The Impact of Awareness of and Concern About Memory Performance on the Prediction of Progression From Mild Cognitive Impairment to Alzheimer Disease Dementia

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Objective: *To investigate the relationship of awareness of and concern about memory performance to progression from mild cognitive impairment (MCI) to Alzheimer disease (AD) dementia.* **Methods:** *Participants (n = 33) had a diagnosis of MCI at baseline and a diagnosis of MCI or AD dementia at follow-up. Participants were categorized as "Stable-MCI" if they retained an MCI diagnosis at follow-up (mean follow-up = 18.0 months) or "Progressor-MCI" if they were diagnosed with AD dementia at follow-up (mean follow-up = 21.6 months). Awareness was measured using the residual from regressing a participant's objective memory score onto their subjective complaint score (i.e., residual<0 indicates overestimation of performance). Concern was assessed using a questionnaire examining the degree of concern when forgetting. Logistic regression was used to determine whether the presence of these syndromes could predict future diagnosis of AD dementia, and repeated measures analysis of covariance tests were used to examine longitudinal patterns of these syndromes.* **Results:** *Baseline anosognosia was apparent in the Progressor-MCI group, whereas participants in the Stable-MCI group demonstrated relative awareness of their memory performance. Baseline awareness scores successfully predicted whether an individual would progress to AD-dementia. Neither group showed change in awareness of performance over time. Neither group showed differences in concern about memory performance at*

Received February 16, 2018; revised April 27, 2018; accepted April 30, 2018. From the Harvard Aging Brain Study (CEM, RAS, JJL), Department of Neurology, Massachusetts General Hospital, Boston, MA; Harvard Medical School (NJD, REA, KVP, GAM, DMR, RAS, JJL, PV), Boston, MA; Center for Alzheimer Research and Treatment (NJD, REA, KVP, GAM, DMR, RAS, PV), Department of Neurology Brigham and Women's Hospital, Boston, MA; Berenson-Allen Center for Noninvasive Brain Stimulation (NJD, AP-L), Division of Cognitive Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; Athinoula A Martinos Center for Biomedical Imaging (GAM, RAS), Massachusetts General Hospital; and the Department of Psychiatry, Massachusetts General Hospital (PV), Harvard Medical School, Charlestown, MA. Send correspondence and reprint requests to Dr. Patrizia Vannini, Massachusetts General Hospital, 149 13th Street, Suite 10025, Charlestown, MA 02129. e-mail: patrizia@bwh.harvard.edu

https://doi.org/10.1016/j.jagp.2018.04.008

baseline or change in concern about performance over time. **Conclusion:** *These data suggest that anosognosia may appear prior to the onset of AD dementia, while anosodiaphoria likely does not appear until later in the AD continuum. Additionally, neither group showed significant changes in awareness or concern over time, suggesting that change in these variables may happen over longer periods.* (Am J Geriatr Psychiatry 2018; 26:896–904)

Key Words: Alzheimer disease, mild cognitive impairment, awareness, subjective memory complaints, clinical progression

Article Highlights

- MCI who progressed to AD overestimated memory performance at baseline.
- MCI who remained stable underestimated memory performance at baseline.
- Progressor MCI group showed more concern about memory at baseline than Stable MCI.
- Only Progressor MCI appeared to show less concern about memory over time.

INTRODUCTION

Lack of awareness of one's own cognitive deficits, referred to as anosognosia, and lack of concern regarding these deficits, referred to as anosodiaphoria, are prevalent in Alzheimer disease (AD) dementia and are also present in other types of dementia.[1–5] However, recent research on the pervasiveness of anosognosia in mild cognitive impairment (MCI) has been inconsistent and research on anosodiaphoria in MCI is lacking.

