Anosognosia predicts default mode network hypometabolism and clinical progression to dementia

Joseph Therriault, BA, Kok Pin Ng, MRCP, Tharick A. Pascoal, MD, Sulantha Mathotaarachchi, MSc, Min Su Kang, BSc, Hanne Struyfs, MSc, Monica Shin, MSc, Andrea L. Benedet, MSc, Ishan C. Walpola, MSc, Vasavan Nair, MD, Serge Gauthier, MD, and Pedro Rosa-Neto, MD, PhD, For the Alzheimer’s Disease Neuroimaging Initiative

Neurology® 2018;0:e1-e8. doi:10.1212/WNL.0000000000005120

Correspondence
Dr. Rosa-Neto
pedro.rosa@mcgill.ca

Abstract

Objective
To identify the pathophysiologic mechanisms and clinical significance of anosognosia for cognitive decline in mild cognitive impairment.

Methods
We stratified 468 patients with amnestic mild cognitive impairment into intact and impaired awareness groups, determined by the discrepancy between the patient and the informant score on the Everyday Cognition questionnaire. Voxel-based linear regression models evaluated the associations between self-awareness status and baseline β-amyloid load, measured by [18F] flurbetapir, and the relationships between awareness status and regional brain glucose metabolism measured by [18F]fluorodeoxyglucose at baseline and at 24-month follow-up. Multivariate logistic regression tested the association of awareness status with conversion from amnestic mild cognitive impairment to dementia.

Results
We found that participants with impaired awareness had lower [18F]fluorodeoxyglucose uptake and increased [18F]flurbetapir uptake in the posterior cingulate cortex at baseline. In addition, impaired awareness in mild cognitive impairment predicted [18F]fluorodeoxyglucose hypometabolism in the posterior cingulate cortex, left basal forebrain, bilateral medial temporal lobes, and right lateral temporal lobe over 24 months. Furthermore, participants with impaired awareness had a nearly 3-fold increase in likelihood of conversion to dementia within a 2-year time frame.

Conclusions
Our results suggest that anosognosia is linked to Alzheimer disease pathophysiology in vulnerable structures, and predicts subsequent hypometabolism in the default mode network, accompanied by an increased risk of progression to dementia. This highlights the importance of assessing awareness of cognitive decline in the clinical evaluation and management of individuals with amnestic mild cognitive impairment.

From the Translational Neuroimaging Laboratory (J.T., K.P.N., T.A.P., S.M., M.S.K., H.S., M.S., A.L.B., P.R.-N.) and Alzheimer’s Disease Research Unit (K.P.N., S.G., P.R.-N.), The McGill University Research Centre for Studies in Aging, Montreal, Canada; Department of Neurology (K.P.N.), National Neuroscience Institute, Singapore; Reference Center for Biological Markers of Dementia (BIODEM) (H.S.), University of Antwerp, Belgium; Center for Mind and Brain (I.C.W.), University of Sydney, Australia; Douglas Hospital Research Centre (V.N.), Department of Psychiatry (V.N.), and Department of Neurology and Neurosurgery (P.R.-N.), McGill University; and Montreal Neurological Institute (P.R.-N.), Canada.

Coinvestigators are listed at links.lww.com/WNL/A236.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.
Anosognosia, a syndrome characterized by a lack of awareness of one’s illness, is commonly observed in Alzheimer disease (AD). Patients with AD with anosognosia are unaware of their cognitive deficits and the difficulties they face when performing activities of daily living. Anosognosia is also correlated with dementia severity in AD. Hence, anosognosia constitutes an important clinical characteristic of patients with AD.

The relationship between anosognosia and AD pathophysiology in the predementia phase of AD is poorly understood. Because anosognosia occurs frequently in AD, further studies focusing on the associations of anosognosia in mild cognitive impairment (MCI) and AD pathophysiology are of paramount importance, given that anosognosia in MCI may represent an important clinical syndrome that signals disease progression.

