Mild behavioral impairment is associated with $\beta$-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals

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Abstract

Introduction: Mild behavioral impairment (MBI) is characterized by the emergence of neuropsychiatric symptoms in elderly persons. Here, we examine the associations between MBI and Alzheimer’s disease (AD) biomarkers in asymptomatic elderly individuals.

Methods: Ninety-six cognitively normal elderly individuals underwent MRI, $^{[18F]}$AZD4694 $\beta$-amyloid-PET, and $^{[18F]}$MK6240 tau-PET. MBI was assessed using the MBI Checklist (MBI-C). Pearson's correlations and voxel-based regressions were used to evaluate the relationship between MBI-C score and $^{[18F]}$AZD4694 retention, $^{[18F]}$MK6240 retention, and gray matter (GM) volume.

Results: Pearson correlations revealed a positive relationship between MBI-C score and $^{[18F]}$AZD4694 retention and global and striatal $^{[18F]}$AZD4694 standardized uptake value ratios (SUVRs). Voxel-based regression analyses revealed a positive correlation between MBI-C score and $^{[18F]}$AZD4694 retention. No significant correlations were found between MBI-C score and $^{[18F]}$MK6240 retention or GM volume.

Conclusion: We demonstrate for the first time a link between MBI and early AD pathology in a cognitively intact elderly population, supporting the use of the MBI-C as a metric to enhance clinical trial enrolment.

KEYWORDS
Alzheimer’s disease, amyloid, mild behavioral impairment, neurodegeneration, neuropsychiatric symptoms, tau
1 | INTRODUCTION

With the failure of over 100 dementia clinical trials to meet primary endpoints, convincing research groups of the relevance of launching new clinical trials on Alzheimer’s disease (AD) progression prevention has become difficult. An often-cited reason for trial failure has been poor recruitment and retention in early phase illness, and better and less costly methods are needed to capture preclinical and prodromal cases. Neuropsychiatric symptoms (NPS), when appropriately measured and operationalized, may offer an opportunity to meet that need to improve.

Although the primary clinical manifestations of AD are impairments of memory and cognitive function, NPS remain a highly prevalent and important source of distress for AD patients and their care partners. NPS include non-cognitive symptoms such as apathy, social withdrawal, anxiety and mood disturbances, irritability, compulsive behaviors, loss of empathy, and delusions, which are clinically associated with increased caregiver burden, greater functional impairment, and faster progression to severe dementia and death, and pathologically linked to greater plaque and tangle burden. In particular, NPS such as depression, anxiety, and agitation have been found to be associated with anomalies of both imaging and fluid AD biomarkers, including hypometabolism as measured by $[^{18}F]$-fluorodeoxyglucose (FDG)–positron emission tomography (PET) imaging, brain $^\beta$-amyloid deposition in the frontal and cingulate cortex as measured by $[^{11}C]$PiB PET, as well as abnormal levels of $^\beta$-amyloid and phosphorylated tau in cerebrospinal fluid in both AD patients and in preclinical populations. Studies have shown that NPS in elderly individuals with normal cognition may be predictive of incipient cognitive decline, and may confer a greater risk of progression to more severe stages of AD in those with mild cognitive impairment (MiCI).

