2.07	0.04*
Baseline age:Time	-0.002	0.001	4552	-1.91	0.06
Baseline A β :Time	-0.13	0.06	4552	-1.98	0.05*
Baseline A β :Baseline DX	-1.65	0.35	4552	-4.72	<.001**
Time:Baseline DX	0.34	0.16	4552	2.13	0.03*
Baseline A β :Time:Baseline DX	-0.36	0.14	4552	-2.63	0.009*

3B.

High Aβ					
	Estimate	SE	DF	<i>t</i>-value	<i>p</i>-value
(Intercept)	0.97	0.37	2303	2.61	0.009*
Baseline age	-0.006	0.005	2303	-1.32	0.19
Time	0.31	0.15	2303	2.12	0.03*
Baseline DX	-1.48	0.12	2303	-12.83	<.001**
Baseline age:Time	-0.005	0.002	2303	-2.42	0.02*
Time:Baseline DX	-0.21	0.05	2303	-3.91	<.001**

Low Aβ					
	Estimate	SE	DF	<i>t</i>-value	<i>p</i>-value
(Intercept)	2.17	0.31	2247	7.02	<.001**
Baseline age	-0.02	0.004	2247	-5.84	<.001**
Time	0.04	0.09	2247	0.42	0.68
Baseline DX	-0.63	0.12	2247	-5.45	<.001**
Baseline age:Time	-0.0006	0.001	2247	-0.54	0.59
Time:Baseline DX	-0.002	0.04	2247	-0.06	0.96

Key: * $p < .05$; ** $p < .001$; SE = standard error; DF = degrees of freedom; A β = beta-amyloid; DX = diagnosis.

Table 4. Effect of amyloid on longitudinal awareness within each diagnostic group

CN					
	Estimate	SE	DF	<i>t</i> -value	<i>p</i> -value
(Intercept)	0.63	0.33	1457	1.91	0.06*
Baseline age	-0.007	0.004	1457	-1.65	0.10
Baseline A β	0.16	0.15	1457	1.11	0.27
Time	0.26	0.12	1457	2.10	0.04*
Baseline age:Time	-0.002	0.001	1457	-1.24	0.22
Baseline A β :Time	-0.12	0.05	1457	-2.36	0.02*

MCI					
	Estimate	SE	DF	<i>t</i> -value	<i>p</i> -value
(Intercept)	1.93	0.36	2792	5.36	<.001**
Baseline age	-0.01	0.005	2792	-2.99	0.003*
Baseline A β	-0.73	0.16	2792	-4.65	<.001**
Time	0.46	0.11	2792	4.25	<.001**
Baseline age:Time	-0.002	0.001	2792	-1.70	0.09
Baseline A β :Time	-0.30	0.05	2792	-6.03	<.001**

Dementia					
	Estimate	SE	DF	<i>t</i> -value	<i>p</i> -value
(Intercept)	-0.48	1.05	295	-0.46	0.65
Baseline age	-0.01	0.01	295	-1.03	0.30
Baseline A β	0.07	0.36	295	0.20	0.84
Time	0.41	0.59	295	0.69	0.49
Baseline age:Time	0.002	0.007	295	0.30	0.76
Baseline A β :Time	-0.57	0.19	295	-3.06	0.002*

Key: * $p < .05$; ** $p < .001$; SE = standard error; DF = degrees of freedom; CN = clinically normal; MCI = mild cognitive impairment; A β = beta-amyloid.

Table 5. Floodlight and spotlight analyses for diagnostic progression

CN to MCI (n=68)					
	Estimate	SE	DF	t-value	p-value
(Intercept) 4y before MCI	0.36	0.09	295	3.77	<.001**
(Intercept) 3y before MCI	0.28	0.08	295	3.40	<.001**
(Intercept) 2y before MCI	0.20	0.08	295	2.64	0.009*
(Intercept) 1y before MCI	0.12	0.08	295	1.56	0.12
(Intercept) at the time of MCI	0.04	0.09	295	0.47	0.64
Time	-0.08	0.03	295	3.12	0.002*

MCI to dementia (n=135)					
	Estimate	SE	DF	t-value	p-value
(Intercept) 4y before dementia	-0.03	0.12	592	-0.23	0.82
(Intercept) 3y before dementia	-0.26	0.10	592	2.67	0.007*
(Intercept) 2y before dementia	-0.49	0.07	592	-6.48	<.001**
(Intercept) 1y before dementia	-0.71	0.06	592	-11.3	<.001**
(Intercept) at the time of dementia	-0.94	0.06	592	-14.72	<.001**
Time	-0.23	0.03	592	-7.68	<.001**

Key: * $p < .05$; ** $p < .001$; SE = standard error; DF = degrees of freedom; CN = clinically normal; MCI = mild cognitive impairment.





