Brain and Cognition 119 (2017) 39–44

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Associations between immunological function and memory recall in healthy adults

Grace Y. Wang[a], Tamasin Taylor[a], Alexander Sumich[a,b], Fabrice Merien[c], Robert Borotkanics[d], Wendy Wrapson[e], Chris Krägeloh[a], Richard J. Siegert[a,*]

[a] Department of Psychology, School of Public Health and Psychosocial Studies, Auckland University of Technology, New Zealand
[b] Division of Psychology, School of Social Sciences, Nottingham Trent University, Nottingham, United Kingdom
[c] AUT-Roche Diagnostics Laboratory, School of Science, Auckland University of Technology, New Zealand
[d] Department of Biostatistics and Epidemiology, School of Public Health and Psychosocial Studies, Auckland University of Technology, New Zealand
[e] National Institute for Public Health and Mental Health Research, School of Public Health and Psychosocial Studies, Auckland University of Technology, New Zealand

ARTICLE INFO

Keywords:
Immunological measures
Memory
T lymphocytes
CD4
Interleukin-6

ABSTRACT

Studies in clinical and aging populations support associations between immunological function, cognition and mood, although these are not always in line with animal models. Moreover, very little is known about the relationship between immunological measures and cognition in healthy young adults. The present study tested associations between the state of immune system and memory recall in a group of relatively healthy adults. Immediate and delayed memory recall was assessed in 30 participants using the computerised cognitive battery. CD4, CD8 and CD69 subpopulations of lymphocytes, Interleukin-6 (IL-6) and cortisol were assessed with blood assays. Correlation analysis showed significant negative relationships between CD4 and the short and long delay memory measures. IL-6 showed a significant positive correlation with long-delay recall. Generalized linear models found associations between differences in all recall challenges and CD4. A multivariate generalized linear model including CD4 and IL-6 exhibited a stronger association. Results highlight the interactions between CD4 and IL-6 in relation to memory function. Further study is necessary to determine the underlying mechanisms of the associations between the state of immune system and cognitive performance.

1. Introduction

A complex network of bidirectional signals exchanged between the nervous, endocrine and immune systems affect cognition and mood (Maier, 2003). For example, chronic stress induces the persistent activation of the hypothalamic-pituitaryadrenal axis and the autonomic nervous system, leading to the release of hormones (e.g. adrenaline, noradrenaline and cortisol) that induce quantitative and qualitative changes in the immune system (Glaser & Kiecolt-Glaser, 2005). Chronic activation of inflammatory pathways, on-the-other-hand, alters synthesis of certain neurotransmitters (e.g. serotonin), increasing stress responsivity and vulnerability to mood disorders (Kiecolt-Glaser, Derry, & Fagundes, 2015). Such alterations to neural chemistry would also be expected to affect several cognitive domains, including learning and memory (Švob Štrac, Pivac, & Mück-Šeler, 2016). Thus, the link between immune system function and cognition is supported in studies of stress (Aas et al., 2014), human immunodeficiency virus (HIV) (Hong & Banks, 2015), cancer (Andreotti, Root, Ahles, McEwen, & Compas, 2015), Alzheimer's disease (Raskin, Cummings, Hardy, Schuh, & A Dean, 2015) and healthy aging (Serre-Miranda et al., 2015). However, the relationship between immunological markers and memory in relatively healthy (nonclinical) young adults remains unclear. Nevertheless, its investigation has important theoretical implications and practical utility with regard to advising on optimum immunological function for psychological wellbeing.

One of the most important components of the adaptive immune response is the lymphocytes, such as T and B lymphocytes. T lymphocytes, or T cells, play a pivotal role in cell-mediated immunity. Primary T cells include helper, killer, regulatory types. T helper cells (TH cells) are involved in the maturation of B cells into antibody producing plasma cells (humoral immunity of the adaptive immune system) and activation of cytotoxic T cells and macrophages. These TH cells are also known as $CD4^+$ T cells because they express the CD4 glycoprotein on their surfaces. Once activated, TH cells divide rapidly and produce cytokines that regulate the immune response. Killer T cells (e.g. $CD8^+$ T) kill tumor cells, cells that are infected (particularly with viruses) and/or damaged cells through complex interactions of molecules between those expressed on the surface of the T cells and derived

* Corresponding author at: Department of Psychology, Auckland University of Technology, 90 Akoranga Drive, Auckland 1142, New Zealand.
E-mail address: richard.siegert@aut.ac.nz (R.J. Siegert).

http://dx.doi.org/10.1016/j.bandc.2017.10.002
Received 27 July 2017; Received in revised form 1 October 2017; Accepted 1 October 2017
Available online 08 October 2017
0278-2626/

from antigen-presenting cells. Multiple surface proteins are known to be upregulated during the immune activation process. CD69 is the earliest inducible surface antigen expressed on lymphocytes after T- or B-cell activation and is absent from resting lymphocytes. Recent evidence supports a regulatory role for CD69 in modulating the inflammatory response (Sancho, Gómez, & Sánchez-Madrid, 2005).

Cytokines modulate the balance between humoral and cell-based immune responses, and regulate the responsiveness of other cell populations important for brain function (Maier & Watkins, 2003). For example, cytokines can influence the metabolism of neurotransmitters (e.g. serotonin, norepinephrine and dopamine) and alter neuroendocrine function. That is, acute Interleukin (IL)-2 administration enhances dopaminergic transmission, while systemic IL-6 administration induces increased noradrenergic and serotonergic transmission (Wilson, Finch, & Cohen, 2002). $CD4^+$ T-cells regulate brain-derived neurotrophic factor (BDNF), a protein critical for synaptic plasticity and memory-processing (Lu, Christian, & Lu, 2008), and contribute to the neurogenic microenvironment (Wolf et al., 2009). On-the-other-hand, excessive or sustained release of inflammatory cytokines produces neurotoxic effects on neurons and glial cells, at least *in vitro* (Allan & Rothwell, 2001; Hanisch, 2002).

