Neurobiology of Aging 37 (2016) 138–146

Contents lists available at ScienceDirect

Neurobiology of Aging

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

The relationship between inflammatory markers and voxel-based gray matter volumes in nondemented older adults

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ARTICLE INFO

Article history:
Received 1 June 2015
Received in revised form 24 September 2015
Accepted 8 October 2015
Available online 22 October 2015

Keywords:
Magnetic resonance imaging
Gray matter
Inflammatory markers
Correlation
Ageing
Voxel-based morphometry

ABSTRACT

Ageing is characterized by chronically elevated inflammatory markers (IMs). Peripheral IM levels have been found in negative correlations with brain structural measures including global and lobar volumes and the hippocampus. This study investigated the relationship between 10 peripheral IMs and voxel-based gray matter (GM) volumes in nondemented older adults (n = 463). Two proinflammatory cytokines (tumor necrosis factor-α [TNF-α] and interleukin-1β) and 2 vascular IMs (vascular cellular adhesion molecule−1 and plasminogen activator inhibitor−1) were negatively correlated with regional GM volumes. TNF-α and interleukin-1β were both significantly correlated with GM volumes in the left occipitotemporal area, left superior occipital gyrus, and left inferior parietal lobule; TNF-α was also significantly correlated with the bilateral medial prefrontal cortices and approached significance for the correlations with the bilateral hippocampi. Significant GM correlations with vascular cellular adhesion molecule−1 were located in the bilateral anterior cingulate cortices, and with plasminogen activator inhibitor−1 in the cerebellum and right hippocampus. The neuroanatomical correlation patterns of 2 proinflammatory cytokines and 2 vascular IMs might be reflective of the effects of neurodegenerative and vascular pathological processes in the ageing brain.

1. Introduction

Inflammatory markers (IMs), the indicators of inflammatory response, are chronically elevated in older adults even in the absence of overt pathogens (Fagiolo et al., 1993; Ferrucci et al., 2005). This phenomenon, termed as "inflammaging," indicates the progressive inflammatory state in older adults (Franceschi et al., 2000). It has been proposed that inflammaging is the consequence of accumulative damaging effects of lifelong immune response (Singh and Newman, 2011). Studies have shown that elevated peripheral IMs are associated with mild cognitive impairment (MCI) and dementia in older adults, indicating that there might be a link between age-related inflammatory changes and neuropathological processes (Bruunsgaard, 2006; De Martinis et al., 2006; McAfoose and Baune, 2009; Trollor et al., 2010).

Inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins (ILs)-1β, -6, -8, -10, and -12, have been implicated in the neurodegenerative process (Gao and Hong, 2008; Perry, 2010). Evidence suggests that TNF-α and IL-1β enhance amyloid β (Aβ) protein deposition and plaque formation, the hallmarks of Alzheimer's disease (He et al., 2007; Liao et al., 2004; Wyss-Coray and Rogers, 2012). Higher peripheral levels of TNF-α, IL-1β, IL-6, IL-8, IL-10, and IL-12 have all been associated with Alzheimer's disease (Metti and Cauley, 2012; Reale et al., 2009; Swardfager et al., 2010; Tan et al., 2007; Wang et al., 2014). One category of IMs has been actively involved in the vascular pathological changes, including vascular cellular adhesion molecule−1 (VCAM-1) and plasminogen activator inhibitor−1 (PAI-1), which are found to play roles in atherosclerosis and thrombosis, respectively (Blann and McCollum, 1994; Carmeliet et al., 1993; Marui et al., 1993). The 2 vascular IMs are also found to be associated with vascular dementia

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http://dx.doi.org/10.1016/j.neurobiolaging.2015.10.008

and late-stage Alzheimer's disease, possibly reflecting the damage of cerebrovascular dysfunction to the ageing brain (Gallacher et al., 2010; Grammas, 2011; Zuliani et al., 2008). Acute-phase proteins such as C-reactive proteins (CRPs) and serum amyloid A (SAA) comprise another category of IMs that rise in concert with the systemic inflammatory response. Elevated CRP and SAA have been associated with increased risk of Alzheimer's disease and vascular dementia (Koyama et al., 2013; O'Bryant et al., 2013; Urieli-Shoval et al., 2000).

A few studies have shown that interindividual variations in peripheral IM levels are associated with individual differences in brain structures in nondemented older adults. TNF-α and IL-6 have been found in negative correlations with total brain volume (Jefferson et al., 2007). Total gray matter (GM) volume was negatively correlated with IL-6 and CRP (Satizabal et al., 2012). One study examined the relationship between lobar atrophy and multiple peripheral IMs and found that atrophy of parietal, temporal, and occipital lobes was not associated with any single IM but significantly associated with a composite factor consisting of IL-4-receptor, IL-6, and IL-8 levels (Baune et al., 2009). Hippocampal volume was also found in a negative relationship with peripheral IL-6 level in middle-aged and older adults (Marsland et al., 2008; Satizabal et al., 2012). Moreover, genetic studies have demonstrated that the polymorphisms of TNF and IL-6 genes are associated with the hippocampal volume (Baune et al., 2012a, 2012b).

