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Correlation between interferon γ and interleukin 6 with PTSD and resilience

Dagmar Bruenig[a,c], Divya Mehta[b], Charles P. Morris[a], Bruce Lawford[a], Wendy Harvey[c], Ross McD Young[b], Joanne Voisey[a,*]

[a] Institute of Health and Biomedical Innovation (IHBI) and School of Biomedical Sciences, 60 Musk Avenue, Queensland University of Technology, Kelvin Grove, Queensland 4059, Australia
[b] Institute of Health and Biomedical Innovation (IHBI) and School of Psychological and Counselling, 60 Musk Avenue, Queensland University of Technology, Kelvin Grove, Queensland 4059, Australia
[c] Gallipoli Medical Research Institute, Greenslopes Private Hospital, Newdegate Street, Greenslopes, Queensland 4120, Australia

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ABSTRACT

Posttraumatic Stress Disorder (PTSD) is a debilitating psychiatric disorder with decreased general health prognosis and increased mortality. Inflammation has been hypothesised to be a link between PTSD and the most common co-morbid medical disorders. However, the relationship between inflammation and PTSD is not clear. Individual inflammatory markers have shown variable associations with PTSD. This study investigates the correlations between serum cytokines, PTSD and resilience in a cohort of Caucasian Vietnam combat veterans (n = 299). After correction for multiple testing, PTSD severity was correlated with small but significant decreases in interleukin 6 and interferon γ (p = 0.004, p = 0.013, respectively) whereas resilience was correlated with increased levels of interleukin 6 and interferon γ (p = 0.023; p = 0.007, respectively). Analyses of sub-symptoms of PTSD revealed that mood and arousal symptoms showed the most significant effect on interleukin 6 and interferon γ. More research is needed to further elucidate the mechanisms underlying the relationship between cytokine levels, PTSD sub-symptoms and trauma outcomes to improve the knowledge base of differences in trauma response and the biological system.

1. Introduction

Posttraumatic Stress Disorder (PTSD) is a debilitating psychiatric disorder (American Psychiatric Association, 2013). Cohorts with high risks of trauma exposure are at particular risk of developing PTSD. For military personnel it is estimated that between 20% and 30% of veterans will develop PTSD (Australian Government, D.o.V.A, 2014; Dohrenwend et al., 2006; Hoge et al., 2004). In addition to the severe negative psychological sequelae, PTSD has also been linked to poorer general health and higher mortality (Boscarino, 2008), especially an increased risk for cardiovascular problems and autoimmune disorders such as rheumatoid arthritis (Edmondson et al., 2013; Lee et al., 2016; Stein et al., 2016; Wolf et al., 2016). The molecular mechanisms underlying the psychological sequelae and medical disorders remain unclear. However, inflammatory pathways have been hypothesised as a potential link (Leonard and Maes, 2012). For example, interferon γ is a cytokine that has been shown to affect serotonin through the tryptophan-kynurenine pathway and is implicated in age-related medical and psychiatric processes (Oxenkrug, 2011). Interleukin 6 is a cytokine that can also cross the blood-brain barrier impacting on the hypothalamus to regulate body temperature but also influencing sleep and stress reactions (Rohleder et al., 2012).

Studies investigating inflammatory markers have consistently shown increased inflammation in PTSD patients (Groer et al., 2015; Lindqvist et al., 2016, 2014; O'Donovan et al., 2015), and two recent genome-wide association studies found associations with genes that are relevant in the context of inflammation (Powers et al., 2016; Stein et al., 2016). Case/control studies investigating individual inflammatory markers and PTSD have shown mixed results (Guo et al., 2012; O'Donovan et al., 2015; von Kanel et al., 2007), and the evidence is even less clear with depression, one of the most frequent co-morbidities of PTSD (Dahl et al., 2014; Schmidt et al., 2016). A recent meta-analysis found increased levels of interleukin 6 (IL6), interleukin 1β (IL1β), tumour necrosis factor α (TNFα) and interferon γ (IFN γ) in a PTSD cohort as opposed to healthy controls. However, heterogeneity of data was high, mostly due to factors such as medication and major depressive disorder (Passos et al., 2015). Only a small number of studies with limited participant numbers for IFNγ analysis were recorded (n = 79) and a potential publication bias for IL 1β was noted (Passos et al., 2015). A replication of the meta-analysis showed that the potential

* Corresponding author.
E-mail address: j.voisey@qut.edu.au (J. Voisey).

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effect size of IL 6 was probably overestimated (Nilsonne et al., 2016).

Two replication studies investigating inflammatory markers in large military cohorts found increased overall levels of inflammation but varying evidence for increased cytokine levels on an individual marker basis (Lindqvist et al., 2016, 2014). The authors consistently found elevated IL 6 levels based on PTSD diagnosis but not in relation to PTSD severity. They did not find a significant association between IFNγ and PTSD. Increased levels of IFNγ in PTSD were found in an Asian cohort (Guo et al., 2012) and a very small study cohort of combat veterans (Hammad et al., 2012), but a study in a much larger military cohort could not replicate these findings (Lindqvist et al., 2016).