The present study aims to characterize the associations of anosognosia and AD biomarkers based on the recently described amyloid/tau/neurodegeneration construct in MCI, using $[^{18}F]$ florbetapir, CSF phosphorylated tau (p-tau), and $[^{18}F]$ FDG, respectively. In addition, we examine the predictive effect of anosognosia on disease progression and changes in brain glucose metabolism at a 24-month follow-up. Because anosognosia occurs frequently in the symptomatic phase of AD, we also hypothesized that anosognosia is related to an increase in neuropathologic features of AD at baseline, and correspondingly to higher rates of diagnostic conversion at 24-month follow-up. The finding of a significant relationship between anosognosia, AD biomarkers, and disease progression would support a framework where assessments of illness awareness constitute an important role in the clinical management of MCI.
sensitivity and specificity, was subsequently used to stratify the participants with MCI into intact and impaired self-awareness groups. See figure 1 for a graphical representation of the determination of intact and impaired awareness groups.

**Cognitive assessments**

Global cognitive abilities were evaluated using the MMSE and the Alzheimer’s Disease Assessment Scale–cognitive subscale (ADAS-Cog). Language abilities were evaluated using the Animals section of the Category Fluency task. The Trail-Making Test part A (TMT-A) was employed to assess psychomotor speed processing, while part B (TMT-B) was used to assess mental flexibility. Finally, the Rey Auditory Verbal Learning Task (RAVLT-IM) was used to assess immediate recall memory and the 30-minute delayed recall (RAVLT-D) was used to assess delayed recall.

**CSF analyses**

CSF β-amyloid (Aβ) and p-tau concentrations were measured with the Luminex (Austin, TX) multiplex platform and Innogenetics (Ghent, Belgium) INNO-BIAALZBio3 immunoassay reagents. CSF biomarker data were obtained from the UPENNBIOMK5-8.csv files from ADNI. In the present study, we employed the most recent measure of CSF Aβ1-42, tau, and p-tau. Complete details of the methods for acquisition and measurement of CSF in ADNI can be found at adni.info.org (accessed February 2017).

**Neuroimaging methods**

A schematic representation of the neuroimaging methods employed is presented in figure e-1 (links.lww.com/WNL/A235). T1-weighted MRI were acquired following the ADNI acquisition protocols. For complete details of the ADNI neuroimaging data acquisition protocol, see adni.loni.usc.edu/methods/ (accessed October 2017). Standardized uptake value ratio (SUVR) maps were obtained for [18F]florbetapir using cerebellar gray matter as the reference region and normalizing for cortical white matter, and [18F]FDG using the pons as the reference region. A global [18F]florbetapir and [18F]FDG SUVR value for each participant was estimated as the mean SUVR of a brain mask comprising the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices. PET images were processed using an established pipeline.9

**Statistical analyses**

Statistical analyses were performed using the R Statistical Software Package version 3.1.2 (r-project.org/; accessed February 2017). Analyses of neuroimaging data were conducted using the RMINC library, a biomedical imaging package that permits Medical Image NetCDF (MINC) files to be analyzed in the R environment.

Baseline demographics were assessed using multiple t tests and χ² tests. To characterize intact and impaired awareness groups on AD biomarkers and neurocognitive functioning, we performed an analysis of covariance (ANCOVA). To account for disease severity, we repeated each ANCOVA model of CSF pathology employing ADAS-Cog scores as an additional covariate.

A voxel-based regression model was used to compare patterns of brain metabolism measured by [18F]FDG PET between groups. Furthermore, we employed a voxel-based regression model to compare patterns of regional amyloid deposition as determined by [18F]florbetapir PET. Of the 124 participants

