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PHYSICAL ACTIVITY, INFLAMMATION, AND VOLUME OF THE AGING BRAIN

M. N. BRASKIE,[a] C. P. BOYLE,[a] P. RAJAGOPALAN,[a†] B. A. GUTMAN,[a] A. W. TOGA,[a] C. A. RAJI,[b] R. P. TRACY,[c] L. H. KULLER,[d] J. T. BECKER,[e] O. L. LOPEZ[f] AND P. M. THOMPSON[a,g*]

[a] *Imaging Genetics Center, Institute for Neuroimaging and Informatics, Dept. of Neurology, Keck/USC School of Medicine, University of Southern California, Los Angeles, CA, USA*

[b] *Department of Radiology, University of California Los Angeles School of Medicine, Los Angeles, CA, USA*

[c] *Departments of Pathology, Biochemistry, and Center for Clinical and Translational Science, University of Vermont, Burlington, VT, USA*

[d] *Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA*

[e] *Departments of Neurology, Psychiatry, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA*

[f] *Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA*

[g] *Depts. of Psychiatry, Engineering, Radiology, & Ophthalmology, Keck/USC School of Medicine, University of Southern California, Los Angeles, CA, USA*

Abstract—Physical activity influences inflammation, and both affect brain structure and Alzheimer's disease (AD) risk. We hypothesized that older adults with greater reported physical activity intensity and lower serum levels of the inflammatory marker tumor necrosis factor α (TNFα) would have larger regional brain volumes on subsequent magnetic resonance imaging (MRI) scans. In 43 cognitively intact older adults (79.3 ± 4.8 years) and 39 patients with AD (81.9 ± 5.1 years at the time of MRI) participating in the Cardiovascular Health Study, we examined year-1 reported physical activity intensity, year-5 blood serum TNFα measures, and year-9 volumetric brain MRI scans. We examined how prior physical activity intensity and TNFα related to subsequent total and regional brain volumes. Physical activity intensity was measured using the modified Minnesota Leisure Time Physical Activities questionnaire at year 1 of the study, when all subjects included here were cognitively intact. Stability of measures was established for exercise intensity over 9 years and TNFα over 3 years in a subset of subjects who had these measurements at multiple time points. When considered together, more intense physical activity intensity and lower serum TNFα were both associated with greater total brain volume on follow-up MRI scans. TNFα, but not physical activity, was associated with regional volumes of the inferior parietal lobule, a region previously associated with inflammation in AD patients. Physical activity and TNFα may independently influence brain structure in older adults. © 2014 Published by Elsevier Ltd. on behalf of IBRO.

Key words: tumor necrosis factor (TNFα), exercise, MRI, supramarginal gyrus, inferior parietal lobule, Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (AD), the most common form of dementia, is characterized by the presence of amyloid plaques (composed of amyloid beta; Aβ) and neurofibrillary tangles (composed of hyperphosphorylated tau protein). However, ~37–44% of older adults who are cognitively normal also show significant AD pathology at autopsy (Bennett et al., 2006) or on amyloid imaging (Mielke et al., 2012). This suggests that other factors, such as baseline differences in brain health when pathology develops, may influence whether disease symptoms are manifest (Stern, 2012). Higher levels of physical activity have been associated with a lower risk of developing AD (Luck et al., 2013). The main mechanisms for this reduced risk are unclear. Physical activity may be associated with lower brain amyloid levels in humans (Liang et al., 2010; Head et al., 2012; Brown et al., 2013), contributing to this effect. In transgenic mouse models of AD, exercise has been associated with lower amyloid deposition and better Aβ clearance as well as reductions in tau phosphorylation. In addition to possible effects on AD pathology, physical activity also promotes human brain regeneration, including in the hippocampus (Pajonk et al., 2010; Erickson et al., 2011), cingulate gyrus and prefrontal cortex (Colcombe et al., 2006; Floel et al., 2010) – regions that are vulnerable in AD. This association between physical activity and larger regional brain volumes in older humans (Colcombe et al., 2006; Erickson et al., 2010; Erickson et al., 2011; Benedict et al., 2013; Boyle et al., in press) may help protect active older adults from developing AD symptoms.

*Corresponding author at: Imaging Genetics Center, Institute for Neuroimaging and Informatics, Dept. of Neurology, Keck/USC School of Medicine, University of Southern California, Los Angeles, CA, USA.; Depts. of Psychiatry, Engineering, Radiology, & Ophthalmology, Keck/USC School of Medicine, University of Southern California, Los Angeles, CA, USA. Tel: +1-323-442-7246; fax: +1-323-442-7247.
E-mail address: pthomp@usc.edu (P. M. Thompson).
URL: http://igc.ini.usc.edu (P. M. Thompson).
† Current address: Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA.
Abbreviations: 3MSE, Modified Mini-Mental State Examinations; AD, Alzheimer's disease; *APOE*4, apolipoprotein E allele ε4; BMI, body mass index; CSF, cerebrospinal fluid; IL-6, interleukin 6; MDT, minimal deformation template; MRI, magnetic resonance imaging; TBM, tensor-based morphometry; TNFα, tumor necrosis factor α.