Unlike research in individuals with preclinical AD who tend to underestimate their own performance on objective tests, results of studies on individuals with MCI are inconsistent.[6,7] Some have shown that awareness is affected in MCI, and these individuals will overestimate their performance on these tests.[8] Moreover, one study showed that those who are unaware show greater cognitive deficits.[9] However, other research has found that insight is maintained in individuals with MCI, unlike those individuals with AD dementia who were more likely to be unaware of cognitive deficits.[10] A meta-analysis done by Roberts et al. in 2009 concluded that there is significant variability in the level of awareness in individuals with MCI, with some underestimating their abilities and others overestimating their abilities. They postulated that lower awareness may be a marker of disease severity and could be a useful factor in predicting future disease progression.[7] No research, to our knowledge, has been published about anosodiaphoria in individuals with MCI, and, to date, there is one study investigating anosodiaphoria in AD dementia.[1]

This controversy regarding awareness in MCI may be due to both the heterogeneity of anosognosia in study samples and the rates of progression in prior research. A recent study showed that approximately 2.6 years prior to dementia diagnosis, awareness of episodic memory performance begins to decline rapidly.[11] However, trials included in that study only reported between 8% and 15% of participants progressing from MCI to AD dementia each year (i.e., the majority of individuals included are not close to the point of progression to AD dementia).[12–15] Therefore, heterogeneity in the study samples might account for the different reports of anosognosia amongst individuals with MCI. Here, we aim to address this variability and investigate how these syndromes relate to clinical progression from MCI to AD by comparing individuals with MCI who remain stable to individuals who progress to AD dementia within the course of a study.

METHODS

Participants

Our sample was comprised of 33 older individuals (mean age = 74.6, standard deviation [SD] = 8.5; 27.3% females) with amnestic MCI (single or multiple domain) who had a global Clinical Dementia Rating (CDR) score of 0.5 at their baseline assessment

TABLE 1. Descriptive Statistics (Mean [SD] or Percentage) at Baseline for the Total Sample and Each Diagnostic Subgroup

	Total sample	Stable-MCI	Progressor-MCI	Test statistic & p Value[a]
N	33	23	10	
Time to Follow-Up (months)	19.1 (8.4)	18.0 (7.9)	21.6 (9.5)	t = −1.135; p = 0.265
Age (years)	74.6 (8.5)	75.7 (7.5)	73.4 (10.5)	t = 0.710; p = 0.483
Sex (% female)	27.3	30.4	20.0	χ^2 = 0.383; p = 0.536
Education (years)	16.7 (2.3)	16.6 (2.5)	16.8 (1.9)	t = −0.214; p = 0.832
AMNART VIQ	121.5 (8.0)	122.9 (7.0)	118.1 (9.6)	t = 1.628; p = 0.114
CDR SB	1.52 (1.0)	1.09 (0.6)	2.7 (1.1)	U = 37.00; p = 0.001[c]
Objective Memory Composite	37.1 (14.6)	41.9 (13.2)	26.0 (11.8)	t = 3.279; p = 0.003[c]
Subjective Memory Complaints[b]	3.86 (1.5)	3.90 (1.5)	3.78 (1.5)	t = 0.214; p = 0.832
Awareness Index Score	0.00 (1.0)	0.42 (0.9)	−0.97 (0.4)	t = 4.873; p < 0.001[c]
Concern Score[b]	3.4 (1.2)	3.2 (1.4)	4.0 (0.5)	U = 53.00; p = 0.347

[a]A χ^2 test was used for the categorical sex variable (df = 1). For all other variables, Levene's test for equality of variances was used to determine whether a parametric or nonparametric significance test should be used. If Levene's test suggested that variances were equal, two-tailed independent sample t tests were used (df = 31). If Levene's test indicated that variances were unequal, two-tailed Mann–Whitney U tests were used based on mean ranks (as there were differences in the shape of distributions between groups).

[b]These scores have been converted to more intuitive reciprocal values for easier interpretation (the nature of the raw data was inverse, such that a lower score indicated greater reports).

[c]Significant at p < 0.05.

(Table 1).[16] All participants were diagnosed as having MCI at baseline assessment based on consensus by experienced clinicians and were diagnosed as having either MCI or AD dementia at follow-up assessment via the same method (mean follow-up = 19.1 months; SD = 8.4). Those who remained MCI at follow-up were classified as "Stable-MCI" and those who progressed to AD dementia at follow-up were classified as "Progressor-MCI" in these analyses.

