ARIC Manuscript Proposal #3916

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1.a. Full Title: Associations of Head Injury with Neuropsychiatric Symptoms (NPS) and Mild Behavioral Impairment (MBI) Domains

b. Abbreviated Title (Length 26 characters): Head Injury and NPS / MBI Domains

2. Writing Group:
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Others Welcome

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

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3. Timeline:
Data for analyses are currently available. Data analysis, conference abstract submission, and manuscript preparation and submission will take place over one year from manuscript proposal acceptance (2021-2022).

4. Rationale:

Research in patients with acute/subacute TBI has demonstrated that changes in emotional regulation and behavior represent relatively common sequelae of recent injury, especially among younger individuals. The frontal regions, in which neural network disruption is frequently observed following TBI, have been well established as mediators of emotional and behavioral processes [1]. Three key frontal neural circuits that have been shown to be affected in TBI patients with emotional regulation/behavioral sequelae are the dorsolateral prefrontal, the orbitomedial frontal, and the anterior cingulate [2]. The dorsolateral prefrontal circuit is responsible for modulating cognitive processes including working memory and executive functions and, when damaged, patients may experience a dysexecutive syndrome, presenting as trouble with shifting attention, organizing, and retrieving information, and problem-solving [2]. The orbitomedial frontal circuit helps guide social behaviors and allows for the ability to self-correct in appropriate social context; damage results in disinhibition, leading to socially inappropriate behavior, impulsivity, and poor social tact [2]. The anterior cingulate circuit is responsible for motivation and reward-related behaviors and, when damaged, leads to apathy with restricted emotional responses and difficulty initiating behaviors [2]. Additionally, emerging evidence suggests that hippocampal atrophy secondary to TBI may result in dysregulation of downstream dopaminergic networks increasing risk of hallucinations and delusions [3]. Damage to one or more of these neural circuits may contribute to the neuropsychiatric symptom (NPS) phenotypes observed among those with TBI. Much of the existing work on post-TBI neuropsychiatric symptoms has been done in younger patients with acute/subacute TBI; **it remains less clear how remote TBI is associated with NPS phenotypes in older adults**.

The construct of mild behavioral impairment (MBI) may prove particularly useful in relating NPS that share underlying neural circuit disruption. MBI refers to the onset of persistent NPS emerging later in life that are not better explained by a common psychiatric disorder such as major depression, in the absence of dementia [4]. The MBI construct and associated diagnostic criteria were first addressed by the International Society to Advance Alzheimer's Research and Treatment in 2012, with the intent of more clearly defining the relationships among MBI, mild cognitive impairment (MCI), and subsequent dementia [4]. The culmination of these efforts in 2016 led to diagnostic criteria and division into five domains. The MBI checklist has been developed as a means of defining and quantifying MBI symptoms and improving case detection [5]. The five MBI domains include decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception/thought content [5]. Each domain is associated with specific NPS. For example, agitation, irritability, and aberrant motor behavior fall under the impulse dyscontrol MBI domain. **Although a construct originally developed for classification of neuropsychiatric symptomatology in those that go on to develop dementia, given that the MBI domains link individual NPS to underlying neural circuit disruption, we believe these same domains have utility when looking at NPS following TBI more broadly.** For example, TBI may affect certain MBI domains more than others. Damage to the orbitomedial frontal circuit may lead to MBI characterized by social inappropriateness and

impulse dyscontrol. Damage to the anterior cingulate circuit may result in MBI with decreased motivation. By contrast, damage to the dorsolateral prefrontal circuit may result in more cognitive symptoms and fewer behavioral ones.

Much of Dr. Peters' previous work has focused on the presence of NPS and MBI domains in those with a history of TBI who go on to develop all-cause dementia. A growing body of literature suggests that TBI may contribute to neuropathological changes consistent with dementia syndromes such as Alzheimer's disease (AD), frontotemporal dementia, Parkinson's disease, among others [6–8]. TBI may exert detrimental effects regardless of age, though it appears that TBI suffered during older adulthood may confer greater dementia risk [9]. Using National Alzheimer's Coordinating Center data (NACC), Dr. Peters' group found that individuals with a history of TBI that progressed to all-cause dementia had increased prevalence and incidence of apathy and motor disturbances, controlling for demographics and type of dementia diagnosis [10]. Earlier anxiety onset was also associated with TBI [9]. Another manuscript from Dr. Peters' group, currently under review and again using NACC data, found TBI to be associated with greater incidence of the impaired impulse dyscontrol and social inappropriateness MBI domains prior to dementia onset, as well as greater incidence of MBI (any domain) and the decreased motivation domain looking across disease progression.