Although early NPS have traditionally been associated with frontotemporal dementia (FTD), the International Society to Advance Alzheimer’s Research and Treatment (ISTAART) NPS Professional Interest Area, a subgroup of the Alzheimer’s Association (AA), developed the ISTAART-AA criteria for mild behavioral impairment (MBI) to foster research into the relationship between NPS and dementias other than FTD. The explicit goal of these criteria is to describe the later-life emergence of sustained NPS as an at-risk state for all causes of dementia, and to describe explicitly the relationship between MBI and MiCI (MBI can emerge before, in concert with, or after MiCI). MBI reflects the neurobehavioral axis of predementia risk states, as a complement to the neurocognitive axis identified by MiCI. Both axes identify individuals who may have increased risk of developing dementia, and there may be some common genetic etiology for MBI and AD. The ISTAART-AA MBI criteria emphasize the importance of a clear change from the person’s usual behavior or personality persisting for at least 6 months in the following domains: decreased drive and motivation (apathy), affective dysregulation (mood and anxiety symptoms), impulse dyscontrol (agitation, impulsivity and abnormal reward salience), social inappropriate ness (impaired social cognition), and abnormal perception and thought content (psychotic symptoms, ie, delusions and hallucinations). MBI, therefore, represents a potential marker for incipient cognitive decline, and for some, MBI is the initial manifestation of a neurodegenerative disease, seen prior to cognitive impairment. In a population with clinically confirmed cognitive impairment, MBI was present in 83.5% of MiCI and 76.5% of subjective cognitive decline (SCD) cases. However, MBI was captured using the Neuropsychiatric Inventory Questionnaire (NPI-Q), in which NPI items were mapped onto MBI domains. The NPI has a 1-month reference range, which does not capture the 6-month symptom duration requirement of the ISTAART-AA MBI, a fundamental feature of the diagnosis. This short reference range can result in poor specificity, inappropriately capturing as cases subjects with transient symptoms and reactive conditions, and therefore, resulting in an inflated prevalence estimate. Similarly, in a population-based community sample, using the same NPI-to-MBI transformation algorithm, MBI prevalence was 27.6% in the public domain.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources (eg, PubMed) and meeting abstracts and presentations. Although the associations between the syndrome of mild behavioral impairment (MBI) and Alzheimer’s disease (AD) pathophysiology have not yet been widely studied, there have been several recent publications describing the clinical aspects of MBI. These relevant publications are cited appropriately.

2. Interpretation: Our findings led to a hypothesis about the neuroimaging correlates of MBI. This hypothesis is consistent with nonclinical and clinical findings currently in the public domain.

3. Future directions: The manuscript proposes a framework for the generation of new hypotheses and the conduct of additional studies. Future directions include further understanding of the capability of MBI in predicting changes in AD pathophysiology in cognitively intact populations through the use of longitudinal data.

HIGHLIGHTS

• Mild behavioral impairment (MBI) is a syndrome characterized by the appearance of neuropsychiatric symptoms in elderly persons.
• MBI is a potential marker of incipient cognitive decline and Alzheimer’s disease (AD).
• MBI is associated with $^\beta$-amyloid deposition in cognitively normal elderly persons.
• MBI may be an early manifestation of AD pathophysiology before cognitive symptoms.
the cognitively unimpaired and 48.9% in MiC1 subjects, again likely reflecting inflated prevalence estimates.\textsuperscript{19} It is notable that if MBI results are to be used to capture an at-risk state, potentially enriched for biomarker positivity, the operationalization of MBI criteria needs to yield specific results in an effort to minimize false positives.

To more precisely capture the higher risk MBI group, the MBI Checklist (MBI-C)\textsuperscript{20} was developed as an MBI case-ascertainment instrument. This checklist mandates that later-life symptoms be sustained for at least 6 months and uses language suitable to functionally independent community dwelling older adults. In a primary care validation study, MBI prevalence was 14.2% in MiC1\textsuperscript{21} and 5.8% in SCD.\textsuperscript{22} These lower frequencies are likely to more accurately represent the actual prevalence of MBI in such populations, and allow defining smaller groups with fewer false positives, for which it is easier and more cost-effective to test for positivity of other biomarkers.

The current study aims to further refine the construct of MBI and to investigate its neuropathological correlates in cognitively asymptomatic elderly individuals. We tested the hypothesis that elevated MBI-C scores are associated with early pathological stages of AD by assessing the relationship between the MBI-C score and AD imaging biomarkers within the context of the A/T/N classification scheme,\textsuperscript{23} specifically brain burden of $\beta$-amyloid as measured with $[18F]$AZD4694 ("A"), brain burden of tau as measured with $[18F]$MK6240 PET ("T"), and regional gray matter (GM) volume using voxel-based morphometry (VBM) ("N"), in a group of cognitively normal elderly participants.

