Anosognosia Is an Independent Predictor of Conversion From Mild Cognitive Impairment to Alzheimer's Disease and Is Associated With Reduced Brain Metabolism

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ABSTRACT

Objective: Anosognosia, or impaired illness awareness, is a common feature of Alzheimer's disease (AD) and less so of mild cognitive impairment (MCI). Importantly, anosognosia negatively influences clinical outcomes for patients and their caregivers and may predict the conversion from MCI to AD. This study aimed to examine (1) the relationship between brain glucose metabolism as measured by fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) and anosognosia in patients with MCI and AD and (2) the predictive utility of anosognosia in patients with MCI for later conversion to AD, even when controlling for other factors, including gender, education, apolipoprotein E ε4 carrier status, dementia severity, and cognitive dysfunction.

Methods: Data for 1,062 participants from the Alzheimer's Disease Neuroimaging Initiative database (2003 to August 2015) classified as having AD (n = 191) or MCI (n = 499) or as healthy comparison (HC) subjects (n = 372) were analyzed. HC participants had Mini-Mental State Examination (MMSE) scores from 24 to 30 and a Clinical Dementia Rating (CDR) of 0. MCI participants had MMSE scores from 24 to 30, a memory complaint, objective memory loss, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, and essentially preserved activities of daily living. AD participants had MMSE scores ≤ 26 and a CDR of ≥ 0.5, and met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD. Anosognosia was measured with the composite discrepancy score of the study partner and participants' scores on the Everyday Cognition scale (ECog). Bivariate correlations and multiple regression analyses were performed to assess the relationship between anosognosia and FDG-PET findings in each group. Lastly, logistic regression and receiver operating characteristic curve analyses were performed in the MCI sample to determine if anosognosia was predictive of conversion from MCI to AD.

Results: Hypometabolism was independently associated with anosognosia in AD, particularly in the posterior cingulate cortex and right angular gyrus. Anosognosia was associated with conversion from MCI to AD within 5 years (OR = 2.74 [95% CI, 1.95 to 3.85], χ^2_1 = 33.65, P < .001), even after including covariates (OR = 1.64 [95% CI, 1.12 to 2.40], χ^2_1 = 6.43, P = .011). ECog-composite scores ≤ −0.75 were 93% sensitive and 15% specific for conversion from MCI to AD.

Conclusions: Anosognosia in AD is related to brain glucose hypometabolism. Further, anosognosia independently predicts conversion from MCI to AD. The absence of anosognosia may be clinically useful to identify those patients that are unlikely to convert from MCI to AD.

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Anosognosia, or impaired illness awareness, is common in Alzheimer's disease (AD) and to a lesser degree in mild cognitive impairment (MCI), becoming more frequent with progressive cognitive decline.[1] Anosognosia has implications for clinical, functional, and quality-of-life outcomes for patients and their caregivers and is a factor associated with treatment nonadherence.[2–4] Whereas intact illness awareness may contribute to depressed mood and reduced quality of life in patients with moderate-to-severe dementia, anosognosia is associated with disinhibition, dangerous behaviors, and caregiver burden.[1,5,6] Less is known about the prevalence and clinical impact of anosognosia in MCI.[3,7,8] Intriguingly, in comparison with patients with mild AD, those with MCI tend to overestimate cognitive impairment in relation to their caregiver's assessment,[9,10] which suggests anosognosia may be a predictor of conversion from MCI to AD.[2,11] For example, anosognosia may distinguish MCI patients whose awareness of cognitive symptoms reflects hypervigilance versus MCI patients who are pathologically unaware due to neurodegeneration in brain regions implicated in anosognosia.[12] In support of this hypothesis, a longitudinal study found that baseline informant data were a better predictor of later conversion to dementia than were participants' subjective memory complaints.[13]

Abnormal brain hypometabolism, particularly within the temporal, parietal, and posterior cingulate cortices, is one of the few biomarkers that can aid in the diagnosis of AD and MCI due to AD and identify those in the preclinical stages of the disease.[14] Imaging studies investigating the neurologic correlates of anosognosia in AD have generally found an association with brain metabolism or cerebral perfusion, as

Clinical Points

- Anosognosia or impaired illness awareness is a common feature of Alzheimer's disease (AD) and less so of mild cognitive impairment (MCI) that negatively influences clinical outcomes for patients and their caregivers and may predict the conversion from MCI to AD.

- Brain glucose hypometabolism as measured by fluorine-18 fluorodeoxyglucose positron emission tomography was independently associated with anosognosia in AD, particularly in the posterior cingulate cortex and right angular gyrus.

- Anosognosia was an independent predictor of conversion from MCI to AD within 5 years. The absence of anosognosia may be clinically useful to identify those patients that are unlikely to convert from MCI to AD.

Figure 1. Flowchart of Participant Selection

Abbreviations: AD = Alzheimer's disease, ECog = Everyday Cognition scale, FDG-PET = fluorodeoxyglucose positron emission tomography, HC = healthy comparison participants, MCI = mild cognitive impairment.

