Neurobiology of Aging xxx (2015) 1–8

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Stroke risk interacts with Alzheimer's disease biomarkers on brain aging outcomes

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ARTICLE INFO

Article history:
Received 19 March 2015
Received in revised form 28 May 2015
Accepted 30 May 2015

Keywords:
Stroke risk
Alzheimer's disease
Biomarkers
Cognition
Hippocampus
Cerebrovascular disease
Aging

ABSTRACT

Alzheimer's disease (AD) biomarkers and stroke risk factors independently predict cognitive impairment, likely through independent disease pathways. However, limited work has sought to describe the dynamic interplay between these important risk factors. This article evaluated the interaction between stroke risk and AD biomarkers on hippocampal volume and cognitive performance. We first evaluated the interaction between stroke risk factors and AD biomarkers using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI, n = 1202). We then extended our findings to an independent autopsy data set from the National Alzheimer's Coordinating Center (NACC, n = 1122) using measures of AD pathology. Stroke risk was quantified using the Framingham Stroke Risk Profile. In ADNI, stroke risk interacted with tau and amyloid levels in relation to baseline and longitudinal cognitive performance. Similarly, in NACC, stroke risk interacted with amyloid and tau positivity on cognitive performance. The effect of stroke risk factors on cognition was strongest in the absence of AD biomarkers or neuropathology, providing additional evidence that AD biomarkers and stroke risk factors relate to cognition through independent pathways.

1. Introduction

Stroke risk factors, such as hypertension and cigarette smoking, have been associated with lower neuropsychological performance in elders with normal cognition (NC) and mild cognitive impairment (MCI; Brady et al., 2001) and in relation to incident Alzheimer's disease (AD; Kivipelto et al., 2002). Although much AD work has focused on classifying "pure" AD in the absence of vascular disease (Jack et al., 2010, 2013), the autopsy literature has clearly demonstrated that the most common presentation of AD is a mixed pathology with contributions from amyloid-β (Aβ) plaques, tau neurofibrillary tangles, and cerebrovascular disease (Schneider et al., 2007a; Schneider and Bennett, 2010; Troncoso et al., 2008). The dynamic interplay among AD and cerebrovascular pathologies remains somewhat elusive, but their co-occurrence leaves open the possibility that risk factors for both may interact in conferring risk for neurodegeneration (e.g., hippocampal volume) and cognitive decline (e.g., neuropsychological performance).

Cerebrospinal fluid (CSF) biomarkers of AD include Aβ-42, total tau, and phosphorylated tau levels based on their strong associations with brain volume (de Souza et al., 2012; Fjell et al., 2010) neuropsychological impairment (Buerger et al., 2005; Jagust et al., 2009), and postmortem AD pathology (Buerger et al., 2006). Similarly, stroke risk factors have shown strong associations with brain volume (Seshadri et al., 2004), neuropsychological impairment (Brady et al., 2001; Jefferson et al., 2015; Kivipelto et al., 2002), and cerebrovascular pathology (Wang et al., 2009; Wolf et al., 1991). In mouse models, there has been some evidence that certain stroke

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[1] 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: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

0197-4580/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2015.05.021

risk factors, such as smoking (Moreno-Gonzalez et al., 2013) and hypertension (Diaz-Ruiz et al., 2009; Gentile et al., 2009), actually exacerbate AD pathology. Thus, there may be differing effects of stroke risk factors on neurodegeneration depending on the presence or absence of AD biomarkers. Yet, despite the depth of research investigating AD biomarkers and stroke risk factors independently, less research has focused on evaluating whether these factors interact in relation to brain volume or neuropsychological performance.

The present study examines the interplay between stroke risk factors and CSF biomarkers in relation to cross-sectional and longitudinal measures of brain aging. First, in the Alzheimer's Disease Neuroimaging Initiative (ADNI) data set, we evaluate interactions between stroke risk factors and AD biomarkers in relation to cross-sectional and longitudinal hippocampal volume. Second, we test the same interactions in relation to cross-sectional and longitudinal neuropsychological performance. Finally, we replicate the observed interaction effects on neuropsychological performance in a second, independent cohort using the National Alzheimer's Coordinating Center (NACC) data set. We could not analyze hippocampal volume in NACC because magnetic resonance imaging data were not available for analysis, so replication analyses focus on cognitive performance. Our hypothesis was that the effect of stroke risk factors on brain aging outcomes would depend on AD biomarker levels whereby vascular risk would exacerbate brain aging in the presence of AD biomarkers.

