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Associations between systemic pro-inflammatory markers, cognitive function and cognitive complaints in a population-based sample of working adults

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ABSTRACT

Background: The knowledge is limited regarding the relation between systemic inflammatory biomarkers and subjective and objective cognitive functioning in population-based samples of healthy adults across the adult age-span. Thus, the aim of this study was to study a selection of four pro-inflammatory biomarkers (IL-6, MCP-1, TNF-α, CRP) in relation to executive cognitive functioning, episodic memory and subjective cognitive complaints (SCC) in a population-based sample of 215 working adults (age 25–67).

Results: Higher levels of MCP-1 were associated with poorer executive cognitive functioning, even after adjustments for demographical factors, health status/conditions, SCC and depressive symptoms. IL-6 and CRP were associated with poorer executive cognitive functioning, but these associations covaried with age especially and were not present after adjustment for demographical factors.

MCP-1 was associated with poorer episodic memory, but this association also covaried with age especially and was not present after adjustment for demographical factors, and CRP was associated with episodic memory only among participants without reported health conditions. Higher MCP-1 levels were also associated with more SCC and this association covaried with depressive symptoms, while higher levels of TNF-α were associated with less SCC.

Conclusion: Low grade inflammatory processes in terms of higher systemic levels of pro-inflammatory biomarkers (MCP-1, IL-6 & CRP) were associated with poorer executive functioning in this sample of working adults, and MCP-1 was so after extensive adjustments. Support for associations between these biomarkers and episodic memory and SCC were more limited. Future research should address the causality of associations between low grade inflammatory processes and cognitive functioning.

1. Introduction

Cognitive functioning is essential to human adaptive behaviour and well-being, including work-ability. Besides genetic factors, a large body of research also suggests that cognitive functions are affected by a multitude of factors, many of which may be modifiable [5]. Research increasingly suggests that inflammatory processes may be one of the mediating mechanisms through which risk modification can occur [77].

Inflammatory processes, central as well as systemic, have been increasingly linked to behaviour and brain functioning (e.g. [68]). It has also been shown that peripheral/systemic cytokines and chemokines can pass the blood-brain-barrier, act as neuromodulators and play a role in e.g. synaptic plasticity and neurogenesis at the molecular level [68,93]. Cytokines and chemokines thus seem to play an intimate role in the molecular and cellular mechanisms subserving cognitive processes in e.g. executive cognitive functioning, learning and memory, as well as affective states, both in the short and long term.

Elevated systemic levels of pro-inflammatory cytokines and chemokines have been implicated in disorders of cognition including e.g. Alzheimer's disease and mild cognitive impairment (MCI), and have been associated with cognitive decline (e.g. [2,9,12,21,22,26,32,39,52,70,73,82,86,96,99]) and poorer cognitive functioning in studies of different clinical groups (e.g. [15]) and population-based elderly/aging samples [51,84,100,38,39,78,98]. Experimental inductions of

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increased cytokine/chemokine levels have also found detrimental effects on executive functioning, learning and memory, in both younger and older adults [48,65,69,83].

However, most studies on systemic inflammatory processes and cognitive functioning have been done on clinical groups and elderly populations with more clearly heightened inflammatory profiles and with conditions that may in parallel be causing both cognitive deficits as well as elevated inflammatory processes. Less is therefore known about the role of systemic pro-inflammatory markers, and low-grade inflammatory processes, in relatively healthy populations across the adult age-span. The present study therefore contributes to fill this gap in the field by including a non-clinical population-based sample of 215 working adults aged 25–67 years, with comprehensive measures of executive cognitive functioning, episodic memory and selected systemic pro-inflammatory cytokines and chemokines (including Interleukin-6: IL-6, monocyte chemotactic protein 1: MCP-1, CRP, and tumour necrosis factor α: TNF-α).

Executive cognitive functioning (including attentional and cognitive control processes and working memory processes) and episodic memory (involving encoding, consolidating and recalling new and learned information or episodes) are key "fluid" cognitive functions that have been found to be vulnerable to elevated levels of proinflammatory cytokines and chemokines [56,58,68]. These functions depend heavily on prefrontal and parietal cortical networks and hippocampal brain regions that have been found to be functionally sensitive to pro-inflammatory cytokines and chemokines, including IL-6, MCP-1, CRP and TNF-α [8,19,33,37,47].

With increasing age these cognitive functions also appear to be the first to decline, while semantic memory (knowledge and recall of vocabulary and generic facts, conceptualized as a "crystallized" cognitive capacity) tends to be preserved longer [1,46,74]. Executive functions and episodic memory have also been found to be particularly sensitive to acute and chronic stress (e.g. [3,76,101,102]).

Therefore, this study focused on the role of inflammatory processes in executive cognitive functioning and episodic memory functioning, since these functions and their neuroanatomical substrates are implicated as especially sensitive to impacts during adulthood.