measured by positron emission tomography (PET) or single photon emission computerized tomography (SPECT), respectively. These investigations implicate a number of regions within the cingulate cortex and frontal, parietal, and temporal lobes.[12,15–24] However, few studies to date have included patients with MCI and healthy comparison (HC) groups[16,22] (Table 1). Lesion studies of stroke patients suggest anosognosia is related to right cerebral hemisphere hypometabolism or perfusion, particularly within the parietal lobe and typically in association with visuospatial hemineglect.[27] Similarly, studies of neurodegenerative disorders indicate an association between anosognosia and brain hypometabolism or perfusion in the right hemisphere, but possibly with less specificity for hemispheric lateralization than in patients with stroke.[15,18,27]
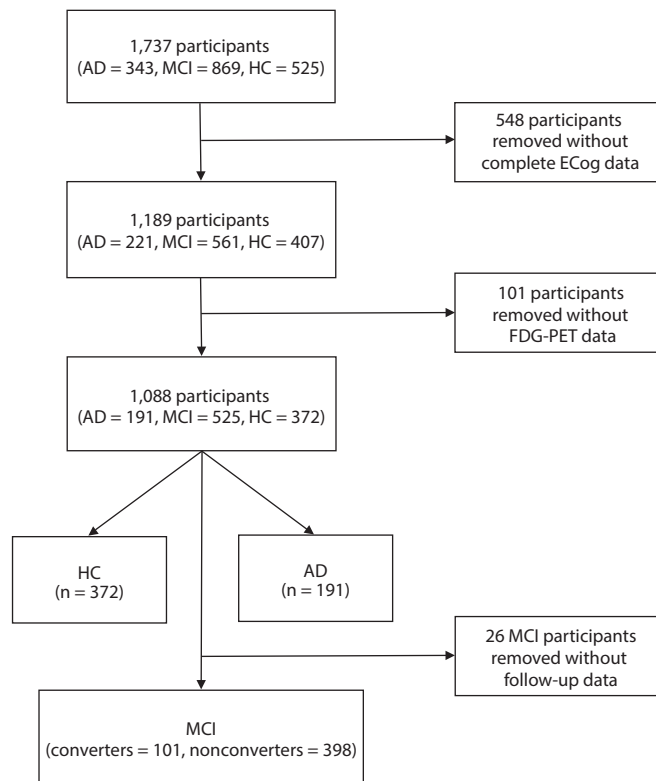
With a large sample, the aims of the current study were to examine (1) the relationship between brain glucose metabolism as measured by fluorine-18 fluorodeoxyglucose PET (FDG-PET) and anosognosia in patients with MCI and AD when controlling for other factors that may be related to brain glucose metabolism or anosognosia in AD, such as age, gender, education, apolipoprotein E ε4 (ApoE4) carrier status, dementia severity, and cognitive dysfunction; and (2) the predictive utility of anosognosia in patients with MCI for later conversion to AD when controlling for brain glucose metabolism and the other aforementioned factors.

METHODS

Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). ADNI was launched in 2003 with the primary goal of combining serial MRI, PET, other biological markers, and clinical and neuropsychological assessments to measure the progression of MCI and early AD. The entire dataset was downloaded from ADNI-1, ADNI-2, and ADNI Grand Opportunity (ADNI-GO) databases on August 7, 2015.[28–30] The region-of-interest (ROI)–based FDG-PET dataset that we used was updated as of July 30, 2015. Data for 1,062 participants were analyzed and consisted of the following classifications: AD (n = 191), MCI (n = 499), and HC (n = 372) (Figure 1). Eligibility criteria for ADNI, ADNI-2, and ADNI-GO are identical.[29,30] Each subject was either an English or a Spanish speaker, was between 55 and 90 years of age, and had a study partner able to provide an independent evaluation of functioning.[29] For our current study, we included only participants with an assessment of anosognosia and an FDG-PET scan. Additionally, MCI participants were included if they had at least 1 follow-up diagnostic assessment within 5 years to determine their conversion status (Figure 1). The diagnostic inclusion criteria for MCI were early MCI, late MCI, normal-to-MCI, and dementia-to-MCI, and the diagnostic inclusion criteria of AD were dementia, MCI-to-dementia, and normal-to-dementia, as defined by the ADNI group. Full details on the inclusion criteria are available in ADNI study protocols at the aforementioned website. In summary, HC participants had Mini-Mental State Examination (MMSE) scores between 24 and 30 (inclusive) and a Clinical Dementia Rating (CDR) of 0 and were nondepressed, non-MCI, and nondemented. MCI participants had MMSE scores between 24 and 30 (inclusive), a memory complaint, objective memory loss measured by

Table 1. The Relationships Between Anosognosia and Brain Metabolism and Anosognosia and Cerebral Perfusion in Alzheimer's Disease and Mild Cognitive Impairment

Authors, Year, Journal	Sample Size	Diagnosis and Stage/Severity	Illness Awareness Assessment	Neuroimaging Technique	Method of Analysis	Study Findings
Jedidi et al, 2014, Soc Cogn Affect Neurosci[26]	AD=37, HC=25	Early-stage, probable AD	Patient-relative discrepancy score on a 40-item personality assessment	FDG-PET	Correlational analysis between the patient-relative discrepancy score for personality changes and FDG-PET metabolism, controlling for age, cognitive impairment severity, and personality changes over time by including these confounding variables in a single design matrix	Hypometabolism in dorsomedial prefrontal cortex
Sultzer et al 2014, Am J Geriatr Psychiatry[17]	AD=88, Delusions=28, No delusions=60	Probable AD	Neurobehavioral Rating Scale (NRS)	FDG-PET	Correlational analysis between NRS inaccurate insight scores and FDG-PET metabolism; univariate ANOVA used to assess differences in those with vs those without delusions for NRS inaccurate insight	Hypometabolism bilaterally in the medial frontal cortex; no qualitative overlap between the regions of hypometabolism associated with delusions and those associated with inaccurate insight
Nobili et al, 2010, J Alzheimers Dis[16]	aMCI=42, HC=29	MCI	Memory Complaint Questionnaire	FDG-PET	"aMCI/unaware" (n=17) vs "aMCI/aware" (n=25), matched for age, sex, education, depression, and neuropsychological test scores; age, sex, and education were included as "nuisance" variables	Hypometabolism in the left inferior parietal lobule, angular gyrus, and superior temporal gyrus
Sedaghat et al, 2010, J Alzheimers Dis[15]	AD=42	Mild or moderate AD	Nonstructured interview with patients and their relatives	SPECT 99mTc HMPAO	"Anosognosia" (n=22) vs "No anosognosia" (n=20) groups and comparison of 4 subgroups: "mild-AD anosognosia" (n=9), "mild AD-No anosognosia" (n=12), "moderate AD-anosognosia" (n=13), and "moderate AD-No anosognosia" (n=8) to control for disease severity	Hypoperfusion in the right inferior parietal and prefrontal regions, and bilaterally in the medial temporal cortex
Hanyu et al, 2008, Dement Geriatr Cogn Disord[18]	AD=38, HC=28	Early AD	Patient-caregiver discrepancy score on Everyday Memory Checklist (EMC)	SPECT I-123-IMP	"Aware" (n=19) vs "Unaware" (n=19) groups	Hypoperfusion bilaterally in the lateral and medial frontal lobes, anterior and posterior cingulate gyri, and left inferior parietal lobe
Shibata et al, 2008, Neurosci Lett[19]	AD=29	Mild dementia, probable AD	Patient-caregiver discrepancy score on a 20-item questionnaire	SPECT I-123-IMP	Correlational analysis to assess the association between anosognosia scores and regional brain perfusion	Hypoperfusion in orbitofrontal cortex
Salmon et al, 2006, Hum Brain Mapp[24]	AD=209	Probable AD	Patient-caregiver discrepancy score on a 13-item questionnaire	FDG-PET	Regression analysis to assess the association between FDG-PET–measured metabolism and impaired illness awareness, controlling for age, MMSE score, IADL score, NPI apathy score, and CDRS score	Hypometabolism in the temporoparietal region bilaterally
Vogel et al, 2005, Int J Geriatr Psychiatry[22]	AD=36, aMCI=25, HC=30	Mild AD	(1) Anosognosia Rating Scale: Semistructured interview of patients and caregivers to characterize patients as "Full Awareness," "Shallow Awareness," "No Awareness," and "Denies Impairment"; (2) Memory Questionnaire patient-caregiver discrepancy score	SPECT 99mTc HMPAO	(1) "Full Awareness" (n=23) vs "Shallow Awareness" (n=25) vs "No Insight" (n=11) groups for frontal regions of interest; (2) correlation analysis to assess association between Memory Questionnaire discrepancy score and frontal regions of interest	Hypoperfusion in the right inferior frontal gyrus in association with Memory Questionnaire discrepancy scores

