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Neuroprotective pathways: lifestyle activity, brain pathology, and cognition in cognitively normal older adults

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ABSTRACT

This study used path analysis to examine effects of cognitive activity and physical activity on cognitive functioning in older adults, through pathways involving beta-amyloid (Aβ) burden, cerebrovascular lesions, and neural injury within the brain regions affected in Alzheimer's disease (AD). Ninety-two cognitively normal older adults (75.2 ± 5.6 years) reported lifetime cognitive activity and current physical activity using validated questionnaires. For each participant, we evaluated cortical Aβ burden (using [^{11}C] labeled Pittsburgh-Compound-B positron emission tomography), cerebrovascular lesions (using magnetic resonance imaging-defined white matter lesion [WML]), and neural integrity within AD regions (using a multimodal neuroimaging biomarker). Path models (adjusted for age, gender, and education) indicated that higher lifetime cognitive activity and higher current physical activity was associated with fewer WMLs. Lower WML volumes were in turn related to higher neural integrity and higher global cognitive functioning. As shown previously, higher lifetime cognitive activity was associated with lower [^{11}C] labeled Pittsburgh-Compound-B retention, which itself moderated the impact of neural integrity on cognitive functioning. Lifestyle activity may thus promote cognitive health in aging by protecting against cerebrovascular pathology and Aβ pathology thought to be relevant to AD development.

1. Introduction

Cognitive and physical engagement are among the modifiable lifestyle risk factors for Alzheimer's disease (AD) (Barnes and Yaffe, 2011), with high potential for preventing or slowing AD progression. Higher levels of cognitive and physical activity are related to lower cross-sectional (Christensen et al., 1996; Floel et al., 2010; Hultsch et al., 1993; Newson and Kemps, 2005) and longitudinal (Wilson et al., 2002b) cognitive decline and decreased risk of AD (Scarmeas et al., 2009; Wilson et al., 2002a, 2002b). Given this importance of lifestyle factors, biological mechanisms through which cognitive and physical activities benefit cognitive health in aging (Thies et al., 2013) need to be delineated.

The recent ability to measure biomarkers thought to be associated with AD pathologic processes (Ewers et al., 2011; Jack et al., 2010) has provided a way to examine effects of lifestyle on brain pathologic burden and cognitive abilities in cognitively normal older adults. Previous research has proposed that the development of AD involves multiple pathologic pathways that converge on temporoparietal brain regions most severely affected in AD. Neural integrity in these AD regions is captured by established AD-sensitive biomarkers such as regional cortical thinning, regional glucose hypometabolism, and hippocampal atrophy (Dickerson et al., 2009; Jack et al., 2012; Knopman et al., 2013).

One associate of neural injury in AD is cerebrovascular disease. Measureable through white matter lesions (WMLs), cerebrovascular disease is frequently observed in neuropathological examinations in combination with AD pathology in older adults (Schneider and Bennett, 2010). Research has further demonstrated that cerebrovascular disease affects brain structure (Cardenas et al., 2012; Wirth et al., 2013c), which itself is correlated with lower cognitive functioning in aging (Raji et al., 2012). Cognitive and physical activities, on the other hand, could protect against cerebrovascular pathology and thereby help to maintain

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cognitive health. Lifestyle factors are known to promote white matter (Gow et al., 2012; Lovden et al., 2010) and gray matter (Erickson et al., 2010, 2011; Floel et al., 2010; Ho et al., 2011) integrity in older adults, by potentially increasing neurogenesis (Erickson et al., 2011), angiogenesis, and/or reducing cerebrovascular risk factors, in particular through physical activity (Kramer et al., 2006).

Furthermore, beta-amyloid (Aβ)-plaque burden can be found in older adults (Braak et al., 2011), where this pathologic hallmark of AD can be detected in vivo using (^{11}C) labeled Pittsburgh-Compound-B (PIB) positron emission tomography (PET) imaging (Klunk et al., 2004; Mintun et al., 2006). Aβ deposition may predict subtle (subclinical) cognitive alterations in cognitively normal older individuals (Hedden et al., 2013) and interact with neural injury in AD-vulnerable regions to aggravate preclinical cognitive decline (Desikan et al., 2012; Wirth et al., 2013a, 2013b). Importantly, lifestyle activities could dampen the risk of Aβ pathology. This is suggested by previous research showing that both greater lifetime cognitive activity and physical exercise are related to lower brain Aβ burden (Landau et al., 2012; Liang et al., 2010).

This study aimed to confirm and extend previous work and construct a comprehensive integrated model that combined lifestyle factors, brain pathologic burden, and cognitive functioning in cognitively normal older adults. Using a cross-sectional design and path modeling similar to previous work (Vemuri et al., 2012), we examined multiple-predictor pathways including cognitive and physical activity, biomarkers reflecting Aβ burden, cerebrovascular burden as well as neural injury within AD regions, and cognitive ability. We first confirmed that separate pathways for cerebrovascular pathology and Aβ pathology are associated with lower cognitive functioning. Adding cognitive and physical activity as exogenous predictors to the pathway model, we conjectured that beneficial effects of lifestyle would be seen on cerebrovascular burden (measured using WML volumes) and on Aβ burden (measured using PIB-PET), which in turn would help to maintain neural integrity (measured using gray-matter thickness, glucose metabolism, and hippocampal volume; Wirth et al., 2013a) and cognitive health.