---

Figure 1 Determination of intact and impaired awareness groups

(A) Steps for determining intact and impaired awareness groups. The threshold for the discrepancy score that optimized sensitivity and specificity at differentiating between patients with Alzheimer disease (AD) and healthy controls is 0.5. (B) Receiver operating characteristic (ROC) curve displays sensitivity and specificity at distinguishing between patients with AD and healthy controls. (C) Distribution of participants with mild cognitive impairment (MCI) according to patient–caregiver discrepancy on everyday cognition (ECog). Patient–caregiver discrepancy scores lower than 0.5 indicate intact awareness (red) and scores above 0.5 indicate impaired awareness (blue). AUC = area under the curve.
with amnestic MCI with caregiver and informant E-Cog data with [18F]FDG PET assessments at both baseline and 24-month follow-up, we employed simple linear regression models to evaluate the effect of awareness group on % change in regional brain metabolism as assessed by [18F]FDG PET. Age, sex, years of education, and APOE e4 status were employed as covariates in all voxel-based regression analyses. Because participants with MCI in the anosognosia group had higher ADAS-Cog scores, we repeated each voxel-based regression model employing ADAS-Cog scores as an additional covariate. All voxel-based regression analyses were corrected for multiple comparisons using random field theory at p < 0.001.

To determine if patterns of brain metabolism were abnormal, we subsequently computed z scores for the mean SUVR from the structures with lower [18F]FDG uptake in individuals with MCI with impaired awareness at baseline and at follow-up. A structure was defined as hypometabolic if the mean [18F]FDG SUVR in the anosognosia group was significantly lower (95% confidence interval [CI]) than that of the healthy individuals. Defining abnormality based on 95% CIs from the healthy population is a commonly employed approach.11,12

To evaluate whether anosognosia is an important risk factor for progression from amnestic MCI to AD, we performed a logistic regression analysis including other known factors related to diagnostic conversion including age, sex, years of education, and APOE e4 status as covariates. We also repeated the logistic regression analysis employing ADAS-Cog scores as an additional covariate to correct for cognitive impairment. Odds ratios (ORs) with respective 95% CIs were calculated.

Results

Of 468 participants with amnestic MCI, 175 had impaired self-awareness and 293 had intact self-awareness. Baseline demographics are summarized in the table.

The impaired awareness group demonstrated lower scores on the ADAS-Cog. Furthermore, participants with MCI in the impaired awareness group also demonstrated a larger deficiency on both the RAVLT-IM and RAVLT-D. No statistically significant differences were observed for MMSE, Category Fluency, TMT-A, or TMT-B (figure e-2, links.lww.com/WNL/A235).

ANCOVAs revealed that compared with individuals with MCI with intact self-awareness, individuals with MCI with impaired self-awareness had higher levels of CSF p-tau, CSF total tau, and global [18F]florbetapir uptake. They also demonstrated lower CSF Aβ (figure 2). Furthermore, significant correlations between patient–caregiver discrepancy on the ECog questionnaire and CSF Aβ (r = 0.14, p = 0.0045), global [18F]florbetapir uptake (r = −0.15, p = 0.0017), CSF p-tau (r = −0.19, p < 0.0001), and CSF total tau (r = −0.20, p < 0.0001)

AD biomarker profiles of intact and impaired awareness groups, corrected for age, sex, years of education, and APOE e4 status. Bars in the box and whisker plots display the 5th and 95th percentiles and the horizontal line shows the median. Bonferroni-corrected p values are displayed for each biomarker. For β-amyloid (Aβ) 1–42, lower scores indicate lower Aβ concentrations in CSF, thus indicating higher concentrations of brain Aβ. When employing Alzheimer’s Disease Assessment Scale–cognitive subscale scores as an additional covariate, only total tau remained significant (p = 0.03). p-tau = phosphorylated tau; SUVR = standardized uptake value ratio.
were observed. Because 0.5 was the threshold for determining intact vs impaired awareness (with impaired awareness participants having scores below 0.5), a negative correlation between AD biomarkers and patient–caregiver discrepancy is expected.

A voxel-based regression model demonstrated that individuals with amnestic MCI in the impaired self-awareness group had higher [18F]florbetapir uptake in the posterior cingulate cortex (PCC) and right lateral temporal and parietal cortices than individuals with intact self-awareness (figure 3A). Results of a voxel-based regression model revealed that individuals with MCI with impaired awareness had decreased metabolism in the PCC and precuneus (figure 3B). Voxel-based regression model demonstrated that impaired self-awareness in MCI predicts lower [18F]FDG uptake at 24-month follow-up in the PCC, bilateral medial temporal lobes, right lateral temporal lobe, and basal forebrain (figure 4).