(continued)

Table 1 (continued).

Authors, Year, Journal	Sample Size	Diagnosis and Stage/Severity	Illness Awareness Assessment	Neuroimaging Technique	Method of Analysis	Study Findings
Harwood et al, 2005, Am J Geriatr Psychiatry[23]	AD=41	Probable AD	Neurobehavioral Rating Scale (NRS)	FDG-PET	Correlational analysis between NRS inaccurate insight scores and FDG-PET metabolism	Hypometabolism in right dorsolateral and lateral frontal regions
Derouesné et al, 1999, Int J Geriatr Psychiatry[12]	AD=78, HC=unknown	Probable AD	Patient-caregiver discrepancy score on Cognitive Difficulties Scale (CDS)	SPECT I-123 IMP	Mean differences in impaired illness awareness for "frontal," "parietotemporal," and "frontotemporoparietal" regions of interest, and right and left hemispheres	Hypoperfusion in the right hemisphere, primarily parietotemporal region
Ott et al, 1996, J Neuropsychiatry Clin Neurosci[21]	AD=40	Possible AD	Clinical Insight Rating Scale (clinician-rated)	SPECT 99mTc HMPAO	Correlational and regression analyses to assess the association between anosognosia scores and regional brain perfusion	Hypoperfusion in the right occipital cortex
Starkstein et al, 1995, Arch Neurol[20]	AD=24	Probable AD	Anosognosia Questionnaire for Dementia: 30-item patient-caregiver discrepancy scale	SPECT 99mTc HMPAO	"Anosognosia" (n=12) vs "No anosognosia" (n=12) groups, matched for age, illness duration, and cognitive impairment	Hypoperfusion in the right hemisphere, primarily the superior and inferior frontal lobes
Reed et al,1993, J Clin Exp Neuropsychol[25]	AD=20	Probable or possible AD	Anosognosia Rating Scale: Semistructured interview of patients and caregivers to characterize patients as "Full Awareness," "Shallow Awareness," "No Awareness," and "Denies Impairment"	SPECT I-123-IMP	"Full Awareness" (n=14) vs "Shallow Awareness" (n=27) vs "No Awareness" (n=13) groups; "Denies Impairment" (n=3) were excluded	Increased perfusion in right dorsolateral frontal lobe for the "Full Awareness" group

Abbreviations: AD=Alzheimer's disease, aMCI=amnestic mild cognitive impairment, ANOVA=analysis of variance, CDRS=Clinical Dementia Rating Scale, FDG-PET=fluorodeoxyglucose positron emission tomography, HC=healthy comparison participants, HMPAO=hexamethylpropyleneamine oxime, IADL=Instrumental Activity of Daily Living scale, I-123-IMP=N-isopropyl-p-[I123] iodoamphetamine, MCI=mild cognitive impairment, MMSE=Mini-Mental State Examination, NPI=Neuropsychiatric Inventory, SPECT=single photon emission computed tomography, 99mTc=technetium-99m.

education adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. Lastly, mild AD participants had MMSE scores between 20 and 26 and a CDR of 0.5 or 1.0 and met NINCDS/ADRDA (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association) criteria for probable AD. To meet inclusion criteria for follow-up, participants must have been originally diagnosed with either MCI or as HC ("Cognitively Normal") and have been willing and able to continue to participate. Participants were asked to continue the trial even if a diagnostic conversion occurred or they were no longer willing and able to continue with neuroimaging or lumbar puncture procedures.

Study Assessments

Assessments were obtained from ADNI-1, ADNI-2, and ADNI-GO databases. Anosognosia was assessed using a caregiver-patient discrepancy strategy,[31] a validated approach to assessing anosognosia in dementia in which the information provided by the caregiver is the standard against which the patient's report is compared.[32] Although this approach is limited by the accuracy of the caregivers' report, clinicians' assessments are correlated with caregivers' reports and do not appear to provide meaningful additional information.[32,33] Study partner-patient discrepancy scores consisted of the composite score (ECog-composite) of the Everyday Cognition–Study Partner Report (ECog-PR) and the Everyday Cognition–Participant Self-Report (ECog-SR).[34] The ECog scales cover 6 cognitive domains that consist of "Everyday" memory, language, visuospatial abilities, planning, organization, and divided attention. Item ratings are made on a 4-point scale: 1=better or no change compared to 10 years earlier, 2=questionable/occasionally worse, 3=consistently a little worse, 4=consistently much worse. A total ECog score is calculated separately for the study partner report and the participant self-report and consists of the sum of all completed items divided by the number of items completed. Thus, total scores range from 1 to 4. ECog-composite scores were calculated as follows: total ECog-PR minus total ECog-SR (ie, ECog-composite=ECog-PR – Ecog-SR). Higher positive scores represent greater anosognosia, whereas lower negative scores indicate greater self-perceived illness.

