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Waheed, Dalton, et al.

1 A Systematic Review of Interleukin (IL) -1 $\beta$  in Post-Traumatic Stress Disorder: Evidence from Human and  
2 Animal Studies

3 (Short Title: Systematic review of IL-1 $\beta$  and PTSD)

4

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20

21 **Keywords:** Interleukin-1beta (IL-1 $\beta$ ), Post-Traumatic Stress Disorder (PTSD), cytokines, biomarker

22

23

24 **Abstract**

25 Pro-inflammatory cytokines, such as IL-1 $\beta$ , have been implicated as underlying pathophysiological  
26 mechanisms and potential biomarkers of Post-Traumatic Stress Disorder (PTSD). This systematic  
27 review examines data regarding IL-1 $\beta$  production/concentration in human and animal studies of PTSD.  
28 In accordance with PRISMA guidelines, relevant articles from PubMed were reviewed from inception  
29 until 10<sup>th</sup> July 2017.

30 Nineteen studies were eligible for inclusion. Animal studies demonstrated increased hippocampal IL-  
31 1 $\beta$  in rodent models of PTSD. Several immunomodulatory drugs were shown to reduce elevated IL-1 $\beta$   
32 levels and anxiety-like behaviours in animals. Human cross-sectional studies showed contradictory  
33 results; serum and plasma IL-1 $\beta$  concentrations in PTSD patients were either elevated or did not differ  
34 from control groups. *In-vitro* IL-1 $\beta$  production by stimulated cells demonstrated no difference  
35 between PTSD and control participants, although spontaneous *in-vitro* production of IL-1 $\beta$  was  
36 increased in the PTSD group. The findings from two longitudinal studies were inconsistent.

37 Given the conflicting findings, it is premature to consider IL-1 $\beta$  as a biomarker of PTSD. Anti-  
38 inflammatory agents may reduce IL-1 $\beta$ , and be a potential basis for future therapeutic agents in PTSD  
39 treatment. More longitudinal research is needed to better understand the role of IL-1 $\beta$  in the  
40 development and/or maintenance of PTSD.

41

42 **Introduction**

43 Post-traumatic Stress Disorder (PTSD) is a chronic psychiatric disorder that can develop in response to  
44 exposure to a catastrophic threat. Triggers can include war, sexual or physical assault, and natural  
45 disasters. Throughout history the condition has had various labels, including 'Shell Shock' and 'Stress  
46 Response Syndrome', although it was not until the late twentieth century that it was included in the  
47 diagnostic classifications used in psychiatry practice today (American Psychiatric Association 2013).  
48 PTSD was first included in the Diagnostic and Statistical Manual (DSM) of the American Psychiatric

49 Association in 1980, followed by inclusion in the World Health Organisation's International  
50 Classification of Diseases (ICD) over a decade later, in 1992 (World Health Organization 1992).  
51 Although similar, the two systems provide differing criteria for which to diagnose patients potentially  
52 suffering from PTSD.

53 PTSD diagnosis and assessment

54 *PTSD diagnosis.* Specifically, the ICD-10 classification requires patients to have been exposed to a  
55 stressful event which is perceived as threatening and causes them distress (World Health Organization  
56 1992). No minimum length of exposure is stated, however, symptoms should begin within six months  
57 of the traumatic exposure. The trauma is regularly revisited by the patient through intrusive dreams,  
58 memories, or flashbacks, particularly if the individual finds themselves in a similar situation to the  
59 initial trauma. Patients actively avoid situations associated with the trauma or block out memories  
60 pertaining to the event. In addition, patients should experience two or more of the following  
61 symptoms in order for the diagnosis to be made: difficulty falling asleep, lability of mood or emotional  
62 outbursts, concentration deficits, hyper-arousal or an increased startle response. These symptoms  
63 ought to be of new onset following the trauma, and are indicative of amplified psychological sensitivity  
64 (World Health Organization 1992).

