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Immune Aberrations in Obsessive-Compulsive Disorder: a Systematic Review and Meta-analysis

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Abstract
Some lines of evidence have indicated that immune dysregulation could play a role in the pathophysiology of obsessive-compulsive disorder (OCD). However, results have been inconsistent across studies. Thus, a systematic review and meta-analysis of studies measuring immune mediators in participants with OCD compared to healthy controls (HC) was conducted. The PubMed/MEDLINE, PsycINFO, and EMBASE electronic databases were systematically searched from inception through June 21, 2018. Sixteen studies met inclusion criteria comprising data from 1001 participants (538 with OCD and 463 were HCs). Levels of TNF-α, IL-6, IL-1β, IL-4, IL-10, and interferon-γ did not significantly differ between participants with OCD and healthy controls. In addition, the ex vivo production of TNF-α and IL-6 by isolated macrophages did not significantly differ between participants with OCD and HCs. Nevertheless, included studies have varied in methodological quality with the enrollment of samples that differed regarding medication status, the proper matching of OCD participants and HCs, age groups, and the presence of psychiatric comorbidities. In conclusion, an association between immune dysregulation and OCD remains unproven. Future studies should consider enrolling larger and more homogeneous samples with OCD.

Keywords Obsessive-compulsive disorder · Meta-analysis · Review · Cytokines · Chemokines · Inflammation

Introduction

Obsessive-compulsive disorder (OCD) is a common mental disorder with an estimated lifetime prevalence of approximately 2.5% in the general adult population [1]. OCD presents a similar gender distribution except during adolescence when the male to female prevalence ratio is 3:1 [2]. In addition, OCD presents a bimodal age of distribution with peaks at 12–14 years (early-onset) and another at 20–22 years (late-onset), while in 30–50% of patients, obsessive-compulsive symptoms emerge during early childhood [3]. It has been suggested that childhood onset OCD may have distinct pathophysiological mechanisms as compared to late-onset forms of the disorder [3]. Although OCD had been previously conceptualized as an anxiety disorder in previous editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM), OCD is no longer considered an anxiety disorder in the 5th edition of the DSM (DSM-5) [2].

Evidence suggests that immune alterations may contribute to the pathophysiology of OCD. The hypothesis of immune dysregulation in OCD was initially proposed based on the association between streptococcal infections and the onset of OCD symptoms [4]. Furthermore, OCD is known to co-occur with Sydenham's chorea, a well-known neuropsychiatric complication of streptococcal infections [4]. Subsequently, the term Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) was coined to encompass a subset of childhood tic disorders and/or OCD which may be causally associated with group Aβ-hemolytic streptococcal infection [5]. In addition to streptococcal infection, other infectious agents including *Borrelia burgdorferi*, mycoplasma, *Toxoplasma gondii*, and Borna disease virus have been associated with OCD [6, 7]. As it became apparent that a multitude of infectious and non-infectious etiological factors may be involved, the term PANDAS later evolved to encompass a wider spectrum of acute neuropsychiatric syndromes referred to as PANS (pediatric acute onset neuropsychiatric syndrome) [7]. These findings

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have led to an increase in research efforts investigating the potential involvement of immune dysregulation in the pathoetiology of OCD, regardless of the fulfillment of diagnostic criteria for PANDAS/PANS [6].

Naïve T cells can differentiate into inflammatory T helper (Th1), Th2, Th17, and regulatory T cells (Tregs). Regarding the association of OCD and inflammatory cytokines, the Th-1-related cytokine TNF-α has been one of the most investigated mediators. A previous systematic review and meta-analysis that included 12 studies found no evidence for an increase in peripheral levels of TNF-α in OCD compared to controls [8]. Since the publication of this previous meta-analysis, several studies have assessed the role of inflammatory mediators in the pathophysiology of OCD. While TNF-α levels did not significantly differ in an adult sample of OCD relative to controls [9], another study found elevated levels of this cytokine in a medication-free pediatric OCD sample [10]. Because the soluble TNF receptors (sTNFR1 and sTNFR2) are thought to be more reliable indicators of an inflammatory response, some studies have investigated those mediators in samples with OCD. While a study found elevated peripheral levels of sTNFR1 and sTNFR2 in adults with OCD relative to controls [9], another study found no evidence of increased levels of these immune receptors in a pediatric OCD sample [10]. IL-1β and IL-12 are also regarded as Th1-related cytokines, and hence, some studies have assessed their potential role in the immunopathogenesis of OCD. However, results across studies have been discrepant. For example, while Leckman et al. [11] found elevated peripheral levels of IL-12 in individuals with co-occurring OCD and tic disorder, another study had found no significant differences between children with OCD coexisting with tic disorder and controls [12]. Moreover, while Brambilla et al. [13] found lower peripheral levels of IL-1β in adults with OCD compared to controls, at least two other studies conducted in adults with OCD failed to replicate those findings [14, 15].

