Systemic inflammation as a predictor of brain aging: Contributions of physical activity, metabolic risk, and genetic risk

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ABSTRACT

Inflammatory processes may contribute to risk for Alzheimer's disease (AD) and age-related brain degeneration. Metabolic and genetic risk factors, and physical activity may, in turn, influence these inflammatory processes. Some of these risk factors are modifiable, and interact with each other. Understanding how these processes together relate to brain aging will help to inform future interventions to treat or prevent cognitive decline.

We used brain magnetic resonance imaging (MRI) to scan 335 older adult humans (mean age 77.3 ± 3.4 years) who remained non-demented for the duration of the 9-year longitudinal study. We used structural equation modeling (SEM) in a subset of 226 adults to evaluate whether measures of baseline peripheral inflammation (serum C-reactive protein levels; CRP), mediated the baseline contributions of genetic and metabolic risk, and physical activity, to regional cortical thickness in AD-relevant brain regions at study year 9.

We found that both baseline metabolic risk and AD risk variant apolipoprotein E ε4 (APOE ε4), modulated baseline serum CRP. Higher baseline CRP levels, in turn, predicted thinner regional cortex at year 9, and mediated an effect between higher metabolic risk and thinner cortex in those regions. A higher polygenic risk score composed of variants in immune-associated AD risk genes (other than APOE) was associated with thinner regional cortex. However, CRP levels did not mediate this effect, suggesting that other mechanisms may be responsible for the elevated AD risk.

We found interactions between genetic and environmental factors and structural brain health. Our findings support the role of metabolic risk and peripheral inflammation in age-related brain decline.

Introduction

Inflammatory processes have been implicated in promoting and resisting degenerative changes in the aging brain. In Alzheimer's disease (AD), neuroinflammation is associated with the classical pathologic hallmarks of the disease: amyloid plaques and neurofibrillary tangles (Akiyama, 2000; Heneka et al., 2015; McGeer and McGeer, 2010). In healthy older adults, peripheral inflammation has been related to cognitive decline and to greater structural change (Alley et al., 2008; Teunissen et al., 2003). In middle-aged adults, chronic peripheral inflammation correlates with higher incidence of dementia (Schmidt et al., 2002).

There is an intriguing overlap between genetic and environmental factors that contribute to inflammation and factors that contribute to dementia. Several of the AD-risk variants discovered in genome wide association studies (GWAS) are implicated in immune reactions and inflammatory processes (Hollingworth et al., 2011; Raz et al., 2005).

Metabolic risk includes factors such as obesity, high blood pressure, dyslipidemia, and insulin resistance (Alberti et al., 2006). These factors are consistently associated with chronic inflammation and with higher...
risk of dementia (Farooqui et al., 2011; Nation et al., 2015; St-Onge et al., 2009; van Himbergen et al., 2012). In older adults, some metabolic factors are associated with measurable brain tissue deficits in the temporal and frontal lobes, the cingulate gyrus, hippocampus, and basal ganglia (Gustafson et al., 2004; Panacciulli et al., 2006; Raji et al., 2010; Taki et al., 2008). Among these regions are those affected most by atrophy as AD progresses (Chetelat et al., 2010; McDonald et al., 2009; Whitwell, 2010).

In contrast, physical activity is associated with lower peripheral inflammation (Bruunsgaard, 2005; Gleeson et al., 2011; Mendham et al., 2011), preserved cognition (Kramer and Erickson, 2007; Lautenschlager et al., 2008; Van Gelder et al., 2004) and greater hippocampal volume (Marsland et al., 2015; Wagner et al., 2015). Exercise may protect cognition in many ways (Kennedy et al., 2016). For instance, physical activity: (1) promotes weight loss, which normalizes metabolic risk factors for dementia, (2) may induce the release of trophic factors that independently protect the brain (Campos et al., 2016), and (3) helps modulate inflammatory processes (Braskie et al., 2014; Ford, 2002; Gleeson et al., 2011; Pedersen, 2011).