65 Similarly, to fulfil a diagnosis of PTSD according to DSM-5 criteria (American Psychiatric Association  
66 2013), patients should have experienced an event involving actual or threat of death, sexual or  
67 physical violence, or serious injury. This may be through direct exposure, witnessing an event, or being  
68 informed that an acquaintance or relative was involved in a traumatic event. Akin to the ICD-10  
69 classification, re-experiencing the trauma is required, although not necessarily as nightmares or  
70 flashbacks. Severe emotional distress or physical reactivity can also be diagnostic. Avoidance of  
71 circumstances or thoughts related to the trauma and two or more negative emotions must also be  
72 present, or become progressively worse following the trauma. These may include feelings of isolation,  
73 persecutory thoughts, or being unable to remember facts relating to the event. The patient also needs

74 to suffer from 2 or more symptoms of hyper-arousal, again equivalent to ICD-10 criteria. Unique to  
75 DSM-5, the patient's symptoms must be severe enough to cause distress and deterioration of normal  
76 function, which cannot be explained by other factors, such as changes in medication or co-morbid  
77 pathology, and should persist for a minimum of one month following the initial trauma. All elements  
78 of the criteria must be fulfilled for over 1 month duration for a confident diagnosis to be made  
79 (American Psychiatric Association 2013).

80 *Assessment of PTSD.* The ICD-10 or DSM-5 criteria are commonly used for research purposes and for  
81 the clinical diagnosis of PTSD. In clinical as well as in research practice, the structured clinical interview  
82 for the DSM-IV axis I disorders (SCID-IV), and more recently the SCID-5, are standard validated  
83 diagnostic tools with good sensitivity and inter-rater reliability that are used to make the diagnosis  
84 according to DSM-IV and DSM-5 (Elhai et al 2008; Lobbestael et al 2011). In research, self-administered  
85 PTSD questionnaires are also used, including the PTSD Checklist (PCL; Blanchard et al 1996; a civilian  
86 and military version are also available, PCL-C and PCL-M respectively; Weathers et al 2013), the Los  
87 Angeles Symptom Checklist (LASC; King et al 1995), and the Posttraumatic Diagnostic Scale (PDS; Foa  
88 et al 1997; Sheeran and Zimmerman 2002). Although quicker to perform, these measures may have a  
89 tendency to over-diagnose patients (Griffin et al 2004). Currently, the gold standard tool for assessing  
90 PTSD symptom severity is the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; American  
91 Psychiatric Association 2013; Blake et al 1995).

92 *Animal models of PTSD.* Rodents are typically used and are subjected to various validated stress-  
93 paradigms in order to simulate a PTSD-like state in the animals (Goswami et al 2013). Two examples  
94 are the Stress-Enhanced Fear Learning (SEFL) model and the Single Prolonged Stress (SPS) procedure.  
95 In SEFL rodents are given multiple electric shocks, at a later time they are then placed in a different  
96 environment and given a single shock as a reminder of the original stressful event. Freezing time  
97 and/or immobility is used as a measure of a learned fear response (Rau et al 2005). In the SPS  
98 procedure, several stressors are administered to the rodent, including restraint, forced swimming, and

99 ether, followed by a period of inactivity (Yamamoto et al 2009). In PTSD models, various behavioural  
100 tests, including the open field test, are then subsequently performed to confirm the presence of pre-  
101 defined PTSD traits, such as hyperarousal and social withdrawal. Following the implementation of an  
102 animal model, medication trials, behavioural experiments, and cellular analysis can then be  
103 performed.

#### 104 The pathophysiology of PTSD

105 An important biological factor involved in the pathophysiology of PTSD seems to be brain morphology  
106 and function. Studies have demonstrated gross morphological differences between the brains of PTSD  
107 patients and healthy controls (Woon and Hedges 2009; Zandieh et al 2016). These include changes to  
108 the hippocampus, amygdala, and prefrontal cortex, which may account for the symptoms of PTSD,  
109 given their involvement in memory, emotion and personality, and behavioural functioning.  
110 Specifically, hippocampal volume and grey matter density were found to be reduced in PTSD patients  
111 compared to healthy controls (Gilbertson et al 2002). Also, studies have demonstrated reduced  
112 amygdala volumes in PTSD patients (Morey et al 2012). Interestingly, stress has been shown to lead  
113 to increases in pro-inflammatory cytokines (Lopez-Castejon and Brough 2011; Wilson et al 2013) and  
114 kynurenine pathway metabolites which can both be neurotoxic in the hippocampus, the amygdala  
115 and prefrontal cortex (Kim and Won 2017).

