SYSTEMATIC REVIEW

The relationship between immune and cognitive dysfunction in mood and psychotic disorder: a systematic review and a meta-analysis

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BACKGROUND: In psychotic and mood disorders, immune alterations are hypothesized to underlie cognitive symptoms, as they have been associated with elevated blood levels of inflammatory cytokines, kynurenine metabolites, and markers of microglial activation. The current meta-analysis synthesizes all available clinical evidence on the associations between immunomarkers (IMs) and cognition in these psychiatric illnesses.

METHODS: PubMed, Web of Science, and Psycinfo were searched for peer-reviewed studies on schizophrenia spectrum disorder (SZ), bipolar disorder (BD), or major depressive disorder (MDD) including an association analysis between at least one baseline neuropsychological outcome measure (NP) and one IM (PROSPERO ID:CRD42021278371). Quality assessment was performed using BIOCRoss. Correlation meta-analyses, and random effect models, were conducted in Comprehensive Meta-Analysis version 3 investigating the association between eight cognitive domains and pro-inflammatory and anti-inflammatory indices (PII and AII) as well as individual IM.

RESULTS: Seventy-five studies (n = 29,104) revealed global cognitive performance (GCP) to be very weakly associated to PII (r = − 0.076; p = 0.003; I² = 77.4) or AII (r = 0.067; p = 0.334; I² = 38.0) in the combined patient sample. Very weak associations between blood–based immune markers and global or domain-specific GCP were found, either combined or stratified by diagnostic subgroup (GCP x PII: SZ: r = −0.036, p = 0.370, I² = 70.4; BD: r = −0.095, p = 0.013, I² = 44.0; MDD: r = −0.133, p = 0.040, I² = 83.5). We found evidence of publication bias.

DISCUSSION: There is evidence of only a weak association between blood-based immune markers and cognition in mood and psychotic disorders. Significant publication and reporting biases were observed and most likely underlie the inflation of such associations in individual studies.

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INTRODUCTION
Cognitive deficits are core features of severe mental disorders, and include memory, reasoning, attention, and information processing problems [1–4]. These deficits have been shown to be predictive of clinical and functional outcome, both cross-sectionally and longitudinally, in psychotic [5, 6] as well as mood disorders [7–9]. Regrettably, traditional treatment options such as antipsychotics [10, 11], mood stabilizers [12, 13], or antidepressants [14, 15] have limited or no beneficial effects on these cognitive symptoms. Besides monoaminergic signaling [16–18], other neurotransmitters including the GABAergic [19], and nicotinicergic [20] systems but also hormonal changes [13, 21] and altered neuroplasticity [22] have been connected with cognitive dysfunctioning. Several potential cognitive enhancers targeting these mechanisms have been investigated with limited success [12], in turn stimulating the search for new treatment targets.

Disruption of the immune system is an important feature of psychotic and mood disorders [23–25] and is characterized by central immune changes such as altered microglial activity [26–28] as well as peripheral changes in cytokine levels [23], alterations in the kynurenine metabolism [29, 30] and white blood cell ratios [31]. While modest beneficial effects of adjunctive therapy with anti-inflammatory agents have been demonstrated for depressive, negative (i.e., apathy, flattened affect, poverty of thought or speech) and psychotic symptoms of severe mental disorders [32–34], it is unclear if this is also the case for cognitive symptomatology [35, 36]. Cognitive dysfunction in psychotic and mood disorders has been associated with elevated blood levels of

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inflammatory cytokines [37–39], kynurenine metabolites [40], and markers of microglial activation [40] in observational studies. However, these associations are typically modest and inconsistent in nature and seem to be subject to reporting bias with several studies only highlighting significant correlations between immune and cognitive markers while leaving other non-significant associations unreported [41–45].

The aim of the current meta-analysis is to synthesize all available evidence on the associations between immunomarkers and cognitive symptomatology in clinical observational studies of patients with psychotic and mood disorders.