Those discrepant findings may be due to differences in sample characteristics (e.g., the presence of comorbid mental disorders, the use of medication, and the enrollment of pediatric versus adult samples) across studies. As a result of the ongoing interest in the search for putative immune mechanisms for OCD, the current work provides an updated systematic review and meta-analysis of studies that assessed immune mediators in participants with OCD compared to healthy controls (HCs). It was anticipated that due to the increase in available evidence, potential sources of heterogeneity across studies could be explored in greater detail.

Methods

This study comprised a between-group systematic review and meta-analysis of studies that compared levels of immune mediators between participants with OCD and HCs. We complied with the Preferred Reported Items for Systematic Reviews and Meta-analysis (PRISMA) statement [16]. The literature search, title/abstract screening, final decision on eligibility after full-text review, and data extraction were independently performed by two investigators (TDC & HE). This study followed an a priori defined protocol that was registered in PROSPERO (number CRD42017077525).

Search Strategy

A systematic search was conducted in the PubMed/MEDLINE, PsycINFO, and EMBASE electronic databases from inception through June 21, 2018. The detailed search strings used in this systematic review are provided in the supplementary material that accompanies the online version of this article. This search strategy was augmented through hand searching the reference lists of eligible articles.

Study Selection

We included original studies published in any language. Eligible studies had to measure immune mediators in any body compartment in participants meeting either DSM [2] or ICD [17] criteria for OCD and a comparison group of HCs. The following exclusion criteria were applied: (i) studies that reported that participants had major medical comorbidities were excluded, (ii) studies that included pregnant women or women in the postpartum period, (iii) case reports or case series ($N < 10$) [18], and (iv) preclinical studies. The authors of meeting abstracts that met inclusion criteria were electronically contacted in at least two separate occasions 1 week apart to provide data.

Data Extraction

For each immune mediator, we extracted means, variance estimates (standard deviation (SD), standard error of the mean (SEM), or 95% confidence interval (CI)), and sample sizes for OCD and HC groups. From studies that provided only results of the comparison of OCD and HC groups, the appropriate measure was extracted (t-score or z-score). In studies that provided median ± IQR or median ± range, the mean ± SD was estimated following a standard method [19]. The following data were also extracted whenever available: (i) first author, (ii) publication year, (iii) sex distribution (% females), (iv) mean age, (v) mean body mass index (BMI), (vi) treatment status (drug-free or not), (vii) % of smokers, (viii) physical comorbidities, and (ix) psychiatric comorbidities.

Characteristics and Methodological Quality of Included Studies

The following characteristics of included studies were extracted: (i) sample source (e.g., plasma, CSF); (ii) assay type (ELISA, RIA, or other); (iii) were participants with OCD and HCs age and gender-matched? (Yes/No); (iv) did the study measure immune mediators ex vivo? (Yes/No); (v) if immune mediators were assayed ex vivo, were immune cells stimulated (Yes/No); (vi) were participants with comorbid mental disorders excluded? (Yes/No); (vii) was the time of sample collection reported? (Yes/No); (viii) was the manufacturer of the assay kit reported? (Yes/No); and (viii) were the coefficient of variation (CV) and sensitivity of the assay kit reported? (Yes/No).

Statistical Analysis

In the current meta-analysis, we used a standardized mean difference and 95%CI (Hedges' *g*) which provides an unbiased effect size adjusted for small sample sizes [20]. Heterogeneity across studies was quantified with the I^2 statistic; values > 50% indicate large heterogeneity [21]. Heterogeneity across studies was further evaluated using the Cochran *Q* test, a weighed sum of the squares of the deviations in individual study ES estimates from the summary ES estimate, and a *P* value of < 0.10 was considered significant (i.e., indicative of heterogeneity). We anticipated a large degree of heterogeneity. Therefore, we pooled ES using a random-effects model, which assumes a genuine diversity across studies results and incorporates a between-study variance into the calculations [22]. Meta-analyses were conducted only for immune mediators which were assessed in at least three independent studies. The level of significance for ES estimates was set at $\alpha = 0.05$.

