ARIC Manuscript Proposal #4098

PC Reviewed: 8/9/22	**Status: _____**	**Priority: 2**
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1.a. Full Title: Associations of Mild Behavioral Impairment (MBI) Domains with Brain Volumetrics in Older Adults

b. Abbreviated Title (Length 26 characters): Neural Correlates of MBI Domains

2. Writing Group: Writing group members:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **_LY_ [please confirm with your initials electronically or in writing]**

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3. Timeline:

Data are currently available. We anticipate that analyses will be performed within 6-12 months of manuscript proposal approval with a goal of submitting an abstract to a conference within this time period. We anticipate submitting the manuscript for publication within 1-2 years of manuscript proposal approval.

4. Rationale:

Neuropsychiatric symptoms (NPS) are core, diagnostically important features of dementia. Examples of NPS include non-cognitive changes in mood, personality, and behavior.[1] Patients with NPS are at higher risk of functional impairment, progressive cognitive decline in multiple domains, institutionalization, and mortality.[2,3] Recent efforts have focused on capturing early NPS manifestations in predementia phases, occurring in patients with mild cognitive impairment (MCI) and in patients with normal cognition before the onset of MCI.[4]

Mild behavioral impairment (MBI) is a syndrome operationalized explicitly to assist in the detection of early-phase neurodegenerative disease, using NPS as the proxy risk markers.[5] However, MBI criteria stipulate that NPS must emerge *de novo* in later life and persist for at least six months to qualify, in order to increase the likelihood that symptoms represent neurodegenerative disease changes rather than life stressors or chronic and recurring psychiatric syndromes. MBI can emerge at any of the pre-dementia stages of the cognitive spectrum (i.e., normal cognition, subjective cognitive decline [SCD], MCI) and the presence of MBI is associated with a greater risk of incident cognitive decline and dementia. Risk is determined based on cognitive status (normal cognition, SCD, MCI) in conjunction with MBI status (MBI+/-).[6] MBI is comprised of five domains: decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception/thought content. Two measures are used to capture MBI symptoms: 1) MBI checklist (MBI-C) (captures symptoms over a >6-month period)[5] and 2) NPI Questionnaire (NPI-Q) (captures symptoms over a 1-month period).[7,8] The MBI-C has 34 items with a cutoff score (6.5 in MCI, 8.5 in SCD) to differentiate MBI from normal.[9] A higher score on either measure represents greater severity and symptomatology. Although the MBI-C was developed explicitly to measure MBI, it is relatively new, whereas the NPI-Q is established and available within many large datasets. Each of the five MBI domains is linked to at least one specific neuropsychiatric symptom from the NPI-Q; thus, MBI global and domain status can be approximated from the NPI-Q.[10]

MBI is associated with significant global brain atrophy; however, specific neural correlates of domain-specific impairment are less clear.[11–13] **Moreover, domain-specific associations with gray matter (GM) volumetrics have not been well studied in dementia-free individuals, particularly using advanced imaging techniques.** The decreased motivation domain has been linked to reduced hippocampal volume.[11] The affective dysregulation score has only been correlated with the left posterior parietal cortex and right middle frontal gyrus in functional connectivity studies, but not volumetric studies.[14] The impulse dyscontrol domain has been linked to reduced volume in specific temporal and frontal gray matter structures, including the left frontal cortex, right thalamus, parahippocampal gyrus, entorhinal cortex (ERC), and hippocampus.[11,12] No neural correlates have been confirmed for social inappropriateness or abnormal perception/thought content in an MBI context. However, in a traumatic brain injury (TBI) population, inappropriate environmentally-elicited behavioral responses were found to be positively correlated with the cerebellum, orbitofrontal cortex (OFC), and prefrontal cortex (PFC), thus implicating pathological pathways in the limbic and frontal lobes.[15]

