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The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: A systematic review and meta-analysis

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SHORT TITLE: Inflammation in anxiety and related disorders

KEYWORDS: anxiety disorders; biological markers; PTSD; SAD; OCD

Abstract

BACKGROUND: Anxiety is characterized by prolonged preparation for real or perceived threat. This may manifest both as psychological and physiological activation, ultimately leading to greater risk for poor health. Chronic inflammation may play an integral role in this relationship given the influential role that it has in chronic illness. The aim of this meta-analysis is to examine levels of chronic inflammation, measured by inflammatory cytokines and CRP, in people with anxiety disorders, PTSD, or OCD compared to healthy controls. Several moderating variables, including specific diagnosis and depression comorbidity, were also assessed. **METHODS:** 76 full-text articles were screened for eligibility with 41 studies ultimately included in analysis. **RESULTS:** Results demonstrated a significant overall difference between HCs and people with anxiety disorders in pro-inflammatory cytokines ($p = .013$, Hedge's $g = -0.39$), which appears to be largely driven by IL-1 β ($p = .009$, Hedge's $g = -0.50$), IL-6 ($p < .001$, Hedge's $g = -0.93$), and TNF- α ($p = .030$, Hedge's $g = -0.56$). Moderation analyses revealed a moderating effect of diagnosis ($p = .050$), as only individuals with PTSD demonstrated differences in inflammation between HCs ($p = .004$, hedge's $g = -0.68$). **CONCLUSIONS:** These data demonstrate the association between inflammatory dysregulation and diagnoses associated with chronic, impactful, and severe anxiety and provides insight into the way that anxiety, and in particular PTSD, is related to certain inflammatory markers. In doing so, these findings may provide an initial step in disentangling the relationship between anxiety and basic health processes.

The association between anxiety, traumatic stress, and obsessive-compulsive disorders and chronic inflammation: A systematic review and meta-analysis

Over the past several decades, the field of psychoneuroimmunology (PNI) has emerged in an effort to understand the interaction between the immune and the nervous system, and the role of behavior in this interaction. The primary goal of the immune system is to fight against infectious or otherwise harmful processes within the body that threaten overall healthy functioning (Sapolsky, 1994). However, many studies also demonstrate an association between stress and inflammation, where acute stress mainly stimulates inflammatory processes, while chronic stress is generally associated with dysregulation or inhibition of immune function (Segerstrom & Miller, 2004; Dhabhar 2014). Conversely, acute experimental inflammation increases anxiety in healthy subjects (Lasselin et al., 2016), and inflammation is increasingly implicated as a co-factor in the pathophysiological processes underlying psychiatric disorders (Goldsmith, Rapaport, & Miller, 2016; Passos et al., 2015). Therefore, detection of threat, either in the environment or in the inner milieu of the body, can connect anxiety with inflammatory activation.

Individuals experiencing chronic, distressing, and impairing anxiety are hypersensitive to threat-related contextual cues, leading to an increased likelihood of experiencing prolonged and/or more frequent physiological activation. Although anxiety disorders, post-traumatic stress disorder (PTSD), and obsessive-compulsive disorder (OCD) are categorically distinct, they share a number of common characteristics and are highly comorbid with one another. Among these, individuals experience distorted thinking due to excessive fear or worry (Turner, Beidel, & Stanley, 1992; Cox, 1996; Falsetti, Monnier, Davis, & Resnick, 2002), greater emotion dysregulation (Mennin, Heimberg, Turk, & Fresco, 2005; Weiss, Tull, Anestis, & Gratz, 2013) and engage in experiential avoidance of anxiety-inducing stimuli (either real or perceived;

Hayes, Wilson, & Gifford, 2015), subsequently putting them at an increased risk for overall psychological and physiological dysregulation regardless of diagnostic category. These individuals are also hypersensitive to contextual cues that may contribute to or maintain anxiety, thus leading to an increased likelihood of experiencing prolonged and/or more frequent physiological activation.

A central aspect of immune functioning is inflammation, which can be characterized as either acute or chronic. An acute inflammatory response is primarily activated when the body suffers illness or injury; cytokines or related proteins are triggered to the affected area by immune cells in the periphery, promoting the healing process by increasing immune activation at the damaged site. In an adaptive acute inflammatory response, following repair, the inflammatory activation is transient and the body returns to a state of homeostasis (Ryan & Majno, 1977). If unabated, however, the immune signaling to the brain can contribute to psychiatric symptoms (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). In addition, chronic low-grade inflammation is associated with an increased likelihood of experiencing a number of negative health outcomes, including congestive heart failure (Kaptoge et al 2013), inflammatory bowel disorder (Halpin & Ford, 2012), Alzheimer's disease (Swardfager, Lanctôt, Rothenburg, Wong, Cappell, & Herrmann, 2010), chronic obstructive pulmonary disease (Gan., Man, Senthilselvan, & Sin, 2004), cancer (Heikkilä et. al, 2009), and stroke (Kuo, Yen, Chang, Kuo, Chen, & Sorond, 2005). The vastness of the literature examining the relationship between chronic inflammation and physical diseases highlights the need to better understand physical and psychological risk factors for high rates of inflammation in an effort to understand the pathophysiology of prevalent disorders and to prevent long-term chronic health issues.

A diagnosis of an anxiety disorder, PTSD, or OCD is relevant to understanding inflammatory dysregulation, as these disorders are characterized by a chronic state of preparation and defense to possible threats and may therefore put the body at potential risk for negative health effects from long-term heightened physiological arousal. These disorders represent chronic, excessive, and severe anxiety as part of their diagnostic criteria (APA, 2013) – i.e. a dysregulated experience of anxiety that is often more severe and debilitating in nature than more normative and briefer states of anxiety. Because these disorders are common and related to substantially increased health care costs for long-term physical health problems, physiological correlates represent an essential avenue for future research.

