Psychoneuroendocrinology (2013) 38, 2196—2208

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Intracellular cytokine production and cognition in healthy older adults

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Received 12 September 2012; received in revised form 10 April 2013; accepted 10 April 2013

KEYWORDS
Intracellular cytokines;
IL-1β;
IL-6;
CANTAB;
Cognition;
Ageing;
Inflammation;
Memory

Summary Elevated concentrations of the pro-inflammatory cytokines IL-1β and IL-6 have been associated with impaired cognitive performance. There are, however, few studies that have examined the relationship between cytokine production and specific aspects of cognition in healthy older individuals. Two-colour flow cytometry was used to determine intracellular cytokine production by activated monocytes, and neuropsychological tests were performed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) in 93 apparently healthy men and women aged 55—70 years. A series of hierarchical regression analyses was carried out to examine the contribution of IL-1β and IL-6 (% expression and production (antibody binding capacity (ABC))) to recognition, attention and working memory, after controlling for socio-demographic variables (age, sex and social class). IL-1β% expression and IL-6 production predicted aspects of working memory. Recognition memory was found to be sensitive to the affects of age and social class. The current study suggests that higher intracellular cytokine production by activated monocytes may be predictive of lower cognitive performance in working memory in healthy older individuals. These findings indicate that utilization of models for *in vivo* cytokine production upon immune challenge may be useful in studying specific aspects of memory affected during inflammatory responses, for example in individuals at risk for cognitive decline owing to age-related inflammatory disorders.

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http://dx.doi.org/10.1016/j.psyneuen.2013.04.007

1. Introduction

Bidirectional communication between the central nervous system (CNS) and the immune system is facilitated by soluble mediators, which include neurotransmitters, cytokines and hormones (Bellinger et al., 2002). Such neuro-endocrine–immune interactions create, within the body, a dynamic network which regulates homeostatic processes and allows for adaptation to environmental stimuli. In normal ageing, cognitive performance and immunity begin to decline concurrently prior to the third decade of life (Burns, 2004; Park et al., 2002), suggesting that the mechanisms underlying these phenomena are inter-related (Rosano et al., 2011). More research is needed to explore how aspects of immune function enhance or impair cognitive performance in healthy ageing.

The cytokines IL-1β and IL-6 are produced predominantly in the periphery by adipose tissue and activated immune cells. These cytokines are pleiotrophic mediators of adaptive immunity, cell proliferation and differentiation, migration and homing, and inflammatory reactions. A specific pattern of physiological, behavioural, and cognitive changes collectively referred to as 'sickness behaviour', during an inflammatory response (Dantzer, 2004) is a classical example of the pro-inflammatory properties of the IL-1β and IL-6 to elicit direct and indirect modulation of the CNS.

There is evidence to suggest that remodelling of the immune system occurs as a natural process of ageing (Franceschi et al., 1996). The process of inflammatory-ageing hypothesizes that a global reduction in the capacity to cope with a variety of stressors and a concomitant progressive increase in proinflammatory status are major characteristics of the ageing process (Franceschi et al., 2000). Furthermore, there also is evidence that genetic variations of IL-1β and IL-6 are associated with a decline in cognitive function in community dwelling adults over the age of 65 years, but it is not yet clear if this is the consequence of changes in cytokine production (Sasayama et al., 2012; Baune et al., 2008) and some disparity remains as to whether serum levels of cytokines are elevated in age-related cognitive disorders. For example, reports that higher concentrations of IL-1β are associated with negative effects on memory in animal and human studies (see Yirmiya and Goshen, 2011, for a review), especially aspects of memory that rely on the hippocampal pathways (Huang and Sheng, 2010), are in contrast to the finding that higher levels of IL-1β were associated with better semantic memory in older women (Lekander et al., 2011). Furthermore, IL-1β is thought to be important for regulating some memory processes (McAfoose and Baune, 2009), such as memory consolidation and synaptic plasticity, and has been reported to be induced into the hippocampus during activation of learning and memory processes (Yirmiya and Goshen, 2011).

Whilst higher levels of IL-6 have been associated with poorer performance on tests of encoding and recall of information (Elderkin-Thompson et al., 2012) and working memory (Troller et al., 2011; Alley et al., 2008; Gimeno et al., 2008; Marsland et al., 2006), this effect may be enhanced in adults over 65 years (Lekander et al., 2011). However, the range of cytokine concentrations reported varies between studies both in the disease groups and the groups of apparently healthy controls (Forlenza et al., 2009; Tan et al., 2007; Cacabelos et al., 1991), and may be attributable to cohort factors, or to methodologies used for measurement of cytokine levels, or to a combination of both.

There is evidence to support a role for inflammatory processes, specifically neuroinflammation, in the development of Alzheimer's disease (AD), although the exact mechanisms are complex and not fully understood (Tuppo and Arias, 2005). However, evidence suggests that cytokines are able to modulate neural systems through direct and indirect action on specific regions of the brain (Britschgi and Wyss-Coray, 2007). Patients with AD are reported to have high abnormal levels of circulating cytokines, which have been found in animal models of AD to influence amyloidosis, neurodegeneration and cognitive function (see Wyss-Coray and Rogers (2013) for a review). However, interventions employing anti-inflammatory drugs have produced disappointing results, with no or little improvement in memory (Imbimbo et al., 2010; Vlad et al., 2008; Aisen, 2002). A number of recent reviews suggest that more research is needed on healthy community dwelling older adults in order to give a better understanding of the clinical relevance of circulating cytokines to memory and ageing (Kawamoto et al., 2013; Czirr and Wyss-Coray, 2012; Fung et al., 2012; Rosano et al., 2011).

Somewhat lacking in previous research are robust measures of cognitive function which are sensitive to changes in neurodegeneration and ageing. This is addressed in the current study by using a well validated test battery called CANTAB (Cambridge Automated Neuropsychololgical Test Battery, Morris et al., 1986), which measures various aspects of cognitive function, including working memory, attention, and visual recognition memory. These tests were chosen as they are reported to be sensitive to normal cognitive ageing (Robbins et al., 1994) and neurodegenerative changes in brain function (Rabbitt and Lowe, 2000; Fray and Robbins, 1996). All of the tests included in the current study have brain to behaviour reliability (Luciana and Nelson, 2002), and activate brain regions that may be affected by changes in the central nervous system (Robbins et al., 1994) and immune function (Lynch, 1998) with age, such as the hippocampus. The ageing process may produce changes in the hippocampal and amygdala regions (visual memory), the temporal and frontal lobe regions (working memory tests) and fronto-striatal circuitry (attention) (Robbins et al., 1998). These changes relate to theories of biochemical and structural changes in the brain with age (Kraup et al., 2011). Such theories suggest the main areas of the brain affected by ageing are the pre-frontal cortex, affecting planning and working memory, while changes to the temporal cortex, the hippocampus and limbic system are related to learning and memory (see Raz and Rodrigue, 2006, for a review). Construct validity for the CANTAB tests is supported by studies of patient groups with various neurological conditions affecting specific brain regions (*e.g.* Owen et al., 1996), neuroimaging studies (*e.g.* Alichniewicz et al., 2012), studies of older healthy adults (*e.g.* Robbins et al., 1994), and those with mild cognitive impairment and AD (*e.g.* Egerhazi et al., 2007). This approach provides a more in-depth look at the relationship between the immune system and neuropsychological functioning and their potential underlying structural components in healthy older adults.