A recent study using a cohort of trauma exposed Nepali child soldiers identified decreased inflammatory gene expression profiles to be associated with increased resilience r (Kohrt et al., 2016). These gene expression profiles were similar to PTSD free civilian children. A study with a female cohort found that women in recovery from PTSD have the same levels of inflammation as healthy controls, suggesting that improved psychological states and associated health perceptions contributed to reduced levels of inflammation (Gill et al., 2013). Another study found that coping factors such as pride and contentment are associated with decreased levels of IL 6 (Stellar et al., 2015). These findings suggest that positive beliefs and emotions are associated with reduced inflammation. Resilience is typically associated with generally positive attitudes and emotions (Bonanno, 2004) and is worthy of closer investigation regarding the association with inflammatory markers.

Given the mixed research findings the correlation between serum cytokine levels and PTSD, symptom severity and resilience in a large Vietnam veteran cohort was investigated. PTSD diagnosis was hypothesised to be associated with increased levels of cytokines. It was further hypothesised that increased symptom severity would positively correlate with the inflammatory marker and resilience negatively correlate with cytokine levels.

2. Method

2.1. Participants

A total of 299 male and age-matched participants were recruited through Greenslopes Private Hospital and the Returned and Services League of Australia by the Gallipoli Medical Research Foundation. Of these, 159 participants met criteria for PTSD diagnosis and the remaining 140 participants were assigned to the control group. PTSD diagnosis was obtained through structured interviews by psychiatrists with substantial clinical expertise in the assessment and differential diagnosis of PTSD. Inclusion criteria included deployment to Vietnam during the Vietnam War in the Australian and New Zealand Defence Force. The mean age of the cohort was 68.82 years (*SD* = 4.2). Clinical psychologists performed further assessments using validated psychological measures. Medical Officers conducted semi-structured interviews to collect a medical history for each participant. Table 1 shows an overview of the characteristics of the cohort by diagnostic status.

2.2. Ethics

Each participant gave written informed consent before commencement of data collection. Ethics approval for the project was obtained from the Human Research Ethics Committees of the Queensland University of Technology and Greenslopes Private Hospital. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.3. Biomarker analysis

A fasting sample of peripheral blood was taken from participants. Whole blood was collected in an 8.5 ml serum separator tube (SST). The tubes were left standing upright for 30 min for clotting to occur and then spun at 1500 g for 10 min at 20 °C. The serum was aliquoted into micro-tubes with a minimum 0.5 ml each. The tubes were stored frozen at −80 °C. A commercial laboratory, Sullivan Nicolaides Pathology, Brisbane, tested a range of cytokines in standard multiplex assay (interleukin-1 α, interleukin-1β, interleukin-6, interleukin-10, tumour necrosis factor α, and interferon γ) in duplicate using Luminex 100 Milliplex cytokine multiplex bead assay (HCYTOMAG-60K; assay sensitivity: 0.8 pg/ml; intra-assay CV% = 1.6; inter-assay CV% = 12.0). Findings relating to Tumour Necrosis Factor Alpha in connection with genetics hypotheses have previously been published by us (Bruenig et al., 2017) The remaining cytokines were further analysed for serum level association of PTSD severity and resilience. Samples (n = 37) that were approaching detectable limit for at least one of the cytokines assayed on the multiplex were reanalysed. Taken together, 299 data points remained for subsequent analyses across all cytokines based on averages from the first run or, if detectable values were observed, from the second run. Data was recoded to 0 if a reading was below lower detection limit (LDT) yielding the following percentage of data below lower detection limit (IL1 α = 53.85%, IL 1β = 91.64%, IL 6 = 85.00%, IL 10 = 66.90%, IFNγ = 43.81%).

Table 1
Demographics and clinical summary.

	PTSD (159)	No PTSD (140)	*p*-value
Age *M* (*SD*)	68.47 (4.16)	69.23 (4.13)	0.113
Marital Status (current)			0.494
Married (current)	116	108	
Divorced/Separated (current)	9	8	
Psychotropic Medication	Yes: 94 No: 51	Yes: 15 No: 112	5.498E-19
Education level			0.005
Less than year 10	26	8	
Year 10	29	23	
Vocational	32	20	
Year 11 or 12	34	33	
University	37	56	
Comorbidities[a]			
Major depression	21	2	4.190E-04
Suicide risk	31	2	2.000E-06
Agoraphobia	33	6	8.000E-05
Social phobia	8	0	0.017
Alcohol dependence	22	6	0.019
Alcohol abuse	4	1	0.029
Generalised anxiety disorder	12	3	0.092
Auto-Immune Disorders			0.806
Rheumatoid Arthritis	3	5	
Psoriasis	2	0	
Other	7	5	

Note. *M* = mean; *SD* = standard deviation.
[a] all comorbidity counts as per Mini International Neuropsychiatric Interview (MINI) for DSM IV (Sheehan et al., 1998). Only a subset of all comorbidities is shown. Rare comorbidities with no current information or both groups = 0 were excluded from the table. Only autoimmune disorders are shown for physical conditions.

2.4. Scales

Clinician-Administered PTSD Scale for DSM 5 (CAPS-5): Clinical psychologists assessed severity of PTSD with the Clinician Administered PTSD Scale for DSM 5 (CAPS-5) (Weathers et al., 2014). Higher scores reflect increased PTSD severity.

The Connor-Davidson Resilience Scale (CD RISC) measures resilience via a range of self-reported behaviours and beliefs thought to be successful in dealing with adverse situations (Connor and Davidson, 2003). The scale has sound psychometric properties (Bezdjian et al., 2016). Higher scores indicate higher resilience. Cronbach's Alpha was high: α = 0.92.

The Mini International Neuropsychiatric Interview DSM IV (MINI), an instrument designed to assess Axis 1 disorders with high validity and