Measures

Subjective memory complaints were assessed as an average of the first 18 questions of the General Frequency of Forgetting subscale of the Memory Functioning Questionnaire.[17] Participants rate "how often remembering or doing certain things presents a problem for [them]" on a Likert scale of 1–7, with 1 indicating "always" (most complaints) and 7 indicating "never" (least complaints). For all analyses, these scores were converted to more intuitive reciprocal values for easier interpretation (i.e., a lower score indicated fewer complaints).

Objective memory performance was assessed using a composite of episodic memory tests, modified from Crane et al.[18] A composite score was utilized to more accurately assess the extent of the participants' memory deficits, as individuals with MCI may exhibit floor effects on certain difficult assessments. The objective memory composite included scores from the Wechsler Logical Memory Assessment (Immediate and Delayed Recall scores), the Rey Auditory Verbal Learning Test (RAVLT) (Total Recall [Trials 1–5], Delayed Recall, 30-minute Delayed Recall), and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) (Total Word Recall [Trials 1–3], Delayed Word Recall)[19–21] (Table 2).

Awareness Index

A measure to assess awareness of memory performance was created by regressing an objective memory

TABLE 2. Objective Memory Composite Breakdown at Baseline

Assessment		Total sample	Stable-MCI	Progressor-MCI	Test Statistic & p Value[a]
Logical Memory	**Immediate Recall**	9.9 (4.5)	11.6 (3.8)	5.2 (3.2)	t = 4.12; p < 0.001[b]
	Delayed Recall	7.2 (5.0)	9.3 (4.2)	2.3 (2.9)	t = 4.75; p < 0.001[b]
ADAS-Cog	**Total Recall**	16.6 (4.2)	17.3 (4.1)	14.9 (4.0)	t = 1.55; p = 0.131
	Delayed Recall	4.6 (2.3)	5.3 (2.0)	3.1 (2.3)	t = 2.80; p = 0.009[b]
RAVLT	**Total Recall**	33.3 (9.2)	35.0 (9.0)	29.3 (8.7)	t = 1.69; p = 0.101
	Delayed Recall	4.2 (2.8)	4.6 (3.0)	3.2 (2.2)	t = 1.33; p = 0.102
	30-minute Delayed Recall	2.6 (3.1)	3.3 (3.1)	1.2 (2.5)	t = 1.84; p = 0.075

[a]Levene's test for equality of variances was used to determine whether each group had equal variance. Since none of the groups significantly differed in terms of variance, two-tailed independent sample t tests were used (df = 31).
[b]Significant at $p < 0.05$.

performance score onto a subjective complaint score to obtain the residual, i.e., the deviation of the objective performance from their subjective rating, as previously described by Wilson et al.[11] This regression was run across the entire sample. This provides a measure of memory awareness, such that a residual of zero would indicate agreement between the subjective rating and actual performance, a positive score would indicate underestimation of objective memory performance (i.e., these individuals believe they are functioning less well than their objective performance would suggest), and a negative score would indicate overestimation of their objective memory performance (i.e., these individuals believe they are functioning at a higher level than their objective memory performance would suggest or have "anosognosia").

Concern Index

As a proxy measure for anosodiaphoria, we used the Seriousness of Forgetting subscale of the Memory Functioning Questionnaire.[17] The questions from this subscale are the same as in the General Frequency of Forgetting subscale, but instead participants were asked to rate "how serious of a problem [they] consider memory failure to be" in each situation when they actually do forget. As with the General Frequency of Forgetting subscale, participants responded with a Likert scale of 1–7, where 1 indicated high concern and 7 indicated low concern. For all analyses, these scores were converted to more intuitive reciprocal values for easier interpretation (i.e., a lower score indicated low concern).

Design and Statistical Analyses

All analyses were conducted using IBM SPSS Statistics software (Versions 23, 24). This study was designed as a mixed 2 x 2 factorial, with the between subject factor being Diagnostic Progression Group (Stable-MCI versus Progressor-MCI) and the within subject factor being Assessment Period (baseline and follow-up). The measures above were assessed at baseline and, for a slightly smaller subset of participants, at follow-up. Given the differences in sample size between groups, we conducted Levene's test for equality of variances (if applicable) and examined distribution pattern and shape for all variables in both groups prior to conducting analyses to determine whether parametric tests or nonparametric tests were indicated.