AD severity was assessed using the Alzheimer's Disease Assessment Scale (ADAS) 11- and 13-item versions[35] and the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB), which is a summation

of disease severity and functional domain scores.[36] Global cognition was assessed using the MMSE and the Montreal Cognitive Assessment (MoCA).[37] Verbal memory performance was assessed using the Rey Auditory Verbal Learning Test (RAVLT),[38] including the immediate recall, learning, forgetting, and percentage of forgetting scores.[39] Higher scores for immediate recall and learning and lower scores for forgetting and percentage of forgetting indicate better verbal memory. Overall function was assessed using the Functional Activities Questionnaire (FAQ).[40] PET scans were performed within approximately 2 weeks of the clinical testing sessions.[41]

FDG-PET Scans and ROI Generation

PET images were acquired from multiple centers using a standardized approach. Details of the ADNI PET data acquisition protocol and image preprocessing are publicly available on the ADNI website (http://adni.loni.usc.edu/) and are described by Landau and colleagues.[41] Predefined ROIs were generated by the ADNI group by identifying regions cited frequently in FDG-PET studies of AD and MCI using a meta-analytic approach. The 5 individual FDG-PET ROI volumes consist of the right and left angular gyri, bilateral posterior cingulate cortex (PCC), and left and right middle/inferior temporal gyrus as well as a combined region created from all 5 subregions.[41]

Statistical Analysis

Demographic, clinical, cognitive, and FDG-PET data. Statistical analyses of demographic, baseline clinical, and FDG-PET ROI variables were carried out with PASW software (PASW Statistics for Windows, Version 18.0. Released 2009. Chicago, Illinois: SPSS Inc). Means and standard deviations were calculated for each variable for HC participants and patients with AD or MCI. Bivariate Pearson correlations were performed between anosognosia (ECog-composite) scores and relevant demographic, clinical, cognitive, and FDG-PET variables. Tests of mean differences and analyses of variance (ANOVAs) were used for group analyses when appropriate. The significance level for tests was established at $P \leq .05$ with Bonferroni correction for multiple testing ($P < .001$).

Relationship of FDG-PET–measured metabolism to anosognosia in MCI and AD. To determine the relationship between FDG-PET–measured metabolism and anosognosia, a series of multiple linear regression analyses were performed after confirming the data met the necessary assumptions. Anosognosia (ECog-composite score) was used as the dependent variable. FDG-PET ROI values were separately entered as the predictor variable. Age, education, gender, ApoE4 carrier status, dementia severity (CDR-SB score), and cognitive impairment (MoCA score) were included as covariates in a stepwise manner.

Anosognosia as a predictor of conversion from MCI to AD. A logistic regression analysis was performed in the MCI sample to determine the odds that anosognosia (ECog-composite score) predicts conversion from MCI to AD

after confirming the data met the necessary assumptions. Follow-up data were available for 499 of the 525 MCI participants up to 5 years after participants' baseline assessment. At the time of this analysis, the mean (SD) duration of follow-up or conversion to AD was 2.5 (1.0) years (range, 0.5 to 5 years). The last reported diagnosis was used to determine participants' conversion status. The aforementioned covariates, in addition to the duration of follow-up and FDG-PET combined ROI values, were added to the analysis.

A receiver operating characteristic (ROC) curve analysis was performed to determine the specificity and sensitivity of anosognosia scores for predicting conversion from MCI to AD.

RESULTS

Demographic and Clinical Data

The demographic and clinical data are presented in Table 2. Within 5 years of follow-up, 73.1% of participants (n = 384) remained classified as having MCI, 19.2% (n = 101) converted to "dementia," and 2.7% (n = 14) reverted to "normal." Therefore, 75.8% (n = 398) were identified as MCI-Nonconverters and 19.2% (n = 101) as MCI-Converters.

There were mean group differences for anosognosia scores ($F_{3,1058} = 162.7$, $P < .001$). Anosognosia was higher in AD subjects than in MCI-Converters (0.60 [95% CI, 0.39 to 0.80], $P < .001$), MCI-Nonconverters (1.07 [95% CI, 0.93 to 1.22], $P < .001$), and HC participants (1.11 [95% CI, 0.96 to 1.25], $P < .001$). Anosognosia was also higher in MCI-Converters than in MCI-Nonconverters (0.47 [95% CI, 0.29 to 0.66], $P < .001$) and HC participants (0.51 [95% CI, 0.33 to 0.70], $P < .001$). Lastly, there was no difference in anosognosia scores between MCI-Nonconverters and healthy participants (0.04 [95% CI, −0.08 to 0.16], $P = 1.000$).

In HC participants, there was no association between anosognosia and demographic, clinical, and cognitive measures (Table 2). Higher ECog-composite scores were associated with worse overall function (ie, FAQ). Similarly, higher ECog-composite scores were modestly associated with dementia severity (ie, CDR-SB); however, this did not survive Bonferroni correction for multiple testing.

In both MCI-Converters and MCI-Nonconverters, higher anosognosia scores were associated with worse overall function (ie, FAQ scores) and dementia severity (ie, CDR-SB scores). Anosognosia was also associated with cognitive impairment, including MoCA, RAVLT-Immediate recall, RAVLT-Learning, and RAVLT-Percent forgotten scores in MCI-Nonconverters, but not after Bonferroni correction for multiple testing.

In AD, similar to MCI, higher ECog-composite scores were associated with worse overall function (ie, FAQ) and dementia severity (ie, CDR-SB). Anosognosia was also associated with cognitive impairment, specifically ADAS-Cog scores, and negatively associated with education; however, these associations did not survive Bonferroni correction for multiple testing.