MATERIALS AND METHODS

We performed a systematic review and meta-analysis of studies reporting on the association between one or more immunomarkers and cognitive functioning in people with psychotic or mood disorders (PROSPERO ID:CRD42021278371, for updates to protocol, see Supplement). The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis PRISMA 2020 standard (Supplementary Table 1) [46].

Search strategy

A multistep procedure was used to conduct the literature search and consequent data assessment. The search included original papers published up to 8 November 2021 on Pubmed, Web of Science, and Psycinfo. The full search strings are available in the Supplement. Two authors independently (MM, CO) performed the literature search and completed the screening of article titles and abstracts for eligibility. In case of disagreement, papers were retained for full-text evaluation.

Inclusion criteria were: (1) Cross-sectional or longitudinal studies in peer-reviewed journals, (2) In vivo human studies on patients with primary diagnosis of schizophrenia (DSM-code: 295.90; ICD-10 code: F20.9), schizophreniform (295.40; F20.81), schizoaffective disorder (295.70; F25.2), brief psychotic disorder (298.8; F23), other psychotic disorder (298.9, F29), major depressive disorder (MDD) (295.70; F25.2), bipolar disorder (296.10; F31.4), (3) The analysis included and reported an association analysis between at least one baseline a) standardized neuropsychological outcome variable and consequent data assessment. The search included original studies reporting on primary diagnoses of either schizophrenia, schizoaffective disorder, bipolar disorder, other (based on Fisher’s z transformation of the r values [49]). This resulted in a single r score reflecting the association of the merged correlational values between the cognitive domain and the pro-inflammatory and anti-inflammatory markers. This method of combining multiple pro-inflammatory markers in a single composite inflammatory score is in line with previous similar efforts in psychosocial stress [50], depression [51], schizophrenia [52], psychological trauma [53], cerebrovascular disease [54], atherosclerosis [55], aging [56] and carcinoma [57] research. Secondary IM outcome variables were individual IM when more than three studies were available. In case of a significant association, exploratory subgroup analyses were performed to define which of the diagnoses contributed to the statistically significant association.

Quality assessment of eligible papers was performed with the BIOCROSS evaluation tool [58], which is specifically developed for biomarker-based cross-sectional studies. Quality assessment of each included study was performed independently by two different authors (MM, CO, EL), and any disagreement was resolved by deliberation.

Data synthesis and analysis

The correlation meta-analyses were conducted in Comprehensive Meta-Analysis version 3 (CMA v3) using random-effect models, which use the Hedges-Olkin method with a Fisher Z transformation of the correlation coefficient [59]. Heterogeneity was estimated with $I^2$ (heterogeneity classification: $I^2 = 25$–$49%$: low; $I^2 = 50$–$74%$: moderate; $I^2 \geq 75%$: high). Because the $p$ value of correlation analysis is known to be strongly influenced by the sample size of the analysis, we opted to evaluate the association based on the strength of the association (using the $r$ value) rather than the $p$ value. Following Evans [60], meta-analytic correlation effect estimates of $|0–0.19|$ were considered to be “very weak”, $|0.20–0.39|$ as “weak”, $|0.40–0.59|$ “moderate”, $|0.60–0.79|$ as “strong” and $|0.80|$ or above as “very strong”.

The primary meta-analysis was performed on the effects of pro-inflammatory and anti-inflammatory markers (see Supplementary Table 4) in all mood and psychotic disorders combined for global cognitive function. Secondary analysis was performed for each cognitive domain, and for individual immunomarkers if at least three studies were available. Subgroup analysis was performed to evaluate differences between diagnostic groups primary and...
The primary meta-analysis was repeated including only high-quality studies as defined by the BIOCROSS quality assessments.

RESULTS

Study selection

The results of the literature search are summarized in the PRISMA Flowchart. Additional data were requested for 88, and granted for 22 papers (response rate 25%). A total of 75 studies [24,41–45,63–130] and 627 NP × IM associations were included in the meta-analysis (see Supplementary Figure 1 for PRISMA Flowchart). Forty-two studies focused on SZ, 17 studies investigated BD, and 18 studies included MDD patients, for a total sample of 29,104 patients (see also Supplementary Tables 5–7). Thirty-one studies reported cognitive associations with a single IM, whereas 44 studies included multiple IM (see Supplementary Table 6).

