Neuropsychiatric symptoms predict hypometabolism in preclinical Alzheimer disease

ABSTRACT
Objective: To identify regional brain metabolic dysfunctions associated with neuropsychiatric symptoms (NPS) in preclinical Alzheimer disease (AD).

Methods: We stratified 115 cognitively normal individuals into preclinical AD (both amyloid and tau pathologies present), asymptomatic at risk for AD (either amyloid or tau pathology present), or healthy controls (no amyloid or tau pathology present) using $[^{18}F]$Florbetapir PET and CSF phosphorylated tau biomarkers. Regression and voxel-based regression models evaluated the relationships between baseline NPS measured by the Neuropsychiatric Inventory (NPI) and baseline and 2-year change in metabolism measured by $[^{18}F]$fluorodeoxyglucose (FDG) PET.

Results: Individuals with preclinical AD with higher NPI scores had higher $[^{18}F]$FDG uptake in the posterior cingulate cortex (PCC), ventromedial prefrontal cortex, and right anterior insula at baseline. High NPI scores predicted subsequent hypometabolism in the PCC over 2 years only in individuals with preclinical AD. Sleep/nighttime behavior disorders and irritability and lability were the components of the NPI that drove this metabolic dysfunction.

Conclusions: The magnitude of NPS in preclinical cases, driven by sleep behavior and irritability domains, is linked to transitory metabolic dysfunctions within limbic networks vulnerable to the AD process and predicts subsequent PCC hypometabolism. These findings support an emerging conceptual framework in which NPS constitute an early clinical manifestation of AD pathophysiology.

Neuropsychiatric symptoms (NPS) represent a common feature of mild cognitive impairment (MCI) and dementia phases of Alzheimer disease (AD).1 In these patients, NPS are associated with a poorer outcome in cognition and functional state.2–3 Although there is an emerging conceptual framework supporting NPS as noncognitive symptoms of preclinical AD,4 the role of NPS as early indicators of AD pathophysiologic progression remains unclear. Studies conducted in patients with AD indicate that NPS are associated with metabolic dysfunction in brain networks subserving mood and cognition.5 Therefore, further studies focusing on the association between NPS and AD pathophysiologic abnormalities are of paramount importance given...
a growing body of evidence proposing subtle NPS as manifestations of emergent disease progression.6

[18F]fluorodeoxyglucose ([18F]FDG) PET is a technique that is sensitive in detecting changes in resting metabolism associated with the neuropsychiatric conditions7 and metabolic declines commonly observed in neurodegenerative conditions.8 In AD, hypometabolism has been considered a part of disease pathophysiology and interpreted as synaptic abnormality or neuronal injury. Thus, modeling the magnitude of symptoms as a function of changes in brain metabolism constitutes a valuable strategy to investigate the neural correlates of NPS in preclinical AD.

Here, in a longitudinal observation of cognitively normal individuals stratified by hallmark AD biomarkers to identify individuals with preclinical AD with the highest risk of progression to clinical AD,9 we test the hypothesis that NPS are associated with metabolic abnormalities in limbic regions and predict pathophysiologic progression in individuals with preclinical AD.

METHODS Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership led by principal investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

In this study, we selected cognitively normal individuals with baseline Neuropsychiatric Inventory (NPI) and Clinical Dementia Rating (CDR) scores, CSF phosphorylated tau (p-tau181p) measurements, [18F]florbetapir PET imaging, both baseline and 2-year follow-up [18F]FDG PET imaging, and ADNI memory composite score (ADNI-mem). We defined cognitively normal individuals as those with a Mini-Mental State Examination score of ≥24, CDR score of 0, and absence of any neuropsychiatric diseases such as depression, MCI, and dementia. The participants were then stratified on the basis of the recent definition of preclinical AD10 into 3 groups: healthy controls, no amyloid or tau pathology present; asymptomatic at risk for AD (AR-AD), either amyloid or tau pathology present; or preclinical AD, both amyloid and tau pathologies present. With this definition,10 the risk of progression to clinical AD is particularly high in preclinical AD. In AR-AD, which may represent cognitively normal individuals who do not follow the temporal sequence in the amyloid cascade hypothesis,11 the risk of clinical evolution still needs to be determined. The inclusion/exclusion criteria adopted by ADNI can be found at www.adni-info.org (accessed October 2016).