#### 116 Current review

117 As PTSD is a heterogeneous disorder, it is likely that there are multiple mechanisms underlying the  
118 development and maintenance of the disorder and therefore, several possible biomarkers.  
119 Inflammatory processes are one possible biomarker of PTSD (Michopoulos et al 2015). Existing  
120 literature indicates that pro-inflammatory cytokines could be a contributing factor to the  
121 pathophysiology of PTSD and play a role in PTSD-related elevated risk for cardiovascular, autoimmune,  
122 and neurodegenerative diseases, although the precise mechanisms remain unclear.

123 The current review will focus upon IL-1 $\beta$  as it is a key cytokine that has been implicated in  
124 neuroplasticity and the process of memory formation (Lopez-Castejon and Brough 2011). Secreted  
125 from macrophages, microglia and astrocytes, IL-1 $\beta$  has roles in host defence, tissue injury during acute  
126 and chronic inflammatory disease, and auto-inflammatory conditions. A recent meta-analysis found  
127 that several pro-inflammatory cytokines, including IL-1 $\beta$ , are elevated in PTSD patients in comparison  
128 to control groups (Passos et al 2015). This meta-analysis focused on human cross-sectional *in-vivo*  
129 measurements and did not account for *in-vitro* measurements, longitudinal investigations, nor animal  
130 studies. Thus, the current review is warranted to provide a more comprehensive and up-to-date  
131 summary of the available literature. The purpose of this systematic review is to summarise the  
132 evidence regarding IL-1 $\beta$  and PTSD in human and animal literature, with a view to adding to current  
133 understanding of the condition and its pathophysiology, and to assess its potential as a biomarker for  
134 PTSD and its treatment. If an association is identified between IL-1 $\beta$  and PTSD, this could provide a  
135 potential future treatment target for PTSD, as blocking medications are available.

## 136 **Methods**

### 137 Selection Criteria

138 Articles were eligible for inclusion in the review if they reported on original research pertaining to both  
139 IL-1 $\beta$  and PTSD in human or animal studies. Specifically, studies of any design that assessed IL-1 $\beta$   
140 production *in-vitro* or IL-1 $\beta$  concentration in the serum, plasma, or cerebrospinal fluid (*in-vivo*) of  
141 individuals with PTSD were eligible for inclusion. Studies were included if they reported a group and/or  
142 longitudinal comparison of IL-1 $\beta$  concentration and/or production. Publications reporting on the  
143 measurement of IL-1 $\beta$  in animal models of PTSD were also included.

144 Studies were excluded if: (i) they did not report group or longitudinal comparisons in concentration or  
145 production of IL-1 $\beta$ ; (ii) they presented purely genetic or IL-1 $\beta$  receptor data; (iii) participants were  
146 not formally diagnosed with PTSD according to a validated assessment tool or diagnostic criteria; and  
147 (v) life trauma, childhood trauma or distress caused by chronic illness, rather than PTSD, was

148 investigated. Review articles, meta-analyses, conference proceedings/abstracts, editorials, letters,  
149 book chapters, and unpublished theses were also not included.

#### 150 Search Strategy

151 Using PubMed and in accordance with the PRISMA guidelines (Moher et al 2009), a search from  
152 inception until 10<sup>th</sup> July 2017 was conducted. The following search terms were used to identify all  
153 potentially eligible records:

154 (("post-traumatic stress disorder"[Title/Abstract]) OR ("PTSD"[Title/Abstract]) OR ("posttraumatic  
155 stress disorder"[Title/Abstract]) OR ("post traumatic stress disorder"[Title/Abstract])) AND  
156 (("interleukin-1"[Title/Abstract]) OR ("interleukin-1 $\beta$ "[Title/Abstract]) OR ("interleukin-1  
157  $\beta$ "[Title/Abstract]) OR ("interleukin-1 beta"[Title/Abstract]) OR ("interleukin-1beta"[Title/Abstract])  
158 OR ("interleukin 1"[Title/Abstract]) OR ("interleukin 1 $\beta$ "[Title/Abstract]) OR ("interleukin 1  
159  $\beta$ "[Title/Abstract]) OR ("interleukin 1 beta"[Title/Abstract]) OR ("interleukin 1beta"[Title/Abstract])  
160 OR ("IL-1"[Title/Abstract]) OR ("IL-1 $\beta$ "[Title/Abstract]) OR ("IL-1  $\beta$ "[Title/Abstract]) OR ("IL-1  
161 beta"[Title/Abstract]) OR ("IL-1beta"[Title/Abstract]) OR ("IL 1"[Title/Abstract]) OR ("IL  
162 1 $\beta$ "[Title/Abstract]) OR ("IL 1  $\beta$ "[Title/Abstract]) OR ("IL 1 beta"[Title/Abstract]) OR ("IL  
163 1beta"[Title/Abstract]))