To expand on this previous work, we propose to first examine NPS and MBI domains by head injury status within the ARIC cohort regardless of cognitive status to investigate associations of remote head injury with NPS and MBI domains. A second manuscript proposal will be submitted specifically to look at NPS and MBI domains by head injury status incorporating risk of subsequent dementia.

5. Main Hypothesis/Study Questions:

1. To investigate the association of prior head injury with NPS, regardless of cognitive status.
    a. We hypothesize that prior TBI history will be associated with certain NPS, including apathy, disinhibition, and depression.
2. To utilize MBI domains to examine the association of prior TBI history with NPS presence, regardless of cognitive status.
    a. We hypothesize that prior TBI history will be associated with certain MBI domains, including decreased motivation, affective dysregulation, impulse dyscontrol, and social inappropriateness.

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: Head injury occurring prior to ARIC visit 5 and NPS/MBI domains measured at ARIC visit 5. We will also consider incorporation of longitudinal analyses from visit 5 to visit 7 (head injury occurring prior to ARIC visit 5 and change in NPS/MBI domains over time) if sample size allows.

Inclusion/Exclusion. We will include white and black participants (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks) with non-missing data on head injury (defined below) whose informants completed the Neuropsychiatric Inventory

Questionnaire (NPI-Q) in Stage 2 at ARIC Visit 5. We will exclude participants with missing cognitive status or covariate data. In sensitivity analyses, we will exclude participants with a diagnosis of dementia at the time of ARIC Visit 5. We will also look stratified by cognitive status (normal; MCI; dementia).

Exposure. *Head Injury Occurring Prior to ARIC Visit 5*. Head Injury will be defined using a combination of self-reported data (from Visits 3, 4, 5, and the brain MRI visit) and ICD-9/10 code data from hospitalizations (ARIC hospitalization surveillance; Centers for Medicare and Medicaid Services [CMS] Fee-for-Service [FFS] data hospitalization and emergency department visits). As secondary exposures, we will also look at number of prior head injuries (0; 1; 2+) and in the subset identified using ICD-9/10 code data, we will look by head injury severity (mild; moderate/severe). These definitions have been used previously in the ARIC cohort (see below for self-reported questions and ICD-9/10 codes) [15-16]. At the time of ARIC Visit 5, approximately 25% of participants have a history of prior head injury.

Self-reported head injury questions.

ARIC Visit 3 (1993-1995) 1. Have you ever had a head injury which led you to see a physician or seek hospital care? 2. How many times has this happened? 3. How many of these head injuries resulted in your losing consciousness, no matter how briefly? 4.In what year was your head injury for which you sought medical care?
ARIC Visit 4 (1996-1998) 1. Have you ever had a major head injury? That is, one that resulted in your losing consciousness, no matter how briefly, or that led you to see a physician or seek hospital care? 2. How many times has this happened? 3. How many head injuries resulted in your losing consciousness, no matter how briefly? 4. In what year was your head injury for which you lost consciousness sought medical care?
ARIC Brain MRI Visit (2004-2006)* 1. Have you ever had a head injury that resulted in loss of consciousness (knocked out)? 2. How many times? 3. In what year or how old were you when this first occurred? 4. In what year or how old were you when this last occurred?
ARIC Visit 5 (2011-2013)* 1. Have you ever had a head injury that resulted in loss of consciousness? 2. Have you had a head injury with extended loss of consciousness (>5 minutes)? 3. Have you had a head injury that resulted in long-term problems or dysfunction?

*Questions asked in a subgroup of ARIC participants selected for brain magnetic resonance imaging (MRI) scans.

ICD-9 and ICD-10 codes used to define head injury.