Neuropsychological assessments. The neuropsychological assessments were performed by certified raters using standardized ADNI protocols. The CDR, NPI, and ADNI-mem datasets used in this study were obtained from the ADNI files CDR.csv, NPI.csv, and UWNPSYCHSUM_01_28_15-5.csv, respectively. In this study, the NPI was used to measure NPS of the participants. The NPI is an instrument that assesses behavioral disturbances occurring in patients with dementia.12 Both the severity and frequency of each symptom are measured, and this information is obtained from a caregiver familiar with the individual’s behavior. ADNI-mem is a validated composite memory score derived from data from the ADNI neuropsychological battery.13 Briefly, a modern psychometric approach was used to analyze the Rey Auditory Verbal Learning Test, AD Assessment Scale–cognition, Mini-Mental State Examination, and Logical Memory tests to obtain a composite memory score. In the ADNI-mem test, lower scores reflect poorer performance. Details of the ADNI protocols for the neuropsychological assessments and the methods for developing the ADNI-mem can be found at www.adni-info.org (accessed October 2016).

CSF analysis. CSF p-tau181p was measured with the Luminex multiplex platform (Luminex, Austin, TX) and Innogenetics INNO-BIA AlzBio3 (Innogenetics, Ghent, Belgium) immunnoassay reagents. The CSF biomarker datasets used in this study were obtained from the ADNI file UPENNBIOMK5-8.csv. An ADNI published cutoff of CSF p-tau181p >23 pg/mL was used to define the presence of tau pathology.13 Details of the ADNI methods for the acquisition and measurement of CSF can be found at www.adni-info.org (accessed October 2016).

MRI and PET methods. MRI and PET standard acquisition protocols were described in the ADNI website at http://adni.loni.usc.edu/methods/ (accessed October 2016). T1-weighted MRI images corrected for field distortions were processed with the CIVET image processing pipeline.14 and the PET images were processed with an established image processing pipeline.15 In summary, the preprocessed images from the ADNI database were spatially normalized to the Montreal Neurological Institute 152 standardized space with the use of transformations obtained for PET native to MRI native space and the MRI native to the Montreal Neurological Institute 152 space. Subsequently, the [18F]florbetapir PET standardized uptake value ratio (SUVR) and the [18F]FDG PET SUVR maps were generated with the cerebellum gray matter and the pons, respectively, as reference regions. [18F]florbetapir PET images were then normalized for the white matter SUVR. The global brain glucose uptake and the global amyloid deposition were defined as the average SUVR calculated from several brain regions characteristic to AD, including the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices in the [18F]FDG and [18F]florbetapir PET images, respectively. Because we do not have access to the pathology data, we used the best operational point of the receiver operating characteristic curve contrasting controls and ADNI patients with AD (n = 90)16 and calculated [18F]florbetapir PET SUVR >1.15 as the threshold for positive amyloid pathology. With this threshold, fewer than one-third of the controls were amyloid positive, which is consistent with the literature.17

Statistical methods. Statistical analyses were performed with the R Statistical Software Package version 3.3.010 with the RMINC library. Descriptive statistics and frequency distributions

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of baseline demographics and cognitive scores were summarized and compared between the 3 groups using analysis of variance for continuous measurements and χ² tests for categorical measurements. Linear regression models evaluated the associations of NPI scores with baseline global [18F]FDG SUVR and global Δ[18F]FDG SUVR over 2 years in each group. Percentage change in [18F]FDG SUVR was defined as [Δ[18F]FDG = [18F]FDG baseline − [18F]FDG follow-up]/[18F]FDG baseline]. An interaction term was added to the regression models to evaluate the interactions of NPI and the biomarker groups on Δ[18F]FDG SUVR:

$$
\Delta [18F]FDG \text{SUVR} = \beta_0 + \beta_1 \text{(baseline NPI)} + \beta_2 \text{(biomarker groups)} + \beta_3 \text{(baseline NPI × biomarker groups)} + \text{covariates} + \varepsilon
$$

Linear regression models also evaluated the associations of individual subcomponents of the NPI with Δ[18F]FDG. In a secondary analysis, we used linear regression models to evaluate the associations between NPI scores and ADNI-mem at baseline and ΔADNI-mem over 2 years in each group as follows: [ΔADNI-mem = (ADNI-mem baseline − ADNI-mem follow-up)/ADNI-mem baseline].