Animal studies support the importance of CD4+ T cells in hippocampal neurogenesis and memory (Jeon et al., 2016). However, levels of $CD4^+$ cells have been inversely associated with immediate and stored memory in children infected with HIV (Ruisenor-Escudero et al., 2016) and short-term verbal memory, verbal working memory in older adults (Serre-Miranda et al., 2015). Other cells were also inversely associated with stored memory, including $CD38^+$ and CD8+ (Ruisenor-Escudero et al., 2016). CD69 is also implicated in memory and has been found on monocytes derived from patients with Alzheimer's disease (Kusdra, Rempel, Yaffe, & Pulliam, 2000). In women with major unipolar depression, which is associated with increases in IL-6, verbal memory performance is negatively associated with IL-6 plasma level after controlling for age, years of education and depression severity (Grassi-Oliveira, Bauer, Pezzi, Teixeira, & Brietzke, 2011). Consistently, an aging population study reported that people with high IL-6 level exhibited poorer attention and sensory memory compared to those having a low level or normal levels of IL-6 (Elwan et al., 2003). These findings provide initial evidence for the relationship between biomarkers of the state of immune system and cognitive function in aging and clinical populations. However, as mentioned, little is known about the relationship between the immune system and cognition in the general young adult population.

The present study was designed to examine whether associations between a set of immunological measures and memory function observed in clinical populations are consistent in healthy populations. Three levels of memory recall were evaluated, including immediate, short- and long delay memory recall. Given findings from Ruisenor-Escudero et al. (2016) and Kusdra et al. (2000) we expected an inverse associations between memory recall and both $CD4^+$ and CD8+. Given those of Grassi-Oliveira et al. (2011), we anticipated an inverse association between memory recall and IL-6. In addition, associations between memory and other measures of the state of immune system (cortisol, CD69) were explored.

2. Materials and methods

2.1. Participants

Participants (n = 30; 10 males, 20 females, M_{age} = 29.50 years, SD_{age} = 11.97; $M_{education}$ = 15.50 years, $SD_{education}$ = 2.5) included undergraduate (n = 25), post-graduate (n = 4) students and staff (n = 1) from a university in Auckland, New Zealand who enrolled in a large study investigating the effect of mindfulness on brain function. All data currently reported were collected prior to their engagement in mindfulness practice and outside of the school exam period, to avoid any possible influence of exam stress on immune system functioning. Exclusion criteria included current severe depression, a history of serious brain injury, epilepsy, drug or alcohol problem, and current prescription of medication for psychiatric illness (e.g. anxiety, depression, schizophrenia). Current depression level was measured using the Depression subscale from the Depression, Anxiety and Stress scale (DASS; (Benjamini & Hochberg, 1995)) and the total score over 20 suggested severe or extremely severe depression. Students of members of the research team were also excluded.

The ethnic makeup included, NZ European (n = 16), Indian (n = 3), Asian (n = 3), Māori (n = 1), Pacific (n = 1), others (n = 4) and Not Specified (n = 2). Ethical approval was granted by Auckland University of Technology Ethics Committee, and written informed consent was given by all participants. Students were gifted a $20 voucher for their time contributed to the study.

2.2. Memory recall and recognition test

Testing for immediate, short and long delay memory recall was taken during normal office hours (9 am–5 pm). Immediate and delayed memory recall was assessed using an Internet-based cognitive battery 'IntegNeuro' (for details see www.brainresource.com). The 'IntegNeuro' test battery has good validity and test-retest reliability (Kemp et al., 2005; Paul et al., 2005; Williams et al., 2010) and meets standardised norms pre-established in 1000 healthy participants (Clark et al., 2006). It has also been validated against traditional paper-and-pencil neuropsychological tests of cognition (convergent validity measures > 0.53) (Paul et al., 2005). This test battery was delivered using an IBM screen interfaced platform with standardised vocal and visual instructions. Instructions were delivered via stereo headphones/microphone at the beginning of each test. Participants were also given a practice set for each test to ensure they understood the instructions.

In the first part, the participants were presented with a list of 12 words, which they were asked to memorise. The list was presented 4 times in total, and the participants were required to recall as many words as possible after each presentation. Immediate recall was measured as the average of the number of words recalled immediately after each presentation.

The participants were then presented with a second list of 12 distracter words, in which none of the words were phonetically or semantically related to the first list, and asked to recall that second list. After this distraction, the participants were asked immediately to recall the previously presented words from the original list. Short delay recall was measured as the number of words recalled from the original list. Long delay recall was measured as the number of words recalled from the original list after a delay of approximately 25 min, during which time participants completed other cognitive tests.

2.3. Blood samples

Blood samples were taken between 10 am and 12:30 pm on a day different from that on which cognitive tests were performed. This was due to logistic reasons, to avoid the effects of cognitive test on immune response and minimise diurinal variation of circulating Interleukin-6 in humans (Nilsonne, Lekander, Åkerstedt, Axelsson, & Ingre, 2016). Also, cortisol levels were expected to be on the decline at this time (10:00–12:30), after the early morning peak (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007). Nevertheless, evidence shows that there is considerable consistency on immune responses to acute laboratory stressors induced by cognitive tasks across time and across similar tasks (Adler et al., 2002; Cohen & Hamrick, 2003).

Blood samples were collected via venepuncture in K2EDTA tubes and tubes with gel SST for serum separation (Surgical Supplies Ltd., Auckland, New Zealand). The EDTA samples were immediately analysed for red and white blood cell counts, haematocrit and haemoglobin concentration on a Sysmex XT automated quantitative haematology