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Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression

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Introduction: **Schizophrenia, bipolar disorder, and major depressive disorder (MDD) have all been associated with immune system dysfunction, including aberrant cerebrospinal fluid (CSF) levels of cytokines and tryptophan catabolites; however, the pattern of alterations has not been compared across disorders. We performed a meta-analysis of CSF cytokine and tryptophan catabolites in patients with these major psychiatric disorders.** ***Methods*****: Articles were identified by searching Pub Med, PsycInfo, and Web of Science, and the reference lists of these studies.** ***Results*****: Twenty-eight studies met the inclusion criteria (16 schizophrenia, 4 bipolar disorder, and 9 MDD). CSF levels of IL-1β and kynurenic acid were significantly increased in patients with schizophrenia and bipolar disorder compared to healthy controls ($P < .001$). CSF levels of IL-6 and IL-8 were significantly increased in patients with schizophrenia and MDD compared to healthy controls ($P \leq .013$).** ***Discussion:*** **There is preliminary evidence for similarities in the pattern of CSF cytokine and tryptophan catabolite alterations across major psychiatric disorders, although findings must be interpreted with caution in light of small numbers of studies/subjects. Many CSF alterations are also concordant with those in the peripheral blood, particularly for schizophrenia. Findings have important implications for our understanding of the pathophysiology and treatment of major psychiatric disorders.**

Key words: schizophrenia/bipolar disorder/major depressive disorder/cerebrospinal fluid/cytokines/inflammation/meta-analysis

Introduction

In recent years, there has been increased attention towards a potential role of the immune system in the pathophysiology of major psychiatric disorders. This interest has been at least partially stimulated by our increased understanding of the interactions that occur between the immune system and the brain in other chronic medical disorders. Advances in molecular biology and genetics have led to the identification of associations between genes involved in the regulation of the immune system and increased risk of schizophrenia, bipolar disorder, and major depressive disorder (MDD).[1–3] These disorders are also associated with abnormalities in blood immune cell numbers, inflammatory markers, tryptophan catabolites, and antibody titers.[4–10] There is mixed evidence in major psychiatric disorders suggesting that adjunctive treatment with immunomodulatory agents may be associated with improvement in psychopathology.[11–14] Taken together, these findings suggest we need to more extensively evaluate the hypothesis that immune dysfunction—manifested by an increase in pro-inflammatory and decrease in anti-inflammatory biomarkers, as well as alterations in tryptophan catabolites—may be involved in the pathogenesis of major psychiatric disorders in some individuals.

Cytokines are key regulators of inflammation that are produced by both immune and nonimmune cells. These signaling molecules coordinate innate and adaptive immunity by binding to specific cytokine receptors on various target cells, and they exert effects in both the periphery and the brain. Cytokine receptors also exist in soluble forms, which can inhibit (eg, soluble interleukin-2 receptor [sIL-2R]) or enhance [eg, sIL-6R]) the biological activity of cytokines. There are also endogenous cytokine receptor antagonists (eg, IL-1 receptor antagonist [IL-1RA]), which compete with cytokines for membrane receptors. Cytokines are key regulators of acute and chronic inflammation, a complex but vital biological

response that impacts all organ systems. In addition to their roles in immune function, cytokines also play a role in a host of other physiological processes throughout the body.[15,16]

A recent hypothesis suggests that the activation of brain microglial cells is associated with increased production of pro-inflammatory cytokines and free radicals that cause neuronal degeneration, white matter abnormalities, and decreased neurogenesis associated with the pathophysiology of schizophrenia.[17] Other studies have observed loss of glial elements in mood-relevant parts of the brain and suggest cytokine effects on glia may be important in the pathophysiology of mood disorders.[18,19] Cytokines can also directly alter the activity of enzymes involved in tryptophan catabolism. Induction of the enzyme indoleamine 2,3-dioxygenase (IDO) by pro-inflammatory cytokines results in increased production of kynurenine (KYN), which is converted in astrocytes to the NMDA receptor antagonist kynurenic acid (KYNA) and to the NMDA receptor agonist quinolinic acid (QUIN).[20,21] NMDA receptor hypofunction has been implicated in the pathophysiology of schizophrenia.[22] Previous studies have found increased blood,[23,24] cerebrospinal fluid (CSF),[25–27] and postmortem brain[28] levels of KYNA, as well as increased IDO activity in patients with schizophrenia.[29] There is also evidence of abnormalities in tryptophan catabolites in the blood and CSF of patients with bipolar disorder and MDD.[8,10,30]