Several hospital-based and memory cohort MRI-imaging studies have been performed on individuals with MBI, with sample sizes ≤800 participants.[16] Only two studies have incorporated voxel-based morphometry (VBM), with conflicting results. While a community-based study indicated no significant correlation between GM volume and MBI-C score (Alzheimer's Disease Research Unit, Montreal),[17] an in-patient neurology cohort reported atrophy in the left postcentral gyrus, right exterior cerebellum, and left superior frontal gyrus, neither examined domain-specific associations of GM volume.[12]

This proposal aims to investigate the cross-sectional associations of global and domain specific MBI positivity with brain GM volume within individuals without dementia in the ARIC cohort. We will examine these associations using both GM volume regions of interest (ROI) and voxel-based morphometry (VBM)) methods. In secondary analyses, we will also consider cortical thickness ROIs.

5. Main Hypothesis/Study Questions:

Aim: To examine the cross-sectional associations of GM volumetrics (ROI- and VBM-based) and cortical thickness ROIs with global and domain-specific MBI positivity in dementia-free participants.

Hypothesis: We hypothesize that global and domain-specific MBI positivity will be associated with lower GM volumes and cortical thickness in *a priori*-selected brain ROIs. Specifically, we hypothesize that the presence of:

(1) Global MBI positivity will be associated with reduced GM volume in the ERC, hippocampus, left postcentral gyrus, left superior frontal gyrus, and left middle frontal gyrus;
(2) Decreased motivation will be associated with decreased GM volume in the right middle temporal gyrus, hippocampus, ventral pallidum, anterior cingulate cortex, and right ventromedial superior frontal gyrus;
(3) Affective dysregulation will be associated with decreased GM volume in the ERC, inferior temporal lobe, amygdala, precentral gyrus, and supplemental motor area (SMA);
(4) Impulse dyscontrol will be associated with reduced GM volume in the parahippocampal gyrus, ERC, hippocampus, dorsolateral prefrontal cortex, and left SMA;
(5) Social inappropriateness will be associated with reduced GM volume in the anterior temporal lobe, left amygdala, right subgenual cingulate gyrus, ventromedial prefrontal cortex, and orbitofrontal cortex (OFC);
(6) Abnormal perception or thought content will be associated with decreased GM volume in the parahippocampal gyrus, dorsolateral parietal cortex, superior temporal gyrus, dorsolateral prefrontal cortex, and OFC.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design:

Cross-sectional (ARIC Visit #5, 2011-2013) study to examine the association between mild behavioral impairment and brain MRI volumetrics.

Inclusion/Exclusion Criteria:

- Inclusions: All ARIC Visit #5 participants without dementia with complete NPI-Q and brain MRI volumetric data.
- Exclusions:
    - Participants with races other than black or white, black participants from the Washington County, Maryland or Minneapolis, Minnesota field centers.
        - Reasoning: The Maryland and Minnesota sites recruited nearly all white participants, the Mississippi site recruited nearly all black participants, and the North Carolina site recruited both races. In adjusted analyses, we plan to create a combined race center variable:
            - MN whites
            - MD whites
            - NC whites
            - NC blacks
            - MS blacks
        - The small number of Indian or Asian race participants will be excluded from analyses.
    - Participants missing data on cognitive status or covariate data.
        - In sensitivity analyses, we will include participants with a diagnosis of dementia at the time of ARIC Visit 5. We will also look stratified by cognitive status (normal; MCI).

Exposure: Mild Behavioral Impairment

NPI-Q symptoms will be mapped to subdomains consistent with MBI subdomains operationalized by the International Society to Advance Alzheimer's Research and Treatment-Alzheimer's Association (ISTAART-AA) research diagnostic criteria (see below).[5,6]

TABLE 1. NPI Domain to MBI Domain Mapping

ISTAART MBI Domains					
	Decreased Motivation	**Affective Dysregulation**	**Impulse Dyscontrol**	**Social Inappropriateness**	**Abnormal Perception or Through Content**
NPI Domains	G. Apathy/Indifference	D. Depression/Dysphoria	C. Agitation/Aggression	H. Disinhibition	A. Delusions
		E. Anxiety	I. Irritability/Lability		B. Hallucinations
		F. Elation/Euphoria	J. Aberrant Motor Behavior		

An MBI domain is considered present if at least one of the constituent NPI domains is endorsed (binary variable). Global MBI positivity is defined as any one or more domains is present. In sensitivity analyses, we will define global MBI positivity as any two or more domains present.