To determine whether the groups were underestimating or overestimating their memory performance, we ran one-sample t tests comparing each group's mean baseline and follow-up awareness index scores against 0, which represents full awareness.

To assess the impact of anosognosia and anosodiaphoria on the prediction of progression to AD dementia, we ran two binary logistic regression models. Our first model used the awareness index score to predict whether a participant was in the

TABLE 3. Subsets of Original Sample Used for Longitudinal Analyses

	Total Sample		Stable-MCI		Progressor-MCI		Test statistic & p Value (follow-up)[a]
	N	Mean follow-up (months)	N	Mean follow-up (months)	N	Mean follow-up (months)	
N (original sample)	33	19.1 (8.4)	23	18.0 (7.9)	10	21.6 (9.5)	t = −1.135; p = 0.265
N (longitudinal awareness index)	33	19.1 (8.4)	23	18.0 (7.9)	10	21.6 (9.5)	t = −1.135; p = 0.265
N (longitudinal concern score)	27	18.0 (7.6)	20	17.1 (7.1)	7	20.6 (9.1)	t = −1.038; p = 0.309

[a]Levene's test for equality of variances was used to determine whether each group had equal variance. Since none of the groups differed significantly in terms of variance, two-tailed independent sample t tests were used (df = 31).

Progressor-MCI or Stable-MCI group, controlling for age at baseline, sex, and education (in years). Our second logistic regression model looked at baseline concern scores as predictive of the Stable-MCI versus Progressor-MCI groups. If either logistic regression was significant, we also planned to run a Cox proportional hazards model as a post-hoc analysis to assess whether a difference in the level of awareness or concern predicted a diagnosis of AD dementia at follow-up. For this model, the diagnosis of AD dementia was the event, time was measured as months to follow-up, and the awareness index score or concern score was used as an independent variable.

To examine the longitudinal patterns of awareness in Stable-MCI versus Progressor-MCI, we ran a two-way repeated measures analysis of covariance (ANCOVA) where the dependent variable was the awareness index score, the group factor was group (Stable-MCI versus Progressor-MCI), and the time point (baseline versus follow-up) was an additional within subject factor, controlling for age, sex, education, and time to follow-up. Another two-way repeated measures ANCOVA was conducted to assess the longitudinal patterns of concern in these groups, using the same model as described above, but using concern score as the dependent variable. While the longitudinal awareness model was run using the same sample as the previous cross-sectional analyses, the longitudinal concern model was run with a smaller subset of participants based on those who had received that portion of the questionnaire at both time points (Table 3). As a post-hoc measure, we ran either paired t tests or Wilcoxon signed-rank tests (a nonparametric analogue of paired t tests) to determine if there were differences in mean awareness index score or concern score between baseline and follow-up within these groups.

RESULTS

We found that 23 participants were categorized as Stable-MCI and 10 were categorized as Progressor-MCI. These two groups showed no significant differences in sex, years of education, months to follow-up, or baseline age or verbal IQ (as measured by the American National Adult Reading Test) (Table 1).[22] The Progressor-MCI group did show significantly higher baseline CDR Sum of Boxes scores and significantly worse baseline objective memory performance composite scores compared to the Stable-MCI group at baseline (Table 1). Looking specifically at the subtests within the objective memory performance composite score, the Progressor-MCI group performed significantly worse on the Logical Memory Immediate and Delayed recall and the ADAS-Cog delayed recall (Table 2). However, the two groups did not significantly differ on amount of subjective complaints (Table 1).