Emerging research in psychoneuroimmunology over the past several decades has provided some preliminary evidence for a coupling between specific psychological diagnoses and inflammatory biomarkers, but the majority of this research has been conducted within PTSD and OCD, while anxiety disorders such as panic disorder, generalized anxiety disorder, and social anxiety disorder have received little attention. Further, no systematic review of psychological diagnoses characterized by heightened, chronic, and impactful anxiety on inflammatory markers. A 2015 meta-analytic review of PTSD and chronic inflammation indicated that individuals with PTSD have significantly higher levels of interleukin-6 (IL-6), interleukin-1 beta (IL-1 β), and interferon gamma (IFN- γ) compared to healthy controls, although this study reported a high degree of heterogeneity among studies (Passos et al., 2015). A 2012 systematic review and meta-analysis of chronic inflammation in people with OCD showed that there were no significant differences in IL-6 or tumor necrosis factor-alpha (TNF- α) between people with OCD and healthy controls (Gray & Bloch, 2012). However, levels of IL-1 β were significantly higher in subjects with OCD. Across generalized anxiety disorder [GAD], social

anxiety disorder [SAD], and panic disorder [PD]), studies have been sparse and somewhat mixed (Furtado & Katzman, 2015). This previous work has highlighted the need to apply more stringent inclusion criteria for systematic analysis and highlights a need for examining specific inflammatory markers in establishing their relationship to these conditions. Further, given symptomatic differences between anxiety disorders, PTSD, and OCD, the field may benefit from a greater understanding of the ways in which inflammatory dysregulation is similar or different across diagnoses. Such an understanding may also provide a first step in understanding mechanisms underlying the link between chronic, impairing, and distressing levels of anxiety and negative long-term health outcomes.

Given the lack of a comprehensive review examining the relationship between inflammatory markers and different anxiety and related diagnoses, the first aim of the current study is to systematically review the existing literature on anxiety and related disorders broadly and inflammation, in an effort to understand the differences between individuals with OCD, PTSD, or anxiety disorders and healthy controls (HCs). The second aim of the current study is to statistically examine the difference between individuals with anxiety disorders, PTSD, and OCD and HCs regarding baseline levels of circulating inflammatory markers using meta-analytic techniques. It is hypothesized that levels of pro-inflammatory markers will be significantly lower in HCs in comparison to those with anxiety disorders. Based on previous research, we also aimed to explore potential diagnostic moderators (i.e., diagnosis type, presence of comorbid depression) and demographic moderators (i.e., proportion of women participants [Garcia-Moll et. al, 2000], proportion of Caucasian participants [Miller et. al, 2007], body mass index [BMI; Festa et. al, 2001], and average participant age [Chung et. al, 2009]) of the relationship between anxiety and inflammation.

Materials and Methods

This study was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2010).

Selection criteria

Eligible studies were in English, peer-reviewed, and included human adult subjects (age 18 and above). Studies were required to include individuals diagnosed with PTSD, OCD, SAD, GAD, PD, or specific phobia and a control group of healthy subjects for comparison. In order to examine the specific effects of an anxiety disorder, studies including participants with chronic physical illnesses were excluded. Additionally, only studies that included individuals with a formal diagnosis of one of the disorders, defined as a diagnosis obtained from a clinician-administered interview or questionnaire, were included. Studies were also required to include at least one measure of inflammation measured in the blood. Each marker identified was categorized as either a pro-inflammatory (IL-1 β , IL-2, IL-3, IL-6, IL-7, IL-8, IL-9, IL-12, IL-15, IL-17, IL-18, TNF- α , IFN- γ , and CRP) or anti-inflammatory marker (IL-4, IL-5, IL-10, IL-11, IL-13, IL-16, IL-19, TGF- β). Finally, all studies were required to include statistics that could be converted into a standardized, uncontrolled effect size. The first author and a research assistant reviewed all studies independently for inclusion and exclusion criteria, and discrepancies were resolved by consensus and consultation with the second author (MSO).

Search strategy

A keyword-based search in the electronic databases PsycInfo and PubMed was conducted to obtain hit results relevant to the key search terms of the current study. Keywords related to inflammation (inflammation OR inflammatory OR cytokine* OR CRP OR “C-reactive protein”

OR chemokine* OR interleukin OR IL-1 β OR IL-2 OR IL-3 OR TNF- α OR IL-6 OR IFN- γ OR IL-12 OR IL-17 OR IL-8 OR IL-4 OR IL-5 OR IL-10 OR IL-15 OR NF-kB) were combined with keywords related to anxiety disorders, PTSD, or OCD (“anxiety disorder” OR anxiety OR “generalized anxiety disorder” OR “social anxiety disorder” OR “social phobia” OR panic* OR “posttraumatic stress disorder” OR “obsessive compulsive*” OR “specific phobia” OR GAD OR PTSD OR OCD OR SAD) to obtain hit results. The earliest studies available were obtained through January 2017. The first author and a research assistant conducted the search in both databases and independently eliminated all duplicate results. In addition, a backward search (snowballing) was conducted of reference lists of identified articles and earlier systematic reviews together with a forward search (citation tracking) until no additional relevant articles were found.

Data extraction

A number of demographic variables were extracted from the studies, including age, percentage of Caucasian participants, percentage of women across studies, and participant’s body mass index (BMI). Studies were also coded for the type of diagnostic tool that was used. The diagnosis was also extracted as well as any comorbid psychological diagnoses. In terms of inflammation, the type of biomarker measured was coded for each study.

