European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro

A systematic review on the association between inflammatory genes and cognitive decline in non-demented elderly individuals

David Stacey[1], Liliana G. Ciobanu[1], Bernhard T. Baune*

Discipline of Psychiatry, School of Medicine, University of Adelaide, Australia

Received 17 July 2015; received in revised form 27 October 2015; accepted 1 December 2015

KEYWORDS
Inflammation;
Cognitive ageing;
Genetics;
GWAS;
Candidate genes

Abstract
Cognitive impairment, or decline, is not only a feature of Alzheimer's disease and other forms of dementia but also normal ageing. Abundant evidence from epidemiological studies points towards perturbed inflammatory mechanisms in aged individuals, though the cause-effect nature of this apparent relationship is difficult to establish. Genetic association studies focusing on polymorphism in and around inflammatory genes represent a viable approach to establish whether inflammatory mechanisms might play a causal role in cognitive decline, whilst also enabling the identification of specific genes potentially influencing specific cognitive facets. Thus, here we provide a review of published genetic association studies investigating inflammatory genes in the context of cognitive decline in elderly, non-demented, samples. Numerous candidate gene association studies have been performed to date, focusing almost exclusively on genes encoding major cytokines. Some of these studies report significant cognitive domain-specific associations implicating Interleukin 1β (IL1β) (rs16944), Tumour Necrosis Factor α (TNFα) (rs1800629) and C-reactive protein (CRP) in various domains of cognitive function. However, the majority of these studies are lacking in statistical power and have other methodological limitations, suggesting some of them may have yielded false positive results. Genome-wide association studies have implicated less direct and less obvious regulators of inflammatory processes (i.e., *PDE7A*, HS3ST4, SPOCK3), indicating that a shift away from the major cytokine-encoding genes in future studies will be important. Furthermore, better cohesion across studies with regards to the cognitive test batteries administered to participants along with the continued application of longitudinal designs will be vital.

*Correspondence to: Discipline of Psychiatry,University of Adelaide, Level 4, Eleanor Harrald Building, Frome Road, Adelaide 5005, Australia. Tel.: +61 8 8222 5141; fax: +61 8 8222 2774.
E-mail address: bernhard.baune@adelaide.edu.au (B.T. Baune).
[1]Equally contributing authors.

http://dx.doi.org/10.1016/j.euroneuro.2015.12.017
0924-977X/

1. Introduction

Cognitive impairment is a defining feature of Alzheimer's disease (AD) and multiple other neurodegenerative diseases that preferentially affect elderly populations (Bettcher and Kramer, 2014). Further, cognitive decline is also characteristic of normal ageing, which not only has an adverse impact on quality of life in elderly populations but the extent of decline is considered a potential marker of prospective pathophysiology (Eshkoor et al., 2015). Although the biological processes and molecular mechanisms mediating cognitive decline in aged populations are not fully understood, abundant evidence highlights immune and inflammatory mechanisms as potential candidates (Li et al., 2014; McAfoose and Baune, 2009; McAfoose et al., 2009). Numerous epidemiological studies have found that peripheral inflammatory markers such as Interleukin 1β (IL1β), IL6, and Tumour Necrosis Factor α (TNFα) are increased in the elderly (Fuchs et al., 2013; Karim et al., 2014; Yaffe et al., 2003), and that this is exaggerated in AD and other dementia patients relative to age-matched healthy controls (Faria et al., 2014; Yarchoan et al., 2013). Likewise, these observations also hold true when sampling from both cerebrospinal fluid and post-mortem brain tissue (Alcolea et al., 2014; Monson et al., 2014; Sudduth et al., 2013). However, these findings are merely correlational and so the cause–effect relationship is not clear.

Although it is not possible to directly manipulate inflammatory mechanisms in humans to investigate subsequent effects on cognitive abilities, Mendelian randomisation represents a viable strategy to explore cause–effect relationships (Smith et al., 2005). By taking advantage of naturally occurring genetic variation known to influence the levels or functioning of inflammatory genes, it becomes possible to determine whether altered inflammatory mechanisms might be causative of cognitive decline whilst also highlighting specific genes in the process – this is of course the implicit premise, or assumption, of genetic association studies (Smith et al., 2005). Thus, in this review we aim to harness findings from published genetic association studies (both candidate-based and genome-wide) investigating inflammatory gene variants and cognitive decline in aged, non-demented, populations in order to glean information concerning cause–effect relationships, particularly as they might relate to different facets of cognition.