When at least ten studies were available, we estimated the likelihood of publication bias with Egger's asymmetry test [23, 24]. We used the following assumptions for the existence of small-study effects, which is an indication of publication bias: (i) the ES of the largest study is more conservative than the pooled ES of the respective meta-analysis and (ii) a *P* value < 0.1 in Egger's test [25, 26]. The trim-and-fill procedure was used to estimate ES when evidence of publication bias was noted [27].

We explored potential sources of heterogeneity across studies using either subgroup (when at least three independent datasets were available per subgroup) or unrestricted maximum likelihood random-effects meta-regression analyses. Meta-regression analyses were conducted only when there were data from at least ten independent datasets. This decision was made a priori because with fewer datasets, this analytic tool may provide spurious results [28]. The following moderators were considered in subgroup analyses: (i) the presence of comorbid mental disorders, (ii) whether participants were drug-free at the time of sample collection, (iii) whether OCD and HC groups were matched for gender and age, and (iv) age group (pediatric vs. adult sample). For meta-regression analyses, the following variables were considered: (i) sample size, (ii) mean age of OCD group, (iii) mean age of HC group, (iv) % females (OCD group), (v) % females (HC group), (vi) mean BMI (OCD group), (vii) mean BMI (HC group), (viii) % smokers (OCD group), (ix) % smokers (HC group), and (x) mean illness duration. Sensitivity analysis where each study was excluded from analysis at a time was also performed to verify whether a single study (i.e., a possible outlier) could be biasing ES estimates. All analyses were conducted in the Comprehensive Meta-Analysis software version 3 for Windows.

Results

After removal of duplicates, the titles/abstracts of 258 unique articles were screened for eligibility, while 33 full texts were scrutinized for eligibility. Finally, 17 references were excluded with reasons, and 16 references met eligibility criteria and were thus included in this systematic review [9–11, 13–15, 29–38] (see Fig. 1). This systematic review synthesized data from 1001 participants (538 with OCD and 463 were HCs).

Characteristics and Methodological Quality of Included Studies

The characteristics of included studies are summarized in supplementary table S1 (available online). In brief, most studies measured immune mediators in the periphery. Only the study by Carpenter et al. [31] assayed IL-6 in the CSF of patients with OCD and HCs. Participants were drug-free at the time of sample collection in 9 (56.2%) studies. Five studies assessed the production of immune mediators in isolated immune cells ex vivo. Of those, 4 used stimulated immune cells. Thirteen studies (81.2%) of studies had OCD and HC groups matched for sex and age. Remarkably, only four studies (25.0%) excluded participants with OCD with comorbid mental health conditions. Finally, all studies provided the manufacturer of the assay kit.

Studies of TNF-α

Eight studies have measured TNF-α in participants with OCD and HCs. There were no significant differences between peripheral levels of this cytokine in participants with OCD compared to HCs ($g = -0.036$; 95%CI − 0.749; 0.677, $P = 0.920$). Heterogeneity was very large ($I^2 = 93.2\%$). Four studies have assayed the production of TNF-α ex vivo in stimulated macrophages from patients with OCD and HCs. Again, there were no significant differences between groups (Table 1 and Fig. 2).

Moreover, TNF-α levels did not differ between participants with OCD and HCs in subgroup analyses that considered studies that included participants with or without comorbid mental disorders, studies that included only participants who were drug-free at the time of