164

165 This search was supplemented by internet searches and hand-searches of reference lists of included  
166 papers and potentially relevant reviews. Citation tracking in Web of Science was also performed. The  
167 abstracts of identified articles were subsequently screened for eligibility according to pre-set inclusion  
168 and exclusion criteria, as described above. Potentially eligible records were further reviewed in full  
169 text. Subsequently, the articles included in the qualitative synthesis were categorized into animal and  
170 human studies and then further divided according to their study design. An overview of the literature  
171 search is shown in Figure 1.

#### 172 Data Extraction



173 The data from all eligible studies was extracted into an electronic summary table by the first author  
174 (AW), which was then checked by another author (BD). Information collected related to the sample  
175 characteristics, method of PTSD assessment and measurement of IL-1 $\beta$ , and relevant findings.

176 **INSERT FIGURE I HERE**

## 177 Results

### 178 Characteristics of included studies

179 A total of 19 articles were eligible for inclusion in this review. Eight of the included articles used animal  
180 models of PTSD to investigate the relationship between IL-1 $\beta$  and PTSD (Aga-Mizrachi et al 2014;  
181 Deslauriers et al 2017; Jones et al 2015; Lazuko et al 2017; Lee et al 2016; Liu et al 2016; Peng et al  
182 2013; Zimmerman et al 2012). Twelve studies assessed IL-1 $\beta$  concentration or production in humans.  
183 Nine of these were *in-vivo* cross-sectional human studies measuring plasma, or serum concentration  
184 of IL-1 $\beta$  (Bersani et al 2016; Hoge et al 2009; Jergović et al 2015; Lindqvist et al 2014; Oganessian et al  
185 2009; Spivak et al 1997; Tucker et al 2004; von Känel et al 2007; Zhou et al 2014). Of these, two studies  
186 also assessed serum IL-1 $\beta$  longitudinally in individuals with PTSD (Jergović et al 2015; Tucker et al 2004)  
187 and one study reported both human and animal data (Zimmerman et al 2012). Two additional human  
188 cross-sectional study assessed IL-1 $\beta$  production *in-vitro* (Gill et al 2008; Gola et al 2013).

### 189 Study findings: Animal studies

190 All included animals studies used rodents in their animal models of PTSD. A variety of animal models  
191 were used (e.g. SPS, SEFL, enhanced SPS, predator scent exposure) to induce PTSD-like traits; the  
192 majority involved applying a shock to the foot of the animal. Most studies measured hippocampal IL-  
193 1 $\beta$  levels (Jones et al 2015; Lee et al 2016; Liu et al 2016; Peng et al 2013), with three remaining studies  
194 measuring serum concentrations of IL-1 $\beta$  (Aga-Mizrachi et al 2014; Lazuko et al 2017; Zimmerman et  
195 al 2012) and the other measuring brain protein levels (Deslauriers et al 2017). The results of these  
196 studies are presented in Table I.

197 Elevated serum IL-1 $\beta$  levels in the PTSD-groups, as compared to the control groups were identified  
198 (Aga-Mizrachi et al 2014; Lazuko et al 2017). In Aga-Mizrachi et al (2014), these elevated serum IL-1 $\beta$   
199 levels were subsequently reduced upon administration of antidepressants (desipramine and  
200 fluoxetine) or methylphenidate, a stimulant of the central nervous system. The combination of the  
201 SSRI fluoxetine and methylphenidate reduced IL-1 $\beta$  to undetectable levels. In contrast, Zimmerman et  
202 al (2012) reported that IL-1 $\beta$  serum levels did not differ between the stressed and non-stressed  
203 groups. However, when stressed mice were administered mEN101, an oligonucleotide with anxiolytic  
204 effects, levels of IL-1 $\beta$  were significantly lower than in the non-treated stress group. Three studies also  
205 reported increased IL-1 $\beta$  levels in the hippocampus of stress-induced rats (Jones et al 2015; Lee et al  
206 2016; Peng et al 2013). Specifically, Jones et al (2015) showed that hippocampal IL-1 $\beta$   
207 immunoreactivity and mRNA expression increased in a time-dependent manner post-stressor. This  
208 effect was most prominently observed in the dentate gyrus of the dorsal hippocampus. Furthermore,  
209 stress-induced rats given morphine 48-hours post-stressor, showed a significant reduction in  
210 hippocampal IL-1 $\beta$  levels. Similarly, in Peng et al., the hippocampal IL-1 $\beta$  levels reduced in a dose-  
211 dependent manner with the administration of gastrodin, a main constituent of a Chinese herbal  
212 medicine. These reductions in IL-1 $\beta$  levels were also associated with improvements in PTSD-like  
213 behaviour. Additionally, Lee et al (2016) found that the elevated levels of IL-1 $\beta$  hippocampal mRNA  
214 expression observed in the stressed rats, was reduced by the administration of fluoxetine to similar  
215 IL-1 $\beta$  levels seen in the non-stressed rats. In contrast, Liu et al (2016) found no significant difference  
216 in hippocampal IL-1 $\beta$  levels between SPS-exposed rats and controls; however, elevated levels of  
217 malondialdehyde, a marker of oxidative stress, were found in the hippocampus (Yang et al 2013).  
218 Deslauriers et al (2017) also found no difference in IL-1 $\beta$  levels in predator stress exposed male  
219 C57BL/6 mice compared to non-exposed mice.