A total of 28.15% of patients with amnestic MCI in the anosognosia group converted to AD dementia, while only 12% in the intact awareness group converted. A multivariate logistic regression analysis demonstrated that impaired awareness of illness predicts diagnostic conversion over 2 years (OR 2.86, 95% CI 1.6–5.25). Notably, the only other factor more closely associated with diagnostic conversion at 24-month follow-up was APOE ε4 status (OR 3.42, 95% CI 1.88–6.39). Anosognosia remained a significant predictor of progression to dementia (OR 2.83, 95% CI 1.44–5.7) when ADAS-Cog scores were employed as a covariate. When each CSF measure of pathology was included in the logistic regression, anosognosia no longer significantly predicted clinical progression (p = 0.09). For the participants with amnestic MCI included in the present analysis, the overall progression rate to probable AD in 2 years was 18.5%. In the intact awareness group, progression to dementia was associated with a significant decline in awareness of illness from baseline (mean 22.27, SD 16.54) to 24-month follow-up (mean −4, SD 33.27, p = 0.0006).

**Discussion**

The present study investigated the relationship among amyloid, tau, neurodegeneration, and anosognosia in amnestic
MCI. The results demonstrate that impaired awareness of illness in MCI is accompanied by an increase in AD pathophysiology as well as decreased metabolism in neural structures vulnerable in AD, independently of sex, education, age, and APOE e4 status. The presence of anosognosia at baseline predicted hypometabolism and clinical progression at 24-month follow-up independently of disease severity. Together, these findings highlight the importance of anosognosia as a clinical feature in amnestic MCI.

While MCIIs in both groups did not differ on MMSE score, participants with MCI with impaired awareness of illness demonstrated lower global cognitive ability from the ADAS-Cog. This divergence may be attributable to the ADAS-Cog being a more sensitive measure of cognitive dysfunction. Furthermore, the impaired awareness group performed worse on verbal memory and delayed recall, consistent with a recent meta-analysis of the neuropsychological correlates of impaired awareness in MCI. Specifically, in participants with MCI with impaired self-awareness, we found increased amyloid deposition in the PCC compared to individuals with intact self-awareness, a feature observed early in the AD process. Higher global amyloid burden has also been linked to decreased awareness of cognitive decline in MCI. Furthermore, results from a longitudinal study reported that individuals with impaired awareness of memory decline demonstrated increased tau pathology postmortem. While these results suggest that anosognosia in MCI is a clinical manifestation of AD pathophysiology, future work is needed to elucidate the role of cognitive impairment in anosognosia. Because relationships between lack of awareness of cognitive impairment and CSF amyloid and CSF p-tau were no longer significant when accounting for cognitive impairment, the regional distribution of neuropathology likely plays a role in the decline of illness awareness.

The association of anosognosia with decreased metabolism and increased amyloid load in the PCC, a key node of the default mode network (DMN), in MCI suggests a link between the PCC and the impairment of self-awareness. The DMN is a large-scale network of brain structures comprising the PCC/precuneus, medial temporal lobes, medial prefrontal cortex, as well as the lateral parietal cortex and is shown to be vulnerable in AD and MCI. Importantly, decreased metabolism in the PCC leading to anosognosia in MCI is not known, multiple functional MRI studies have suggested that the PCC plays a key role in mental processing related to oneself and is involved in the retrieval of autobiographical memories. Furthermore, previous research has shown that less neuronal activity in the PCC is observed when patients with MCI with impaired awareness of illness engaged in a self-referential mental task compared to patients with MCI with intact awareness. It is possible that patients’ decreased mental activity relating to themselves may result in patients failing to integrate information about their recent functional difficulties and cognitive decline into their knowledge about themselves.