2. Methods

2.1. Selection of participants

The sample included 92 community-dwelling cognitively normal older people from the Berkley Aging Cohort (BAC), an ongoing longitudinal study. For the present sample, eligibility criteria included a Geriatric depression scale score (Yesavage et al., 1982) ≤10, Mini mental status examination (Folstein et al., 1975) score ≥25, normal memory functions (all memory scores within −1.5 standard deviations [SD] of age-, gender-, race- and years of education-adjusted norms), and age between 60 and 90 years at first visit. Individuals reported no current serious medical, neurologic, or psychiatric illnesses (except hypertension [32% of the cases], hyperlipidemia [37%], and diabetes mellitus [3%]). This sample included all 65 individuals from a previous publication (Landau et al., 2012) that exclusively investigated associations of lifetime cognitive activity and cortical PIB retention.

Each participant underwent a standardized neuropsychological test session as well as magnetic resonance imaging (MRI) and PET scanning (Table 1). For individuals with multiple assessments, the neuropsychological evaluation closest to MRI scanning was chosen. Written informed consent was obtained from each participant in accordance with the Institutional Review Boards of the University of California, Berkeley and Lawrence Berkeley National Laboratory (LBNL).

Table 1
Characteristics of participants

Participants, number	92
Age at MRI, y (SD), span	75.2 (5.6), 63–88
Women, number (%)	58 (63)
Education, y (SD), span	16.9 (1.9), 12–20
MMSE, mean score (SD), span	28.7 (1.4), 25–30
Measurement characteristics	
Δ_{time} (MRI − FDG), y (SD), span	0.1 (0.4), 0.0–1.8
Δ_{time} (FDG − PIB), y (SD), span	0.0 (0.0), 0.0–0.1
Δ_{time} (NTS − MRI), y (SD), span	0.3 (0.2), 0.0–0.8
Lifestyle activity	
Cognitive activity, mean score (SD), span	3.5 (0.5), 2.0–4.6
Physical activity[a], mean score (SD), span	10,766.8 (9541.8), 0.0–53,856.5
Biomarkers	
WML (mm^3), median (SD), span	2229.0 (2024.3), 922.0–10,789.0
PIB index, median (SD), span	1.04 (0.18), 0.82–1.76
Cortical thickness (mm), mean (SD), span	2.8 (0.2), 2.1–3.1
FDG-PET, mean (SD), span	1.5 (0.1), 1.3–1.7
HV (mm^3), mean (SD), span	3532.6 (430.1), 2141.0–4828.5

Mean or median and standard deviation (SD) and span are provided.
Key: Δ, absolute difference; HV, hippocampal volume; MMSE, Mini Mental Status Examination; MRI, magnetic resonance imaging; NTS, neuropsychological test session; PET, positron emission tomography; PIB, Pittsburgh-Compound-B; WML, white matter lesion; FDG, Fludeoxyglucose.
[a] The physical activity score was divided by a factor of 10 for descriptive purposes.

2.2. Assessment of cognitive and physical activity

2.2.1. Cognitive activity

Cognitive activity was measured using a cognitive activity interview, described elsewhere (Wilson et al., 2003). In brief, a 25-item interview was administered, in which the frequency of relatively common cognitively demanding activities, such as reading books, newspapers and magazines, writing letters, going to the library, and playing games was recorded across age epochs at age of 6, 12, 18, 40 years (retrospectively), and at the current age. Responses were provided on a 5-point frequency scale ranging from 1 (once a year or less) to 5 (every day or almost every day). For each participant, we calculated the mean of each age epoch and created 3 cognitive activity measures: early (average over the age epochs 6, 12, and 18), middle life (average over the age epoch 40), and current (average over the current age epoch) life.

A test–retest analysis was conducted for 75 of our participants, who completed at least 2 cognitive activity interview measurements with an average time interval of 1.63 years (SD = 0.50). Test–retest reliability was measured using the intra-class correlation coefficient (ICC) and indicated good reliability for the age-epoch related measures, that is for early life cognitive activity (ICC: $r = 0.92$, 95% confidence interval [CI]: 0.88, 0.95), for middle life cognitive activity an ICC of $r = 0.89$, 95% CI: 0.83, 0.93, and for current cognitive activity the ICC was $r = 0.79$, 95% CI: 0.67, 0.87. The results replicate earlier retest correlation reports based on an independent sample (Wilson et al., 2003) and a smaller BAC sample (Landau et al., 2012). Evaluating the reproducibility using t tests, cognitive activity measures for early life ($t[74] = 0.27$, $p = 0.90$), middle life ($t[74] = 0.27$, $p = 0.79$), and current life ($t[74] = 0.64$, $p = 0.52$) did not differ significantly between first and second administration of the questionnaire and there was no significant variation across age epochs, as indicated by a repeated-measure ANOVA ($F[2, 148] = 0.28$, $p = 0.76$).

2.2.2. Physical activity

Current physical activity was measured using a previously validated physical activity interview based on the modified Minnesota leisure-time activities questionnaire (Geffken et al., 2001; Taylor et al.,