Anosognosia in Stable-MCI Versus Progressor-MCI

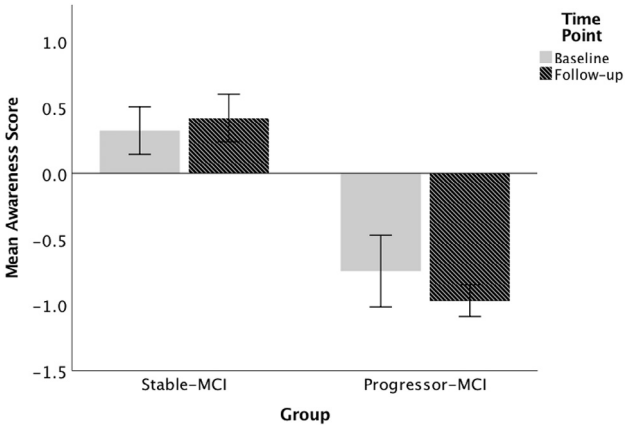
One-sample t tests comparing baseline awareness index scores for each group against 0 (which would indicate close to full awareness) revealed that the Stable-MCI group had a mean awareness index score that was not significantly different from 0 (t[22] = 1.801, p = 0.085), indicating that they had close to full insight into their memory performance. Conversely, the

Progressor-MCI group had a mean awareness index score significantly less than 0, suggesting a tendency to overestimate their memory performance (t[9] = –2.716, p = 0.024), consistent with anosognosia. Independent samples t tests between the groups revealed that the Progressor-MCI group had significantly lower awareness index scores than the Stable-MCI group (Table 1).

A logistic regression analysis was conducted to predict the probability of being in the Progressor-MCI group using the awareness index score, while controlling for age, sex, and education. The overall model was significant, indicating the model reliably distinguished between those within the Progressor-MCI group and those within the Stable-MCI group ($\chi^2 = 11.85$, p = 0.019, df = 4). Nagelkerke's R^2 of 0.427 indicated a moderate relationship between prediction and grouping. Prediction success overall was 84.8% (91.3% for Stable-MCI and 70.0% for Progressor-MCI). The Wald criterion demonstrated that only awareness index score made a significant contribution to prediction (B = –2.112, Wald = 5.510, Exp[B] = 0.121, df = 1, p = 0.019). This model indicated that as awareness decreased, the odds of being in the Progressor-MCI group increased.

The post-hoc Cox proportional hazards model to assess the risk of progressing to AD dementia given awareness index score value was run as a backward elimination model, including age, sex, education, and time to follow-up as covariates. During the fourth and final iteration, only the awareness index score remained, as all other covariates had been eliminated, indicating that they did not significantly contribute to the model (inclusion threshold = $p < 0.05$). The final model was significant (χ^2 d = 5.982, df = 1, p = 0.014), and only the awareness index score significantly contributed to the model (B = –1.050, Wald = 5.282, df = 1, p = 0.018, hazard ratio = 0.350, 95% CI for hazard ratio [0.143, 0.857]), suggesting that as awareness index score increases by one unit (i.e., indicating greater awareness, or, at the extreme, underestimation of performance), risk for progressing to AD dementia decreases by 65.0%. This model was re-run using time-dependent covariates and an interaction term between awareness index score and time to test the proportional hazards assumption. Although the overall model was significant, the interaction term was not significant, indicating that the hazards were proportional over time.

FIGURE 1. Longitudinal awareness index scores in Stable-MCI and Progressor-MCI. This graph demonstrates the awareness scores at baseline and follow-up for the Stable-MCI and Progressor-MCI groups. The awareness score is the residual obtained from regressing subjective memory ratings onto objective memory performance, such that an awareness score of 0 would indicate perfect awareness of one's own performance. A higher awareness score indicates a participant is underestimating their own performance and a lower awareness score indicates that a participant is overestimating their own performance. A logistic regression model showed that baseline awareness index score reliably distinguished between those within the Progressor-MCI group and those within the Stable-MCI group (overall model: $\chi^2 = 11.85$, p = 0.019, df = 4, Nagelkerke's $R^2 = 0.427$, prediction success = 84.8%). A repeated measures ANCOVA indicated that awareness score did not significantly change over time for either group (F[1,27] = 0.150, Wilks's lambda = 0.994, p = 0.702).