Fifteen studies did not include effect sizes or means and standard deviations for the inflammatory markers measured. The authors of those studies were contacted via e-mail to request the relevant data, with a follow-up e-mail also sent if authors did not respond within a three-week time period. Four authors responded and were able to provide the data, while three responded that they no longer had access to the data. In instances where the data was not accessible, we were able to obtain other statistics from which an effect size could be estimated. If

means and standard deviations were unavailable, an alternative test statistic was used to compute an effect size, such as a t -value ($k = 1$) or N and a p -value ($k = 3$). When the appropriate statistics were not mentioned in the study, a direction of the effect was not indicated within the manuscript, and we could not get the necessary information from the author of the study, a given inflammatory outcome was excluded. This resulted in the exclusion of three outcomes from two different studies. When authors reported that there were no significant differences between groups on an inflammatory outcome but appropriate statistics were not provided, the effect size was set to zero in an effort to retain the data. This resulted in an effect size set to zero for four different inflammatory outcomes in two studies. This approach may be too conservative; therefore, analyses were conducted with and without these four studies to examine differences in overall results.

All codings and ratings were provided by the first (MR) and third (PS) authors. Disagreements were discussed and solved by consensus and in consultation with the second author (MSO). Literature search and data extraction protocols are available upon request.

Analytic overview

All analyses were conducted using the Comprehensive Meta-Analysis program, version 3.3.070 (Comprehensive Meta-Analysis, 2014). Meta-analyses were performed to determine the between-group differences in those with a diagnosis, with all disorders combined, and individual inflammatory markers. Meta-analyses were performed on individual inflammatory markers if the number of studies that included that specific marker was equal to or exceeded three. These main analyses were based on random-effects models. A number of exploratory moderation analyses were conducted with meta-ANOVAs (for categorical criterion variables) and meta-regression analyses (for continuous criterion variables). Effect sizes were expressed as Hedge's g , thereby

attempting to adjust for a potential bias to overestimate the effect size in small samples (Hedges & Olkin, 1985), and a p -value < 0.05 was considered significant. Each effect size was weighted by its precision (inverse variance), so that studies with larger samples contributed more to the estimate of the overall effect size. Heterogeneity was explored using Q and I^2 statistics. Q -tests concern the probability that results reflect systematic between-study differences. The I^2 statistic is an estimate of the degree of heterogeneity and is unaffected by the number of studies. An I^2 value of 0% indicates no observed heterogeneity. Values of 25%, 50%, and 75% are considered low, moderate, and high, respectively (Higgins & Thompson, 2002).

A risk of publication bias is introduced in that positive and negative findings may not be equally likely to get published. Therefore, the distribution of effect sizes was visually inspected using funnel plots (Light, Singer, & Willet, 1994), and statistically tested using Egger's test (Egger, Davey, Schneider, & Minder, 1997). The file-drawer problem, defined as the possibility that unpublished studies with null findings may alter any significant findings, was evaluated by Rosenthal's fail-safe number (Rosenthal, 1979). If the fail-safe number exceeded $5K + 10$, with K being the number of studies included in the meta-analysis, the file drawer problem was considered low enough to not warrant further investigation (Rosenthal, 1991). When these tests indicated a possible file drawer problem, an adjusted effect size was estimated using Duval and Tweedie's (2000) trim-and-fill method, which imputes missing results and then recalculates the effect size.

Results

Study inclusion

A total of 1,265 unique citations were identified as a result of the search with an additional citation identified through citation tracking. Of these, 1,190 were deemed irrelevant

and therefore excluded based on the following determinations: 1) study did not consist of physically healthy participants, 2) study did not consist of participants with a formal anxiety disorder, PTSD, or OCD diagnosis, 3) study did not measure at least one inflammatory marker, 4) study did not include a control group, 5) study examined children or adolescents rather than adults, 6) study was not an original/empirical study (i.e., review or meta-analysis). Seventy-six full-texts were evaluated with 39 papers ultimately included. An examination of previously published reviews and meta-analyses yielded the inclusion of one additional study. The forward search method of citation tracking did not yield any additional studies to be included. Two of the included studies were comprised of two independent studies within themselves; consisting of two different diagnostic groups (i.e., PTSD and PD) with separate control groups, thus resulting in a total number of studies included in the overall meta-analysis of 41. See Figure 1 for the study flowchart on inclusion and exclusion.

Study characteristics

The studies reviewed included a total of 1,077 people with an anxiety disorder, PTSD, or OCD and 1,006 HCs. The median number of participants with one of these disorders in the included studies was 26, while the mean number of control participants in each study was 22. Of the 41 studies that met inclusion criteria, the diagnostic breakdown included PTSD ($n = 22$), OCD ($n = 6$), panic disorder ($n = 10$), social anxiety disorder ($n = 1$), and generalized anxiety disorder ($n = 2$). In terms of diagnostic breakdown, 63.8% ($n = 687$) were diagnosed with PTSD, 14.2% ($n = 153$) with OCD, and 22.0% ($n = 237$) with other anxiety disorders, including panic disorder ($n = 182$), social anxiety disorder ($n = 15$), and generalized anxiety disorder ($n = 40$). No studies included individuals diagnosed with a specific phobia. For a review of study characteristics, see Table 1.