In a meta-analysis, we found that blood levels of 2 cytokines (IL-6, TNF-α), 1 soluble cytokine receptor (sIL-2R), and 1 cytokine receptor antagonist (IL-1RA) were significantly increased in acutely ill patients with schizophrenia, bipolar mania, and MDD compared to controls.[31] The overall similarities in the pattern of blood cytokine alterations in schizophrenia, bipolar disorder, and MDD during acute and chronic phases of illness raises the possibility of common underlying pathways for immune dysfunction. However, measurements of peripheral blood cytokines and tryptophan catabolites may not necessarily reflect the immunological activity in the brain. At this time, we do not know if changes in these blood markers are mirrored in the CSF. Despite the evidence for cytokine alterations in major psychiatric disorders, there is tremendous between-study heterogeneity with respect to: specific cytokines; effects of potential confounding or moderating factors (eg, medications, smoking, body mass index, assay methodology, fasting status); and associations between immune markers and psychopathology. Meta-analysis is one approach that can bring increased clarity to an area of research with significant heterogeneity,[32] and thus is well suited to the study of immune alterations in major psychiatric disorders. This article presents meta-analyses comparing and contrasting the patterns of CSF cytokine and tryptophan catabolite alterations across schizophrenia, bipolar disorder, and MDD. We chose to investigate tryptophan catabolites in addition to cytokines because of the evidence linking these pathways. In doing so, we extend our investigation of potential common underlying pathways for immune dysfunction across these disorders, identify important gaps in the literature, and discuss implications for the research agenda in this field.

Methods

Study Selection

Studies of CSF cytokine (and cytokine receptor or antagonist) and tryptophan catabolite levels in schizophrenia, bipolar disorder, and MDD were identified by a systematic search using Medline (PubMed, National Center for Biotechnology Information, US National Library of Medicine, Bethesda, Maryland), PsycInfo (via Ovid, American Psychological Association, Washington, DC), and Thomson Reuters (formerly ISI) Web of Science (Science Citation Index and Social Sciences Citation Index, Thomson Reuters, Charlottesville, Virginia) in June 2015 and again in March 2016. The primary search strategies were: (1) "(CSF OR "cerebrospinal fluid") AND (inflammation OR cytokine OR interleukin OR interferon OR "tumor necrosis factor" OR kynurenine OR "kynurenic acid") AND (schizophrenia OR psychosis)", (2) "(CSF OR "cerebrospinal fluid") AND (inflammation OR cytokine OR interleukin OR interferon OR "tumor necrosis factor" OR kynurenine OR "kynurenic acid") AND (bipolar OR mania)", and (3) "(CSF OR "cerebrospinal fluid") AND (inflammation OR cytokine OR interleukin OR interferon OR "tumor necrosis factor" OR kynurenine OR "kynurenic acid") AND (depression OR "major depressive disorder"), limiting results to human studies in English. From all sources, we identified 212 potential studies for schizophrenia, 49 for bipolar disorder, and 276 for MDD. The majority of initial matches were excluded because they were review articles, did not present CSF data, or were genetic studies related to cytokines or tryptophan catabolites.

The inclusion criteria were studies assessing CSF cytokine or tryptophan catabolite levels in patients with schizophrenia, bipolar mania, or MDD and healthy controls. The exclusion criteria were: (1) studies without a control group, (2) studies that did not present either mean and SDs or median and interquartile range (IQR) for cytokine levels (after attempting to contact the study authors), (3) significant overlap in study population, and (4) genetic studies related to cytokines or tryptophan catabolites. Due to the potential for low concentrations of some markers, the methods of the potential studies were reviewed to evaluate assay sensitivity. An individual marker was excluded if: (1) the mean concentration was less than the lower limit of assay detection, (2) concentrations were not detectable in >50% of subjects, or (3) either the intra-assay coefficient of variation (CV) was >10% or the inter-assay CV was >15%.

After independent searches, review of study methods by both authors (A.K.W. and B.J.M.) and attempts to contact other authors, 28 studies met the inclusion criteria (16 schizophrenia, 4 bipolar disorder, and 9 MDD—1 study reported on both schizophrenia and MDD).[25–27,33–57] There was universal agreement on the included studies. A flow chart summarizing the study selection process is presented in supplementary material.