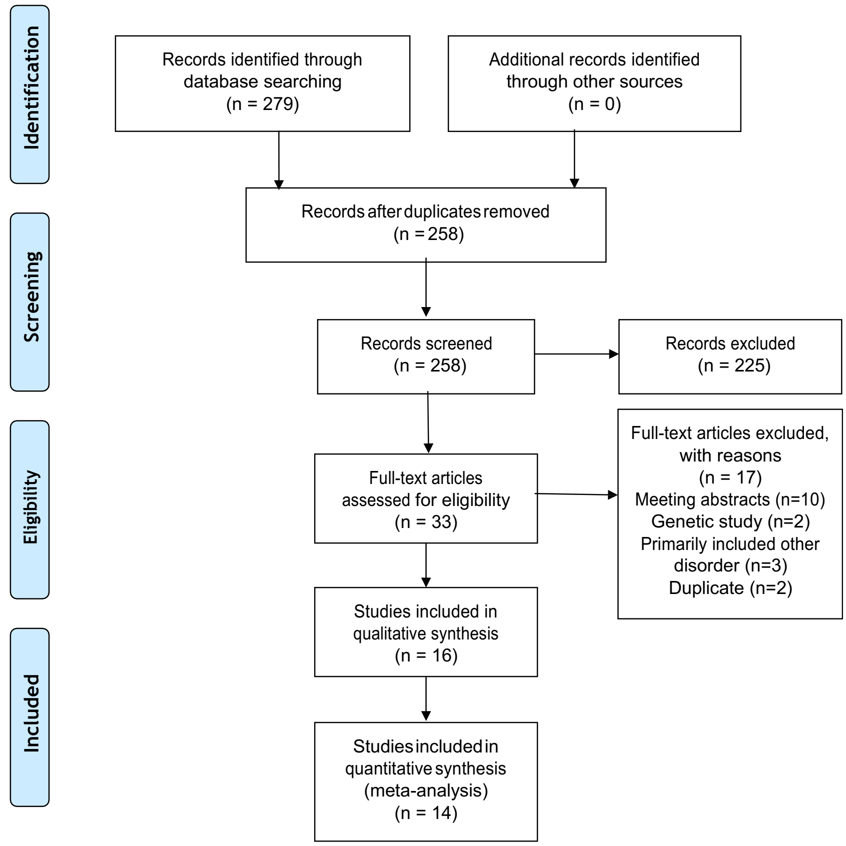

Fig. 1 PRISMA flowchart of study selection

sample collection or studies that enrolled adult samples (Table 2). Heterogeneity remained high in all subgroup analyses. In addition, results remained non-significant and heterogeneity was high in all planned subgroup analyses of studies that assayed TNF-α production ex vivo (Table 2). In sensitivity analyses that excluded one study at a time from analyses, results remained non-significant (see supplementary Figures S1 and S2, available online), thus indicating that no single outlier was biasing the ES estimates.

Studies of IL-6

Seven studies assayed IL-6 levels in participants with OCD and HCs (Table 1; Fig. 3a). There were no significant differences in IL-6 levels between participants with OCD and HCs ($g = 0.129$; 95%CI − 0.383; 0.641, $P = 0.621$). Moreover, 4 studies have assessed the ex vivo production of IL-6 in stimulated macrophages in patients with OCD compared to HCs and no between-group differences were observed (Table 1; Fig. 3b). In both meta-analyses, heterogeneity was high (Table 1).

Table 1 Primary meta-analyses of studies measuring immune mediators in individuals with OCD vs. healthy controls

Mediator	No. of studies	OCD *n*	Controls *n*	ES (95%CI)*	*P* value (overall)	I^2
TNF-α	8	292	277	− 0.036 (− 0.749; 0.677)	0.920	93.2
TNF-α[#]	4	194	130	0.187 (− 1.608; 1.982)	0.841	97.8
IL-6	7	204	189	0.129 (− 0.383; 0.641)	0.621	84.1
IL-6[#]	4	165	100	0.209 (− 1.400; 1.817)	0.799	96.9
IL-1β	5	143	140	− 0.266 (− 0.848; 0.316)	0.371	82.7
IL-4	4	140	125	0.203 (− 0.320; 0.725)	0.447	77.7
IL-10	4	140	125	0.194 (− 0.200; 0.589)	0.334	61.3
IFN-γ	3	106	91	0.199 (− 0.310; 0.707)	0.444	67.9

CI confidence intervals, *ES* effect size, *OCD* obsessive-compulsive disorder, *Y* yes, *N*, no, *NA* non-applicable