The following IM were included in the meta-analysis: C-reactive protein (hs-PCR), cytokines/chemokines (CCL-11; CCL-17; CCL-22; CXCL-10; IFN-g; IL-1; IL-1b; IL-2; IL-3; IL-4; IL-6; IL-7; IL-10; IL-12; IL-12p70; IL-15; IL-16; IL-17; IL-18; IL-33; MCP-1; sST2; sTNF-R1; sTNFR2; TGF-b; TNF-a) or kynurenine metabolites (Tryptophan (TRP); Kynurenine (KYN); Kynurenine Acid (KA); 3-hydroxykynurenine (3-HK); Quinolinic Acid (QUIN)). A single study [130] looked into the association of cognition with immunomarker levels in CSF while all other studies focused on peripheral assessments (serum/plasma). Therefore, CSF data were not included in the current meta-analysis. No studies investigated associations between NP and leukocyte IM.

P11 correlation scores were calculated for a total of 18 out of 39 studies in the verbal memory domain, 6 out of 14 studies in visual memory, working memory (14 out of 15 studies); attention (12 out of 35 studies); processing speed (12 out of 23 studies); reasoning (18 out of 42 studies); language (9 out of 22 studies) (see Supplementary Table 7).

Association of pro-inflammatory (P11) and anti-inflammatory index (AII) with global cognitive performance (GCP)

P11 and AII × GCP interactions were available for 53 studies (n = 27,908). Over the three eligible diagnostic groups (MDD, SZ, BD), GCP was very weakly associated with P11 (P11 × GCP r = −0.076; 95% CI = −0.116 to −0.027, z = −3.011; p = 0.003, F = 77.4; see Table 1; Supplementary Figures 2–9), an association that can be considered to be negligible.

Subgroup analysis revealed no significant differences between the three diagnostic groups (Q(2) = 2.302; p = 0.316), with very weak associations in each group for P11 × GCP (SZ: n studies = 27, r = −0.036, p = 0.370, F = 70.4; BD: n studies = 13, r = −0.095, p = 0.013, F = 44.0; MDD n studies = 13, r = −0.133, p = 0.040 (not significant after FDR correction), F = 83.5); see Table 1).

While only five studies yielded All × GCP interactions, no significant associations were found (see Table 2; Supplementary Figures S10–S14).

Association of P11 and AII with domain-specific cognitive performances

Overall association measures for P11 were smaller than |0.10| for all domain-specific cognitive outcome variables. In the diagnostic subgroups analysis, significant but very weak associations were observed for visual memory in SZ, and for visual and verbal memory, working memory, and language in BD (see Table 1).

Notably, the analyses reporting a statistically significant association in the diagnostic subgroups typically contained a lower number of included studies and smaller total sample sizes than analyses reporting non-significant associations. Meta-regression analysis for P11 × GCP associations in the total sample (with sample size as covariate) did not reveal a significant confounding effect (coefficient (SE) = 0.00 (0.00); z = 0.97; p = 0.330).

No significant associations were found between All and specific domains such as verbal memory, processing speed, and reasoning (see Table 2).

The BIOCROSS evaluation tool [58] was used to assess the quality of the included studies (see Supplementary Table 8). Thirty-seven papers had high quality, 35 papers were rated as having moderate quality, two papers had low quality. When only studies of high quality were retained, the overall correlation between P11 and the composite score became non-significant (r = −0.042; z = −1.955; p = 0.051). Similarly, when only considering high quality studies this correlation disappeared in all diagnostic subgroup (BD: k = 7, r = −0.032, z = −1.301, p = 0.193; MDD: k = 6, r = −0.120, z = −1.051, p = 0.293; SZ: k = 14, r = −0.064, z = −1.363, p = 0.173).