We begin by providing a brief primer outlining the "cytokine model of cognitive function" (McAfoose and Baune, 2009) and applying this specifically to cognitive decline in the non-demented elderly. We then provide a systematic review of all published genetic association studies investigating immune genes in elderly populations, where we summarise the major findings and offer critical appraisal to assess reliability and validity. Finally, we highlight some of the major limitations of this research whilst making recommendations as to further research directions in this area.

2. Primer on the "cytokine model of cognitive function" and possible relevance for cognitive decline in non-demented elderly

Although the precise nature of the relationship between immune/inflammatory mechanisms and elderly cognitive decline is not known, there is ample evidence to indicate that inflammatory molecules – particularly the major cytokines – are certainly capable of influencing cognitive function through the regulation of various biological substrates of cognition. We refer the reader to McAfoose and Baune (2009) for a more comprehensive accounting of this evidence, though here we provide a brief primer. The vast majority of research in this area has focused on hippocampal-dependent learning and memory using murine models of perturbed inflammatory genes or mechanisms. For example, intracranial injections of IL1β and IL1RN in rats has been shown to impact memory performance as evidenced by altered performance in classic behavioural tests such as the Morris water maze and the inhibitory avoidance task (Brennan et al., 2003; Depino et al., 2004; Pugh et al., 2001; Yirmiya et al., 2002). Likewise, studies utilising transgenic and knock out mouse models have also implicated TNFα and IL6 as additional regulators of memory and learning performance (Aloe et al., 1999; Baune et al., 2008b; Fiore et al., 2000).

In accord with these behavioural studies, numerous molecular studies in animals have highlighted a role for these same cytokines in various biological processes underlying cognitive function. In particular, IL1β, TNFα, and IL6 have been heavily implicated in the regulation of two opposing forms of classical Hebbian synaptic plasticity, particularly in hippocampal tissue: long-term potentiation (LTP) and long-term depression (LTD) (Balschun et al., 2004; Butler et al., 2004; Schneider et al., 1998). Furthermore, evidence from animal studies also suggests that neurogenesis in the hippocampus is under the influence of inflammatory cytokines such as IL1β and IL6 (Koo and Duman, 2008; Vallières et al., 2002), whereas TNFα has been shown to be important for a non-Hebbian form of synaptic plasticity called synaptic scaling, which functions to facilitate Hebbian synaptic plasticity by promoting homoeostasis during periods of prolonged synaptic inactivity or hyperactivity (Stellwagen and Malenka, 2006). Thus, based on these lines of evidence, McAfoose and Baune (2009) have outlined a "cytokine model of cognitive function" whereby the pleiotropic cytokines IL1β, IL6, and TNFα – amongst other cytokines – are proposed to play a major role in memory, learning, and relevant underlying mechanisms.

Despite this animal evidence clearly indicating "causal" capability, it remains to be determined how the cytokine model of cognitive function might relate to cognitive decline as a consequence of normal ageing. Indeed, as mentioned above, the up-regulated inflammatory markers observed in aged populations (Fuchs et al., 2013; Karim et al., 2014; Yaffe et al., 2003) and dementia patients (Faria et al., 2014; Yarchoan et al., 2013) may in fact be a consequence of cognitive decline as opposed to a "cause" or an exacerbating factor, which again underscores the importance of assessing genetic association studies in this field. Further, even if we assume inflammatory mechanisms do exert a "causal" effect, it is not clear as to which biological substrate – or substrates – outlined within the cytokine model of cognitive function might be affected, or whether ageing- and pathology-specific factors such as amyloid plaque toxicity might in fact be more applicable.

Nevertheless, in the context of the current work, a basic, logical extension of the cytokine model of cognitive function assumes that the majority of non-demented elderly individuals are able to tolerate the increased cytokine

Please cite this article as: Stacey, D., et al., A systematic review on the association between inflammatory genes and cognitive decline in non-demented elderly individuals. European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.12.017