Data Extraction and Meta-analysis

Data were extracted (sample size, mean/SD or median/IQR for patients and controls), for every cytokine and tryptophan catabolite assessed in each study for each disorder. If necessary, we estimated the mean/SD from the median/IQR using the following formulas: (1) mean = $(2m + a + b)/4$, where m is the median and a and b are the 25th and 75th percentiles, respectively,[58] and (2) IQR = 1.35 × SD.[59] One author (A.K.W.) extracted all data, which was independently verified by another author (BJM). We then calculated effect size ES estimates (Standard Mean Difference [SMD]) for every marker in each study for each disorder, and these data are included in supplementary material. Fixed effects pooled ES estimates and 95% CIs were calculated using the method of Mantel and Haenszel. Separate meta-analyses were performed for each individual marker for each disorder (vs controls). P values were considered statistically significant at the $\alpha = .05$ level. Given the preliminary nature of this study, we did not correct P-values for multiple comparisons. The statistical analyses were performed in Stata 10.0 (StataCorp LP).

The meta-analysis procedure also calculates a χ^2 value for the heterogeneity in ES estimates, which is based on Cochran's Q-statistic,[60] and I^2, the proportion of the variation in ES attributable to between-study heterogeneity. Heterogeneity (χ^2) was considered significant for $P < .10$.[61] For many cytokines for each disorder, χ^2 was significant, so we performed a sensitivity analysis. This was done by removing 1 study at a time and repeating the meta-analysis procedure, to examine its impact on the OR and between-study heterogeneity.[62]

Given the significant heterogeneity for many markers, we performed a series of meta-regressions for IL-6 in schizophrenia and MDD (the marker most frequently studied in each disorder) to explore possible moderating variables of age and sex. We were not able to perform meta-regression analyses for other markers due to the small number of available studies, nor other possible moderating variables (eg, illness duration, smoking, and body mass index) due to the absence of adequate data. Potential for publication bias was examined with Sterne's funnel plot analysis[63] and Egger's regression intercept.[64]

Results

To summarize our findings: CSF levels of IL-6 (small–medium ES = 0.40) and IL-8 (small–medium ES, range 0.35–0.57) were significantly increased in patients with schizophrenia and MDD compared to controls ($P \leq .013$ for each); IL-1β (small–medium ES, range 0.31–0.75) and KYNA (medium-large ES, range 0.59–0.79) were significantly increased in patients with schizophrenia and bipolar disorder compared to healthy controls ($P \leq .013$ for each). CSF levels of KYN (large ES = 1.22) were significantly increased and CSF sIL-2R levels (large ES = −0.84) were significantly decreased in patients with schizophrenia compared to healthy controls ($P < .02$ for each). Findings for each disorder are presented in greater detail below (see also table 1 and figures 1 and 2).

Schizophrenia

CSF levels of IL-1β, IL-6, IL-8, KYN, and KYNA were all significantly increased ($P < .02$ for each), and CSF levels of sIL-2R were significantly decreased ($P < .02$) in schizophrenia vs controls. There was not a significant ES difference for IL-1α, IL-2, or sTNFR2. Between-study heterogeneity was significant for IL-1β and KYN. In sensitivity analyses, heterogeneity was no longer significant, but the ES remained significant after removing 1 study for KYN.[45] A funnel plot and results of Egger's test showed no evidence for publication bias for IL-6 ($P > .05$). In meta-regression analyses, age and sex were both unrelated to IL-6 in schizophrenia ($P > .05$ for each).

Bipolar Disorder

CSF levels of IL-1β ($P = .02$) and KYNA ($P < .001$) were both significantly increased in patients with bipolar disorder vs controls, and IL-8 was increased at the trend level ($P = .087$). There was not a significant ES difference for IL-6. Between-study heterogeneity was significant for IL-1β, IL-6, and IL-8, but not for KYNA. Sensitivity analysis was not possible for any markers due to the small number of studies.

Major Depressive Disorder

CSF levels of IL-6 and IL-8 were both significantly increased in MDD patients vs controls ($P < .01$). There was not a significant ES difference for IL-1β and TNF-α. Between-study heterogeneity was significant for IL-1β and IL-6, but not for IL-8 or TNF-α. In a sensitivity analysis, heterogeneity was no longer significant, but the ES remained significant, after removing 1 study for IL-6.[42] Sensitivity analysis was not possible for IL-8 due to the small number of studies. A funnel plot and results of Egger's test showed no evidence for publication bias for IL-6 ($P > .05$). In meta-regression analyses, age and sex were both unrelated to IL-6 in MDD ($P > .05$ for each).