Peripheral IM levels, such as TNF-α, IL-6, and CRP, have been found to be in negative relationships with brain structural measures in nondemented older adults. However, a comprehensive investigation on the IM-GM relationship is still lacking, especially for the IMs that have been shown to be involved in different types of dementia. Therefore, we selected 10 IMs that were elevated in Alzheimer's disease and/or vascular dementia, including 6 inflammatory cytokines (TNF-α, IL-1β, -6, -8, -10, and -12), 2 vascular IMs (VCAM-1 and PAI-1), and 2 acute-phase proteins (CRP and SAA). Moreover, composite markers (CMs) that combined different IMs of one category were generated. We used the approach of voxel-based morphometry to partition the brain into fine-grained units. Each IM or CM was correlated with the whole-brain voxel-based GM volumes in a large group of community-dwelling, nondemented older adults (n = 463). On the basis of prior findings, we hypothesized that peripheral IM and/or CM levels might be negatively correlated with voxel-based GM volumes. Moreover, the neuroanatomical correlation patterns of different IMs and/or CMs might be diverse, reflecting specific influences of distinct neuropathological processes that involve different IMs on the ageing brain.

2. Methods

2.1. Subjects

Participants in the present study were drawn from wave 1 of the Sydney Memory and Ageing Study (MAS). The MAS participants (n = 1037) were randomly recruited from community-dwelling elderly adults aged 70–90 years (Sachdev et al., 2010), with the following exclusion criteria: dementia based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria (American Psychiatric Association, 1995); Mini–Mental State Examination score <24, adjusted for age, education, and non–English-speaking background (Anderson et al., 2007; Folstein et al., 1975); developmental disability; history of psychosis; multiple sclerosis; motor neuron disease; progressive malignancy; or inadequate English to complete basic psychometric assessments.

Of all MAS participants, 542 individuals had T1-weighted scans. To minimize confounding effects on brain structure, the individuals who had been diagnosed with the following conditions were excluded from this study: stroke (n = 12), Parkinson's disease (n = 8), epilepsy (n = 4), severe head injury (unconsciousness >24 hours, n = 2), brain cancer (n = 1), benign meningioma (n = 2), brain infection (n = 6), and transient global amnesia (n = 3). After further excluding participants who had missing information on IMs (n = 25), *APOE* genotype (n = 15), Mini–Mental State Examination score = 24 (n = 1), or poor magnetic resonance imaging (MRI) quality including image artifacts and error in data saving or converting (n = 11), a total of 463 participants were included in the analysis.

The study was approved by the ethics committee of UNSW, Australia, and written informed consent was obtained from each participant.

2.2. Inflammatory markers

Following an overnight fast, the early morning blood samples of all participants were collected, clotted, aliquoted, and frozen by an accredited laboratory. The concentrations of 10 IMs were measured, including TNF-α, IL-1β, IL-6, IL-8, IL-10, IL-12, VCAM-1, PAI-1, CRP, and SAA. The procedures to measure their concentrations have been described previously (Trollor et al., 2010). Briefly, the serum concentrations of VCAM-1, PAI-1, and SAA were measured using commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The serum VCAM-1 and PAI-1 ELISA kits were obtained from Bender Medsystems GmbH (Austria). The SAA ELISA kit was obtained from United States Biological (USA). The serum concentrations of TNF-α, IL-1β, -6, -8, -10, and -12 were measured using cytometric bead array (BD Biosciences, San Diego, CA, USA) and flow cytometer (FACSCalibur TM, BD Biosciences). The plasma concentration of CRP was measured via near infrared particle immunoassay rate methodology using the Beckman Coulter Synchron LXi (Beckman Coulter, CA, USA). The concentrations of 10 IMs were all transformed to Z-scores for the statistical analysis.

2.3. MRI acquisition

Of the 463 subjects, 254 were scanned using a Philips 3T Intera Quasar scanner (Philips Medical Systems, Best, The Netherlands). The remaining 209 subjects were scanned on a Philips 3T Achieva Quasar Dual scanner which replaced the original one in 2007 due to reasons outside of the investigators' control. Acquisition parameters for all T1-weighted structural MRI scans were: repetition time = 6.39 ms, echo time = 2.9 ms, flip angle = 8°, matrix size = 256 × 256, field of view = 256 × 256 × 190, and slice thickness=1 mm with no gap between; yielding 1 × 1 × 1 mm^3 isotropic voxels. The subject recruitment was randomly distributed, and the scanning was consecutive. No significant difference on total GM volumes was found between the participants scanned by the 2 scanners ($p = 0.85$). A binary variable accounting for each of the scanners was included in the statistical analysis as a controlled covariate to minimize the scanner effect.

2.4. Image processing

All T1-weighted MRI images were processed following the voxel-based morphometry approach, described previously (Zhang et al., 2011). Briefly, after visually inspecting MRI scans for structural abnormalities, the hidden Markov random field option in the unified segmentation of the Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm) was used to segment T1 images into different tissues with the most commonly used ICBM152 atlas as the template. Next, the toolbox of Diffeomorphic Anatomical Registration Through and Exponentiated Lie