*Effect sizes estimated as Hedges' *g*

[#] Ex vivo lipopolysaccharide-stimulated macrophages

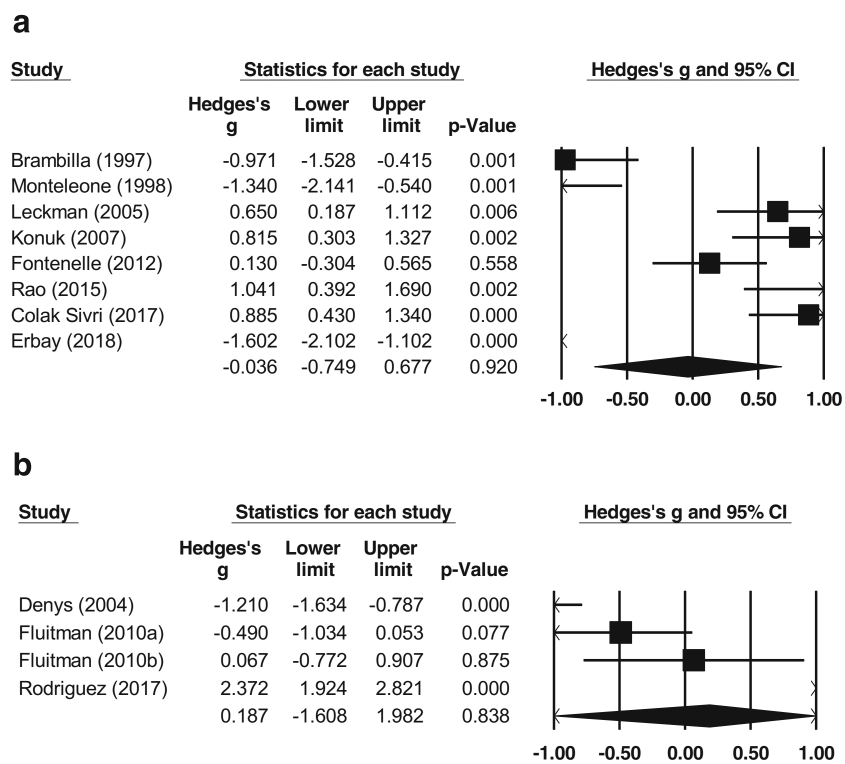

Fig. 2 Forest plot of studies measuring TNF-α (**a**) or the ex vivo production of TNF-α (**b**) in individuals with OCD compared to HCs using Hedges' *g* in random-effects model. The sizes of squares are proportional to the sample size. The squares depict the individual studies and the diamond depicts the pooled effect size

In subgroup analyses, IL-6 levels still did not differ between patients with OCD and HCs (Table 2). However, in subgroup analyses, the ex vivo production of IL-6 was higher in OCD patients compared to HCs in studies that included participants without mental disorders, in studies in which OCD and HC groups were matched for gender and age and in studies that enrolled adult samples (Table 2). In those estimates, heterogeneity was low.

In sensitivity analyses where one study was removed at a time, IL-6 levels were significantly higher in participants with OCD compared to HCs after excluding the study by Erbay et al. [38] from analyses (Figure S3, available online). Moreover, in sensitivity analyses, the ex vivo production of IL-6 by stimulated macrophages was significantly higher in participants with OCD after excluding the study by Rodriguez et al. [37] from analyses (Figure S4, available online).

Studies of IL-1β

Five studies have assessed IL-1β levels in patients with OCD compared to HCs (Table 1 and supplementary Figure S5, available online). Levels did not significantly differ between patients with OCD and HCs ($g = -0.266$; 95%CI -0.848; 0.386, $P = 0.371$). Moreover, heterogeneity was large (I^2 = 82.7%). However, IL-1β levels were significantly higher in the OCD group compared to the HC group in studies that enrolled participants who were drug-free at the time of sample collection with low heterogeneity (Table 2). In addition, IL-β was significantly higher in the OCD group after excluding the study by Erbay et al. [38] from analyses (see supplementary Figure S6, available online).

Studies of IL-4

Four studies have assessed levels of IL-4 in patients with OCD and healthy controls (Table 1; supplementary figure S7, available online). No significant between-group differences were verified. In sensitivity analyses, no potential outlier was identified (supplementary figure S8, available online).

Studies of IL-10

No significant overall differences in peripheral levels of IL-10 between patients with OCD and HCs were observed across 4 studies (Table 1; supplementary figure S9, available online). Moreover, in sensitivity analyses, no outlier was identified (supplementary figure S10, available online).

Studies of IFN-γ

Across 3 studies, INF-γ levels did not significantly differ between participants with OCD and HCs (Table 1; supplementary figure S11, available online).