Discussion

Overall, there is preliminary evidence for some similarities in the ES direction and, to a lesser extent, magnitude

Table 1. CSF Cytokine and Tryptophan Catabolite Alterations in Patients With Schizophrenia, Bipolar Disorder, and MDD vs Controls

Marker	*N*			Mean ES	95% CI		*P* Value	Heterogeneity		I^2	References
	Studies	Pt	Control					χ^2	*P* Value		
Schizophrenia											
IL-1α	2	70	31	−0.33	−0.77	0.11	.143	3.44	.06	70.9	43,44
IL-1β	3	57	45	0.75	0.29	1.21	**.001**	40.30	<.01	95.0	33,38,54
IL-2	4	114	52	−0.01	−0.35	0.33	.954	6.14	.11	51.2	33,35,43,44
sIL-2R	2	19	20	−0.84	−1.50	−0.18	**.013**	0.66	.42	0.0	33,46
IL-6	7	244	180	0.40	0.20	0.60	**<.001**	6.12	.53	0.0	27,33,37,38,53,54,56
IL-8	3	112	101	0.35	0.07	0.63	**.013**	1.01	.60	0.0	27,37,54
TNF-α											
sTNF-R2	2	56	45	−0.09	−0.49	0.30	.646	2.56	.11	61.0	37,46
KYN	3	60	92	1.22	0.86	1.58	**<.001**	14.66	<.01	86.4	25,27,44
KYNA	4	148	141	0.59	0.34	0.83	**<.001**	2.87	.41	0.0	25–27,44
Bipolar disorder											
IL-1α											
IL-1β	2	151	101	0.31	0.05	0.58	**.020**	27.51	<.01	96.4	39,54
IL-2											
sIL-2R											
IL-6	2	151	101	−0.13	−0.39	0.12	.310	12.94	<.01	92.3	39,54
IL-8	2	151	101	0.22	−0.03	0.48	.087	6.97	<.01	85.7	39,54
TNF-α											
sTNF-R2											
KYN											
KYNA	2	74	35	0.79	0.36	1.21	**<.001**	0.36	.408	0.0	48,49
MDD											
IL-1α											
IL-1β	2	30	57	0.27	−0.21	0.75	.266	12.28	<.01	91.9	41,45
IL-2											
sIL-2R											
IL-6	7	127	222	0.40	0.17	0.63	**.001**	21.49	<.01	67.4	34,41,45,47,50,53,57
IL-8	2	38	114	0.57	0.20	0.95	**.003**	2.12	.15	52.9	45,57
TNF-α	3	48	82	0.26	−0.10	0.63	.161	1.18	.55	0.0	41,45,47
sTNF-R2											
KYN											
KYNA											

Note: CSF, cerebrospinal fluid; MDD, major depressive disorder; KYN, kynurenine; KYNA, kynurenic acid. Bolded *P* values were significant at the $P < .05$ level.

of alterations in CSF cytokine and tryptophan catabolite levels in schizophrenia, bipolar disorder, and MDD compared to controls. Levels of 3 cytokines (IL-1β, IL-6, and IL-8) and 1 tryptophan catabolite (kynurenic acid) were significantly elevated in 2 of 3 syndromes. In addition, levels of kynurenine were significantly increased and levels of sIL-2R were significantly decreased in patients with schizophrenia vs controls.

We found some evidence of concordance between cytokine alterations in the CSF identified in the present study with those found in our previous meta-analysis of cytokine alterations in the peripheral blood,[31] particularly for schizophrenia (table 2). Both blood and CSF IL-1β, IL-6, and IL-8, but not IL-2, are increased in patients with schizophrenia vs controls.[31] By contrast, CSF sIL-2R levels were significantly decreased, whereas blood levels are significantly increased in schizophrenia.[31] In bipolar disorder, increased blood and CSF IL-1β was a concordant finding. By contrast, blood IL-6 levels were significantly increased in bipolar disorder, whereas CSF IL-6 levels were nonsignificantly decreased. In MDD, increased blood and CSF IL-6 and nonsignificant alterations in IL-1β were concordant findings. Blood and CSF findings were discordant for IL-8 and TNF-α in MDD. However, the majority of findings for blood and CSF cytokines are based on independent studies. We identified 4 studies with available data on blood and CSF cytokines in the same patients. Sasayama et al[31] found significantly higher CSF than blood IL-6 levels in schizophrenia, and a trend for higher levels in MDD. However, blood and CSF IL-6 levels were not correlated. van Kammen et al[56] found lower CSF than blood IL-6 levels in schizophrenia, but did not report on the correlation between these measures. Katila et al[40] found lower CSF than blood IL-1β levels in schizophrenia, and no correlation between the 2 measures. Lindqvist et al[46] found lower levels of IL-1β, IL-6, and TNF-α, and higher IL-8 levels in CSF than blood in suicide attempters with