2 METHODS

2.1 Participants

For this study, we selected participants with normal cognition (CN; $n = 96$) from our Translational Biomarkers of Aging and Dementia (TRIAD) cohort (triad.tnl-mcgill.com). Informed written consent was obtained for all experimentation in human subjects. All participants underwent extensive clinical assessments, including neuropsychological evaluation, structural MRI, $\beta$-amyloid PET with $[18F]$AZD4694, tau PET with $[18F]$MK6240, and genotyping for APOE$\varepsilon$.\textsuperscript{4} All individuals were over the age of 55. CN individuals were defined as having no objective cognitive impairment, and all were asked to report any subjective memory complaint in a questionnaire given during screening. Diagnosis was confirmed by an expert consensus panel of clinicians, neuropsychologists, and nurses based on neuropsychological and imaging data. None of the participants met criteria for any major neuropsychiatric disorder.

2.2 Cognitive assessment

Global cognition was evaluated using Mini-Mental State Examination (MMSE) and clinical dementia rating (CDR). Participants underwent neuropsychological evaluation of four cognitive domains: (1) language (Delis-Kaplan executive function system (D-KEFS) Verbal Fluency Test, Boston Naming Test, Wechsler abbreviated scale intelligence (WASI)-II Vocabulary Test), (2) visuospatial function (Birmingham object recognition battery (BORB) Object Decision Test, BORB Orientation Test, WASI-II Matrix Reasoning), (3) memory (delayed recall trials of the Rey Auditory Verbal Learning Test, Logical Memory Test, Free and Cued Selective Reminding Test, Aggie Figure Learning Test, Face-Name Association Task), and (4) executive function (WAIS-III Digit Symbol and Digit Span Tests, D-KEFS Color-Word Interference Test, Trail Making Test). All tests were administered by a neuropsychologist. In addition, the Geriatric Depression Scale (GDS) and the Generalized Anxiety Disorder 7 (GAD7) scale results were used to rule out major depression and anxiety.

2.3 Assessment of mild behavioral impairment

MBI was assessed using the MBI-C,\textsuperscript{20} a scale available for use in the public domain with multiple language versions, including English and French (freely available at www.MBItest.org). The MBI-C was completed by the participant’s primary informant, most frequently their spouse. The MBI-C is a simple scale composed of 34 questions subdivided into five domains: (1) decreased drive and motivation (apathy), (2) affective dysregulation (mood and anxiety symptoms), (3) impulse dyscontrol (agitation, impulsivity, and abnormal reward salience), (4) social inappropriateness (impaired social cognition), and (5) abnormal perception and thought content (psychotic symptoms). Each question is answered with “Yes” or “No,” and a severity rating is accorded to each question answered “Yes” of either 1 = mild, 2 = moderate, or 3 = severe. To be given a “Yes” rating, symptoms must have persisted for at least 6 months, either continuously or intermittently, and represent a marked change from the normal pattern of behavior. An overall numerical score can be generated for the MBI-C by summing the severity ratings (with symptoms rated as “No” having a score of 0). The possible total scores for the MBI-C range from 0 to 102. Individual scores for each domain of the MBI-C can similarly be generated by summing the severity scores for reported symptoms in each category. A cut-off score of 8.5 on the MBI-C was used to confer a diagnosis of MBI to participants, based on a validation study of the MBI-C conducted in people with SCD.\textsuperscript{22}

2.4 Genetic analyses

Determination of APOE genotypes was performed using the polymerase chain reaction amplification technique, followed by restriction enzyme digestion, standard gel resolution, and visualization processes. Full details of this procedure can be found elsewhere.\textsuperscript{24}

2.5 Radiosynthesis

$[18F]$AZD4694 was prepared by radiofluorination of its corresponding N-Boc-protected nitro precursor followed by acidic deprotection.\textsuperscript{25} $[18F]$MK6240 was prepared in one step by the concurrent radiofluorination and thermal deprotection of its corresponding di-Boc-protected nitro precursor.\textsuperscript{26,27}
2.6 MRI acquisition and processing