Outcome: Brain MRI:

A subsample of participants who attended visit #5 (2011-2013) was selected for brain MRI scans. Briefly, ARIC study selection criteria for a visit #5 brain MRI scan included: 1) absence of MRI contraindications, 2) prior participation in the ARIC Brain MRI Ancillary Study,[18] 3) all participants with evidence of cognitive impairment at visit #5 (low Mini-Mental State Exam [MMSE] score [<21 for whites and <19 for blacks] *or* low visit #5 domain z-scores on 2 or more cognitive domains [< -1.5 SD] *and* cognitive decline on the Delayed Word Recall Test, the Digit Symbol Substitution Test, or the Word Fluency Test [defined as visit #5 score minus highest

previous score <20th percentile on 1 or more tests or <10th percentile on 2 or more tests]), and 4) a random sample of participants without evidence of cognitive impairment at visit #5.

The ARIC visit #5 brain MRI scans (2011-2013) were performed using 3-Tesla scanners (Maryland: Siemens Verio [vb17 software]; North Carolina: Siemens Skyra [D11 software]; Minnesota: Siemens Trio [vb17 software]; Mississippi: Siemens Skyra [D13 software]. Brain volume was measured from MP-RAGE sequences (Statistical Parametric Mapping [https://www.fil.ion.ucl.ac.uk/spm/] image analysis software).

Our analyses will use the following brain volumes as outcomes. We hypothesize *a priori* that GM volumes will be associated with MBI groups in regions of interest known to be associated with endorsement of their respective domains or global MBI positivity (see table).

Domain	Non-frontal Brain Regions	Frontal Brain Regions
MBI Global	Entorhinal cortex Hippocampus Left postcentral gyrus	Left superior frontal gyrus Left middle frontal gyrus
MBI Decreased motivation	Right middle temporal gyrus Hippocampus Ventral pallidum	Anterior cingulate cortex Right ventromedial superior frontal gyrus
MBI Affective dysregulation	Entorhinal cortex Inferior temporal lobe Amygdala	Precentral gyrus Supplementary motor area
MBI Impulse dyscontrol	Parahippocampal gyrus Entorhinal cortex Hippocampus	Dorsolateral prefrontal cortex Left supplementary motor area
MBI Social inappropriateness	Anterior temporal lobe Left amygdala Right subgenual cingulate gyrus	Ventromedial prefrontal cortex Orbitofrontal cortex
MBI Abnormal perception/thought content	Parahippocampal gyrus Dorsolateral parietal cortex Superior temporal gyrus	Dorsolateral prefrontal cortex Orbitofrontal cortex

Covariates:

All covariates will be measured at visit 5, except sex, race, education and APOE ε4 genotype, which were measured at visit 1. The following covariates (assessed at ARIC visit #5 unless otherwise specified) will be included in statistical models:

- **Age** (years; continuous);
- **Sex** (male; female);
- **Race/center** (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks);
- **Education** (assessed at ARIC visit 1, <high school; high school, GED, vocational school; college, graduate, or professional school);
- **Physical activity** (assessed at ARIC visit 1, ordinal scale);

- **Hypertension** (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or medication use);
- **Diabetes** (self-report physician diagnosis, medication use, fasting glucose ≥126 mg/dl, or HbA1c ≥6.5%);
- **Alcohol use** (never; former; current);
- **Stroke up to start of visit 5** (adjudicated event);
- **Smoking status** (never; former; current);
- **Apolipoprotein ε4 (APOE ε4) genotype** (0; 1 or 2 ε4 alleles);
- **Cognitive status** (normal; MCI).