Cognitive performance and individual IM

Only for the immunomarkers CRP, IL-1b, IL-6, TNF-a, and IFN-g, there were at least three studies available that assessed their association with cognitive performance in mood and psychotic disorders (Supplementary Table 7; Supplementary Figures S15–S19).

CRP (22 studies; 25,948 patients) was significantly but very weakly associated with GCP (r = −0.124; p < 0.001, F = 79.8), as well as with verbal and visual memory, working memory, reasoning, and language in the total patient cohort. Follow-up subgroup analyses revealed a significant but very weak association with global cognition to be reflected in schizophrenia (r = 0.139; p = 0.013) and bipolar disorder (r = 0.126; p = 0.016), but not in MDD. Associations remained significant after FDR correction. Significant and weak correlations were observed between CRP and attention, verbal memory and visual memory in SZ, and verbal memory, processing speed, reasoning, and language in BD.

IL-6 (27 studies; n = 2,250) was significantly but very weakly associated with global cognition (r = −0.167; p < 0.001), verbal memory, and processing speed but not with any of the other cognitive domains in the total patient cohort.

IL-1b (10 studies; n = 988), TNF-a (23 studies; n = 1,868), and IFN-g (five studies; n = 203) were not associated with either the composite cognitive score or any of the separate cognitive domains.

Seven studies probed relations between several tryptophan catabolism (TRYCAT) metabolites (TRP, KYN KA, 3-HK, QUIN) and cognitive performance in mood and psychotic disorders. Again, none of the metabolites interacted significantly with cognition (see Table 4).

Covariate assessment

For the association between pro-inflammatory cytokines and global cognition, publication year (coefficient(SE) = −0.02(0.01); z = −0.30; p = 0.7035), mean patient age (coefficient(SE) = 0.01 (0.01); z = 0.36; p = 0.720), mean Duration of Illness (coefficient(SE) = 0.000(0.02); z = −0.17; p = 0.862), BMI (coefficient(SE) = −0.01(0.04); z = −0.40; p = 0.689), gender ratio (coefficient(SE) = 0.000(0.01); z = 0.46; p = 0.642) and smoker/non-smoker ratio (coefficient(SE) = 0.01(0.00); z = 1.24; p = 0.217) all proved non-significant covariates in meta-regression analyses.

Assessment of publication bias

Out of the included 75 papers, a total number of 627 out of the potential 1810 associations (number of cognitive measures ×
number of immunomarkers) were at disposition for the current meta-analysis (i.e., 35%). On average, 53% of the potential total number of associations were reported per study (MDD: 63%; SZ: 53%; BD: 43%).

Visual inspection of the funnel plots of the standard errors by Fisher’s Z scores for associations between GCP and PI, CRP and IL-6 respectively (see Supplementary Figures 20–22) indeed suggested the presence of a publication bias in favor of more pronounced...
negative correlations. The Egger regression test confirmed the potential presence of a publication bias (intercept $= -1.30; t = 4.26; p < 0.0001$). However, when conducted for each diagnosis independently, Egger’s test was only significant for MDD (intercept $= -1.74; t = 2.68; p = 0.023$), but not for SZ (intercept $= 0.64; t = 0.68; p = 0.501$) or bipolar disorder (intercept $= -0.94; t = 1.37; p = 0.199$).