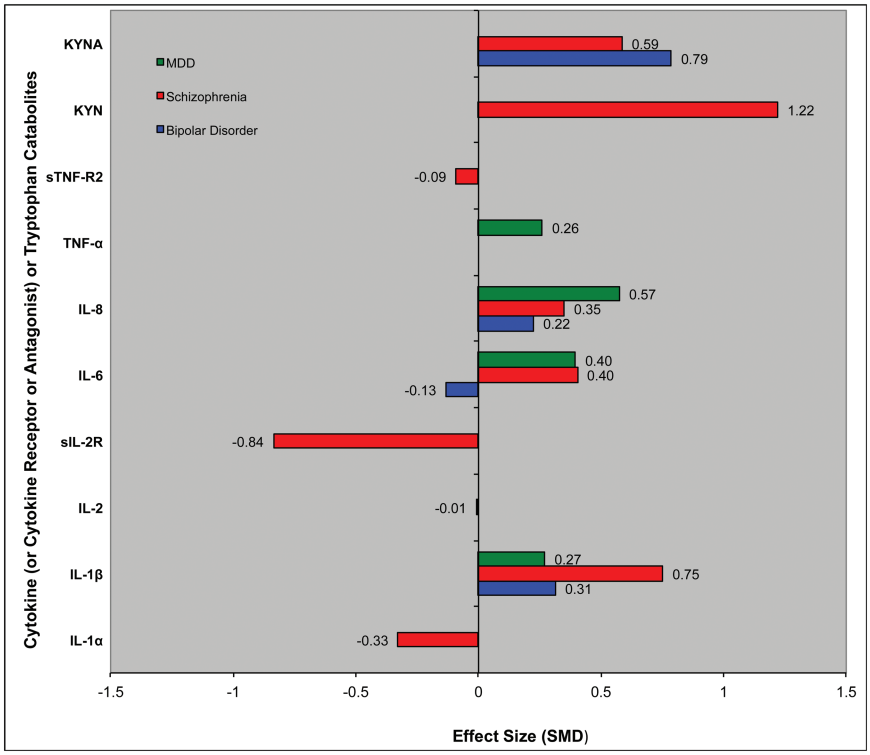

Fig. 1. Cerebrospinal fluid (CSF) cytokine and tryptophan catabolite alterations in patients with schizophrenia, bipolar disorder, and major depressive disorder vs controls.

depression. Blood and CSF levels were not correlated for any of the cytokines.

One potential explanation for discordant results is that the CSF findings are generally based on much smaller sample sizes than those for blood. Another potential contributing factor is that we were unable to control for the clinical status of subjects in the analysis of CSF cytokines, whereas previous findings for blood cytokines were stratified based on this variable (eg, first-episode, acutely ill, and chronically ill subjects).[31] Alternatively, it is possible that there are differences in regulatory mechanisms in the CNS compared to the periphery which contribute to the observed discrepancies. There is evidence for discordant findings for blood and CSF cytokine levels in other disorders, including neuropsychiatric lupus and multiple sclerosis.[65,66]

It is intriguing that all 3 cytokines that were elevated in patients (IL-1β, IL-6, and IL-8) are modulated through the Nuclear Factor-kappa B (NF-κB) signaling pathway that is commonly activated in inflammatory and autoimmune disease.[67–69] Elevations in the CSF cytokines IL-1β and IL-6 suggest the possibility of microglial activation, which has been reported in patients with schizophrenia.[70–72] These findings are broadly consistent with elevations in CSF kynurenic acid in schizophrenia and bipolar disorder, as cytokines can modulate the activity of tryptophan catabolism in astrocytes and microglia. However, none of the included studies reported correlative data between levels of cytokines and tryptophan catabolites.