The majority of studies ($n = 25$) included at least two different inflammatory markers, with the mean number of inflammatory markers included in a study being 3.27. Of the different inflammatory markers measured, the most common was IL-6, with 58.54% ($k = 24$) of studies having it included. A large percentage of studies also included TNF- α ($k = 20$), IL1 β ($k = 18$) and IL-2 ($k = 16$). Additionally inflammatory markers used included the following: IFN- γ ($k = 8$), CRP ($k = 8$), IL-10 ($k = 7$), IL-12 ($k = 1$), IL-13 ($k = 2$), IL-15 ($k = 2$), IL-1 α ($k = 3$), IL-2r ($k = 1$), IL-3 ($k = 1$), IL-4 ($k = 5$), IL-5 ($k = 3$), IL-7 ($k = 2$), IL-8 ($k = 8$), IL-1 α ($k = 1$).

The majority of study designs ($k = 35$) were cross-sectional examinations of inflammatory markers between people with anxiety disorders and healthy controls, of which inflammation was only measured at one time. The remaining studies ($k = 6$) involved a medication intervention. Subsequently, inflammatory marker data from these studies were the participants' baseline assessment prior to beginning the intervention. The majority of studies ($k = 38$) controlled for diurnal variation when collecting the serum samples for analysis of inflammatory cytokines (e.g., time of day serum samples were collected).

Pooled effect sizes and between-study differences

The overall between-group difference in pro-inflammatory cytokines across studies was significant and of a small to moderate magnitude (Hedge's $g = -0.39$, 95% CI [-0.70 - -0.08] both with and without adjusting for publication bias, indicating that individuals with a diagnosis of PTSD, OCD, or an anxiety disorder had an overall higher rate of pro-inflammatory cytokines compared to HCs. See results in Table 2. In order to evaluate the influence of possible outliers the standard deviation for Hedge's g for the pro-inflammatory cytokines was first estimated ($SD = 1.2$). A search for outliers above or below two standard deviations from the pooled effect size (range: -2.79 to 2.01) was conducted. Three studies fell outside of this range (Han, 2013; Gill,

2008; and Jergovic, 2014). The effect size for these studies was winsorized by replacing it with the lower or upper value of the range, thereby retaining the studies with an attenuated influence (cf. Lipsey & Wilson, 2001; O'Toole, Zachariae, Renna, Mennin, & Applebaum, 2016). Re-analyzing the overall between-group difference across outcomes with the winsorized effect size revealed an effect of a similar magnitude ($g = -0.40$, 95% CI $[-0.70 - -0.10]$). Consequently, subsequent analyses were based on the non-winsorized effect sizes.

There were no between-group differences in anti-inflammatory cytokines (Hedge's $g = -0.15$, 95% CI $[-0.86 - 0.57]$). In order to evaluate the influence of possible outliers the standard deviation for Hedge's g for the anti-inflammatory cytokines across outcomes was first estimated ($SD = 1.6$). A search for outliers above or below two standard deviations from the pooled effect size (range: -1.75 to 1.45) was conducted. One study fell outside of this range (Jergovic, 2014). The effect size for this study was winsorized by replacing it with the lower value of the range. Re-analyzing the overall between-group difference across outcomes with the winsorized effect size revealed an effect of a similar magnitude ($g = 0.06$, 95% CI $[-0.54 - 0.65]$). Figure 2 provides a forest plot of effect sizes for all included studies.

When exploring group differences in the individual inflammatory markers, three out of the 10 analyses were significant, that is, IL-1 β ($g = -0.50$, $p = .009$) and IL-6 ($g = -0.93$, $p < .001$), and TNF- α ($g = -0.56$, $p = .030$).

Moderator analyses

Results for the moderator analyses can be found in Table 3. Given that a significant difference was only demonstrated for pro-inflammatory, and not anti-inflammatory cytokines, only pro-inflammatory markers were utilized in moderation analyses. Examining type of diagnosis revealed a significant moderation effect ($p = .050$). Results indicated that the

difference between patients with PTSD and HCs was significant ($g = -0.68, p = .004$), but not for patients with OCD ($g = 0.10, p = .680$) and patients with anxiety disorders ($g = -0.09, p = .714$). Comorbid depression also did not significantly moderate the relationship between anxiety disorders and inflammatory markers. None of the continuous moderators (i.e., age, percent of women, percent of Caucasian participants, BMI) explored in individual meta-regression analyses demonstrated significance.

Heterogeneity and publication bias

A relatively large systematic variation in effect sizes between studies was detected. On average, the included studies demonstrated a high degree of heterogeneity ($I^2 > 90$) when combining outcomes. This pattern of high levels of heterogeneity remained both when investigating between-group differences at the cytokine level (see Table 2) and within-group effect sizes (i.e., anxiety type and depressive comorbidity; Table 3).

For all statistically significant results, the risk of publication bias was evaluated. For the overall pro-inflammatory cytokines analysis as well as the specific IL-6 analysis, effect sizes were asymmetrically distributed as determined by a significant Egger's test, indicating potential publication bias. Adjusted effect sizes can be found in Table 2. The fail-safe number for the between-group effect concerning pro-inflammatory markers failed to meet the criterion, indicating a lack of robustness of this result.

Discussion

The aim of the current systematic review and meta-analysis was to examine the overall difference in chronic inflammation between people with anxiety disorders, PTSD, or OCD and healthy controls. Findings indicate a small to moderate effect size for the difference between pro-inflammatory markers, indicating that people with one of these disorders have a significantly

higher level of pro-inflammatory markers compared to controls in the pooled analysis. There were no significant differences in anti-inflammatory markers between people with PTSD, OCD, or anxiety disorders compared to HCs. Although each inflammatory marker was identified as pro- or anti-inflammatory, some markers, such as IL-6, have both pro- and anti-inflammatory properties, as only one of two of IL-6's signaling pathways indicate an increase of inflammation in the body (Del Giudice & Gangestad, 2018) thus creating some ambiguity in the interpretation of the IL-6 findings. Consistent with previous research identifying links between inflammatory markers and psychopathology, the current study considered IL-6 as a pro-inflammatory marker (Dowlati et. al, 2010; Gray et. al, 2012).