Potential Effect Modifiers:

We will formally test for interaction by age, sex, race, cognitive status, and APOE ε4 genotype. We will perform stratified analysis if we observe evidence for effect modification.

Data Analyses:

All analyses with brain MRI outcomes will incorporate sampling weights (derived by the ARIC coordinating center) to account for the visit #5 brain MRI selection process that was designed to oversample cognitively impaired individuals (see above).

We will use adjusted linear regression models to assess the association of MBI groups with brain volume ROIs. The distributions of these volumes may be non-normal, so we will explore and transform distributions of these data as appropriate. We will also consider adjustment for multiple comparisons as although our ROIs were selected *a priori* based on a literature review, we are still proposing many different comparisons. In secondary analyses, we will also consider cortical thickness ROIs.

We will perform two statistical models:

- Model 1: adjusted for demographic variables: age, sex, race/field center, and education.
- Model 2: adjusted for Model 1 + physical activity, hypertension, diabetes, alcohol use, cognitive status, stroke, smoking status, and APOE ε4 genotype.

For the VBM analysis, each participant's T1-weighted MRI scan will be segmented into GM, white matter, and CSF probability map images using SPM12 unified segmentation with the Mayo Clinic Adult Lifespan Template (MCALT; nitrc.org/projects/mcalt/) tissue priors and population-optimized segmentation settings.[19] We will spatially normalize, modulate, and smooth GM images, then use them in a general linear model framework to estimate models of associations between the MBI groups and GM volume on a voxel-wise basis with FDR correction for multiple comparisons. The models will be adjusted for age, sex, race/center, and education (Model 1 above). Six VBM maps will be created using the following pair-wise comparisons: +/- positivity in each of the 5 domains (decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception/thought content) and +/- global MBI positivity.

Limitations:

This study has certain limitations. First, the proposed design is cross-sectional and thus, does not provide information on the changes in MBI or GM volumes over time. However, the distinction of cognition domain groups takes into consideration individuals' 20-year prior trajectory of changes in cognitive function. Second is the use of the transformed NPI-Q to

approximate MBI. MBI prevalence may be inflated due to the NPI-Q evaluating symptoms within a 1-month range, limiting diagnostic specificity. However, the transformed NPI-Q for MBI case detection has been validated.[8] Additionally, as with any observational study, we will not be able to rule out the possibility of residual confounding in our analyses. Third, it is possible that the low number of participants endorsing social inappropriateness and abnormal thoughts and perceptions will limit our ability to analyze associations with these domains.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _X_ Yes ___ No
(APOE ε4 genotype)

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _X_ Yes ___ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the website at: **_X_ Yes ___ No**

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

#2288: Associations of Brain Imaging with Cognitive Change over 20 Years (David Knopman)
#3978: Associations between Head Injury and Mild Behavioral Impairment (MBI) Domains
#2586: Neural Correlates of Prior Domain-specific Cognitive Decline: A Voxel-based Morphometry Study (Andrea Schneider)
#3423: Neural Correlates of Anosmia Among Persons With and Without Mild Cognitive Impairment: A voxel-based Morphometry (VBM) Study (Vidya Kamath; Andrea Schneider)
#3527: Hearing & Neuropsychiatric Symptoms among Older Adults with Cognitive Impairment (Carrie Nieman; Jennifer Deal)
#3830: Association of Midlife Vascular Risk Factors with Late Life Neuropsychiatric Symptoms (Carla Rodriguez; Keenan Walker)
Across the Cognitive Spectrum (Nicholas Daneshvari)
#3916: Associations of Head Injury with Neuropsychiatric Symptoms (NPS) and Mild Behavioral Impairment (MBI) Domains (Lisa Richey)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes ___ No

11.b. If yes, is the proposal
_X_ A. primarily the result of an ancillary study (list number* 2009.29)

___ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*** _____ _____ _____**)**

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

Understood.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

Understood.

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