Table 2 Subgroup analyses of studies measuring immune mediators in individuals with OCD vs. healthy controls

Variable	No. of studies	ES (95%CI)*	*P* value (overall)	I^2	*Q*	*P* value[a]
TNF-α						
Comorbid mental disorders						
Yes	3	− 0.154 (− 1.428; 1.121)	0.813	88.7	17.81	< 0.001
No	5	0.030 (− 0.952; 1.013)	0.952	95.3	85.27	< 0.001
Drug-free						
Yes	5	− 0423 (− 1.334; 0.488)	0.363	95.1	82.18	< 0.001
No	3	0.599 (− 0.570; 1.767)	0.315	65.8	5.86	0.053
Adult or pediatric sample						
Adult sample	6	− 0.312 (− 1.096; 0.471)	0.435	93.4	76.43	< 0.001
TNF-α[#]						
Comorbid mental disorders						
No	3	− 0.612 (− 1.320; 0.096)	0.090	77.6	8.94	0.011
Age/gender matched						
Yes	3	− 0.612 (− 1320; 0.096)	0.090	77.6	8.94	0.011
Adult or pediatric sample						
Adult	3	− 0.612 (− 1320; 0.096)	0.090	77.6	8.94	0.011
IL-6						
Comorbid mental disorders						
No	4	0.192 (− 0.667; 1.051)	0.661	91.9	37.94	< 0.001
Drug-free						
Yes	4	− 0.025 (− 0.858; 0.807)	0.952	89.0	27.27	< 0.001
Age/gender matched						
Yes	5	0.067 (− 0.586; 0.719)	0.842	88.8	35.69	< 0.001
Adult or pediatric sample						
Adult	4	0.521 (− 0.039; 1.080)	0.068	14.4	3.50	0.320
Pediatric	3	− 0.342 (− 0.942; 0.258)	0.264	87.1	16.41	< 0.001
IL-6[#]						
Comorbid mental disorders						
No	3	− 0.615 (− 0.950; 0.279)	< 0.001	0	1.93	0.380
Age/gender matched						
Yes	3	− 0.615 (− 0.950; 0.279)	< 0.001	0	1.93	0.380
Adult or pediatric sample						
Adult	3	− 0.615 (− 0.950; 0.279)	< 0.001	0	1.93	0.380
IL-1β						
Comorbid mental disorders						
No	4	− 0.274 (− 0.977–0.429)	0.444	87.0	23.12	< 0.001
Age/gender matched						
Yes	4	− 0.170 (− 0.851; 0.511)	0.625	85.3	20.47	< 0.001
Drug-free						
Yes	4	− 0.522 (− 0.798; − 0.245)	< 0.001	0	2.41	0.491
Adult or pediatric sample						
Adult	4	− 0.245 (− 1.033; 0.543)	0.542	86.4	22.16	< 0.001
IL-4						
Age/gender matched						
Yes	3	0.115 (− 0.549; 0.779)	0.734	81.0	10.52	0.005
IL-10						
Age/gender matched						
Yes	3	0.289 (− 0.248; 0.844)	0.285	71.21	6.94	0.031

[a] Of *Q* test of heterogeneity

[#] Ex vivo lipopolysaccharide-stimulated macrophages

Discussion

This systematic review and meta-analysis provides no consistent evidence for the involvement of immune mediators in the pathophysiology of OCD. A previous meta-analysis had found a decreased level of IL-1β in participants with OCD relative to HCs [8]. Yet the current work synthesizes a larger amount of evidence, with respect to number of studies, total participants, and number of immune mediators examined. For example, in the previous meta-analysis, only three cytokines, namely IL-1β, TNF-α, and IL-6, had sufficient data to undergo meta-analysis, while this systematic review was able to provide meta-analytic estimates for six immune mediators (TNF-α, IL-1β, IL-6, IL-4, IL-10, and IFN-γ).

Our results should be interpreted in the context of some limitations. First, OCD is a heterogeneous phenotype. Therefore, although we observed that heterogeneity was large in all meta-analytic estimates, this may also reflect genuine

a

Study	Hedges's g	Lower limit	Upper limit	p-Value
Maes (1994)	0.401	-0.228	1.030	0.211
Monteleone (1998)	0.101	-0.619	0.820	0.784
Leckman (2005)	-0.108	-0.559	0.344	0.640
Konuk (2007)	0.555	0.053	1.056	0.030
Rao (2015)	0.992	0.347	1.637	0.003
Simsek (2016)	0.192	-0.279	0.663	0.423
Erbay (2018)	-1.111	-1.578	-0.645	0.000
	0.129	-0.383	0.641	0.621

b

Study	Hedges's g	Lower limit	Upper limit	p-Value
Denys (2004)	-0.733	-1.223	-0.244	0.003
Fluitman (2010a)	-0.699	-1.251	-0.147	0.013
Fluitman (2010b)	-0.069	-0.909	0.770	0.871
Rodrigues (2017)	2.318	1.835	2.800	0.000
	0.209	-1.400	1.817	0.799