Analyses revealed that this effect was largely driven by significant differences between people with anxiety, PTSD, or OCD and HCs in IL-6, IL-1 β , and TNF- α . These findings are consistent with previous meta-analytic findings examining depression and inflammation, which identified some (i.e., IL-6 and TNF- α), but not all, inflammatory markers significantly differed between people with depression and healthy controls (Dowlati et. al, 2010). A large prospective study of individuals with agoraphobia also demonstrated significantly higher levels of CRP and TNF- α over time, but no differences in IL-6 and IL-1 β (Wagner et. al, 2015). Taken together, these findings, along with the findings from the current meta-analysis, provide provisional evidence for differences in inflammatory markers that relate to different forms of anxiety and related pathology. Because increased inflammation is generally related to increased risk for ill-health, it is important to better disentangle what patterns of inflammatory activation that are related to chronic, distressing, and impairing anxiety and other forms of psychopathology.

A number of exploratory moderation analyses were also conducted. These moderators were selected based on previous research demonstrating that these variables may have a potential

impact on inflammation. Age (Chung et. al, 2009), BMI (Festa et. al, 2001), percentage of female participants (Garcia-Moll et. al, 2000), and percentage of Caucasian participants (Miller et. al, 2007) were not associated with the magnitude of the between-group difference. This is in contrast to a previous cohort study examining the relationship between anxiety and inflammation that found significant differences in CRP for men, but not women, with anxiety disorders versus HCs (Vogelzangs, Beekman, de Jonge, & Penninx, 2013) such that men had higher levels of CRP compared to HCs. A significant moderation effect was found for diagnosis type, and analyses revealed that the significant differences between groups were largely driven by a significant and moderate effect for PTSD. There were no significant differences between individuals with OCD or an anxiety disorder and HCs, highlighting a potential difference in physiological activation between people with PTSD and OCD or an anxiety disorder. This finding is consistent with a 2012 systematic review and 2015 meta-analysis examining inflammatory markers in people with PTSD compared to HCs, which showed an overall difference between the two groups (Gill et. al, 2009; Passos et al., 2015). Overall, numerous findings have highlighted the presence of altered immune and physiological functioning in PTSD and the potential mechanistic role that the dysregulation of these systems may play in linking the disorder to negative health outcomes (Kibler, Tursich, Ma, Malcolm, & Greenbarg, 2014). Although PTSD was the only diagnosis that demonstrated significant differences in pro-inflammatory markers compared to HCs, consistent with this previous research, this meta-analysis extends the previous PTSD findings by analyzing differences between different diagnostic categories.

The moderation effect for diagnosis type highlight that although the disorders examined in the current study share similar symptom presentations, the diagnostic categories may

differentially relate to physical functioning. It can however not be excluded that the diagnosis type may be a proxy for symptom severity, indicating that those with PTSD may be demonstrating greater physiological and emotional dysregulation compared to those with OCD or an anxiety disorder, rather than a genuine difference between diagnoses. Unfortunately, too few studies included in the current meta-analysis examined the relationship between symptom severity for individuals in the anxiety disorders groups and inflammatory markers. Future research examining psychopathology and inflammatory processes should attempt to further examine the impact that symptom severity may have on these basic biological processes. Research moving forward should also attempt to expand the examination of traditional anxiety disorders (e.g., generalized anxiety disorder, social anxiety disorder), as the number of studies that included participants with these diagnoses was very small. This resulted in participants in these diagnostic groups to be lumped together into the “other” category, limiting statistical power and prohibiting definitive conclusions regarding differences between anxiety disorders, OCD, and PTSD.

A comorbid diagnosis of depression did not moderate these results, indicating an independent association between anxiety and higher levels of pro-inflammatory markers. Although depression has been studied more widely in relation to inflammation (Schiepers, Wichers, & Maes, 2005; Dowlati et. al, 2010), it is important to understand if the anticipatory-based state of anxiety may produce dysregulated inflammatory responses (or vice versa) and put an individual at an increased risk of experiencing long-term negative health consequences. Further, these findings support several other studies that highlight the potential for trait anxiety to be associated with a dysregulated immune response (O’Donovan et al., 2010; Hou et al., 2017). The findings of the current meta-analysis are somewhat contrasting to a previous meta-

analysis of OCD and inflammation, which identified depression moderating the relationship between OCD and TNF- α (Gray & Bloch, 2012). Future research should therefore attempt to address diagnostic comorbidity between anxiety and depressive disorders more explicitly in relation to inflammatory markers to determine differential impacts that these disorders have on immunological processes.

Although these findings advance the overall understanding of the relation between a diagnosis of an anxiety disorder, PTSD, or OCD and inflammatory functioning, an important next step in terms of research is to examine the physiological, cognitive, and behavioral mechanisms that may underlie this link. In response to anxiety and fear, the stress response is exacerbated among individuals with these disorders. The stress response may, in turn, promote a cascade of psychological and physiological processes, which is mediated by hypothalamic-pituitary-adrenal axis (HPA) dysregulation (Michopoulos et al., 2017). Through glucocorticoid insensitivity, HPA dysregulation is theorized to contribute to a state of low-grade inflammation, which might put an individual at risk for negative health consequences (Cohen, Janicki-Deverts, Doyle, Miller, Frank, Rabin, & Turner, 2012). Cognitive processes that are central to a number of these disorders, such as worry (McEvoy, Watson, Watkins, & Nathan, 2013), self-criticism (Sowislo & Orth, 2013), and intolerance of uncertainty (Carleton, 2012) may impact immunological responding, as these processes tend to prolong physiological activation through cognitive activation that is difficult to control. Finally, in terms of behavioral mediators, people who experience severe, chronic, and impactful anxiety may be less likely to engage in a healthy lifestyle. Notably, these individuals may be more likely to suffer from sleep disturbances, be less likely to engage in exercise, and may utilize alcohol, smoking, food, or drugs in an effort to regulate their anxiety and fear, subsequently putting them at risk for experiencing a number of

poor health outcomes over the long term (Michopoulos et al., 2017; Pederson 2017). Taken together, an essential avenue for future research is to take a more mechanistic approach to understanding the physical, cognitive, and behavioral processes that may impact the relationship between an anxiety disorder, PTSD, or OCD and inflammatory dysregulation.

