Psychoneuroendocrinology (2014) 40, 108—118

Available online at www.sciencedirect.com

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

Markers of low-grade inflammation and endothelial dysfunction are related to reduced information processing speed and executive functioning in an older population — the Hoorn Study

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Received 10 September 2013; received in revised form 26 October 2013; accepted 11 November 2013

KEYWORDS
Low-grade inflammation;
Endothelial dysfunction;
Cognitive functioning;
Vascular risk factors;
Cardiovascular disease

Summary Low-grade inflammation and endothelial dysfunction are related to cognitive decline and dementia, in a complex interplay with vascular factors and aging. We investigated, in an older population, low-grade inflammation and endothelial dysfunction in relation to detailed assessment of cognitive functioning. Furthermore, we explored this association within the context of vascular factors.

377 participants (73 ± 6 years) of the population-based Hoorn Study were included. In plasma samples of 2000—2001 (n = 363) and/or 2005—2008 (n = 323), biomarkers were determined of

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0306-4530/$ — see front matter
http://dx.doi.org/10.1016/j.psyneuen.2013.11.011

low-grade inflammation (CRP, TNF-alpha, IL-6, IL-8, SAA, MPO, and sICAM-1) and endothelial dysfunction (vWF, sICAM-1, sVCAM-1, sTM, sE-selectin). In 2005—2008, all participants underwent neuropsychological examination. Composite z-scores were computed for low-grade inflammation and endothelial dysfunction at both time points, and for six domains of cognitive functioning (abstract reasoning, memory, information processing speed, attention and executive functioning, visuoconstruction, and language). The association between low-grade inflammation and endothelial dysfunction, and cognitive functioning was evaluated with linear regression analysis. In secondary analyses, we explored the relation with vascular risk factors and cardiovascular disease.

Low-grade inflammation and endothelial dysfunction were associated with worse performance on information processing speed and attention and executive functioning, in prospective and cross-sectional analyses (standardized betas ranging from −0.20 to −0.10). No significant relation with other cognitive domains was observed. Adjusting for vascular factors slightly attenuated the associations. Low-grade inflammation and endothelial dysfunction accounted for only 2.6% explained variance in cognitive functioning, on top of related vascular risk factors and cardiovascular disease. Bootstrapping analyses show that low-grade inflammation and endothelial dysfunction mediate the relation between vascular risk factors and cognitive functioning.

This study shows that low-grade inflammation and endothelial dysfunction contribute to reduced information processing speed and executive functioning in an older population.

1. Introduction

Cognitive impairment and dementia are important public health problems. To date, no cure is available, but some factors contributing to cognitive decline are potentially modifiable. These include vascular risk factors such as diabetes, hypertension, dyslipidemia, obesity, and smoking, which are part of a complex cascade of subclinical vascular abnormalities that occurs in aging (Knopman and Roberts, 2010). Eventually, such abnormalities can lead to cardiovascular events such as ischemic heart disease and stroke, but also to more insidious global changes in the brain and to cognitive decrements. In this vascular cascade, chronic low-grade inflammation and endothelial dysfunction are thought to play an important role (Gorelick, 2010).

The relation between low-grade inflammation and endothelial dysfunction, vascular risk factors, cardiovascular disease, and cognitive functioning is complex (see Fig. 1). Low-grade inflammation and endothelial dysfunction are closely linked: inflammatory cytokines can induce endothelial dysfunction, and endothelial dysfunction is a pro-inflammatory state (Zhang, 2008). These processes may have a direct effect on the brain due to their role in neurotransmitter and neuroendocrine responses (Wilson et al., 2002). However, low-grade inflammation and endothelial dysfunction may also affect the brain through vascular insufficiency. Low-grade inflammation, endothelial dysfunction and vascular risk factors reinforce each other (Esposito and Giugliano, 2004; Dharmashankar and Widlansky, 2010; Granger et al., 2010) and can lead to cardiovascular and cerebrovascular disease, by themselves and in interaction (Cosentino and Volpe, 2005; Granger et al., 2010). Furthermore, ischemia as a result of vascular disease may lead to an inflammatory response (Galea and Brough, 2013). Moreover, inflammatory and vascular disease do not only result in cognitive decrements but also in depressive symptoms (Alexopoulos and Morimoto, 2011), which are known to interact with cognitive performance (Taylor et al., 2013; Thomas and O'Brien, 2008).

Low-grade inflammation and endothelial dysfunction could thus have their own influence on cognitive performance and at the same time may be intermediate processes between vascular risk factors, cardiovascular disease and cognitive impairment. Results from previous studies provide evidence for associations between biomarkers of inflammation and/or endothelial dysfunction and cognitive dysfunctioning (Kuo et al., 2005; Gorelick, 2010; Quinn et al., 2011; Hedges et al., 2012; Bettcher and Kramer, 2013). To our knowledge however, thus far no studies have addressed this relation by combining multiple circulating biomarkers for both low-grade inflammation and endothelial dysfunction with extensive neuropsychological examination on a wide range of cognitive domains.

The aim of the present study was to examine the relation between circulating biomarkers of low-grade inflammation and of endothelial dysfunction and a detailed assessment of cognitive functioning, in a population-based sample of older individuals. We provide additional analyses to further explore the complex relation between low-grade inflammation, endothelial dysfunction, cognitive functioning, vascular factors, and depressive symptoms.

2. Methods

2.1. Participants

The Hoorn Study is a population-based cohort study on glucose metabolism, which started in 1989 and included 2484 participants aged 50—75 years at baseline. Follow-up examinations of this cohort were performed in 1996—1998, 2000—2001 and 2005—2008. Details on the design of the baseline study and the follow-up have been described elsewhere (Mooy et al., 1995; De Vegt et al., 2001; Van den Berg et al., 2008). Circulating biomarkers of low-grade inflammation and endothelial dysfunction were determined in 2000—2001 (n = 765) and again in 2005—2008 (n = 450), cognitive functioning was assessed in 2005—2008 (n = 385). For the present analyses, we included all persons with at least one