Table 2. Demographic, Clinical, Cognitive and FDG-PET Data and Their Relationship With Anosognosia in AD, MCI, and HC Participants

	HC (n=372)			MCI (n=499) Nonconverters (n=398)			MCI (n=499) Converters (n=101)			AD (n=191)		
Variable	%, Mean (SD), Range	IIA, z^a / F test^b / r^c	P	%, Mean (SD), Range	IIA, z^a / F test^b / r^c	P	%, Mean (SD), Range	IIA, z^b / F test^b / r^c	P	%, Mean (SD), Range	IIA, z^a / F test^b / r^c	P
Female	53.5	−1.11	.265	43.2	−2.01	.045*	43.6	−0.72	.474	40.8	z=−1.69	.092
ApoE4 carrier (% of 0:1:2 Alleles)	71.8:25.5:2.2	F=2.05	.130	58.0:34.4:7.5	F=0.15	.857	29.7:54.5:15.8	F=1.62	.203	36.6:44.5:18.3	F=0.30	.744
Age, y	74.6 (6.6), 56.2–90.1	0.06	.227	72.3 (7.8), 55.0–91.4	0.10	.057	73.6 (7.5), 55.0–89.5	−0.09	.383	75.3 (8.0), 55.6–90.3	0.13	.074
Education, y	16.5 (2.6)	0.01	.896	16.1 (2.7)	−0.07	.185	16.0 (2.7)	0.11	.281	15.9 (2.7)	−0.24	.001*
Illness awareness score												
Anosognosia (ECog-composite)^d	−0.19 (0.36)	…	…	−0.15 (0.65)	…	…	0.32 (0.77)	…	…	0.91 (0.83)	…	…
ECog-patient	1.39 (0.33)	−0.65	<.001**	1.79 (0.53)	−0.63	<.001**	1.89 (0.56)	−0.49	<.001**	1.88 (0.61)	−0.63	<.001**
ECog-study partner	1.2 (0.29)	0.50	<.001**	1.63 (0.52)	0.62	<.001**	2.22 (0.70)	0.71	<.001**	2.79 (0.66)	0.69	<.001**
Brain glucose metabolism, SUVR												
FDG-PET combined	6.566 (0.570)	−0.07	.191	6.419 (0.611)	−0.13	.012*	5.813 (0.594)	−0.09	.377	5.360 (0.744)	−0.21	.004*
Left angular	1.326 (0.138)	−0.08	.136	1.291 (0.146)	−0.14	.006*	1.151 (0.142)	0.04	.697	1.054 (0.181)	−0.14	.062
Right angular	1.321 (0.131)	−0.08	.143	1.299 (0.134)	−0.14	.007*	1.165 (0.158)	−0.11	.286	1.074 (0.189)	−0.19	.009*
PCC	1.395 (0.161)	−0.04	.411	1.373 (0.167)	−0.14	.007*	1.247 (0.141)	−0.20	.041*	1.141 (0.167)	−0.36	<.001**
Left temporal	1.273 (0.123)	−0.08	.126	1.241 (0.134)	−0.06	.254	1.111 (0.145)	0.00	.967	1.016 (0.168)	−0.07	.325
Right temporal	1.252 (0.113)	−0.01	.809	1.229 (0.124)	−0.09	.088	1.140 (0.140)	−0.06	.548	1.076 (0.159)	−0.14	.047*
Function												
FAQ score	0.3 (1.2)	0.31	<.001**	2.1 (3.2)	0.36	<.001**	5.8 (4.8)	0.54	<.001**	14.1 (7.1)	0.59	<.001**
Illness severity												
CDR-SB score	0.1 (0.2)	0.12	.024*	1.3 (0.8)	0.24	<.001**	2.2 (1.0)	0.39	<.001**	4.8 (1.8)	0.44	<.001**
Cognitive measures score												
MoCA	25.6 (2.5)	−0.03	.569	23.8 (3.1)	−0.11	.034*	21.4 (7.3)	0.12	.242	17.2 (4.7)	−0.12	.108
MMSE	29.0 (1.3)	0.02	.693	28.3 (1.6)	−0.02	.703	27.1 (1.9)	0.02	.863	22.4 (3.0)	−0.11	.149
ADAS-Cog 11	5.7 (3.0)	0.04	.442	8.2 (3.6)	0.09	.080	13.2 (5.4)	−0.02	.822	20.5 (7.6)	0.18	.012*
ADAS-Cog 13	9.0 (4.5)	0.07	.197	13.3 (5.6)	0.09	.080	21.3 (7.3)	−0.02	.885	30.8 (9.1)	0.19	.008*
RAVLT-Immediate recall	45.7 (10.4)	0.07	.182	38.5 (10.7)	−0.12	.016*	28.9 (8.1)	0.02	.858	22.4 (7.7)	−0.07	.324
RAVLT-Learning	5.9 (2.4)	−0.08	.126	5.0 (2.5)	−0.14	.005*	3.4 (2.4)	−0.16	.122	1.9 (1.8)	−0.14	.059
RAVLT-Forgetting	3.9 (2.8)	−0.06	.258	4.6 (2.5)	0.08	.116	5.5 (2.4)	0.18	.083	4.4 (2.2)	0.00	.998
RAVLT-Percent forgotten	36.7 (27.9)	−0.06	.258	50.7 (30.4)	0.15	.002*	77.5 (27.7)	0.24	.018*	87.0 (41.5)	0.03	.692