The current findings have a number of potential implications that may help to inform future research, particularly within the context of PTSD. Given that the majority of research examining inflammation in psychopathology has focused on depressive rather than anxiety disorders, the results of the current study provide evidence for the necessity of understanding the relationship between different anxiety and related disorders and inflammation. It may be particularly important to move beyond categorical diagnoses and examine underlying transdiagnostic processes such as apprehension, hypervigilance, and anhedonia to help determine what specific phenomenology of these psychopathological states may be most likely to lead to chronic inflammation. Further, these findings provide more nuanced information regarding the association between anxiety, and specifically PTSD, on physiological dysregulation, in terms of examining specific markers that have been shown to be associated with numerous chronic health conditions – lending support for the necessity to treat anxiety in an effort to improve physical health overall. The potential benefits of psychotherapy for anxiety as a protective factor for physical health should be further explored, as it may promote greater physiological and immunological regulation (O'Toole, Bovbjerg, Renna, Lekander, Mennin, & Zachariae, in press) and subsequently reduce the link between anxiety and physical health problems (Sareen, Jacobi, Cox, Belik, Clara, & Stein, 2006). Given the associations demonstrated between PTSD and heightened levels of pro-inflammatory markers in the current study, future research should seek to explore whether dysregulated inflammation may serve as a predictor of treatment response,

similar to what has been indicated in treatment for depression (Strawbridge, Aarnone, Denese, Papadopoulos, Vines, & Cleare, 2015).

For the purposes of the current meta-analysis, studies utilizing participants diagnosed with chronic health conditions were excluded given that the presence of chronic illness may alter circulating levels of inflammatory markers. This exclusion criterion omitted several studies from our initial hit results. Future research should, however, explore these relationships in an effort to understand how psychiatric disorders or symptoms may be a co-factor contributing to the increased inflammation, which is demonstrated also in non-communicable disorders (Slavich 2015).

The current meta-analysis has several limitations that should be noted. Primarily, given that many studies did not include the examination of a relationship between inflammatory markers and symptom severity, it is difficult to establish any conclusions about the data beyond mere group differences. Future research should therefore target a better understanding about how symptom severity may influence higher rates of pro-inflammatory markers, or vice versa. Additionally, few studies have utilized experimental approaches to examine mechanisms underlying the relationship between anxiety and inflammation. A number of the moderation analyses did not yield significant results; however, this may have been limited due to the fact that only a small number of studies were included in some analyses. An additional consideration in interpreting the current findings is that heterogeneity was relatively high, indicating systematic variation between studies included in the current meta-analysis. Lastly, as mentioned above, the number of studies examining anxiety disorders was small in comparison to OCD and PTSD. It would therefore be optimal for future research to expand the understanding of each diagnosis in regards to inflammatory dysregulation and to examine these diagnoses together with an emphasis

on the mechanisms underlying this relationship. In interpreting these data, it is important to keep in mind that the only significant differences between diagnostic groups and HCs was in PTSD, while no signs of inflammatory dysregulation in people with OCD or an anxiety disorder compared to healthy people were observed.

Conclusion

Despite these limitations, this meta-analysis demonstrates the association between inflammatory dysregulation and diagnoses associated with chronic, impactful, and severe anxiety in a comprehensive manner that has not yet been available otherwise. Further, these findings suggest that a diagnosis of PTSD may differ from OCD or anxiety disorders in terms of inflammatory activation. However, the restricted number of studies investigating inflammation in anxiety disorders renders conclusions from the current study provisional. The synthesis of these data therefore provides an initial opportunity for researchers to consider the relation between anxiety and certain inflammatory markers as a potential way to disentangle why anxiety increases the risk for long-term negative health outcomes.

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RUNNING HEAD: Inflammation in anxiety disorders, PTSD, and OCD

Table 1.
Study characteristics

Study (country)	N Controls	N Anxiety	Diagnosis Group(s)	Diagnostic Tool	Inflammatory Markers	M age Controls	M age Anxiety	% Caucasian Controls	% Caucasian Anxiety	% Women Controls	% Women Anxiety
Baker 2001	8	11	PTSD	SCID & CAPS	IL-6	41	42	n/a	n/a	0	0
Bersani 2016	65	56	PTSD	SCID	CRP ↑ IFN-γ IL-1β IL-6 ↑ TNF-α ↑	33	34	n/a	n/a	0	0
Brambilla 1999	10	10	PD	SCID	TNF-α	32	33	100	100	60	60
Brambilla 1994	10	10	PD	SCID	IL-1β ↑	32	33	100	100	60	60
Brambilla 1997	27	27	OCD	SCID	TNF-α ↓ IL-1β ↓	35	34	100	100	44	44
Fontenelle 2012	31	40	OCD	MINI	IL-1β TNF-α IL-1ra	38	38	n/a	n/a	48	48
Gill 2010	14	18	PTSD	SCID & CAPS	IL-6 ↑	34	37	57	39	71	28
Gill 2013	24	26	PTSD	SCID	CRP ↑ IL-6 ↑	35	35	71	58	100	100
Gill 2008	21	26	PTSD	CAPS	IL-1β IL-6 ↑ TNF-α ↑	43	45	12	21	100	100
Gola 2013	25	35	PTSD	MINI & CAPS	IL-6 IL-8 IL-10 TNF-α	29	33	92	82	68	46
Guo 2012	50	50	PTSD		IL-2 ↑ IL-4 ↑ IL-6 ↑ IL-8 ↑ IL-10 ↑ TNF-α ↑	41	42	n/a	n/a	50	56
Han 2013	30	30	PTSD	SCID	IL-2 ↑ IL-6 ↑ IL-8 ↑	38	38	n/a	n/a	33	33