Because inflammation plays a key role in brain aging, we hypothesized that measures of inflammation would mediate the effect of genetic risk, metabolic risk, and physical exercise on brain health in older, cognitively intact adults. We analyzed blood levels of C-reactive protein (CRP), which is elevated in AD patients with more severe cognitive decline (Gong et al., 2015). CRP is associated with the release of several inflammatory mediators such as tumor necrosis factor alpha (TNF-α), and interleukin-1 and -6 (IL-1 and IL-6; Rochemonteix et al., 1993). In addition, CRP increases blood-brain-barrier permeability (Hsuchoh et al., 2012) and interacts with cells involved in brain immune surveillance (Zhang et al., 2015). Finally, CRP is directly influenced by metabolic risk factors (Ebrahimi et al., 2016; Ridker, 2001). Overall, circulating CRP is a relevant marker for chronic peripheral inflammation and may induce or reflect conditions leading to neuroinflammatory processes in the brain.

We used structural equation models (SEM) to assess whether inflammation mediates an effect between brain structure in regions relevant to both AD and aging, and modulators thought to promote cognitive decline, specifically, genetic risk, metabolic risk, and physical activity. This is the first study to evaluate how all these disease risk factors affect brain structure and how they interact, in a unified statistical model.

Methods

The Cardiovascular Health Study Cohort

The study participants were selected from the Cardiovascular Health Study Cohort (CHS; https://chs-nhlbi.org), a 9-year observational study of individuals aged 65 and older who were cognitively intact at baseline. CHS was initiated in 1991 to identify factors associated with coronary heart disease and stroke (Fried et al., 1991). We examined year-9 high resolution MRI and baseline measures of peripheral inflammation, cardiovascular health, and physical activity (Table 1). The MR scans acquired at the study baseline were not comparable to the follow-up scans and were only used to visually detect the presence of infarcts. A physician performed this inspection at the time of participant inclusion in CHS.

Participant selection

Presymptomatic amyloidosis can occur years before onset of clinical symptoms (Braskie et al., 2010; Johnson et al., 2012; Sabuncu, 2011) and could cause specific neurodegenerative and homeostatic changes not easily discerned from environment or age-related homeostatic imbalance. To limit the level of measured inflammation likely to arise from AD neuropathology, we focused our analyses on cognitively healthy older individuals, and excluded those who developed AD incidentally, by year 9 of the study when the MRI scans we used were acquired. This helped us to reduce variability in chronic inflammation that is unrelated to the metabolic risk and physical activity on which we focused here.

Mild cognitive impairment (MCI) was classified following the CHS-CS diagnostic criteria (Lopez et al., 2003a). A MCI amnestic-type diagnosis, required participants to have impairments (defined as performance > 1.5 standard deviations below age/education appropriate means) in delayed recall of verbal or non-verbal material (or both); the cognitive deficits also must represent a decline from a previous level of functioning. Cognitive functions must otherwise fall within normal limits. A diagnosis of dementia was based on a deficit in performance in two or more cognitive domains that was of sufficient severity to affect activities of daily living, with a history of normal intellectual function before the onset of cognitive abnormalities; a memory deficit was not required for the diagnosis of dementia (Lopez et al., 2003b).

Participants were classified by an Adjudication Committee comprised of experts in dementia, who first classified participants as demented, MCI, or cognitively intact, and then decided upon the specific type of dementia or MCI. The Adjudication Committee had access to the historical CHS cognitive test scores from 1989 to 1999, and the neuropsychological battery from 1998 to 99, as well as depression measures, vision and hearing testing, history of alcohol intake, vital status, date of death, history of hospitalizations, medications to treat dementia, MRI scans (1992-94, 1997-98), the neurological exam, the NPI obtained in 1998-99, and hospital records. For AD, this classification relies on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) which do not rely on the use of a biomarker of amyloid pathology (amyloid PET or CSF...
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