aMann-Whitney U test.
bOne-way ANOVA, HC: df=2, 367; MCI Nonconverters, df=2, 395; MCI Converters, df=2, 98; AD df=2, 187.
cPearson correlations: HC, df=370; MCI Nonconverters, df=497; MCI Converters, df=99; AD df=189.
dAnosognosia group differences, $F_{3,1058}=162.7$, $P<.001$.
*Significant at α≤.05.
**Significant at α<.001.
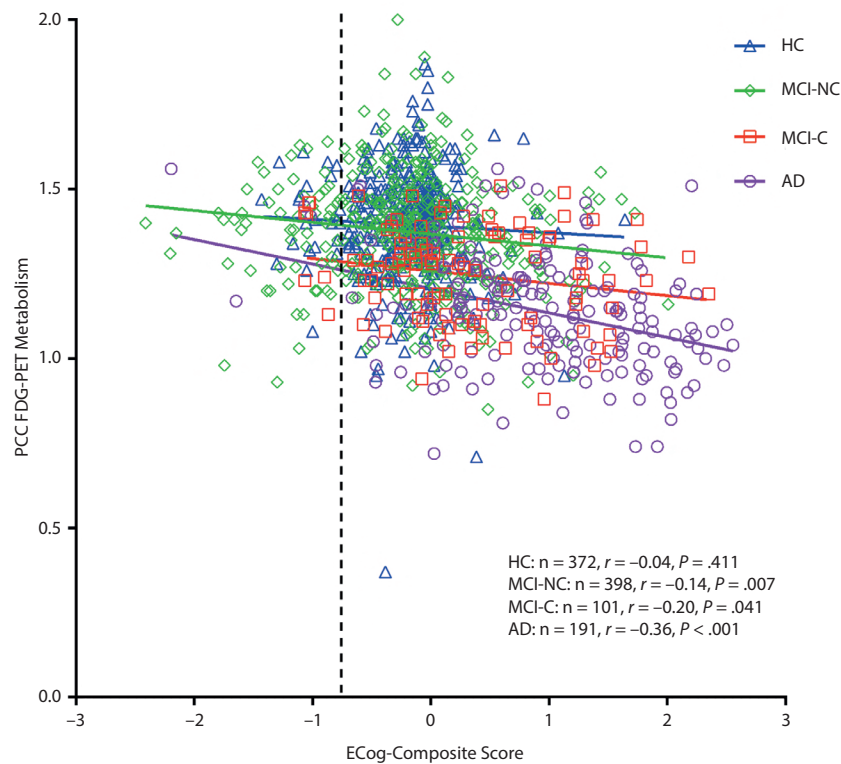Abbreviations: AD=Alzheimer's disease, ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive, ANOVA=analysis of variance, ApoE4=apolipoprotein E ε4, CDR-SB=Clinical Dementia Rating Scale Sum of Boxes, ECog-composite=Everyday Cognition scale study partner report minus participant self-report, FAQ=Functional Assessment Questionnaire, FDG-PET=fluorodeoxyglucose positron emission tomography, HC=healthy comparison participants, IIA=impaired illness awareness, MCI=mild cognitive impairment, MMSE=Mini-Mental State Examination, MoCA=Montreal Cognitive Assessment, PCC=posterior cingulate cortex, RAVLT=Rey Auditory Verbal Learning Test, SD=standard deviation, SUVR=standardized uptake value ratio.
Symbol: …=not applicable.

Figure 2. Relationship Between FDG-PET Metabolism in the Posterior Cingulate Cortex (PCC) and Anosognosia in Subjects With Alzheimer's Disease (AD), Mild Cognitive Impairment Converters (MCI-C) and Nonconverters (MCI-NC), and Healthy Comparison Participants (HC)[a,b]

HC: n = 372, r = −0.04, P = .411
MCI-NC: n = 398, r = −0.14, P = .007
MCI-C: n = 101, r = −0.20, P = .041
AD: n = 191, r = −0.36, P < .001

[a]Higher scores on the ECog-composite indicate greater anosognosia.
[b]The dotted vertical line represents an ECog-composite cutoff score of ≤ −0.75 (n = 72/525), which is 93% sensitive and 15% specific for conversion from MCI to dementia within 5 years. In other words, of the 72/525 MCI participants with baseline anosognosia scores ≤ −0.75, 61 (84.7%) were nonconverters and 7 (9.7%) were converters to AD.
Abbreviations: ECog = Everyday Cognition scale, FDG-PET = fluorodeoxyglucose positron emission tomography.

Relationship Between FDG-PET Metabolism and Anosognosia in AD and MCI

As expected, in the HC group, FDG-PET–measured metabolism was not associated with ECog-composite scores in the combined or any other ROI (Table 2, Supplementary eTable 1, and Figure 2).

In MCI-Nonconverters, anosognosia was associated with FDG-PET–measured hypometabolism in the combined, PCC, and angular ROIs, while in the MCI-Converters, anosognosia was associated with FDG-PET–measured hypometabolism only in the PCC ROI (Table 2 and Figure 2). However, none of these associations remained after including covariates (Supplementary eTable 1).

Lastly, in the AD group, anosognosia was associated with FDG-PET–measured hypometabolism in the combined, PCC (Figure 2), right angular, and right temporal ROIs (Table 2) and in the combined and PCC ROIs after including covariates (Supplementary eTable 1).

Anosognosia as a Predictor of Conversion From MCI to AD

For the logistic regression analyses, anosognosia (ECog-composite scores) was associated with increased odds of

converting from MCI to AD within 5 years (OR = 2.74 [95% CI, 1.95 to 3.85], χ^2_1 = 33.65, P < .001). In the initial model, anosognosia as the sole independent variable explained 11.4% (Nagelkerke R^2) of the variance in MCI-Converters versus MCI-Nonconverters and correctly classified 80.8% of cases. Sensitivity was 8.9%, specificity was 99.0%, positive predictive value was 69.2%, and negative predictive value was 81.1% for this model. In the second model, anosognosia remained associated with increased odds of converting from MCI to AD after including the covariates (OR = 1.64 [95% CI, 1.12 to 2.40], χ^2_1 = 6.43, P = .011) (Table 3). The model explained 40.4% of the variance in MCI-Converters versus MCI-Nonconverters and correctly classified 83.7% of cases. In addition to anosognosia, ApoE4 carrier status, FDG-PET combined ROI, CDR-SB score, and MoCA score were predictors of converting from MCI to AD.