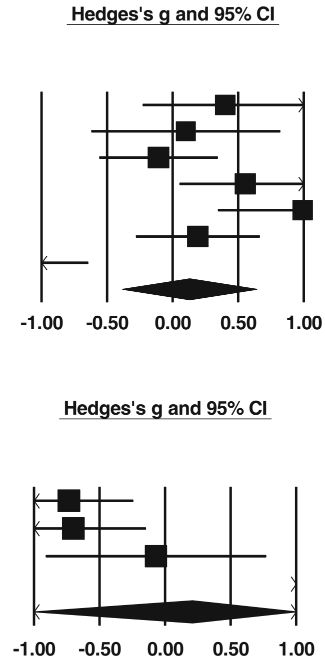

Fig. 3 Forest plot of studies measuring IL-6 (**a**) or the ex vivo production of IL-6 (**b**) in individuals with OCD compared to HCs using Hedges' *g* in random-effects model. The sizes of squares are proportional to the sample size. The squares depict the individual studies and the diamond depicts the pooled effect size

heterogeneity. Second, OCD frequently co-occurs with other mental disorders, most notably with depression and other anxiety disorders [1]. A large body of evidence including recent meta-analyses indicates that immune mechanisms may be involved in the pathophysiology of depression [18, 39, 40], and hence, this may confound findings derived from studies included in this review. For example, when only studies that excluded participants without comorbid mental disorders were considered, the ex vivo production of IL-6 by stimulated immune cells was higher in participants with OCD compared to HCs. Third, some studies have included participants who were not drug-free at the time of sample collection. This is relevant because a large body of clinical and preclinical evidence suggests that medications that are used as first-line treatments for OCD (e.g., selective serotonin reuptake inhibitors) may affect the immune system in their own right [41]. It is worthy to note that when only studies that included drug-free participants were pooled, peripheral IL-1β levels were found to be significantly more elevated in participants with OCD relative to controls. Fourth, other potential confounders that may affect immune function have not been evenly reported across studies. Those confounders include BMI/obesity (and other components of the metabolic syndrome) [42] and smoking status [43]. Fifth, some outliers could have biased some ES estimates. For example, in sensitivity analyses, after excluding the study by Erbay et al. [38] from analyses, levels of both IL-6 and IL-1β were observed to be significantly higher in participants with OCD compared to HCs.

Moreover, although the "periphery as a window to the brain" hypothesis has provided relevant insights into the pathophysiology of major mental disorders, it remains unclear how peripheral immune activation would mirror neuroinflammation. However, it has been proposed that there are reciprocal communications between the periphery and the central nervous system that play a role in governing immune regulation and inflammation [44]. Carpenter et al. [31] conducted the only study that assayed levels of immune mediators in CSF and found that levels of IL-6 did not differ between patients with OCD and HCs. More recently, a PET study found evidence of increased microglia activation within the neurocircuitry of OCD [45]. Nevertheless, this study enrolled a relatively small sample of participants with OCD ($n = 20$), and some participants had a history of depression.

The current systematic review opens relevant research directions. First, future studies should enroll more homogeneous populations and take into account potential confounders such as the presence of comorbid mental disorders (e.g., depression), the use of drugs, BMI, and smoking status as well as provide a proper matching of OCD and HC groups. Further studies assaying CSF levels of immune mediators in participants with OCD and HCs may provide greater insights, alongside studies examining the role of exposure to trauma—particularly in at an early age.

In conclusion, although a putative role for immune mechanisms in the pathophysiology of OCD has been proposed, the current systematic review and meta-analysis indicates that an associative role is yet to be established. The current systematic review and meta-analysis opens important research directions. Future studies should enroll more homogeneous samples with OCD and provide a better control for confounding variables (for example, psychiatric comorbidity and exposure to early-life trauma).

Compliance with Ethical Standards

Conflict of Interest DJS is supported by the Medical Research Council of South Africa and has received research grants and/or consultancy honoraria from Abbott, Astrazeneca, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah, and Wyeth. The other authors declare no conflict of interest.

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