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Association between genetic variants of IL-1β, IL-6 and TNF-α cytokines and cognitive performance in the elderly general population of the MEMO-study

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Summary
This study is to investigate the associations between specific polymorphisms in three cytokine genes and domains of cognitive functioning in a population based study in the elderly. In a cross-sectional study of 369 community dwelling elderly subjects we examined the relationships between the polymorphisms IL-1β-1418C→T, IL-6-572G→C and TNF-α-308G→A and the cognitive function domains memory, processing speed and motor function using an extensive neuropsychological test battery. Linear regression models were used in the analysis and results adjusted for multiple comparisons. A significant association between the IL-1β-1418C→T polymorphism and memory performance was found with carriers of the T allele (dominant model) having worse memory performance than those with the C allele. In addition, a significant association between the TNF-α-308G→A polymorphism and processing speed was observed, indicating better performance for heterozygous or homozygous carriers of the A allele. These results remained significant after adjustment for known confounders of cognitive function and additional Bonferroni correction for multiple comparisons. Our study provides first results on detrimental effects of the IL-1β-1418C→T polymorphism on memory performance and neuroprotective effects of the TNF-α-308G→A polymorphism on processing speed in elderly individuals. Further research is needed to prospectively examine changes in cognitive performance in relation to cytokine genotypes.

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1. Introduction

The capacity of the brain to activate an inflammatory reaction in response to an immune challenge in the periphery is well established (Tonelli and Postolache, 2005). This reaction involves the production of various cytokines. Interleukin-1β (IL-1β) is the cytokine that responds with the most widespread pattern of expression in the brain (Tonelli and Postolache, 2005). Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are two other cytokines which share this pattern. The evidence that cognitive decline such as dementia is associated with cytokines is supported by studies showing an association between increased peripheral cytokine levels of IL-6 (Weaver et al., 2002),TNF-α, and IL-1β (Bruunsgaard et al., 1999; Holmes et al., 2003; van Exel et al., 2003; Dik et al., 2005) and cognitive decline and by several genetic studies that reported associations between different IL1-polymorphisms (IL-β polymorphisms (Ehl et al., 2003; Sciacca et al., 2003; Licastro et al., 2004; Wang et al., 2005; Ravaglia et al., 2006; Wehr et al., 2006), IL-6 polymorphisms (Shibata et al., 2002; Capurso et al., 2004; van Oijen et al., 2006) or TNF-α polymorphisms (Perry et al., 2001; Culpan et al., 2003; Bruunsgaard et al., 2004; Lio et al., 2006) and cognitive decline. However, these studies are limited by the use of the diagnostic entity of dementia rather than domains of cognitive function such as memory, processing speed and motor function, which would allow a better understanding of the association between cytokines, cytokine genotypes and specific domains of cognitive functioning.

Recent studies provided an initial understanding of the neuronal effects of cytokines on normal brain functioning. In the normal brain, accumulated evidence strongly indicated that the "proinflammatory" cytokines IL-1β and TNF-α were constitutively expressed and are modulators of neuronal activities. Both cytokines were involved in several processes subserving cognition, such as in autonomic and behavioral (Vitkovic et al., 2000) and neurodegenerative processes (Bruunsgaard et al., 1999; Holmes et al., 2003), apoptosis and excitotoxicity, modulation of neurotransmitters (Dunn et al., 1999), neuroendocrine responses (McCann et al., 2000) and modulation of neuronal and glial cell function (Griffin et al., 1998). More specifically for TNF-α, it has been suggested that the continual presence of TNF-α is required for preservation of synaptic strengths at the excitatory synapse (Beattie et al., 2002) and that neurotransmitter metabolism and neuro-developmental processes were altered by TNF-α (Stellwagen and Malenka, 2006).

Initial studies have investigated effects of genotypes of other cytokines such as IL-6 on cognitive function. A study among newborns reported a relationship between specific IL-6 genotypes and cognitive function showing that the IL-6-572C-allele (CC/GC genotypes) is associated with impaired cognitive development among children (Harding et al., 2005). Further evidence for a role of IL-6 was found in an animal study examining cognitive function in transgenic mice not expressing IL-6 (IL-6 KO). Compared to wild type (WT) genotype IL-6 KO mice showed better performance in various cognitive tests, suggesting a possible involvement of IL-6 in memory processes (Braida et al., 2004).

These previous human genetic-cognition association studies are also limited by not considering potential effects of the corresponding peripheral cytokine on cognitive function. Moreover, reports on the associations between these cytokine genotypes and domains of cognitive function in older adults in the community are still lacking.

In this study, we selected the TNF-α-308G$\rightarrow$A (rs1800629) polymorphism due to previous reports in relation to cognitive decline in the elderly (Bruunsgaard et al., 2004) and the IL-6-572G$\rightarrow$C (rs1800796) polymorphism was chosen following reports on its detrimental effects on cognitive development in children (Harding et al., 2005). Finally, the IL-1β-1418A$\rightarrow$G (rs16944) polymorphism was selected as IL-β polymorphisms were widely investigated in dementia (Shibata et al., 2002; Capurso et al., 2004; van Oijen et al., 2006) and it seems to play a role in vascular disease (Le Flem et al., 2001) (it predicts an Ala 455 Val substitution in the sixth epidermal growth factor-like Thrombomodulin module) that has potentially relevance to impaired cognitive function. This SNP, however, appears not to be investigated specifically in relation to cognitive function in the elderly.

Thus, the aim of our study was to investigate the associations between the IL-1β IL-6 and TNF-α genotype and the cognitive domains of memory, processing speed and motor function in an elderly, general population.

2. Methods

2.1. Sample

The Memory and Morbidity in Augsburg Elderly (MEMO-Study) is a follow-up project of the 1989/1990 WHO MONICA Survey Augsburg, Germany (Monitoring Trends and Determinants in Cardiovascular Disease) (Keil et al., 1998; Schmidt et al., 2004). For the MEMO-Study, all participants of the MONICA-survey aged 65 years and older were re-contacted. The overall response proportion for the MEMO-Study was 60.6% yielding a total of 385 participants. The ethics committee of the University of Muenster, Germany, approved the study. After a complete description of the study to the subjects, written informed consent was obtained. All cognitive test examinations were performed under controlled conditions in the study centre. The data presented in this analysis are based on $N = 369$ participants with complete data and laboratory analyses.

3. Measures

3.1. Cognitive test battery

The cognitive test battery which was used in the Memo-Study consisted of tests assessing short-term memory, attention, processing speed and motor function (Nilsson et al., 2005). Details of the single cognitive tests have been described extensively elsewhere (Baune et al., 2006). In brief, short-term memory was assessed by three word recall tests on the basis of the Tulving and Colotla (1970) lag measures (Nilsson et al., 1997). Higher scores in the recall test are associated with better memory performance. Word fluency was assessed by the use of the production