220

**INSERT TABLE I HERE**

221 Study findings: Human Studies

222 *PTSD assessment.* In the majority of studies, PTSD diagnosis had been made using versions of the DSM  
223 or ICD. The majority of studies also used validated questionnaires to measure PTSD symptom severity  
224 in the study. The CAPS was used in 8 studies, 2 of these used it in combination with the SCID (Bersani  
225 et al 2016; Tucker et al 2004) and one with the PCL-M (Zhou et al 2014). One study (Hoge et al 2009)  
226 used the Short Post-Traumatic Stress Disorder Rating (SPRINT; Connor and Davidson 2001) , one used  
227 the LASC (Jergović et al 2015) and one the Hebrew version of the PTSD Inventory (Spivak et al 1997).

228 *Cross-sectional studies measuring IL-1 $\beta$  in-vivo.* Five of the included cross-sectional studies identified  
229 elevated IL-1 $\beta$  concentrations in the plasma or serum of PTSD participants, as compared to a control  
230 group (Hoge et al 2009; Oganessian et al 2009; Spivak et al 1997; Tucker et al 2004; Zimmerman et al  
231 2012). The remaining five studies found no difference in serum or plasma concentrations of IL-1 $\beta$   
232 between participants with and without PTSD (Bersani et al 2016; Jergović et al 2015; Lindqvist et al  
233 2014; von Känel et al 2007; Zhou et al 2014). Details of these studies are presented in Table II.

234 Of note, plasma IL-1 $\beta$  concentration were found to positively correlate with recognised PTSD  
235 symptoms, including re-experiencing, avoidance and co-morbid anxiety and depression, although  
236 when controlling for co-variables, such as depression, the results became insignificant (von Känel et al  
237 2007). Spivak et al (1997) reported a positive correlation between serum IL-1 $\beta$  concentration and PTSD  
238 symptom duration. This association remained even when adjusting for subject demographics.  
239 Additionally, Oganessian et al (2009) noted a positive correlation between IL-1 $\beta$  and CH50 levels, a  
240 marker-measure of activation of the classic complement pathway, suggestive of an immunological  
241 component to PTSD pathophysiology. Zimmerman et al (2012) identified a significant inverse  
242 correlation between IL-1 $\beta$  serum levels and hippocampal volume in a subset of PTSD patients (n=5).  
243 No correlations were identified between IL-1 $\beta$  serum levels and other brain structures.

244 *Cross-sectional studies measuring IL-1 $\beta$  in-vitro.* Two studies assessed IL-1 $\beta$  production using *in-vitro*  
245 methods; details regarding these are presented in Table II. Gola et al (2013) assessed spontaneous  
246 and lipopolysaccharide (LPS)-induced IL-1 $\beta$  production in peripheral blood mononuclear cells (PBMCs)

247 of refugees, with and without PTSD. Participants with PTSD were found to spontaneously produce  
248 elevated levels of IL-1 $\beta$ , as compared to those without PTSD. Spontaneous IL-1 $\beta$  production and PTSD  
249 symptom severity (in PTSD group only) were found to be correlated at trend level. However, no  
250 difference in LPS-induced IL-1 $\beta$  production was observed between these groups. Similarly, Gill et al  
251 (2008) found no differences between females with PTSD, females who experienced trauma but did  
252 not go on to develop PTSD, and healthy females in stimulated phytohaemagglutinin (PHA) combined  
253 with LPS production of IL-1 $\beta$  from whole blood samples.