The primary strength of our study is the comparison of CSF cytokine and tryptophan catabolite alterations across 3 major psychiatric disorders, which has not been previously performed. There are several limitations of the present work. Our findings should be interpreted with caution in light of small numbers of studies and cumulative sample size available for many of the markers, including cytokines that were not studied in some of the disorders.13 of the 17 markers were reported in 3 or fewer studies. This is itself an important finding: the need to replicate many of the observed alterations, as well as studies of specific markers in order to facilitate comparisons across disorders. A second limitation is that one cannot account for either the clinical status or the type/length of pharmacologic intervention employed, as there were an insufficient number of studies to conduct subgroup analyses. One also needs to acknowledge the problem of important potential confounding, and some potentially moderating, factors such as smoking, BMI, medical comorbidities, level and type of psychopathology, genetic heterogeneity, sample collection and processing, time of day, type of assay employed and how long samples are stored before being analyzed.[73–78] Subjects were medicated in the majority of studies included in the present analysis. There is evidence that antipsychotics (as a class) increase sIL-2R and decrease IL-1β and interferon-gamma (IFN-γ) levels in the blood in patients with schizophrenia.[78] In vitro studies of the effects of antipsychotics on cytokines are heterogeneous, with evidence

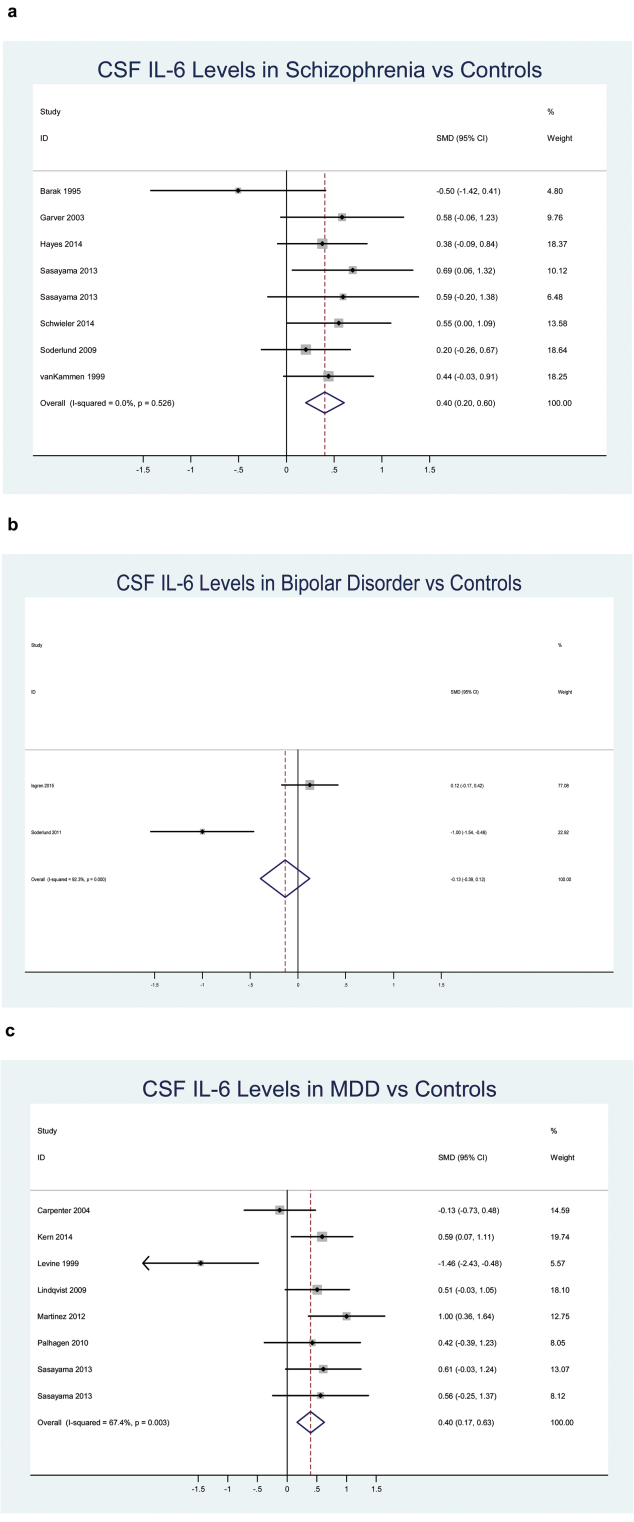

Fig. 2. Forest plots of cerebrospinal fluid (CSF) IL-6 alterations in patients with schizophrenia, bipolar disorder, and major depressive disorder (MDD) vs controls. (a) Schizophrenia, (b) bipolar disorder, and (c) MDD.