ICD-9 Codes	
800.xx	Fracture of vault of skull
801.xx	Fracture of base of skull
803.xx	Other and unqualified skull fractures
804.xx	Multiple fractures involving skull or face with other bones

850.xx	Concussion
851.xx	Cerebral laceration and contusion
852.xx	Subarachnoid, subdural, and extradural hemorrhage following injury
853.xx	Other and unspecified intracranial hemorrhage following injury
854.xx	Intracranial injury of other and unspecified nature
959.01	Head injury, unspecified
ICD-10 Codes	
S02.0	Fracture of vault of skull
S02.1X	Fracture of base of skull
S02.8	Fractures of other unspecified skull and facial bones
S02.91	Unspecified fracture of skull
S04.02	Injury of optic chiasm
S04.03X	Injury of optic tract and pathways
S04.04X	Injury of visual cortex
S06.X	Intracranial injuries, concussion, traumatic cerebral edema, diffuse and focal traumatic brain injury, traumatic epidural, subdural, and subarachnoid hemorrhage
S07.1	Crushing injury of skull

Outcomes.

Neuropsychiatric Symptoms. Late-life psychiatric and behavioral changes were measured using the Neuropsychiatric Inventory Questionnaire (NPI-Q). The NPI-Q was obtained via informant report from participants who were selected for Stage 2 Assessment at ARIC Visit 5. The NPI-Q measures the presence and severity of depression, apathy, agitation, delusion, hallucination, anxiety, euphoria, disinhibition, irritability, aberrant motor behavior, sleep, and eating/appetite. NPS presence will be a binary variable (no symptom [0] versus yes symptom [1-3]), however, we will also look at the severity of each NPI-Q symptom (rated on scale of 0 to 3) and total NPI-Q symptom severity range (0-36).

Mild Behavioral Impairment. NPI-Q symptoms will also 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) [4-5].

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 NPI domains is positive (binary variable). For example, presence of depression/dysphoria would map to presence of the MBI domain of affective dysregulation regardless of anxiety and elation/euphoria NPI domain.

Covariates. Covariates included in statistical models will include: age, sex, race/field center (MN whites; MD whites; NC whites; NC blacks; MS blacks), education (<high school; high school, GED, vocational school; college, graduate, or professional school), alcohol use (never; former; current), apolipoprotein ε4 (APOE ε4) genotype (0 ε4 alleles; 1 or 2 ε4 alleles, and cognitive status (normal; MCI; dementia). We will also consider adjustment for global cognitive function (MMSE or global cognitive factor variable). All covariates will be measured at visit 5, except education and APOE ε4 genotype, which were measured at visit 1).

Statistical Analyses. Threshold for statistical significance for all tests will be set *a priori* as α=0.05. Baseline characteristics will be presented overall and stratified by head injury status. Differences between head injury groups will be assessed using Welch's T-tests (for continuous variables) and Chi-square tests with Yates' continuity correction applied (for categorical variables). Associations between head injury (and in sensitivity analyses, head injury frequency and head injury severity) and presence of each of the NPS and MBI domains will be assessed using logistic regression. Associations of head injury with NPI symptom severity (0-3 range for each symptom and 0-36 range divided into quartiles for overall) will be assessed using ordinal/multinomial logistic regression models. All statistical models will be adjusted for covariates described above. In supplemental analyses, we will stratify our population by cognitive status (normal; MCI; dementia) and will also perform analyses excluding participants with a diagnosis of dementia at ARIC Visit 5. If sample size allows, we will look at associations of head injury with worsening of NPS over time (from visit 5 to 7) using logistic regression models (worse NPS versus stable/improved NPS). We will formally look for interaction effects of age and sex.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No

(The 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 current derived consent file ICTDER05 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 web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

_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)?

#2768: The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study (Andrea Schneider)
#3668: The Risk of Post-traumatic Epilepsy in the ARIC Study (Andrea Schneider)
#2767: The Association of Head Injury with Brain MR and Brain PET Amyloid Imaging in the ARIC Study (Andrea Schneider)
#2769: The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality in the ARIC Study (Andrea Schneider)
#3830: Association of Midlife Vascular Risk Factors with Late Life Neuropsychiatric Symptoms (Carla Rodriguez; Keenan Walker)
#3527: Hearing & Neuropsychiatric Symptoms among Older Adults with Cognitive Impairment (Carrie Nieman; Jennifer Deal)

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

___ A. primarily the result of an ancillary study
_X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* Brain MRI Study 1999.01)

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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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