254 *Longitudinal studies measuring IL-1 $\beta$  in-vivo.* Two of the included studies employed a longitudinal  
255 design (Jergović et al 2015; Tucker et al 2004). The results of these studies are presented in Table II.  
256 In Jergović et al (2015), serum IL-1 $\beta$  was measured on two separate occasions, three months apart, in  
257 male Croatian combat veterans with PTSD. An increase in IL-1 $\beta$  concentration was found between the  
258 first and second assessment. Of note, IL-1 $\beta$  was not detectable in a proportion of participants at both  
259 time points. Tucker et al (2004) performed a double-blind randomised controlled trial of selective  
260 serotonin reuptake inhibitors (sertraline and citalopram) and placebo treatment in outpatients with  
261 PTSD. In contrast to Jergović et al (2015), serum IL-1 $\beta$  was found to significantly decrease over the trial  
262 for all treatment groups.

263 **INSERT TABLE II HERE**

## 264 Discussion

265 The current review summarises and integrates the existing data on concentrations and production of  
266 IL-1 $\beta$  in PTSD. Data from the included animal studies demonstrated an increase in serum IL-1 $\beta$   
267 concentration and a time-dependent elevation in hippocampal IL-1 $\beta$  levels in PTSD-modelled rats  
268 (Aga-Mizrachi et al 2014; Jones et al 2015; Lazuko et al 2017; Lee et al 2016; Peng et al 2013). In  
269 particular, this was observed in the dentate gyrus of the dorsal hippocampus, suggesting that  
270 inflammation in this neural region, with roles in memory processing and autonomic functions, may be  
271 integral to PTSD pathophysiology. Conversely, no difference in IL-1 $\beta$  levels between PTSD-modelled

272 rats and controls was observed in three studies (Deslauriers et al 2017; Liu et al 2016; Zimmerman et  
273 al 2012), highlighting the need for further research into cytokine levels in animal models of PTSD. As  
274 a centre for emotional processing, dysregulation of inflammatory processes in the amygdala may  
275 equally contribute to PTSD symptoms, particularly those effecting mood (Shin et al 2006). However,  
276 Jones et al. identified no increase in IL-1 $\beta$  in the basolateral amygdala. More research is needed to  
277 assess IL-1 $\beta$  levels in alternative neural regions that have been implicated in PTSD.

278 Interestingly, in the animal studies a range of treatment medications were found to reduce both IL-1 $\beta$   
279 levels and PTSD-like behaviours, including antidepressants (Aga-Mizrachi et al 2014), apocynin, an  
280 inhibitor of NADPH oxidase (Liu et al 2016), and gastrodin, an inhibitor of nitric oxide synthase (Peng  
281 et al 2013). This not only contributes further evidence to the role of oxidative stress and inflammatory  
282 mechanisms in PTSD pathophysiology, but also suggests that such compounds may be useful as future  
283 pharmacological therapies for PTSD. Similarly, morphine was found to decrease IL-1 $\beta$  in the dorsal  
284 hippocampus (Jones et al 2015), suggestive of a protective role of opioid signalling in the physiological  
285 response to trauma. In summary, the majority of animal studies suggest an associative link between  
286 elevated IL-1 $\beta$  and PTSD; however, the small number of animal studies identified in this review makes  
287 drawing solid conclusions difficult, particularly concerning serum IL-1 $\beta$ , where only three studies were  
288 available.

289 Half of the human cross-sectional studies found that serum or plasma IL-1 $\beta$  concentrations were  
290 elevated in those with PTSD compared to control participants (Hoge et al 2009; Oganessian et al 2009;  
291 Spivak et al 1997; Tucker et al 2004; Zimmerman et al 2012). Spontaneous production of IL-1 $\beta$  was  
292 also found to be elevated in PTSD compared to non-PTSD groups (Gola et al 2013). The remaining  
293 studies found no significant difference in serum or plasma IL-1 $\beta$  concentrations between PTSD  
294 patients and controls (Bersani et al 2016; Lindqvist et al 2014; von Känel et al 2007; Zhou et al 2014)  
295 (Jergović et al 2015). Stimulated production of IL-1 $\beta$  also did not differ between PTSD and control  
296 groups (Gill et al 2008; Gola et al 2013). One factor that may contribute to the variable outcomes