Anosognosia in amnestic MCI predicted hypometabolism in the PCC, bilateral medial temporal lobes, right lateral temporal lobe, and basal forebrain at 2-year follow-up. AD and MCI are characterized by significant loss of cholinergic neurons in the basal forebrain. Our results are also in line with previous results demonstrating that patients with AD with anosognosia had decreased glucose metabolism in the PCC and medial temporal lobes. Crucially, the PCC and medial and lateral temporal lobes are DMN structures particularly vulnerable in AD, suggesting that the presence of anosognosia in MCI may be an important marker of incipient AD dementia. Correspondingly, individuals with amnestic MCI with impaired awareness of cognitive decline were 2.86 times more likely to progress to AD within a 2-year time frame than those with intact awareness. Our results are in agreement with previous research demonstrating that lack of awareness of cognitive decline typically appears 2–3 years before the onset of dementia.

Awareness of cognitive decline is not incorporated into screening procedures such as the Alzheimer’s Association recommendations for operationalizing the detection of cognitive impairment. If replicated, these findings demonstrating an increase in AD pathophysiology indicate that awareness assessments are a reasonable method to clinically screen individuals for interventions targeting AD pathophysiology in MCI. Indeed, anosognosia could provide clinicians with insights regarding clinical progression to dementia, though future work is needed to determine the methodology to most accurately assess awareness of illness.

While multiple procedures exist for assessing the extent of lack of awareness of cognitive decline, there is currently no ubiquitously accepted gold standard. Currently, approaches to quantifying lack of awareness of cognitive deficits fall into 3 main categories: (1) assessing the difference between subjective ability and objective score on a neuropsychological task, (2) assessment by a clinician, and (3) the discrepancy between patient and caregiver ratings of cognitive impairment. Because structured interviews with informants are already well-established in current clinical care (such as the Clinical Dementia Rating and the Informant Questionnaire...
on Cognitive Decline in the Elderly [IQCODE][9], clinicians may be able to gain important prognostic information by assessing a patient’s awareness of illness with an informant.

Some methodologic considerations make replication of these findings highly desirable. The first is our operational measure of anosognosia; ECog is a measure of activities of daily living and not a measure of self-awareness in the strict sense. Another limitation of ECog is that it requires patients to recall their memories of past cognitive functioning, a faculty impaired in the anosognosia group. Despite the novelty of using the discrepancy of the ECog scores, the methodology of subtracting patient from caregiver scores has wide empirical support and is commonly employed in investigations of anosognosia across the AD spectrum.2,3,22,33 Furthermore, awareness of illness is not a binary phenomenon and future work is needed to establish the most appropriate method of determining the degree of awareness of illness across the AD spectrum. Another limitation of this research is that ADNI participants are self-selected, and thus may have been interested in participating due to having noticed a decline their cognitive abilities. Therefore, replication in another population-based cohort will strengthen confidence in these findings. However, a unique advantage of the ADNI cohort is that participants do not need to express a concern about their cognitive decline in order to be enrolled in the cohort, thus permitting the study of anosognosia for cognitive decline in MCI.

The results of the present study demonstrated that anosognosia in amnestic MCI is related to an increase in neuropathologic features of AD and increased risk of clinical progression to dementia. Overall, our findings highlight the importance of including assessments of self-awareness in medical diagnostic settings in order to provide additional insights into disease severity and clinical management across the AD spectrum.

Author contributions
J. Therriault, Dr. Ng, Dr. Pascoal: study concept, design, analysis and interpretation of data, creation of figures and manuscript draft. M.S. Kang, H. Struyfs, M. Shin, A.L. Benedet, I. Walpola, and V. Nair report no disclosures relevant to the manuscript. S. Gauthier received honoraria for serving on the scientific advisory boards of Alzheon, Axovant, Lilly, Lundbeck, Novartis, Schwabe, and TauRx and on the Data Safety Monitoring Board of a study sponsored by Eisai and studies run by the Alzheimer’s Disease Cooperative Study and by the Alzheimer’s Therapeutic Research Institute. P. Rosa-Neto reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Disclosure
J. Therriault, K.P. Ng, T.A. Pascoal, S. Mathotaarachchi, M.S. Kang, H. Struyfs, M. Shin, A.L. Benedet, I. Walpola, and V. Nair report no disclosures relevant to the manuscript.