The area under the curve for the ROC analysis of the ECog-composite score's ability to predict progression from MCI to AD was 0.668 (SE = 0.31 [95% CI, 0.606 to 0.729]). The coordinates of the curve are presented in Supplementary eTable 2. A single cutoff score of 0 is 61% sensitive and 64% specific for conversion from MCI to AD within 5 years, which is of little clinical utility. By comparison,

Table 3. Logistic Regression Analysis to Determine the Odds That Anosognosia Predicts Conversion From MCI to AD Within 5 Years, Including FDG-PET Metabolism and Other Covariates

Predictor	Odds Ratio	95% CI	Wald	df	P
Anosognosia (ECog-composite)	1.64	1.12 to 2.40	6.43	1	.011*
Duration of follow-up (maximum of 5 years)	1.16	0.87 to 1.56	1.04	1	.308
Age	1.00	0.97 to 1.04	0.01	1	.929
FDG-PET combined ROI	0.28	0.17 to 0.47	24.90	1	<.001*
CDR-SB	1.98	1.46 to 2.69	19.21	1	<.001*
MoCA	0.83	0.79 to 0.95	8.70	1	.003*
Sex	0.73	0.42 to 1.26	1.30	1	.255
ApoE4 carrier status	2.60	1.47 to 4.60	10.79	1	.001*

*Significant at α ≤ .05.
Abbreviations: AD = Alzheimer's disease, ApoE4 = apolipoprotein E ε4, CDR-SB = Clinical Dementia Rating Scale Sum of Boxes, ECog-Composite score = Everyday Cognition scale study partner report minus participant self-report, FDG-PET = fluorodeoxyglucose positron emission tomography, MCI = mild cognitive impairment, MoCA = Montreal Cognitive Assessment, ROI = region of interest.

ECog-composite scores ≤ −0.75 were 93% sensitive and 15% specific for conversion from MCI to AD. In other words, of the 72 of 525 MCI participants with baseline anosognosia scores ≤ −0.75, 61 were MCI-Nonconverters (84.7%) and 7 (9.7%) were MCI-Converters to AD within 5 years of follow-up. Interestingly, of the 23 of 525 MCI participants with baseline anosognosia scores ≤ −1.25, 22 (95.7%) were MCI-Nonconverters.

DISCUSSION

To the best of our knowledge, this study is the largest to date investigating the association between anosognosia and FDG-PET–measured brain metabolism in AD, MCI, and HC participants and the predictive utility of anosognosia for identifying patients with MCI that will progress to AD. Our study revealed 3 main results. First, FDG-PET–measured brain hypometabolism was associated with anosognosia in AD even when controlling for variables commonly associated with reduced brain metabolism and anosognosia. Second, anosognosia was an independent predictor of conversion from MCI to AD within 5 years. Third, anosognosia was associated with greater cognitive impairment, dementia severity, and functional impairment in MCI and AD.[8,42,43] Intriguingly, functional impairment and dementia severity were also associated with the degree of anosognosia in HC participants.

FDG-PET–measured hypometabolism is one of the few biomarkers available to substantiate the diagnosis of AD and differentiate it from other neurodegenerative disorders and brain lesions.[41] Our results suggest FDG-PET–measured hypometabolism is related to anosognosia in AD, particularly in the PCC, and to a lesser degree, the right angular gyrus (Supplementary eTable 1). This finding is consistent with prior literature that suggests anosognosia or impaired illness awareness is associated with brain hypometabolism or hypoperfusion, even when controlling for the confounders of cognitive dysfunction or dementia severity.[15,18,20,22–26] In both SPECT and FDG-PET studies of AD, anosognosia is associated with hypoperfusion or hypometabolism in multiple brain regions within the frontal,[15,18,22–25] parietal,[15,18,24] cingulate,[18] and temporal cortices[15,24] (Table 1). Contrary to our finding, the only prior FDG-PET study of anosognosia in amnestic MCI (n = 42) found that anosognosia was associated with reduced brain metabolism in the left angular region.[16] However, our results, in a much larger sample of MCI participants, indicate anosognosia is more generally associated with brain hypometabolism in the PCC and, to a lesser degree, both angular gyri (Table 1), but not after inclusion of covariates (Supplementary eTable 1). We suspect that anosognosia was not independently associated with brain hypometabolism in MCI participants as it was likely overshadowed by the degree of cognitive dysfunction, but later emerged in AD independent of cognitive dysfunction with the progression of neurodegeneration.

Based on the diversity of brain regions associated with anosognosia in MCI and AD, it is difficult to come to any definitive conclusions about the underlying neural correlates. Our results of lower FDG-PET–measured metabolism in the PCC and right hemisphere, particularly the right angular gyrus, in association with anosognosia in AD is consistent with existing structural brain lesion and functional imaging studies attributing impaired illness awareness to right hemisphere dysfunction relative to the left, ultimately resulting in left hemisphere dominance.[27] While the posterior parietal cortex, which includes the angular gyrus, is primarily associated with visuospatial reasoning and attention, it is also related to a range of other cognitive functions that may be implicated in illness awareness[44,45] and establishing a coherent sense of self or self-awareness.[46–50]

Anosognosia was an independent predictor of conversion from MCI to AD within 5 years, with an odds ratio of 2.74 (1.64 after controlling for confounding variables) (Table 3). Moreover, ECog-composite scores ≤ −0.75 were 93% sensitive and 15% specific for conversion from MCI to AD, which suggests this cutoff could be used clinically to identify those patients who subjectively report cognitive impairment (eg, in the context of anxiety and mood disorders), but who are unlikely to convert from MCI to AD in 5 years (Supplementary eTable 2 and Figure 2). Even lower anosognosia scores demonstrated greater confidence in ruling out conversion from MCI to AD. These results are consistent with prior studies that identified discrepancy between caregiver and self-reported cognitive and functional impairment to be a predictor of conversion from MCI to AD.[11,51] Relatedly, a longitudinal study found that baseline informant data better predicted later conversion to AD than participants' subjective cognitive complaints.[13]

The results of the present study also substantiate prior findings of the association of anosognosia with cognitive dysfunction, dementia severity, and functional impairment.[8,42,43] In the literature, illness awareness is associated with depressed mood and reduced quality of life.[1] Intriguingly, any protective effects of anosognosia

in preventing reduced quality of life and symptoms of depression appear to come at the expense of greater functional impairment and increased caregiver burden.[1,6,42,43]