All participants underwent structural MRI acquisition procedures at the Montreal Neurological Institute. Images were acquired on a 3T Siemens Magnetom using a standard head coil. A volumetric magnetization prepared rapid gradient echo (MPRAGE) MRI (repetition time [TR]: 2300 ms, echo time [TE]: 2.96 ms) sequence was employed to obtain a high-resolution T1-weighted anatomic image of the entire brain (9° flip angle, coronal orientation perpendicular to the double spin echo sequence, and 1 x 1 mm^2 in-plane resolution with 1 mm slab thickness). T1-weighted MR images were corrected for field distortions, segmented, non-uniformity corrected, and processed following an optimized VBM protocol. The anatomic images were segmented into probabilistic GM and white matter (WM) maps using the statistical parametric software (SPM) 12 segmentation tool. Each GM and WM probability map was then non-linearly registered with modulation to the Alzheimer disease neuroimaging initiative (ADNI) (adni.loni.usc.edu) template using Darten, an algorithm for diffeomorphic image registration. Images were smoothed with a Gaussian kernel with a full width at half maximum (FWHM) of 8 mm. All images were visually inspected to ensure proper alignment to the ADNI template.

2.7 PET acquisition and processing

PET scans were acquired with a Siemens high-resolution research tomograph. [18F]MK6240 images were acquired between 90 and 110 minutes after an intravenous bolus injection of the tracer. Scans were reconstructed with the ordered subset expectation maximization (OSEM) algorithm on a four-dimensional (4D) volume with four frames (4 x 300 s). [18F]AZD4694 images were acquired between 40 and 70 minutes post-injection and scans were reconstructed with the OSEM algorithm on a 4D volume with three frames (3 x 600 s). A 6-minute transmission scan was conducted with a rotating ^137Cs point source at the end of each acquisition for attenuation correction purposes. All images were subsequently corrected for dead time, decay, and random and scattered coincidences. A head holder was used to reduce head motion during the scan time. In addition, possible movements during the scanning procedure were corrected using a coregistration-based method that performs frame realignment and compensates for emission–transmission mismatches.

Image analysis was performed using our in-house image processing pipeline. PET images were automatically registered to their corresponding T1-weighted image space, and the T1-weighted images were linearly and non-linearly registered to the ADNI template space. Subsequently, a PET non-linear registration was performed using the linear and non-linear transformations from each T1-weighted image to the ADNI space and the PET to T1-weighted image registration. The PET images were spatially smoothed to achieve a final resolution of 8 mm FWHM. [18F]MK6240 standardized uptake value ratio (SUVR) maps were generated using the inferior cerebellar GM as a reference region and [18F]AZD4694 SUVR maps were generated using the cerebellar GM as a reference region. A global SUVR was estimated for each participant by averaging the SUVRs from the precuneus, prefrontal, orbitofrontal, parietal, temporal, anterior, and posterior cingulate cortices. Amyloid positivity was assessed by visual inspection of the [18F]AZD4694 PET scan.

2.8 Statistical analyses

Descriptive statistics of baseline demographics and scores of the MBI-C for the sample were summarized using the R Statistical Software Package (www.r-project.org/). We performed several correlation and regression analyses to explore the association between total score on the MBI-C and AD biomarkers, specifically brain β-amyloid and tau burden as determined by [18F]AZD4694 and [18F]MK6240 PET, respectively, and GM volume as measured by VBM. Scores on the MBI-C were treated in all following analyses as continuous variables. First, Pearson correlation analyses were performed between total score on the MBI-C and both global and striatal [18F]AZD4694 SUVRs using the R Statistical Software Package. Pearson correlation analyses were similarly performed between the total MBI-C score and global [18F]MK6240 SUVR, as well as [18F]MK6240 SUVR corresponding to stages 1 and 2 of the Braak staging scheme of tau protein distribution. Then, voxel-based analyses of neuroimaging data were carried out using the VoxelStats toolbox (github.com/sulantha2006/VoxelStats), a MATLAB-based analytical framework that allows for the execution of voxel-wise multimodal neuroimaging analyses. We employed voxel-based linear regression models to evaluate the interaction between the total MBI-C score and β-amyloid and tau deposition in the CN sample. Voxel-based linear regression models were also used to evaluate the associations between total score on the MBI-C and regional GM volume. Age, sex, years of education, and APOE ε4 status were used as covariates in all voxel-based regression analyses. Random field theory with a cluster threshold of P < 0.001 was used to correct all voxel-based regression analyses for multiple comparisons.