Study funding
This work was supported by the Canadian Institutes of Health Research (MOP-11-51-31), the Alan Tiffin Foundation, the Alzheimer’s Association (NIRG-12-92090, NIRP-12-259245), the Fonds de Recherche du Québec–Santé, and the Centre for Studies on Prevention of AD (StoP-AD Centre). Data collection and sharing for this project was funded by the ADNI (NIH grant U01 AG024904) and DOD ADNI (Department of Defence award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through contributions from the following: AbbVie; Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Arclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb; CereSpir, Inc.; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd. and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC; Johnson & Johnson Pharmaceutical Research & Development LLC; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research also provides funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the NIH (fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the AD Cooperative Study at the University of California, San Diego. ADNI data were disseminated by the Laboratory for Neuroimaging at the University of Southern California.

References
1. Starkstein SE. Anosognosia in Alzheimer’s disease: diagnosis, frequency, mechanism and clinical correlates. Cortex 2014;61:64–73.
2. Starkstein S, Jorge R, Mirzahi R, Robinson RG. A diagnostic formulation for anosognosia in Alzheimer’s disease. J Neurol Neurosurg Psychiatry 2006;77:719–725.
3. Gauthier S, Reisberg B, Zaudig M, et al. Mild cognitive impairment. Lancet 2006;367:1262–1270.
4. Jack CR, Bennett DA, Blennow K, et al. A new classification system for AD, independent of cognition A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. Neurology 2016;1:1–10.
5. Farias ST, Mungas D, Reed BR, et al. The measurement of everyday cognition: scale development and psychometric properties. Neuropsychology 2008;22:531–544.
6. Cacchione PZ, Pawlishka KK, Grant EA, Buckles VD, Morris JC. Accuracy of collateral source reports in very mild to mild dementia of the Alzheimer type. J Am Geriatr Soc 2003;51:819–823.
7. Jorm AF. Assessment of cognitive impairment and dementia using informant reports. Clin Psychol Rev 1996;16:51–73.
8. Tierney MC, Szalai JP, Snow WG, Fisher RH. The prediction of Alzheimer disease: the role of patient and informant perceptions of cognitive deficits. Arch Neurol 1996;53:423–427.
9. Pascoal TA, Mathotaarachchi S, Mohades S, et al. Amyloid-β and hyper-phosphorylated tau synergy drives metabolic decline in preclinical Alzheimer’s disease. Mol Psychiatry 2016;21:6–13.

10. Worsley KJ, Taylor JE, Tomaiuolo F, Lerch J. Unified univariate and multivariate random field theory. Neuroimage 2004;23(suppl 1):S189–S195.

11. Ng KP, Shin M, Gauthier S. Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease. Neurology 2017;88:1814–1821.

12. Gräbeck R. The evolution of the reference value concept. Clin Chem Lab Med 2004;42:692–697.

13. Benge JF, Balas S, Geraci L, Massman PJ, Doody RS. How well do the ADAS-cog and its subscales measure cognitive dysfunction in Alzheimer’s disease? Dement Geriatr Cogn Disord 2009;28:63–69.

14. Piras F, Piras F, Orfei MD, Caltagirone C, Spalletta G. Self-awareness in mild cognitive impairment: quantitative evidence from systematic review and meta-analysis. Neurosci Biobehav Rev 2016;61:90–107.

15. Spalletta G, Piras F, Piras F, et al. Neuroanatomical correlates of awareness of illness in patients with amnestic mild cognitive impairment who will or will not convert to Alzheimer’s disease. Cortex 2014;61.

16. Buckner RL. Molecular, structural, and functional characterization of Alzheimer’s disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci 2005;25:7709–7717.

17. Vannini P, Amariglio R, Hanseeuw B, et al. Memory self-awareness in the preclinical and prodromal stages of Alzheimer’s disease. Neuropsychologia 2017;99:343–349.

18. Wilson RS, Boyle PA, Yu L, et al. Temporal course and pathologic basis of unawareness of memory loss in dementia. Neurology 2015;85:984–991.

19. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain’s default network: anatomy, function, and relevance to disease. Ann NY Acad Sci 2008;1124:1–38.

20. Mevel K, Chetelat G, Eustache F, Desgranges B. The default mode network in healthy aging and Alzheimer’s disease. Int J Alzheimers Dis 2011;2011:553816.

21. Pengas G, Hodges JR, Watson P, Nestor PJ. Focal posterior cingulate atrophy in Alzheimer’s disease. J Neuropathol Exp Neurol 2002;61:85–92.

22. Nestor PJ, Fryer TD, Smielewski P, Hodges JR. Limbic hypometabolism in Alzheimer’s disease. J Neuropathol Exp Neurol 2005;64:1317–153.

23. Braik H, Braik E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991;82:239–259.

24. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Metabolic reduction in the posterior cingulate cortex in very early Alzheimer’s disease. Ann Neurol 1997;42:85–94.

25. Davey CG, Pujol J, Harrison BJ. Mapping the self in the brain’s default mode network. Neuroimage 2016;132:390–397.

26. Andrews-Hanna JR, Reider JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain’s default network. Neuron 2010;65:550–562.

27. Northoff G, Heinzel A, de Greck M, Brempolo F, Dobrowolny H, Panksepp J. Self-referential processing in our brain: a meta-analysis of imaging studies on the self. Neuroimage 2006;31:440–457.

28. Addis DR, Wong AT, Schacter DL. Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. Neuropsychology 2007;21:1363–1377.

29. Ries ML, Jakab BM, Schmitt TW, et al. Anosognosia in mild cognitive impairment: relationship to activation of cortical midline structures involved in self-appraisal. J Int Neuropsychol Soc 2007;13:450–461.

30. Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, Delon MR. Alzheimer’s disease and senile dementia: loss of neurons in the basal forebrain. Science 1982;215:1237–1239.

31. Mufson EJ, Ma SY, Dills J, et al. Loss of basal forebrain P75(NTR) immunoreactivity in subjects with mild cognitive impairment and Alzheimer’s disease. J Comp Neurol 2002;444:136–153.

32. Perrotin A, Desgranges B, Landeau B, et al. Anosognosia in Alzheimer disease: disconnection between memory and self-related brain networks. Ann Neurol 2015;78:477–486.

33. Salmon E, Perani D, Herholz K, et al. Neural correlates of anosognosia for cognitive impairment in Alzheimer’s disease. Hum Brain Mapp 2006;27:588–597.

34. Cordell CB, Borson S, Boustani M, et al. Alzheimer’s Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimers Dement 2013;9:141–150.

35. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.

36. Cherbuin N, Francis Jorm A. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). In: Abou-Saleh MT, Katona C, Kumar A, et al, editors. Principles and Practice of Geriatric Psychiatry, 3rd ed. Chichester, United Kingdom: John Wiley & Sons, Ltd.; 2010:147–151.
Anosognosia predicts default mode network hypometabolism and clinical progression to dementia
Joseph Therriault, Kok Pin Ng, Tharick A. Pascoal, et al.
Neurology published online February 14, 2018
DOI 10.1212/WNL.0000000000005120

This information is current as of February 14, 2018

Updated Information & Services
Including high resolution figures, can be found at:
http://n.neurology.org/content/early/2018/02/14/WNL.0000000000005120.full

Citations
This article has been cited by 2 HighWire-hosted articles:
http://n.neurology.org/content/early/2018/02/14/WNL.0000000000005120.full##otherarticles

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Alzheimer disease
http://n.neurology.org/cgi/collection/alzheimers_disease
Assessment of cognitive disorders/dementia
http://n.neurology.org/cgi/collection/assessment_of_cognitive_disorders_dementia
MCI (mild cognitive impairment)
http://n.neurology.org/cgi/collection/mci_mild_cognitive_impairment
PET
http://n.neurology.org/cgi/collection/pet

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.neurology.org/about/about_the_journal#permissions

Reprints
Information about ordering reprints can be found online:
http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.