Voxel-based regression models were used to test the associations of NPI scores with baseline [18F]FDG SUVR and Δ[18F]FDG SUVR over 2 years in each group:

$$
\Delta [18F]FDG \text{SUVR} = \beta_0 + \beta_1 \text{(baseline NPI)} + \text{covariates} + \varepsilon
$$

We extracted and scored the mean SUVR at baseline and at follow-up from the regions where significant associations between NPI scores and Δ[18F]FDG were observed. We defined the presence of hypometabolism if the mean [18F]FDG SUVR was significantly lower (95% confidence interval) than the biomarker-negative individuals, under the assumption that these individuals had a normal metabolic trajectory.

Bonferroni correction was used to correct the aforementioned linear regression analysis for multiple-comparison tests. The statistical parametric maps presented in this study were false discovery rate corrected for multiple comparisons with a threshold of $p < 0.001$. All statistical models presented here were corrected for age, sex, education, and APOE ε4 status.

**RESULTS**

Baseline demographics, APOE status, and biomarker characteristics of the 3 groups are summarized in the table.

We found that individuals with preclinical AD with higher NPI scores had higher [18F]FDG uptake in the posterior cingulate cortex (PCC), ventromedial prefrontal cortex (vmPFC), and right anterior insula (AI) at baseline (figure 1). However, this finding was not observed in the AR-AD or healthy control group at baseline. NPI scores did not have an effect on baseline global [18F]FDG uptake in any of the groups.

We further found that high NPI scores predicted global [18F]FDG uptake decline over 2 years in the preclinical AD group ($β = 0.52, SE = 0.17, p = 0.01$) but not in the AR-AD or healthy control group. A significant interaction between NPI and the groups confirmed that this effect was higher in those with preclinical AD than the other individuals ($β = 0.44, SE = 0.19, p = 0.02$). Subcomponent analysis indicated that only the combined sleep/nighttime behavior disorders and irritability/lability components of NPI predicted global [18F]FDG uptake decline in the preclinical AD group ($β = 0.51, SE = 0.17, p = 0.008$). NPI scores did not predict ADNI-mem scores in any of the groups at baseline or over 2 years.

The voxel-based analysis indicated that high NPI scores predicted regional [18F]FDG uptake decline over 2 years in the PCC and vmPFC of individuals with preclinical AD (figure 2). The mean [18F]FDG uptake at the 2-year follow-up declined below normality in the PCC ($t = 2.89, p = 0.006$) (figure 3B) but remained within a normal range, compared with biomarker-negative individuals, in the vmPFC (figure 3A).

### Table: Baseline demographics and sample characteristics

|                      | Healthy controls (n = 22) | AR-AD (n = 60) | Preclinical AD (n = 33) | p Value |
|----------------------|---------------------------|----------------|------------------------|---------|
| **Age, mean (SD), y**| 75.16 (7.17)              | 74.08 (6.54)   | 76.86 (6.24)           | 0.15    |
| **Male, n (%)**      | 14 (63.6)                 | 34 (66.7)      | 13 (39.4)              | 0.15    |
| **Education, mean (SD), y** | 17.77 (7.70)       | 16.38 (7.73)   | 16.15 (2.33)           | 0.06    |
| **MMSE score, mean (SD)** | 29.05 (1.48)       | 29.17 (1.12)   | 28.91 (0.94)           | 0.58    |
| **APOE ε4 carriers, n (%)** | 1 (4.5)                | 16 (26.7)      | 12 (36.4)              | 0.02    |
| **Follow-up, mean (SD), y** | 2.01 (0.07)       | 1.99 (0.17)    | 2.02 (0.16)            | 0.55    |
| **CSF p-tau181p, mean (SD), pg/mL** | 39.38 (2.63)*a,b,c | 36.28 (15.08)*a, b,c | 46.21 (16.67)*a, b,c | <0.001  |
| **[18F]Florbetapir, mean (SD) SUVR** | 1.06 (0.03)*a,c | 1.08 (0.08)*b,c | 1.30 (0.09)*a,c | <0.001  |

**Abbreviations:** AD = Alzheimer disease; AR-AD = asymptomatic at risk for Alzheimer disease; MMSE = Mini-Mental State Examination; p-tau181p = phosphorylated tau; SUVR = standardized uptake value ratio.

p values were assessed with analyses of variance for each variable except sex and APOE ε4, for which a χ² test was performed.