					TNF- α ↑						
Han 2013	30	30	PTSD	SCID	IL-2 ↑ IL-6 ↑ IL-8 ↑ TNF- α ↑	40	36	n/a	n/a	37	33
Herrán 2005	21	33	PD	MINI	CRP ↑	31	32	n/a	n/a	69	66
Hoge 2009	27	27	PTSD	SCID	IFN- γ ↑ IL-1 β ↑ IL-1 α ↑ IL-2 ↓ IL-4 ↑ IL-5 IL-6 ↑ IL-7 ↑ IL-8 ↑ IL-10 ↑ IL-13 ↑ IL-15 ↑ TNF- α ↑	42	41	77	86	50	50
Hoge 2009	21	21	PD	SCID	IFN- γ ↑ IL-1 β ↑ IL-1 α ↑ IL-2 ↑ IL-4 ↑ IL-5 IL-6 ↑ IL-7 ↑ IL-8 ↑ IL-10 ↓ IL-13 ↑ IL-15 ↑ TNF- α ↑	42	41	77	86	50	50
Jergović 2015	15	32	PTSD	LASC	CRP IFN- γ IL-1 β IL-2 IL-6 IL-8 ↓ TNF- α	46	47	n/a	n/a	0	0

Jergović 2014	16	27	PTSD	MINI & CAPS	IFN- γ ↓ IL-2 ↓ TNF- α	47	46	n/a	n/a	0	0
Koh 1998	28	28	GAD/PD		IL-2 ↓	27	28	0	0	52	52
Koh 2004	42	42	PD		IL-2 ↓	35	36	0	0	45	45
Kokai 2002	16	5	PD	SCID	IL-18 ↑	34	38	n/a	n/a	56	62
Konuk 2007	31	31	OCD	SCID	IL-6 ↑ TNF- α ↑	33	33	n/a	n/a	48	55
Lindqvist 2014	51	51	PTSD	SCID	CRP IFN- γ ↑ IL-1 β IL-6 IL-10 TNF- α ↑	34	34	28	26	0	0
Maes 1999	32	13	PTSD	SCID & CIDI	IL-6 ↑	45	47	n/a	n/a	84	69
Maes 1994	19	19	OCD	SADS	IL-1 β IL-6	30	34	n/a	n/a	32	42
Miller 2001	8	15	PTSD		CRP	n/a	n/a	n/a	n/a	n/a	n/a
Monteleone 1998	14	14	OCD		IL-1 β IL-6 TNF- α ↓	32	33	n/a	n/a	50	50
Newton 2014	26	15	PTSD	CAPS	IL-6	55	54	92	87	100	100
O'Donovan 2015	132	40	PTSD	SCID & CAPS	IL-6	45	42	75	60	14	23
Oganesyan 2009	31	31	PTSD		IL-1 β ↑ IL-6 ↑ TNF- α ↑	39	42	n/a	n/a	13	13
Rapaport 1994a	15	15	SAD	SCID	IL-2	37	32	100	100	40	40
Rapaport 1994b	18	14	PD	SCID	IL-1 α IL-1 β IL-2	34	38	100	100	100	100
Söndergaard 2004	30	32	PTSD	CAPS	CRP ↓	n/a	n/a	n/a	n/a	n/a	n/a
Song 2007	34	34	PTSD	CIDI	IL-2 ↓ IL-6 IL-8 ↓	38	40	n/a	n/a	65	65
Spivak 1997	19	19	PTSD	SCID	IL-1 β ↑	32	25	n/a	n/a	0	0
Tucker 2004	21	58	PTSD	SCID & CAPS	IL-1 β ↑	n/a	38	n/a	89	n/a	75

Tükel 2012	23	23	PD	SCID	IFN- γ ↓ IL-2 IL-6 IL-12 ↓ TNF- α	31	34	n/a	n/a	61	48
Vieira 2010	20	20	GAD	SCID	IFN- γ ↓ IL-1 β IL-2 ↓ IL-4 ↓ IL-5 ↓ IL-6 IL-10 ↓ IL-17 ↑ TNF- α ↑	30	29	n/a	n/a	60	60
von Känel 2007	14	14	PTSD	CAPS	CRP IL-1 β ↑ IL-4 IL-6 IL-10 TNF- α ↑	33	33	n/a	n/a	36	36
Weizman 1996	22	22	OCD	SADS	IL-1 β IL-2	32	32	n/a	n/a	45	55
Weizman 1999	19	24	PD	SCID	IL-2 IL-3	36	3 8	n / a	n / a	6 3	7 1