3 RESULTS

3.1 Baseline demographic characteristics

Baseline demographics are summarized in Table 1. A total of 96 CN individuals were included in the present study. Participants were from 57 to 85 years of age.

3.2 Analysis of MBI based on the MBI-C

MBI-C data were collected for all individuals in the sample. A summary of MBI-C data can be found in Table 2. Overall, the total score of the MBI-C were low, with 58 participants (60.4%) scoring 0. The mean score ± SD on the MBI-C was 1.94 ± 4.37. The MBI-C domain with the highest overall score was emotional dysregulation (0.76 ± 1.82), whereas the lowest was for abnormal thoughts and
perception (0.08 ± 0.54). Of the 96 participants, seven (7.29%) reached the cut-off for a diagnosis of MBI.

### 3.3 | Pearson's correlations

Results from Pearson correlation between the total MBI-C score and global [\(^{18}\text{F}\)]AZD4694 SUVR showed a moderate positive linear relationship (R = 0.27, P < 0.0074; Figure 1A). SUVRs for [\(^{18}\text{F}\)]AZD4694 were also computed only for the striatum, and results from Pearson correlation between total MBI-C scores and striatal [\(^{18}\text{F}\)]AZD4694 SUVR found a slightly stronger positive correlation (R = 0.3, P < 0.0028; Figure 1B). None of the Pearson correlation analyses between total MBI-C score and [\(^{18}\text{F}\)]MK6240 SUVRs for global, Braak stage 1, and Braak stage 2 regions reached significance (Figure 2).

### 3.4 | Voxel-based regression analyses

Voxel-based linear regression investigating the relationship between [\(^{18}\text{F}\)]AZD4694 retention and the total MBI-C score revealed significantly positive associations, with higher MBI-C scores being associated with increased [\(^{18}\text{F}\)]AZD4694 retention in the left frontal cortex, the left posterior cingulate cortex, as well as in subcortical areas including the caudate nucleus and the thalamus (Figure 3). Voxel-based regression analysis between the total MBI-C score and [\(^{18}\text{F}\)]MK6240 retention did not reveal any significant correlations. Furthermore, voxel-based linear regression analysis between the regional GM volume and MBI-C score did not show significant correlation in any brain region.

### 4 | DISCUSSION

We performed an exploratory study of the associations between MBI and AD pathology in the context of the A/T/N scheme for AD biomarkers in cognitively unimpaired individuals. With regards to the \(\beta\)-amyloid biomarker category, we found that higher MBI-C scores predicted higher \(\beta\)-amyloid PET uptake in the left frontal cortex, left posterior cingulate cortex, left caudate nucleus, and left thalamus. This
**FIGURE 2** Pearson correlations between [18F]MK6240 SUVR and total MBI-C score. Scatter plots representing total MBI-C scores and global (A), Braak stage 1 (B), and Braak stage 2 (C) [18F]MK6240 SUVR values with results of Pearson correlations in CN individuals (n = 96).

**FIGURE 3** Voxel-based regression analyses between [18F]AZD4694 retention and total MBI-C score. Images of voxel-based statistical parametric maps (left-to-right: horizontal, left medial, coronal) overlaid on a template structural MRI scan show significant correlation between mild behavioral impairment checklist (MBI-C) total score and [18F]AZD4694 retention. Voxel-based analyses were corrected for age, gender, education, and APOE ε4 status, and were corrected for multiple comparisons using random field theory at P < 0.001.