*Post hoc analysis provided significant group differences from AR-AD.

b Post hoc analysis provided significant group differences from preclinical AD.

c Post hoc analysis provided significant group differences from healthy controls.
DISCUSSION Our study showed that the magnitude of NPS is linked to a transient metabolic dysfunction in limbic networks that are vulnerable to early AD pathophysiology in individuals with preclinical AD. While individuals with preclinical AD with higher NPI scores had higher $^{18}$F-FDG uptake in the PCC, vmPFC, and right AI at baseline, high NPI scores predicted subsequent hypometabolism in the PCC. These metabolic dysfunctions were driven by the sleep/nighttime behavior disorders and irritability components of the NPI.

The finding of worse NPS with higher $^{18}$F-FDG uptake in the PCC, vmPFC, and right AI in individuals with preclinical AD at baseline suggests a link
between specific brain regions involving early AD pathophysiology and behavioral control. Our results are in line with recent evidence from both functional and metabolic imaging studies. For example, a positive correlation has been shown between increased functional connectivity in the anterior cingulate and right insula regions of the salience network (SN) and irritability, agitation, disinhibition, aberrant motor behavior, and euphoria symptoms in patients with AD, while NPS changes have been proposed to reflect aberrant increases in SN functional connectivity. Most recently, NPS are found to be associated with increased glucose metabolism in the left insula, anterior cingulate gyrus, and superior frontal gyrus of patients with early-onset AD. Together, these results support a metabolic dysfunction in limbic networks affected by early AD pathophysiology, leading to NPS manifestations.

The AI, which is a key node of the SN, plays a key role in generating appropriate behavioral responses by integrating affective, homeostatic, and higher-order cognitive processes. Hyperactivity in the AI may lead to enhanced salience detection, which is associated with NPS such as irritability or anxiety, while hypoactivity in the AI is associated with cognitive slowing and attentional deficits. The vmPFC regulates behavioral responses particularly in the context of changing reinforcement contingencies, emotional regulation, and decision-making tasks. Higher NPI scores and higher \(^{18}\)F-FDG uptake in the right AI and vmPFC at baseline may explain the enhanced neuropsychological presentations in these cognitively normal individuals who have both amyloid and tau pathologies.

Our findings of higher \(^{18}\)F-FDG uptake in the PCC in individuals with preclinical AD with higher NPI scores at baseline may represent a change in tissue metabolism in response to amyloid-related neurotoxicity to stabilize neuropsychiatric manifestations in the early stages of the disease. The PCC, a central part of the default mode network, is a highly connected and metabolically active region that plays a key role in supporting cognition. While hypometabolism in the PCC has been consistently observed in early AD pathophysiology, our findings suggest an early and transient neuronal compensation as a manifestation of cognitive reserve to preserve function that has been shown previously in cognitively normal individuals and those with MCI in association with amyloid deposition. As amyloid pathology progressively accumulates in the brain, metabolic decline occurs in response to the demands of the neuronal injury. In line with this concept, we showed that individuals with preclinical AD with worse NPS had subsequent hypometabolism in the PCC at the 2-year follow-up.

In addition, sleep/nighttime behavior disorders and irritability/lability were the NPI components that drove the metabolic dysfunctions in individuals with preclinical AD. Both symptoms have been shown to be associated with early AD pathophysiology. For example, in the National Alzheimer’s Coordinating Center data, noncognitive symptoms of early AD presented in 3 phases, and both irritability and
nighttime behavior changes were found to be some of the first symptoms to occur. In a longitudinal study of the Massachusetts Alzheimer’s Disease Research Center Cohort in which participants were cognitively normal, had subjective cognitive concerns, or were diagnosed with MCI, worse affective factor score predicted time to progression to a worse diagnosis in all 3 groups, driven by depression, agitation, and irritability. In the Mayo Clinic Study of Aging, baseline irritability in cognitively normal adults increased the risk of developing MCI over a median of 5 years (hazard ratio 1.84, 95% confidence interval 1.31–2.58). Irritability and lability are NPS linked to abnormal emotional processing, associated with the vmPFC and PCC. In fact, reduced volume of the PCC gray matter has been shown to contribute to emotional instability. Sleep disturbances are common symptoms of AD and may be early indicators of amyloid pathology and dementia. Sleep deprivation can exacerbate amyloid pathology and mediate neuronal injury, while circadian dysfunction may also lead to cerebral oxidative stress and synaptic damage. Worse sleep quality is also shown to be associated with amyloid deposition in the preclinical AD stage. Patients with obstructive sleep apnea and daytime somnolence have decreased brain metabolism in the precuneus, middle and posterior cingulate gyrus, and parieto-occipital and prefronral cortices, while healthy adults with dream enactment behavior have significantly lower glucose metabolism in brain regions, including the PCC. Hence, the finding of sleep/nighttime behavior disorders and irritability/lability symptoms predicting hypometabolism in the PCC supports these NPS as early manifestations of AD pathophysiology.