Furthermore, subjective cognitive complaints (SCC), involving self-perceived cognitive problems such as memory and concentration difficulties, are common across the age span. For example, a recent study showed that 10% in the Swedish work force reported at least one type of cognitive difficulty (incl. problems with concentration, memory, decision making, and thinking clearly) "often" or "always" [88].

In general and working populations, SCC have been associated with lower quality of life [80], poorer performance on objective tests of executive cognitive functioning and memory [13,89] and are cardinal symptoms in conditions that constitute major causes of sick-leave today [29,30], including chronic stress/exhaustion and depressive disorders [44,80,88]. Chronic stress and depressive conditions are in turn associated with actual cognitive deficits, especially in executive cognitive functioning and episodic memory (e.g. [60,102,64,76]). SCC have also been found to be a key factor which reduces work ability even in phases that are not characterized by clinical illness in the frame of depressive and chronic stress conditions (e.g. [25,85]), as well as a predictor of cognitive decline and brain degeneration in studies of cognitive aging [91].

Inflammatory processes have been linked to degenerative processes in the brain over time, and cytokines seem to play a central role in the modulation of brain and cognitive functions also in the shorter time span [56,58,68]. Hence, it is possible that inflammatory processes also contribute to SCC in working adults (i.e. without dementias or known neurodegenerative disorders).

Elevated levels of the cytokines IL-6, TNF-α, and CRP and the chemokine MCP-1 have also been linked to mental health problems common in the working population, like depression [14,19,23,28,36,41,58] and burnout or exhaustion [4,97], although no such association was found by Jonsdottir et al. [43]. These conditions are also associated with cognitive complaints and deficits, especially in executive cognitive functioning and episodic memory (e.g. [60]; Grossi et al. 2015; [64,76]).

While higher levels of pro-inflammatory cytokines have generally been implicated as malicious to cognition, some cytokines have also been shown to exert physiologically protective [103,104,105], including neuroprotective [106,107,108], functions [114]. Specifically, it has been found that genetic variants of TNF-α may have protective effects on cognitive functioning such as perceptual speed in a population-based study of elderly [7]. In an animal model of cytokine-mediated cognitive function including memory and learning, the presence of TNF has also been shown to be essential for normal functioning of memory and learning under immunologically non-challenged conditions [6]. Following this research, one may consider the possibility that the relation between systemic TNF-a and cognitive functioning may differ in relatively more healthy and younger populations (with TNF-a concentrations at the very low end of the spectrum) compared to clinical groups and elderly (with more elevated TNF-a levels).

In sum, there is a lack of studies that have investigated the relationship of systemic inflammatory markers with both objective and subjective cognitive functioning in general working populations (as opposed to specific clinical groups or elderly). Studying this type of population can contribute to increased understanding of the role of low grade inflammatory processes for cognitive functioning outcomes in this population.

Thus, the purpose of this study was to investigate the potential role of inflammatory processes in cognitive functioning and SCC in a population-based sample of adults, while adjusting for important covariates, including depressive and chronic stress/exhaustion symptoms, in order to also evaluate the extent to which these symptoms covary with and may explain associations between inflammatory markers and cognitive outcomes. Based on previous research and data availability, the systemic biomarkers that were investigated were MCP-1, IL-6, CRP and TNF-α.

It was hypothesized that higher levels of MCP-1, IL-6 and CRP would be associated with poorer cognitive outcomes.

2. Methods

2.1. Participants

Participants were recruited in the context of a study on cognitive functioning and SCCs in the working population (see [88,89]) and were drawn from the 2010 wave of the Swedish Longitudinal Occupational Survey of Health (SLOSH). SLOSH is a longitudinal study of work life and health among Swedish employees, conducted biennially on an approximately representative sample of the Swedish work force (see e.g. [50]). The SLOSH 2010 sample is based on the respondents to the nationally representative Swedish Work Environment Surveys (SWES) conducted biennially. (See, e.g., [50,54]). Participants from SWES 2003, 2005 and 2007 are included in SLOSH 2010 and the age range of the sample is 16–64 years. Compared to the Swedish population, women, older subjects (aged 50 +) and married/cohabiting subjects as well as men and women with high education are slightly overrepresented in SLOSH.

A total of 11,525 subjects participated (57% response rate) in SLOSH 2010 and 9132 of the participants were gainfully employed - i.e. they were in gainful employment during the past three months at a level of 30% of full time or more.

Gainfully working participants in Stockholm county and the counties including and surrounding the city of Gothenburg were invited to the in-depth study of cognitive functioning and SCC based on their recently reported levels of cognitive complaints (SCC) in SLOSH 2010.

SCC were measured on a 4-item scale asking about difficulties during the past 3 months with concentration, memory, decision-mak-