297 observed is participant's use of corticosteroid treatments (e.g. prednisone, prednisolone and  
298 dexamethasone). These medications have anti-inflammatory effects (Greaves 1976), however, long-  
299 term steroid treatment was an exclusion criteria in only one study (Zhou et al 2014). Given the mixed  
300 findings and the lack of control for potential confounders such as glucocorticoid treatment, it would  
301 be premature to consider IL-1 $\beta$  as a biomarker of PTSD. Moreover, given that other pro-inflammatory  
302 cytokines (e.g. IL-6 and TNF- $\alpha$ ) were also shown to be elevated in patients with PTSD, as compared to  
303 controls, a combined pro-inflammatory cytokine score/index may be most appropriate as a biomarker.  
304 In addition, levels of these cytokines, and others, are typically elevated in people with moderate to  
305 severe depression (Dahl et al 2014). Therefore, cytokine levels may be a general marker of  
306 psychopathology, rather than specifically for PTSD.

307 There is much evidence from animal studies showing that both chronic and acute stress paradigms  
308 result in elevated levels of pro-inflammatory cytokines (e.g. Cosen-Binker et al 2004; Liu et al 2012).  
309 This includes elevated protein and mRNA levels of IL-1 $\beta$  in the brain (e.g. Minami et al 1991; Nguyen  
310 et al 1998; Pugh et al 1999). Furthermore, in humans, acute psychological stress has been shown to  
311 increase IL-1 $\beta$  gene expression (Brydon et al 2005). The mechanisms as to how stress leads to an  
312 increase of pro-inflammatory cytokine production is still unclear. Pro-inflammatory cytokines,  
313 including IL-1 $\beta$ , have an effect on the brain, and therefore, behaviour, via several mechanisms (Quan  
314 2008). For example, they have been shown to have effects on neurotransmitter synthesis, release and  
315 reuptake; neuroendocrine activity; neural plasticity; and changes in brain circuitry (Capuron and Miller  
316 2011). Therefore, stress may results in an increased production of pro-inflammatory cytokines and  
317 consequently trigger neurobiological changes, which may contribute to the development and/or  
318 maintenance of psychiatric disorders, such as PTSD and depression.

319 As previously mentioned, the hippocampus is a key brain structure implicated in PTSD (e.g. Kitayama  
320 et al 2005; O'Doherty et al 2015). In the animal studies described above, elevated IL-1 $\beta$  was observed  
321 in the hippocampi of PTSD-modelled rats and in one of the included human studies, IL-1 $\beta$  serum levels

322 were found to be inversely correlated with hippocampal volume in PTSD patients (Zimmerman et al  
323 2012) which may imply that elevated IL-1 $\beta$  production possibly leads to a decrease in hippocampal  
324 volume. Moreover, it has been suggested that elevated IL-1 $\beta$  concentration in the hippocampus may  
325 impair synaptic plasticity and memory (Patterson, 2015). However, the mechanisms as to how IL-1 $\beta$   
326 influences hippocampal volume and synaptic plasticity are not clear.

327 Only two longitudinal studies of IL-1 $\beta$  levels in PTSD patients were identified in this review, reporting  
328 contradictory findings in terms of IL-1 $\beta$ , however, both finding improvements in PTSD symptoms  
329 (Jergović et al 2015; Tucker et al 2004). Specifically, in a randomised controlled trial of anti-depressant  
330 medications (placebo vs. sertraline vs. citalopram), all treatment groups showed decreases in serum  
331 IL-1 $\beta$  at the end of treatment, compared to baseline (Tucker et al 2004). In contrast, Jergović et al  
332 (2015) found that serum concentrations of IL-1 $\beta$  increased over a period of 3-months. However, in  
333 approximately half of the samples IL-1 $\beta$  could not be detected, and this therefore limits our ability to  
334 draw firm conclusions. As there is limited longitudinal data on IL-1 $\beta$  concentrations in PTSD, future  
335 research should measure IL-1 $\beta$  over the treatment course to better determine how IL-1 $\beta$  is related to  
336 changes in PTSD symptom severity and associated treatment response. Given not everyone who is  
337 exposed to a traumatic event will go on to develop PTSD, prospective studies would also be of benefit  
338 in elucidating the role of cytokines in the development and maintenance of PTSD (Keane et al. 2009).