Although baseline NPI score predicted [18F]FDG uptake decline, it did not predict memory decline using the ADNI-mem. Given that our study population is composed of a group of highly educated individuals, high cognitive reserve and education might play a role in stabilizing the cognitive function in the early stages of the disease. In addition, NPS may precede cognitive manifestations in early AD pathophysiology. In the Alzheimer’s Disease Cooperative Study Prevention Intervention Project, the presence of baseline behavioral symptoms predicts conversion to a CDR score ≥0.5 over 4 years in cognitively healthy older individuals, while in the National Alzheimer’s Coordinating Center Data, a significantly earlier presence of NPS is found in cognitively normal people who progressed in CDR score compared to those who did not progress. This further supports NPS as early manifestations of AD pathophysiology.

There are limitations to our study. Although NPI is the most widely used instrument to measure NPS, it was initially designed for dementia studies, not for preclinical AD studies. Hence, the sensitivity of NPI in diagnosing NPS in individuals with preclinical AD is not known. In addition, given that the NPI is based on responses from an informed caregiver, the NPI scores may not accurately reflect the NPS of study participants. The ADNI database is made up of highly educated individuals who volunteered to participate in the study that focused on AD research. This may introduce selection bias in that the study population is a self-selected group of individuals who may have concerns about their cognition. The self-selected character of our study population and the relatively small sample size of our study limit the generalizability of our findings to a broader community. Therefore, our findings will need to be confirmed in a larger population-based cohort.

Our findings support an emerging conceptual framework that NPS, driven by sleep behavior and irritability domains, are early manifestations of AD pathophysiology. Therefore, early NPS may further contribute to the characterization of the preclinical AD stage.

AUTHOR CONTRIBUTIONS
Kok Pin Ng: study concept, design, analysis and interpretation of data, compose figures and manuscript draft. Tharick A. Paciol: study design, analysis and interpretation of data, compose figures and manuscript draft. Sulanthi Marthottarachchi, Chang-Oh Chung, Andela L. Benedet, Monica Shin, Min Su Kang: image data processing and manuscript draft. Xiaofeng Li, Mayeen Ba: manuscript draft. Nagaendran Kandiah: study concept, design and manuscript draft. Pedro Rosa-Neto, Serge Gauthier: study concept, design, study supervision, and critical review of manuscript for intellectual content.

STUDY FUNDING
This work was supported by the Canadian Institutes of Health Research (CIHR) (MOP-11-51-31), Canadian Consortium of Neurodegeneration in Aging (CIHR-CCNA), the Weston Brain Institute, and the Alzheimer’s Association (NIRG-08-92090). Pedro Rosa-Neto is supported by the Fonds de la recherche en santé du Québec (chercheur boursier), and Kok Pin Ng is supported by the National Medical Research Council, Research Training Fellowship, Singapore. Pedro Rosa-Neto and Serge Gauthier are CIHR-CCNA members. Data collection and sharing for this project were funded by the ADNI (NIH grant U01 AG024944) and Department of Defense ADNI (award W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, by the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer’s Association, Alzheimer’s Drug Discovery Foundation, Arcterion Biotech, Bioclinica, Inc; Biogen; Bristol-Myers Squibb Co; CereSpir, Inc; Cogstate; Eisai Inc; Elan Pharmaceuticals, Inc; El Lilly and Co; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc; Fujirebio; GE Healthcare; IXICO Ltd; Janssen Alzheimer Immunothera-
Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

DISCLOSURE
K. Ng, T. Pascual, S. Mathoossaratchi, C. Chung, A. Benolet, M. Shin, M. King, X. Li, M. Ba, N. Kandiah, and P. Rosa-Neto report no disclosures relevant to the manuscript. S. Gaulthier received honoraria for serving on the scientific advisory boards of Alteon, 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. Research was funded by CIHR and NIH. Go to Neurology.org for full disclosures.

Received October 14, 2016. Accepted in final form February 17, 2017.

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