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Brain morphology links systemic inflammation to cognitive function in midlife adults ☆

Anna L. Marsland *, Peter J. Gianaros, Dora C.-H. Kuan, Lei K. Sheu, Katarina Krajina, Stephen B. Manuck

Department of Psychology, University of Pittsburgh, Center for the Neural Basis of Cognition, University of Pittsburgh and Carnegie Mellon University, United States

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ABSTRACT

Background: Inflammation is linked to cognitive decline in midlife, but the neural basis for this link is unclear. One possibility is that inflammation associates with adverse changes in brain morphology, which accelerates cognitive aging and later dementia risk. Clear evidence is lacking, however, regarding whether inflammation relates to cognition in midlife via changes in brain morphology. Accordingly, the current study examines whether associations of inflammation with cognitive function are mediated by variation in cortical gray matter volume among midlife adults. *Methods:* Plasma levels of interleukin (IL)-6 and C-reactive protein (CRP), relatively stable markers of peripheral systemic inflammation, were assessed in 408 community volunteers aged 30–54 years. All participants underwent structural neuroimaging to assess global and regional brain morphology and completed neuropsychological tests sensitive to early changes in cognitive function. Measurements of brain morphology (regional tissue volumes and cortical thickness and surface area) were derived using Freesurfer. *Results:* Higher peripheral inflammation was associated with poorer spatial reasoning, short term memory, verbal proficiency, learning and memory, and executive function, as well as lower cortical gray and white matter volumes, hippocampal volume and cortical surface area. Mediation models with age, sex and intracranial volume as covariates showed cortical gray matter volume to partially mediate the association of inflammation with cognitive performance. Exploratory analyses of body mass suggested that adiposity may be a source of the inflammation linking brain morphology to cognition. *Conclusions:* Inflammation and adiposity might relate to cognitive decline via influences on brain morphology.

1. Introduction

Aging engenders declines in multiple cognitive domains, including episodic and working memory, attention, and executive functioning (Salthouse, 2004). Typically, these cognitive declines begin in the late 20s and progress across adulthood (Salthouse, 2004). Trajectories of cognitive aging are heterogeneous, however, with some individuals showing minimal declines and others more precipitous deterioration (Raz et al., 2005). Understanding factors that account for individual differences in cognitive aging is critical because age-related impairments in cognitive function confer risk for dementia (Barberger-Gateau et al., 1999; De Lepeleire et al., 2004), injuries (Sattin, 1992), hospitalization, and death (Bennett, 1997).

Preclinical changes in brain morphology precede and may contribute to cognitive declines among healthy aging individuals, as well as predict risk for dementia (Burgmans et al., 2009; den Heijer et al., 2006; Driscoll et al., 2009; Kramer et al., 2007; Persson et al., 2012; Raz et al., 2005; Walhovd et al., 2011). These changes include reductions in total brain and gray matter volume and in white matter integrity that accompany advancing age (Burgmans et al., 2009; DeCarli et al., 2005; Fjell et al., 2013; Kennedy and Raz, 2009; Raji et al., 2012; Raz et al., 2005; Ryan et al., 2011). On average, reductions in gray matter volume begin around age 35 and accelerate thereafter (Fjell et al., 2013; Hedman et al., 2012), associating with concomitant and future declines in cognitive function (Burgmans et al., 2009; Fjell and Walhovd, 2010; Kramer et al., 2007). Individuals differ in rates of age-related brain atrophy, with accelerated gray matter loss associated with earlier progression to dementia (Whitwell et al., 2008). Thus, gray matter atrophy represents a midlife preclinical predictor of cognitive aging. At present, however, the biological

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* Corresponding author at: Behavioral Immunology Laboratory, Department of Psychology, 3943 O'Hara Street, Pittsburgh, PA 15260, United States. Tel.: +1 (412) 624 4530; fax: +1 (412) 624 9108.
E-mail address: marsland@pitt.edu (A.L. Marsland).

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bases for early deterioration of global and regional gray matter volumes remain unclear. On a cellular level, explanations for brain atrophy in aging are manifold and include apoptosis, axonal degeneration, reduced dendritic spine density, dendritic simplification, cell shrinkage, and reduced vascularity (von Bohlen und Halbach, 2010). However, factors that affect these cellular changes and consequent changes in gross morphology remain to be determined. In this regard, recent evidence suggests that inflammation may play a critical role.

Peripheral inflammatory mediators (e.g., interleukin (IL)-6) can cross the blood–brain barrier to modulate central inflammatory processes that result in neurodegeneration and impair cognitive function (Arai et al., 2001; Ek et al., 2001; Heyser et al., 1997; Monje et al., 2003; Poluektova et al., 2005; Pugh et al., 1998; Richwine et al., 2008; Trapero and Cauli, 2014; Yirmiya and Goshen, 2011). Within the brain, proinflammatory cytokines and their receptors are expressed by many cell subtypes throughout the cerebral cortex (Hampel et al., 2005). Chronic increases in peripheral inflammation, such as those that accompany aging, "prime" microglia to switch to an inflammatory phenotype, increasing central inflammatory responses to peripheral inflammation (Chen et al., 2008; Perry et al., 2007; Ye and Johnson, 1999) and possibly playing a pathogenic role in age-related neurocognitive decline. Human studies support this possibility, with increases in circulating mediators of inflammation, whether the result of exogenous administration or acute/chronic inflammatory conditions, relating inversely to disturbances of, attention, memory, executive and global cognitive function (Bucks et al., 2008; Capuron et al., 1999; Kozora et al., 2001; Krabbe et al., 2005; Reichenberg et al., 2001; Smith et al., 1988). Poorer cognitive function also associates with peripheral inflammation among the well-functioning elderly (Marioni et al., 2009; Rafnsson et al., 2007; Schram et al., 2007; Weaver et al., 2002; Wright et al., 2006; Yaffe et al., 2003), with higher levels predicting future cognitive decline in some (Marioni et al., 2009; Rafnsson et al., 2007; Schram et al., 2007; Tilvis et al., 2004; Weaver et al., 2002; Yaffe et al., 2003), but not all studies (Alley et al., 2008; Dik et al., 2005; Teunissen et al., 2003). We have extended this evidence previously by showing an inverse association of circulating IL-6 with performance on memory and executive function tasks among cognitively normal adults of mean age 43 years (Marsland et al., 2006), raising the possibility that systemic inflammation represents an early marker of cognitive risk.