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The effects of physical activity on brain volume may stem from other factors that arise from exercise and are likewise associated with brain integrity. For instance, exercise promotes better sleep (Dzierzewski et al., 2014) and cardiorespiratory fitness (such as the maximum volume of oxygen consumption), both of which are associated with a lower risk of dementia (Defina et al., 2013; Benedict et al., 2014; Di Meco et al., 2014) and with larger regional brain volumes including in frontal and parietal cortices (Altena et al., 2010; Hayes et al., 2013). Exercise also reduces obesity, inflammation, and modulates levels of the stress hormone cortisol (Tsukui et al., 2000; Mastorakos et al., 2005; Cotman et al., 2007; Rasmussen et al., 2011), all of which are implicated in AD (Gustafson et al., 2003; Kivipelto et al., 2005; Razay and Vreugdenhil, 2005; Whitmer et al., 2005; Doorduin et al., 2009; Fitzpatrick et al., 2009; Lee et al., 2010; Xu et al., 2011; Hinterberger et al., 2013; Krstic and Knuesel, 2013) and associated with smaller regional brain volumes (Marsland et al., 2008; Ho et al., 2010a; Ho et al., 2011; Rajagopalan et al., 2012; Kesler et al., 2013) (Fig. 1).

Physical activity reduces pro-inflammatory conditions in the brain (Cotman et al., 2007), which link to poorer cognition in rodents, and less hippocampal gray matter in humans (Marsland et al., 2008). Inflammation contributes to AD (Lee et al., 2010) symptoms, and several confirmed AD risk genes (Harold et al., 2009; Lambert et al., 2009; Hollingworth et al., 2011; Morgan, 2011; Naj et al., 2011) relate to inflammatory processes. Interleukin 6 (IL-6) is a measure of systemic inflammation, typically acting as a pro-inflammatory cytokine (Rasmussen et al., 2011). Higher serum IL-6 levels relate to greater hippocampal inflammation and poorer cognition in rodents, and less hippocampal gray matter in humans (Marsland et al., 2008). Paradoxically though, IL-6 may also reduce inflammation, making a high measure of IL-6 difficult to interpret. In response to exercise, active muscles and the brain release IL-6, and its mRNA expression is up-regulated in the hippocampus (Rasmussen et al., 2011). It then down-regulates tumor necrosis factor α (TNFα), another pro-inflammatory cytokine, reducing peripheral and hippocampal inflammation in rodents (Schindler et al., 1990; Funk et al., 2011). TNFα is both pro-inflammatory and decreased with exercise (Schindler et al., 1990; Funk et al., 2011), so high values can be consistently interpreted as detrimental. Higher peripheral IL-6 levels are associated with lower hippocampal gray matter in healthy middle-aged adults (Marsland et al., 2008), but in breast cancer survivors, higher IL-6 levels are associated with larger left hippocampal volumes (Kesler et al., 2013). In contrast, higher serum TNFα was associated with smaller hippocampal volumes in breast cancer survivors (Kesler et al., 2013).

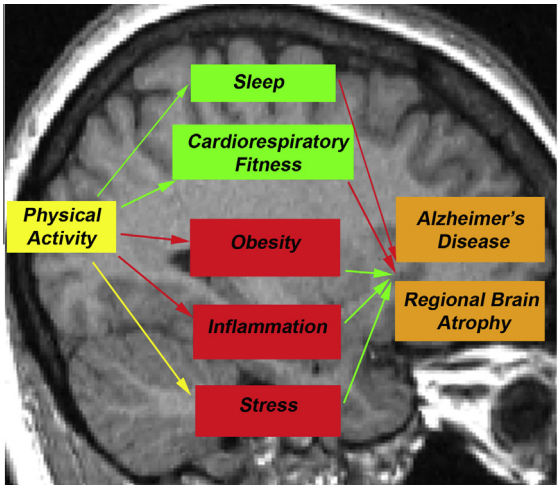

Fig. 1. In physical activity intervention studies, physical activity over a period of time has numerous effects in the body. These effects have been previously associated with both lower regional brain atrophy and lower risk of developing AD. Red arrows indicate a decreased result; green arrows indicate an increased result. The yellow arrow between physical activity and stress demonstrates the complex relationship between the two in which acute physical activity increases cortisol levels, but over time, decreases the body's reactivity to stress (Mastorakos et al., 2005). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Here, we investigate whether lower systemic inflammation contributes to the effect of physical activity on brain volume in older adults who have AD or are cognitively intact. The level of physical activity intensity was assessed for each subject based on self-reported recent activities upon admission into the Cardiovascular Health Study (CHS; see Experimental procedures). We included these physical activity intensity measures and serum TNFα levels in a model that predicts brain volume, while controlling for other factors known to be associated with regional brain volumes, including body mass index (BMI; a measure of obesity) (Raji et al., 2010; Ho et al., 2010a; Ho et al., 2010b). We examine brain volume in two ways: whole-brain volume as a percentage of intracranial volume (listed as "total brain volume" for the remainder of this paper) and voxelwise volume assessed using tensor-based morphometry (TBM), a method for mapping profiles of atrophy in 3D throughout the brain. We hypothesized that greater physical activity intensity would be associated with greater brain volume on a follow-up magnetic resonance imaging (MRI) scan. We further hypothesized that variability in systemic inflammation, as measured by serum TNFα, would explain part of this effect.

EXPERIMENTAL PROCEDURES

Participants

Subjects were selected from the Cardiovascular Health Study (Fried et al., 1991; Lopez et al., 2003b), a population-based longitudinal study of coronary heart disease and stroke in adults aged 65 and older. Subjects were recruited from a Medicare database, and all were ambulatory and living outside an institution. Those included here had neurological and neuropsychological exams in 1998–99 (year 9 of the study). Of those with T1-weighted volumetric brain MRI scans at that time, we identified 517 without a history of infarct but with measures of baseline exercise intensity available. Of these, 85 had available serum TNFα levels at year 5. Three of