2. Materials and methods

Data used in the preparation of this article were obtained from the ADNI launched in 2003 (adni.loni.usc.edu). The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI-2. To date these 3 protocols have recruited >1500 adults, ages 55–90 years, excluding serious neurological disease other than AD, history of brain lesion or head trauma, and history of psychoactive medication use (for full inclusion and/or exclusion criteria see www.adni-info.org). Informed written consent was obtained from all participants at each site.

The replication sample was drawn from the NACC, which maintains a database of participant information collected from 34 past and present National Institute on Aging-funded Alzheimer's Disease Centers. In 2005, NACC implemented a standard protocol (i.e., Uniform Data Set), including clinical, medical, neurological, and neuropsychological data (Beekly et al., 2004). Analysis of both publically available databases was approved by our local Institutional Review Board.

2.1. Participants

We accessed publicly available data from ADNI on June 1, 2014. Participants were enrolled based on criteria outlined in the ADNI protocol (http://www.adni-info.org/Scientists/AboutADNI.aspx). For the present analyses, we included all participants who had CSF biomarker data, full vascular risk factor data needed to calculate a stroke risk score, and the outcome measure of interest. For the neuroimaging analyses, participants had to have a FreeSurfer measure of hippocampal volume derived from 1.5 T magnetic resonance imaging data, yielding 1082 participants. For cognitive analyses, participants had to have a composite measure of episodic memory and EF, yielding 1202 participants with all measures of interest.

For the replication sample, we used neuropathology data because NACC does not have CSF biomarker data available for analysis. NACC participants between 55 and 90 years of age evaluated between September 1, 2005 and September 29, 2014 with neuropathology, neuropsychological, and stroke risk data were included, yielding 1122 participants.

2.2. Framingham Stroke Risk Profile

To assess systemic vascular health, we calculated Framingham Stroke Risk Profile (FSRP) at baseline in the ADNI data set and at the last visit before death in the NACC data set. FSRP assigns points for age, systolic blood pressure (accounting for antihypertensive treatment), history of diabetes, current cigarette smoking, prevalent cardiovascular disease (i.e., history of myocardial infarction, angina pectoris, coronary insufficiency, intermittent claudication, or heart failure), left ventricular hypertrophy, and history of atrial fibrillation (D'Agostino et al., 1994). In this study, the FSRP calculation is modified because left ventricular hypertrophy information is not available in ADNI or in NACC. FSRP values range from 0 to 44 with higher values indicating more adverse risk of stroke.

2.3. CSF biomarker processing (ADNI) and autopsy measures of neuropathology (NACC)

ADNI's CSF protocol, including the quantification of Aβ-42 and tau, has been outlined in detail elsewhere (Jagust et al., 2009; Shaw et al., 2011). For the present analyses, we compiled a data set across the UPENN1–UPENN5 data sources available for download on the ADNI site and used the first measure of total tau and Aβ-42 available for each subject. Biomarker levels were entered as continuous predictors in statistical models.

In the NACC data set, we used the semiquantitative Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque staging to classify participants as either "amyloid positive" or "amyloid negative". Individuals with no plaques or sparse plaques were considered amyloid negative, and those with moderate or frequent plaques were considered amyloid positive. Similarly, we used the semiquantitative Braak neurofibrillary tangle staging to identify participants as either "tau positive" or "tau negative." Braak stages 0, I, and II were considered "tau negative," and Braak stages III–VI were considered "tau positive."

2.4. Composite neuropsychological measurements

The ADNI neuropsychological protocol has been reported in detail, including calculation of composite measures of episodic memory and EF (Crane et al., 2012; Gibbons et al., 2012). We leveraged both the memory (ADNI-MEM) and the executive function (ADNI-EF) scores in the present analyses. Briefly, a single factor model based on item level data from the Rey Auditory Verbal Learning Test, the AD Assessment Scale-Cognitive Subscale, the Mini-Mental State Examination, and the Logical Memory test were used in the calculation of the ADNI-MEM score. Item level data from the Trail Making Test (A and B), digit span backward, digit symbol, animal naming, vegetable naming, and the clock drawing test were used in the calculation of the ADNI-EF score.

We used a well-validated psychometric approach to cocalibrate memory and executive functioning scores from the ADNI and NACC databases (Crane et al., 2008). Cocalibration refers to combining test scores across studies into a single metric. Briefly, we cocalibrated ADNI-MEM and ADNI-EF scores with NACC item level data to obtain NACC memory (NACC-MEM) and executive function (NACC-EF) scores on the same metric as ADNI using previously published methods (Crane et al., 2008; Mez et al., Under Review). Common memory measures in NACC and ADNI (i.e., Logical Memory Immediate and Delayed Recall) and common EF measures (i.e., digit span backwards, verbal fluency, vegetable fluency, and Trail Making Test parts A and B) served as anchors for cocalibration. We calculated