for the same antipsychotic showing pro- and anti-inflammatory effects across different studies.[79] Furthermore, in vitro studies have found that among antidepressants, fluoxetine and clomipramine tend to decrease IL-6, IFN-γ, and TNF-α production, whereas mirtazapine and venlafaxine may increase production of these cytokines.[79] However, the effects of psychotropic medications on CSF cytokines have not been characterized. Although we did not find evidence for moderating effects of age or sex on IL-6 levels in either schizophrenia or MDD, this does not preclude moderating effects between such clinical and demographic factors and other markers. These factors should be carefully considered regarding the significance of our meta-analytic findings. Based on the lack of available data, we were also not able to perform a meta-analysis of other molecules/markers that are involved in immune/inflammatory mechanisms (eg, chemokines).

Our findings raise many questions. What are the most important CSF markers to measure across disorders? We suggest that some of the most important CSF cytokines for further study include IL-1β, sIL-2R, IL-6, IL-8, and TNF-α, because of (1) existing evidence of alterations in the peripheral blood and/or CSF, (2) some of these markers have not been studied in the CSF in some psychiatric disorders (eg, TNF-α in schizophrenia and bipolar disorder, sIL-2R in bipolar disorder and MDD), and/or (3) the opportunity to address discordant findings (eg, blood vs CSF). Other issues in such an approach include statistical

Table 2. Comparison of Blood and CSF Cytokine Alterations in Patients with Schizophrenia, Bipolar Disorder, and MDD vs Controls

Marker	Blood[31]			CSF
	First-Episode	Acutely Ill	Outpatient	
Schizophrenia				
IL-1β	↑	↑	↑	↑
IL-2	NS	NS	NS	NS
sIL-2R	↑	↑	↑	↑
IL-6	↑	↑	↑	↑
IL-8	↑	↑	↑	↑
TNF-α	↑	↑	↑	
Bipolar disorder				
IL-1β			↑	↑
IL-2				
sIL-2R				
IL-6		↑	↑	NS
IL-8				NS
TNF-α		↑	NS	
MDD				
IL-1β		NS	NS	NS
IL-2		NS	↑	
sIL-2R			NS	
IL-6		↑	↑	↑
IL-8			NS	↑
TNF-α		↑	NS	NS

Note: CSF, cerebrospinal fluid; MDD, major depressive disorder; NS, not significant; ↑, Significantly increased in patients vs controls; ↓, Significantly decreased in patients vs controls.

considerations of multiple comparisons due to the potential for type 1 error, and whether investigators should focus on a composite "inflammatory score" rather than individual markers. Studies measuring both cytokines and tryptophan catabolites would be informative regarding the relationship of these pathways across disorders. What is the relationship of CSF markers to demographic and clinical features (eg, psychopathology and cognition)? Relationships between cytokine levels and psychopathology have not been considered in the majority of previous studies. It would therefore be informative to investigate if there are any symptom dimensions, which may cut across diagnostic categories, which may be more strongly associated with inflammation. Studies in first-episode drug-naïve subjects would clarify whether alterations in cytokines and tryptophan catabolites are more attributable to the disorder itself or medication effects. Studies of changes in these CSF markers across the course of the disorder, including acute illness episodes and treatment-resistant illness would also be particularly informative. Is there a level of concordance in findings that would justify preferential use of peripheral blood vs CSF markers, particularly if findings in blood were coupled with brain imaging?

In conclusion, there is some preliminary evidence for similarities in the pattern of CSF cytokine and tryptophan catabolite alterations in subjects with schizophrenia, bipolar disorder and MDD most consistent with an inflammatory profile, although many findings are based on a small number of studies/subjects and there was substantial between-study heterogeneity. Our findings do not rule out the possibility of common underlying pathways for the expression of immune dysfunction in patients with these disorders, and this hypothesis warrants further evaluation. Many CSF alterations are also concordant with those in the peripheral blood, particularly for schizophrenia. The moderate effect sizes observed most likely reflects that fact that immune system involvement occurs in only a subset of patients with each of these syndromes, which is an important consideration for future studies of immune function and anti-inflammatory therapies. The results from this meta-analysis reflect a need to more rigorously evaluate how and what we measure in the immune system. More extensive and systematic investigation in this area is clearly warranted.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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