Note. *M* = mean, *PTSD* = post-traumatic stress disorder, *PD* = panic disorder, *OCD* = obsessive compulsive disorder, *GAD* = generalized anxiety disorder, *SAD* = social anxiety disorder, *IL-1alpha* = interleukin 1 alpha, *IL-1 β* = interleukin 1 beta, *IL-2* = interleukin 2, *IL-3* = interleukin 3, *IL-4* = interleukin 4, *IL-5* = interleukin 5, *IL-6* = interleukin 6, *IL-7* = interleukin 7, *IL-8* = interleukin 8, *IL-9* = interleukin 9, *IL-10* = interleukin 10, *IL-13* = interleukin 13, *IL-15* = interleukin 15, *IL-17* = interleukin 17, *IFN- γ* = interferon gamma, *TNF- α* = tumor necrosis factor alpha, *CRP* = c-reactive protein, *SCID* = Structured Clinical Interview for Diagnosis, *MINI* = Mini International Diagnostic Interview, *CAPS* = Clinician-Administered PTSD Scale, *SADS* = Schedule for Affective Disorders and Schizophrenia, *LASC* = Los Angeles Symptom Checklist, *IDC* = International Diagnostic Checklist, *CIDI* = Composite International Diagnostic Interview, *n/a* = data not available, ↑ = inflammatory marker rates significantly higher in patients with anxiety disorders than healthy controls, ↓ = inflammatory marker rates significantly lower in patients with anxiety disorders than healthy controls.

Table 2.
Pooled effect sizes across outcomes and levels of moderator variables.

Outcome ^b	Sample size		Heterogeneity				Global effect sizes ^a			Failsafe N ^e	Criterion
	K	N	Q ^c	df	<i>p</i>	I ²	Hedge's <i>g</i>	95 % CI	<i>p</i>		
Pro-inflammatory cytokines	41	2083	427.0	40	<.001	90.6	-.39	-.70 - -.08	.013	454	215
<i>Adjusted for publication bias</i>	<i>(48)</i>						-.39	-.70 - -.08			
<i>Winsorized effect</i>	<i>41</i>		410.5	40	<.001	90.3	-.40	-.70 - -.10	.009	490	235
Anti-inflammatory cytokines	9	527	118.2	8	<.001	93.2	-.15	-.86 - .57	.689	-	-
<i>Winsorized effect</i>	<i>41</i>		87.9	8	<.001	90.9	.06	-.54 - .65	.855	-	-
IL-1 β	18	1020	144.9	18	<.001	87.6	-.50	-.87 - -.012	.009	174	105
IL-2	16	866	346.0	15	<.001	95.7	-.25	-1.00 - .50	.517	-	-
IL-4	5	264	121.0	5	<.001	95.9	-.10	-1.17 - 1.17	.881	-	-
IL-5	3	136	8.5	2	.014	76.6	-.11	-.81 - .59	.759	-	-
IL-6	24	1421	346.0	23	<.001	93.4	-.93	-1.39 - -.47	<.001	947	130
<i>Adjusted for publication bias</i>	<i>(29)</i>						-1.32	-1.82 - -.81			
IL-8	8	701	177.5	7	<.001	96.1	-.71	-1.68 - .26	.150	-	-
IL-10	7	426	59.0	6	<.001	89.8	.18	-.45 - .80	.580	-	-
TNF- α	20	1147	275.2	19	<.001	93.1	-.56	-1.02 - -.05	.030	312	110
IFN- γ	8	495	89.6	7	<.001	92.2	.46	-.27 - 1.19	.219	-	-

CRP	8	543	20.8	7	.004	66.3	-.12	-.43 - .19	.465	-	-
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Note: K and N do not necessarily add up due to exclusion of non-independent samples/studies from the comparison analyses. Statistically significant results are highlighted in **bold**.
a: Effect size = Hedge’s g. Standardized mean difference, adjusting for small sample bias. A positive value indicates an effect size in the hypothesized direction, i.e., improvement following CBT. To ensure independency, if a study reported results for more than one measure, effect sizes were combined (mean), ensuring that only one ES per study was used in the calculation. Conventions: small (<0.3); medium (0.5); Large (0.8>).
b: Possible publication bias was examined with funnel plots and Egger’s test, followed by imputation of missing studies (Duval & Tweedie, 2000). (K) = K + number of imputed studies.
c: Q-statistic: p-values < 0.1 taken to suggest heterogeneity. I² statistic: 0% (no heterogeneity), 25% (low heterogeneity), 50% (moderate heterogeneity), 75% (high heterogeneity).
d: Random effects model.
e: In case of statistically significant effect sizes, it was planned to examine the robustness of findings by calculating the Failsafe N (number of non-significant studies that would bring the p-value to non-significant (p > 0.05) (Rosenthal, 1979).

RUNNING HEAD: Inflammation in anxiety disorders, PTSD, and OCD

Table 3.

Proposed moderators: Meta-ANOVA and meta-regression results.

Meta-ANOVAs	K	N	Q ^c	df	<i>p</i>	I ²	Hedge's <i>g</i>	95 % CI	<i>p</i>
Anxiety type	41	1077	6.0	2	.050				
PTSD	23	687					-.68	-.1.13 - -.22	.004
OCD	6	153					.10	-.36 - .55	.680
Other	12	237					-.09	-.56 - .38	.714
Depression comorbidity	31	817	<.1	1	.862				
No depression	18	394					-.52	-1.14 - .11	.105
Depression	13	423					-.45	-.95 - -.06	.084
Meta-regression analyses	K		B	SE	<i>p</i>				
Age	35		-.03	.03	.308				
% women	38		-.01	.01	.354				
% Caucasian	17		<.01	.01	.660				
BMI	15		-.05	.10	.626				

RUNNING HEAD: Inflammation in anxiety disorders, PTSD, and OCD

Figure 1.
Study Inclusion Flowchart

RUNNING HEAD: Inflammation in anxiety disorders, PTSD, and OCD

Figure 2.
Forest Plot