Our study is limited by a few factors. First, as with other ADNI studies, our investigation relies on clinical diagnoses of MCI and AD for group classification of participants. As a result, the prediction models of conversion from MCI to AD are limited by the accuracy of the clinical classifications. However, although imperfect, clinical assessments are often more predictive of progression of cognitive decline than available biomarkers.[52] Second, although a caregiver-patient discrepancy strategy is a consistently used approach for the assessment of anosognosia in dementia (Table 1),[31] there are inherent flaws in relying on a caregiver's report as a single proxy, including lack of knowledge, denial of the patient's dysfunction, or exaggeration due to caregiver distress. However, a clinician's assessment is similarly biased and may be influenced by a lack of adequate exposure to the patient's deficits and behavior, a propensity to pathologize behavior, or a lack of knowledge of dementia. Interestingly, although a caregiver-patient discrepancy strategy is limited by the accuracy of the caregivers' report, clinicians' assessments are correlated with caregivers' reports and do not appear to provide meaningful additional information.[32,33] Third, our study lacked the inclusion of variables that may possibly influence conversion rates, anosognosia scores, or the relationship between anosognosia and FDG-PET–measured metabolism, such as metabolic factors, mood symptoms, and history of other neuropsychiatric illness. That being said, the influence of these variables is most likely accounted for by measures of cognitive impairment and dementia severity. Future studies should consider incorporating these possible confounding variables. Fourth, our FDG-PET analysis was restricted to the ADNI group's predefined FDG-PET ROIs, which consist of right and left angular gyri, bilateral PCC, and left and right middle/inferior temporal gyri, as well as a combined region created from all 5 subregions.[41] The ADNI group selected these ROIs as they are the regions most frequently cited as determined by a meta-analytic approach of FDG-PET studies in AD and MCI.[41] Notably absent were frontal regions, which are regularly implicated in brain metabolic and perfusion studies of anosognosia (Table 1). Future neuroimaging biomarker studies of FDG-PET in AD and MCI using large samples should consider including frontal ROIs or adopting a whole brain analytic approach to identify subregions associated with anosognosia.

In summary, anosognosia is related to reduced brain metabolism in AD, particularly in the PCC and, to a lesser degree, the right angular gyrus. Clinically, anosognosia, as measured by the discrepancy between caregiver and patient reports, independently predicts conversion from MCI to AD. Using a prospective longitudinal design, future studies should test the predictive utility of anosognosia scores to facilitate clinical decision-making in MCI, and also HC participants, for whom we found an association between anosognosia and functional impairment and, to a lesser degree, dementia severity. Specifically, anosognosia scores may be beneficial in identifying those MCI patients who may have another etiology for their cognitive impairment or require careful monitoring.

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Supplementary material follows this article.

Supplementary Material

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List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1. Stepwise linear regression analyses to determine the relationship between anosognosia (ECog-composite) and FDG-PET brain metabolism after including covariates.

Predictors	B	95% CI	Partial Correlation	p
Healthy Comparison[a]				
CDR-SB	0.210	0.044 to 0.375	0.130	0.013
MCI Nonconverters[a]				
CDR-SB	0.185	0.110 to 0.259	0.238	<0.001
MCI Converters[a]				
CDR-SB	0.284	0.145 to 0.422	0.380	<0.001
_AD_[b]				
CDR-SB	0.219	0.154 to 0.283	0.446	<0.001
Education	-0.070	0.154 to 0.283	-0.242	0.001
MoCA	0.037	0.010 to 0.064	0.199	0.007
FDG-PET combined	-0.178	-0.335 to -0.022	-0.166	0.026
FDG-PET PCC	-1.468	-2.111 to -0.826	-0.319	<0.001
FDG-PET Right Angular	-0.591	-1.188 to 0.006	-0.144	0.052

AD=Alzheimer's Dementia; MCI=Mild Cognitive, Impairment; FDG-PET=fluorine-18 fluorodeoxyglucose positron emission tomography; MoCA=Montreal Cognitive Assessment; CDR-SB=Clinical Dementia Rating Scale Sum of Boxes; PCC=posterior cingulate cortex.
[a] Variables excluded due to statistical insignificance: gender, ApoE4 carrier status, education, age, MoCA, and all FDG-PET ROIs.
[b] Variables excluded due to statistical insignificance: gender, ApoE4 carrier status, age, MoCA, left temporal, right temporal, and left angular ROIs.

Supplementary eTable 2. Sensitivity and specificity of anosognosia (i.e ECog-composite) cut-off scores to predict conversion from MCI to dementia within 5 years.

Cut point	Sensitivity	Specificity	Total (n=525)	Converters (%)	Nonconverters (%)	Missing (%)
≤-1.25	1.00	0.05	23	0 (0)	22 (95.7)	1 (4.3)
≤-1.00	0.95	0.09	44	5 (10.9)	39 (84.8)	2 (4.3)
≤-0.75	**0.93**	**0.15**	**72**	**7 (9.7)**	**61 (84.7)**	**4 (5.6)**
≤-0.50	0.88	0.25	117	13 (11.1)	99 (88.4)	5 (4.3)
≤-0.25	0.76	0.39	194	24 (12.4)	161 (83.0)	9 (4.6)
0	0.61	0.64	525	101 (19.2)	398 (75.8)	26 (5.0)
≥0.25	0.58	0.76	141	47 (32.0)	94 (63.9)	6 (4.1)
≥0.50	0.49	0.87	88	37 (40.2)	51 (55.4)	4 (4.3)
≥0.75	0.38	0.92	61	30 (47.6)	31 (49.2)	2 (3.2)
≥1.00	0.29	0.96	39	22 (55.0)	17 (42.5)	1 (2.5)
≥1.25	0.15	0.98	26	16 (61.5)	10 (38.5	0 (0.0)

ECog-composite=Everyday Cognition – Study Partner Report (ECog-PR) minus the ECog – Participant Self-Report (ECog-SR); MCI=Mild Cognitive Impairment