Findings from studies of healthy older adults show inverse associations of markers of systemic inflammation with aspects of brain morphology that decline with age, including total brain volume (Jefferson et al., 2007), total gray matter volume (Satizabal et al., 2012), temporal lobe volume (Bettcher et al., 2012; Taki et al., 2013), hippocampal volume (Satizabal et al., 2012) and white matter integrity (Wersching et al., 2010). Our earlier work extended these findings to a midlife community sample, showing associations of higher IL-6 and CRP with lower total gray matter volume and white matter integrity throughout the brain, and with lower regional gray matter volume of the hippocampus and PFC (Gianaros et al., 2013; Marsland et al., 2008; Verstynen et al., 2013). However, it is still unknown whether these global or regional aspects of brain structure provide a plausible pathway linking inflammation to preclinical neurocognitive decline among midlife adults.

Accordingly, the goals of this study were (1) to confirm inverse associations of markers of systemic inflammation (IL-6 and CRP) with a broad range of cognitive functions and with global and regional measures of brain structure among midlife adults and (2) to extend our prior work by examining whether global or regional measures of gray matter volume statistically mediate associations between inflammation and cognitive function. In regard to brain structure, our early work was informed by animal models and focused on relationships between inflammation and the structure and function of the hippocampus (Marsland et al., 2008). More recently, however, we have found inflammation associated with global aspects of brain morphology as well (Gianaros et al., 2013; Verstynen et al., 2013). In the current study we explored two possibilities. One is that inflammatory associations are localized to specific brain regions; the other is that they are global. Finally, in light of evidence that adipocytes are a primary source of circulating IL-6 (Mohamed-Ali et al., 1997) and that body fat covaries positively with IL-6 (Bermudez et al., 2002; Khaodhiar et al., 2004) and inversely with gray matter volume (Marsland et al., 2008; Taki et al., 2008), cognitive function (Marsland et al., 2006), and accelerated cognitive aging (Ho et al., 2011), we explored whether inflammation accounts for associations of BMI with brain atrophy and associated cognitive performance.

2. Methods and materials

2.1. Participants

Participants were 408 adults 30–54 years of age drawn from the Adult Health and Behavior Project – Phase 2 (AHAB-II) project (see Table 1). AHAB-II is an epidemiological registry of biobehavioral correlates of cardiovascular disease risk among midlife adults. Participants were recruited between 2008 and 2011 by mass-mail solicitation from Western Pennsylvania (principally Allegheny County). To be eligible, participants had to be in good general health and working at least 25 h/week outside of the home (a sub-study involving this cohort focused on occupational stress and CHD risk). Participants were excluded if they (a) had a history of cardiovascular disease, schizophrenia or bipolar disorder, chronic hepatitis, renal failure, major neurological disorder, chronic lung disease, or hypertension (BP $\geqslant$ 160/100 mm Hg); (b) reported drinking $\geqslant$35 portions of alcohol per week; (c) took fish-oil supplements (because of the requirements for another sub-study); (d) were prescribed insulin or glucocorticoid, anti-arrhythmic, antihypertensive, lipid-lowering, psychotropic, or prescription weight-loss medications; (e) were pregnant or lactating; (f) had less than 8th grade reading skills; or (g) were shift workers. Remaining exclusion criteria were claustrophobia, presence of medical devices, implants, or other metal objects in or on the body that could not be removed, tattooed eyeliners, or a body habitus prohibiting MR scanning.

Of the 490 participants in AHAB-II, 448 had reliable measures of CRP and IL-6, excluding 8 individuals who did not have blood drawn, 36 taking medications known to impact immune function (e.g., cold medications/antihistamines) and 1 individual with rheumatoid arthritis. In addition, we excluded 9 individuals with CRP levels >10 ng/ml, which is outside the normal range and suggests acute illness at the time of blood draw (Biasucci, 2004;

Table 1
Characteristics of the Sample (n = 408).

Characteristic	Mean (SD) or %
Sex (%)	47% male
Age (years)	42.8 (7.3)
Race (%)	83% white, 15% black
Education (years)	17.0 (2.9)
BMI (kg/m^2: mean ± SD)	26.7 (5.0)
Current smokers (%)	15%
Alcohol use (drinks/week)	3.27 (4.7)
Systolic blood pressure	115 (11)
IL-6 (pg/ml)	1.10 (.97)
CRP (ng/ml)	1.51 (1.86)

BMI, body mass index; IL-6, interleukin-6; CRP, C-reactive protein.

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