A repeated measures ANCOVA examining the interaction between group and time on awareness index score did not reach the statistical threshold for significance (F[1,27] = 1.017, Wilks's lambda = 0.964, p = 0.322), indicating that the awareness index score did not change over time differentially when comparing groups and controlling for age, sex, education, and time to follow-up (Figure 1). Given the interaction was not significant, the main effect tests become of interest. The main effect for time was not significant (F[1,27] = 0.150, Wilks's lambda = 0.994, p = 0.702), indicating that with both groups pooled, there was no change in awareness score across time. The main effect for group

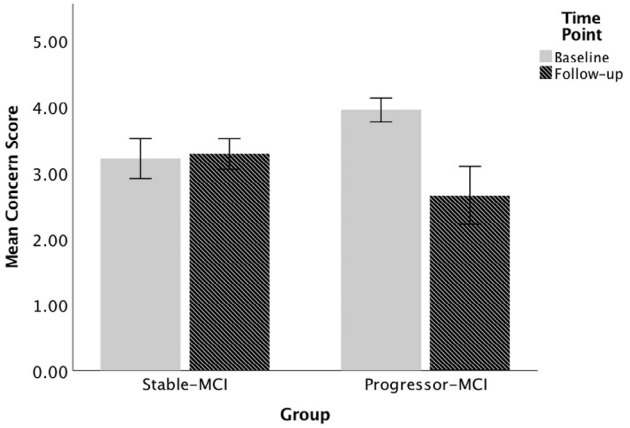
between subjects was significant (F[1,27] = 21.562, p < 0.001), reflecting the fact that the Progressor-MCI group had lower awareness index scores at both time points.

Anosodiaphoria in Stable Versus Progressor-MCI

A logistic regression model used baseline concern score to predict group, controlling for age, sex, and education. The overall model was not significant ($\chi^2 = 3.502$, p = 0.478, df = 4), indicating that baseline concern score was not reliable in distinguishing between Stable-MCI and Progressor-MCI groups.

The repeated measures ANCOVA investigating the interaction between group and time on concern score was statistically significant (F[1,27] = 7.767, Wilks's lambda = 0.730, p = 0.011) when controlling for age, sex, education, and time to follow-up (Figure 2). However, Wilcoxon signed-rank tests revealed that the concern scores in neither the Progressor-MCI group (z = –1.690, p = 0.091) nor the Stable-MCI group (z = –0.523, p = 0.601) significantly changed over time. A two-tailed Mann-Whitney U test based on mean ranks showed that there was no significant difference between the two groups in concern scores at follow-up (U = 47.50, p = 0.213).

FIGURE 2. **Longitudinal concern scores in Stable-MCI and Progressor-MCI. This graph demonstrates the concern scores (i.e., ratings of concern about memory) for the Stable-MCI and Progressor-MCI groups at baseline and follow-up visits. A higher concern score indicates greater concern about memory performance. A logistic regression model using baseline concern scores to predict group was not significant ($\chi^2 = 3.502$, p = 0.478, df = 4), indicating baseline ratings of concern about memory performance do not seem to reliably predict which individuals with MCI will progress to AD dementia. A repeated measures ANCOVA investigating the interaction between group and time on concern scores was significant, indicating differential change over time for one group compared to the other, although neither group individually showed change that was statistically significant.**



DISCUSSION

The results of this study suggest that anosognosia and anosodiaphoria may have different patterns of expression in individuals with MCI.

Anosognosia, or unawareness of memory impairment, was present at baseline in the Progressor-MCI group, whereas participants in the Stable-MCI group demonstrated close to full insight into their own memory performance. The Progressor-MCI group significantly overestimated their memory performance compared to the Stable-MCI group at baseline. Additionally, individuals with MCI who displayed characteristics of unawareness were at an increased risk for progression to AD dementia, although the extent of this risk is as yet unclear in these early analyses. These data are in line with previous studies that suggest that individuals with MCI who demonstrate anosognosia tend to overestimate their performance on objective memory assessments, but this pattern may only be apparent in those close to a diagnosis of AD dementia.[4,23]

In terms of longitudinal change in awareness scores between groups, there was no significant change over time in either the Stable-MCI group or the Progressor-MCI group. This may suggest the length of time between baseline assessment and follow-up assessment was not long enough to see significant change in awareness score despite some participants progressing to AD dementia, or it could be a reflection of the small sample size of this preliminary study.