suggests a link between MBI and increased amyloid pathology, representing preclinical AD in the A/T/N framework. The areas in which we found the strongest associations between elevated MBI-C scores and β-amyloid PET uptake correspond to regions that are known to exhibit amyloidosis in the first phases of hierarchical amyloidosis in AD, specifically the neocortex, including frontal neocortex, followed by the striatum. This further strengthens the hypothesis of a link between MBI and early AD-related pathological changes. Our findings extend previous research demonstrating that certain NPS such as anxiety are associated with subcortical amyloidosis, as well as previous reports on the associations between NPS such as apathy and anxiety and β-amyloid deposition in the frontal and cingulate...
Our results are further supported by reports linking NPS with neurobiological correlates in frontal-subcortical circuits in AD.\textsuperscript{25} Investigation of the association between MBI-C score and the tau biomarker category, specifically [\(^{18}\text{F}\)]MK6240 uptake, led to no significant associations in global or voxel-wise analyses. We, therefore, suggest that in cognitively normal elderly individuals, MBI is not associated with increased amounts of tau PET uptake, a reliable marker of tau pathology in AD. This result is not unexpected, as significant tau aggregation is rarely observed in cognitively unimpaired individuals. Indeed, this serves to strengthen our original hypothesis by demonstrating that MBI is associated with early and not with later-stage AD pathophysiology. With regard to the neurodegeneration biomarker category, in this case, regional GM volume, we show that VBM analysis of MRI data indicated no significant correlations between GM volume and MBI-C score. Although previous research reveals many associations between NPS and GM atrophy in AD populations,\textsuperscript{36–38} our result is expected for our cognitively normal population, given the lack of association between MBI and tau burden, and the temporal ordering of AD-related pathologies.\textsuperscript{23}

To our knowledge, our study is the first to assess the association between imaging markers of AD and MBI using an appropriate case ascertainment instrument, the MBI-C. We present in vivo evidence that MBI is linked to early AD pathology, specifically \(\beta\)-amyloid pathology, in pre-clinical AD populations. Together, our results suggest that MBI, as measured by the MBI-C, may be used as an indicator of the preclinical stages of dementia and as a non-cognitive marker of neurodegenerative disease, further validating the research or clinical use of this diagnostic entity. Our results are concordant with those of previous studies associating MBI with incident cognitive decline and increased risk for progressing to dementia.\textsuperscript{39,40} Our suggestion that the MBI-C detects preclinical AD pathophysiology in advance of cognitive decline provides compelling evidence for clinicians and researchers to use the MBI-C as a screening tool for the enrichment of disease-modifying clinical trial cohorts, allowing for less expensive, more targeted case detection, and potentially addressing the poor recruitment and retention of early phase illness that has contributed to clinical trial failures. Furthermore, preliminary and simpler detection of preclinical AD may allow for earlier intervention with agents that either reduce amyloid, prevent tau hyperphosphorylation, or modify the amyloid-mediated generation of tangles.

The present study has methodological limitations that must be acknowledged. To begin with, MBI-C scores were obtained through the independent completion of the MBI-C by the study participant’s informant, following given instructions. As a result, there is likely considerable variability in the reporting and scoring of behavioral symptoms, with certain persons considering some behavioral symptoms to be normal and not worthy of being reported, whereas others rating a behavioral symptom as much more severe than others. This is further influenced by who the participant’s informant is (i.e., their spouse, friend, child, neighbor, and so on) as well as how much time they spend with the participant, ultimately affecting their ability to determine if a certain behavior in the participant was sustained or intermittent for a period of at least 6 months. This is a further source of variation in our primary MBI measure, the MBI-C score, and affects our results. The MBI-C has since been validated for self-report,\textsuperscript{41} and further iterations of this study can include MBI-C self-report to determine validity versus the traditional informant-based NPS approach. Another limitation to our study is the lack of longitudinal data for both the MBI-C and for PET acquisitions. Further investigation of MBI should incorporate longitudinal data in order to determine the ability of the MBI-C to predict changes in AD pathophysiology, and outcomes from this study would prove valuable in cementing the MBI syndrome as a prodromal stage of AD dementia as well as encourage its use in clinical settings and in treatment research. In addition, the sample size utilized in this analysis might have contributed to the negligible association between MBI-C score and tau burden. Finally, as we concentrated on evaluating markers for AD only, we have no way of estimating the specificity of this test for AD detection when other neurodegenerative conditions might be present.

In conclusion, our study supports the conceptual framework in which MBI, measured by the MBI-C, constitutes an early clinical manifestation of AD pathophysiology, before cognitive decline is detected. This study contributes to establishing MBI as a preclinical stage of dementia in some and may contribute to an expanded use of MBI-C as a tool for disease-modifying intervention clinical trials in the recruitment phase of preclinical AD populations.

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CONFLICT OF INTEREST

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