339 *Methodological considerations of the included studies.* Many of the included studies did not covary for  
340 potential confounding variables in their analyses or study design that could affect the cytokine  
341 concentration, for example, BMI, smoking, medication (e.g. corticosteroid treatments), blood sugar  
342 level and total cholesterol. High co-morbid rates of dyslipidaemia, coronary heart disease, smoking  
343 and obesity amongst PTSD sufferers have been observed. Given that factors associated with these  
344 (e.g. BMI, physical illnesses, medication, smoking; Dugué et al 1996) have been shown to impact upon  
345 cytokine concentrations, it would be important for future studies to take factors such as these into  
346 consideration. Another factor to take into consideration is that the studies included in the current

347 review used different PTSD assessment/diagnostic tools. The measures used to assess PTSD symptoms  
348 vary considerably on a range of factors, including number of items, response format, time frame, and  
349 degree of detailed enquiry. Therefore, studies may not be directly comparable with regards to PTSD  
350 symptom severity.

351 There are also several limitations of the included studies based on factors related to the sample that  
352 limit the generalisability of the findings. Generally, sample sizes are small and the majority of study's  
353 samples consisted of exclusively or predominantly males. This may be attributable to the inclination  
354 to study combat-associated PTSD, with males being more highly represented in armed services.  
355 However, considering the increased incidence of PTSD in females (Carmassi et al 2014), the presented  
356 data may not be able to account for potential sex differences in IL-1 $\beta$  levels and may not be  
357 generalisable to females with PTSD. Furthermore, many samples are limited to veterans with trauma  
358 exposure due to combat. We cannot be sure that individuals with different experiences of trauma  
359 exposure (e.g. with regards to time, type and extent of trauma exposure) will demonstrate similar  
360 alterations in cytokine levels (Wang and Young 2016). Future studies should consider investigating  
361 cytokine levels in non-military PTSD patients. Finally, several of the included studies used trauma  
362 controls, i.e. people that had previously been exposed to trauma (e.g. combat) but did not go on to  
363 develop PTSD, which may account for the findings observed in some of the studies. Although not  
364 meeting the clinical threshold for a formal PTSD diagnosis, the experience of trauma may cause  
365 intrinsic changes in cellular processes, which may result in a heightened pro-inflammatory status in  
366 the control group participants. For example, MRI studies have since shown cingulate isthmus and  
367 prefrontal volume reduction, not only in PTSD individuals, but also in those without diagnosed PTSD  
368 who have been previously exposed to traumatic events (Eckart et al 2011). However, it is still unclear  
369 as to what extent trauma exposure can influence inflammatory markers, even without the  
370 development of PTSD (Passos et al 2015).



371 *Limitations of the current review.* Our systematic review has a number of limitations. Firstly, PubMed  
372 was the only source of articles searched, potentially excluding some of the published literature on the  
373 subject. However, a hand-search was also conducted to identify any that may have been missed  
374 through the initial search. Secondly, given that several other pro- and anti-inflammatory cytokines  
375 have been implicated in PTSD, the exclusive focus on IL-1 $\beta$  may be deemed too narrow. Thirdly, as  
376 several of studies in this review, both animal and human, reported elevated IL-1 $\beta$  in PTSD groups,  
377 publication bias must also be taken into account.

## 378 Conclusion

379 Animal studies suggest that IL-1 $\beta$  expression/production, particularly in the hippocampus, may be  
380 involved in the underlying pathophysiology of PTSD. Anti-inflammatory agents were shown to reduce  
381 elevated IL-1 $\beta$  levels in animal studies, and therefore may be a potential basis for future therapeutic  
382 agents in PTSD treatment. The conflicting findings from human studies suggest that it is premature to  
383 consider IL-1 $\beta$  as a biomarker of PTSD. However, these findings need to be considered in light of a  
384 range of methodological issues, such as confounding variables and sample characteristics. Therefore,  
385 more research, taking into account these issues, is needed to determine whether IL-1 $\beta$  can be  
386 considered a specific biomarker of ~~PTSD~~ and therefore a potential therapeutic target for PTSD.  
387 Longitudinal research is needed to better understand the role of IL-1 $\beta$  in the development and/or  
388 maintenance of PTSD.

389

## 390 Author Disclosure Statement

391 No competing financial interests exist.

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