Heterogeneity over studies was moderate to high (see Tables 1–4), especially for immunomarkers investigated in a larger number of studies. When evaluating individual biomarkers (see Table 4), heterogeneity tended to be higher for those associations with cognitive performance that yielded statistically significant correlations.
abnormalities instead of volatile “snapshots” of individual compounds may be more informative to assess the relationship with cognitive functioning. Furthermore, while peripheral immunomarker levels fluctuate heavily over time [138], cognitive deficits are a more stable or slowly progressive phenomenon in mood and psychotic disorders [139]. As such, the temporal resolution of cross-sectional assessments of blood-based immunomarkers may not be sufficient to detect the long-term and/or long-ago repercussions of immunological causes on cognitive performance. Peripheral CRP and several cytokines (including IL-6 and TNF-α) have been demonstrated to be highly state-dependent in mood and psychotic illness [23, 24, 140–143], suggesting they are more relevant as biomarkers for episodic symptoms like psychosis or mania. Alternatively, longitudinal characterization of immunomarkers and cognitive outcomes over longer time periods may be more informative than single cross-sectional assessments. Another consideration is that peripheral blood concentrations may not reflect latent or undetected central immune-related processes [144, 145] that do interfere with cognitive performance. Undoubtedly, the lack of studies focusing on central assessments of immune activity in major psychiatric disorders is hampering our ability to determine the interplay between the immune system and cognitive function. The few available studies of central inflammatory responses are mostly small-scale and cross-sectional in nature, and typically do not include neuropsychological assessments [26, 27]. Even so, the most investigated of these molecules (CRP, IL-6, IL-1β) are potent but nonspecific immune markers that are produced by a variety of cells and have a myriad of pleiotropic effects in the brain [146, 147], rendering the interpretation of their potential impact on cognitive functioning difficult. It has been proposed that kynurenine metabolites are more closely related to cognitive functioning, due to their interaction with the glutamatergic and nicotinergic systems [25] and while the current meta-analysis did not reveal an association with cognitive functioning, the number of studies focusing on these immune markers was very limited, and studies with larger sample sizes are needed. Finally, a few studies demonstrated increases of anti-inflammatory cytokines in processes associated with low-grade systemic inflammation [148, 149]. As a result, it has been questioned to what extent these changes that may be comparable to those seen in psychiatric illness actually represent anti-inflammatory properties in such conditions.

Several limitations should be acknowledged. Meta-analysis of correlation measures remains methodologically challenging, and this is particularly true for associations between two complex dimensions without standardized outcome measures, as is the case for immunological assays and neuropsychological testing in psychiatric disorders. The method used by meta-analysis software CMA tends to overestimate pooled effects [150], especially when correlation coefficients are higher. However, these coefficients tended to be low in the current series of meta-analyses, and even when present would only confirm the conclusions drawn in the current review. Moreover, although efforts were made to mitigate account for publication and reporting biases, they were demonstrably present and will have fundamentally impacted the results.
of the current meta-analysis. Several studies had small to very small sample sizes and were of moderate quality, which seems to have impacted the results, as analyses only including high-quality papers revealed even more modest associations between immune markers and cognition. The moderate to high overall heterogeneity might be attributable to several meta-analyses of inherent and individual study design-related factors. First, the calculated pro- and anti-inflammatory indexes amalgamate individual inflammatory compounds into two potentially arbitrary categories, at the risk of oversimplification or effect diffusion. Another limitation to be kept in mind is that basal blood levels of immunomarkers do not necessarily reflect the in vivo reactivity upon immune challenge. It should also be noted that both cognitive and immune assessments have methodological limitations contributing to measurement errors and other forms of noise that may mask the detection of an actual association. Finally, while we did not find a significant influence of publication year, age, gender, and duration of illness as covariates, other sources of confounding such as medication status or psychiatric symptom severity were not well accounted for in the included studies [151].

In conclusion, we found evidence of only a weak association between blood-based immune markers and cognition in mood and psychotic disorders. Although assuming an interaction between immune changes and cognitive symptomatology is appealing, evidence to convincingly support such a relationship in severe mental disorders is weak. Significant publication and reporting biases were observed and most likely underlie the inflation of such associations in individual studies. Efforts including central measures of immune activity, trait markers, longitudinal data, and immune challenges might prove more fruitful to uncover a hypothetical relationship between immune alterations and cognitive functioning in mood and psychotic disorders. Potentially, an extant relationship between these parameters can merely not be unveiled by the currently available methodologies and requires assessment techniques with higher resolution.

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AUTHOR CONTRIBUTIONS

MM and LDP designed the protocol of the study. MM and CO performed the literature search and data extraction. MM, CO, and EL performed quality assessments of the included studies. MM conducted the statistical analyses and wrote the first draft. All authors contributed to the final manuscript.

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