Baseline measures of anosodiaphoria (i.e., concern about memory performance) were not predictive of progression to AD dementia in this sample of participants with MCI. Longitudinal analyses investigating the change over time in concern scores revealed a significant interaction between group and time point,

reflecting a decline in mean score for the Progressor-MCI group as compared with a slight increase for the Stable-MCI group. However, post-hoc analyses indicated that neither group individually showed a statistically significant change over time in concern scores. This may again reflect the small sample size in the present study and could be an avenue for future research with a larger set of participants. It is also possible that change in concern scores happens more gradually over a longer time period than is covered in this study or occurs at later stages of AD dementia.

Overall, these results suggest that, although anosognosia may not be present in all individuals diagnosed with MCI, a higher degree of anosognosia can be found in those who are close to the point of progression to AD dementia or who are at increased risk for progression to AD dementia within a short time period. As longitudinal analyses within the two groups were not significant, it appears that awareness and concern scores may take longer to change than the time between our baseline and follow-up assessments. It will be important to investigate the change of awareness across the spectrum of preclinical and prodromal AD, as there has been some controversy over whether individuals in the preclinical phase of AD demonstrate intact or impaired awareness. One recent study found that that awareness is low even in individuals with preclinical AD.[24] However, another suggested that individuals with preclinical AD tend to be hyperaware of subtle memory changes prior to any detectable memory impairment.[25] Furthermore, the tipping point for showing symptoms of anosodiaphoria may occur in close temporal proximity to the diagnosis of AD dementia.[26] Along these lines, it appears that individuals who are closer to a diagnosis of AD dementia may initially show more concern about their memory impairment prior to AD dementia, a concern which then lessens after the onset of AD dementia.

Delineating patterns of anosognosia and anosodiaphoria symptoms in individuals with MCI could inform diagnosis, clinical care, and future research. A patient's level of self-awareness and self-concern can impact the treatment they receive and the success of their medical care and pose challenges for researchers analyzing subjective report data from participants with impairment. Therefore, it is essential for clinicians and researchers to consider the impact of these variables in assessing individuals with MCI.

The current study has several limitations. Given the small sample size, additional data are required to estimate more accurately the true size of certain effects in our analyses and to substantiate the longitudinal relationships between group and awareness or concern that remained at a trend level of significance in this study. It is also likely that the longitudinal results for the awareness index might be driven by the greater baseline memory impairment of the Progressor-MCI group given that awareness scores did not significantly decrease between baseline and follow-up. Future research will expand the sample and follow participants for longer periods of time, with special attention to those classified as Stable-MCI, to better characterize differences in awareness of and concern about memory impairment across time in early AD. Another future direction, suggested by the work of Scherling et al, would be to examine anosognosia in nonmemory domains, such as executive function, and how this relates to prediction of progression from MCI to AD dementia.[27]

CONCLUSIONS

In conclusion, our results suggest that anosognosia may be present in individuals with MCI who are close to progression to AD dementia, but anosodiaphoria is not likely present until a diagnosis of AD dementia has already been made. Awareness of or concern about memory impairment did not significantly change over the follow-up period, indicating that change in these variables may remain constant over time or change more gradually over time.

This research was supported by the National Institute on Aging of the National Institutes of Health *under grants* K01AG048287 *(PV),* K24 AG035007 *(RAS),* R01 AG027435-S1 *(RAS),* P01AG036694 *(RAS), and* P50AG00513421 *(RAS). The authors have received research salary support from Eisai Inc. (NJD, GAM) and Eli Lilly and Company (NJD, GAM). The authors have no conflicts of interest to report.*

All authors were provided with a file that included the complete text of the acknowledgments and financial disclosures when signing their individual disclosure forms. All authors have reviewed this text and have agreed that it is accurate.

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