Brain, Behavior, and Immunity xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Chemokine alterations in bipolar disorder: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Cytokine
Chemokine
Inflammation
Immunity
Peripheral marker
Bipolar disorder

ABSTRACT

We aimed to perform a systematic review and meta-analysis of studies examining the levels of chemokines in peripheral blood of patients with bipolar disorder (BD) and healthy controls. Meta-analysis was based on random-effects models with Hedges' g as the effect size estimate. We included 13 eligible studies (1221 BD patients and 663 controls). The following chemokines were analysed: interleukin-8 (IL-8), monocyte-chemoattractant protein-1 (MCP-1), eotaxin-1, eotaxin-2 and interferon-γ-induced protein 10 (IP-10). The levels of IL-8 ($N = 8$, $g = 0.26$, 95%CI: 0.11–0.41, $p < 0.001$), MCP-1 ($N = 8$, $g = 0.40$, 95%CI: 0.18–0.63), eotaxin-1 ($N = 3$, $g = 0.55$, 95%CI: 0.21–0.89, $p = 0.001$) and IP-10 ($N = 4$, $g = 0.95$, 95%CI: 0.67–1.22, $p < 0.001$) were significantly higher in BD patients as compared with controls. Subgroup analyses revealed that elevated levels of IL-8 ($N = 5$, $g = 0.75$, 95%CI: 0.42–1.07, $p < 0.001$) and MCP-1 ($N = 4$, $g = 0.57$, 95%CI: 0.28–0.86, $p < 0.001$) appeared only in BD patients during their depressive phase. Illness duration was associated with significantly lower levels of IL-8 in meta-regression analysis. In turn, elevated levels of IP-10 were present during euthymia ($N = 2$, $g = 0.76$, 95%CI: 0.43–1.10, $p < 0.001$) but not depression ($N = 2$, $g = 1.81$, 95%CI: −0.16 to 3.77, $p = 0.072$). The analysis of eotaxin-1 levels was mainly based on studies of euthymic BD patients ($N = 3$). Our results suggest that chemokine alterations in BD might be related to mood state. Elevated levels of IL-8 and MCP-1 might be specific to depression. Available evidence indicates that increased levels of eotaxin-1 and IP-10 appear in euthymia; however, more studies are needed to address these alterations in other mood states.

1. Introduction

Bipolar disorder (BD) represents one of most disabling mental disorders and affects 2–3% of worldwide population (Merikangas et al., 2011). The etiology of BD remains largely unknown; however, accumulating evidence indicates the role of aberrant immune-inflammatory processes. Clinical observations revealed that patients with BD are at risk of systemic autoimmune diseases (Fries et al., 2019). Consistently, autoimmune diseases and certain prenatal infections may increase a risk of BD (Oliveira et al., 2017). Several studies have also demonstrated that neuroinflammation, in terms of microglial activation and elevated cytokine levels, can be found in post-mortem brain samples of BD patients (Giridharan et al., 2019).

Interestingly, it has been reported that some immune-inflammatory alterations are detectable in the peripheral bloodstream of patients with BD (Misiak et al., 2019). Several studies in this field have focused on the role of pro- and anti-inflammatory cytokines in the pathophysiology of BD. Cytokines represent small molecules that regulate immune reactions as well as responses to infections and injuries. Importantly, cytokines can cross the blood-brain barrier (BBB) and impact serotonin-

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https://doi.org/10.1016/j.bbi.2020.04.013
Received 24 January 2020; Received in revised form 3 April 2020; Accepted 6 April 2020

catecholamine-related pathways as well as the hypothalamus-pituitary-adrenal (HPA) axis (Banks, 2005; Sayana et al., 2017). Relatively recent meta-analyses revealed that some cytokine alterations observed in BD patients become apparent during symptomatic relapses (Munkholm et al., 2013b,a; Rowland et al., 2018), meaningfully associated with cognitive deficits, representing one of core psychopathological characteristics of BD (Misiak et al., 2017). For instance, the levels of tumour necrosis factor-α (TNF-α) and its soluble receptor (sTNFR1) appear to be elevated during manic and depressive episodes though unaltered in euthymia (Munkholm et al., 2013b; Rowland et al., 2018). In turn, increased levels of interleukin (IL)-6 have been found in euthymia and mania (Rowland et al., 2018).

However, less is known about the involvement of chemokine alterations in the pathophysiology of BD. Chemokines are a subgroup of cytokines that are able to induce directed chemotaxis to the sites of inflammation or injuries. They have been classified into four main subfamilies: CXC, CC, CX3C and XC. All chemokines interact with the G protein-linked transmembrane receptors that are also expressed on the vasculature of the BBB (Williams et al., 2014). Chemokines might exert several activities that are relevant to neuropsychiatric disorders and include neuromodulator and neurotransmitter-like effects, as well as regulation of neurogenesis (Stuart and Baune, 2014). On the basis of a meta-analysis, we have recently reported several chemokine alterations in patients with schizophrenia and early psychosis (Frydecka et al., 2018). Specifically, we could uncover elevated levels of monocyte-chemoattractant protein-1 (MCP-1) in first-episode psychosis and multiple-episode schizophrenia patients. In turn, elevated levels of other chemokines, such as IL-8, eotaxin-1 and macrophage inflammatory protein (MIP)-1β were found in multiple-episode schizophrenia patients but not among those with first-episode psychosis. There is also evidence that some chemokine alterations might occur in major depression. Eyre et al. (2016) demonstrated increased levels of MCP-1 and unaltered levels of IL-8 in this group of patients.

The involvement of chemokine alterations in the pathophysiology of BD remains unclear, since relevant studies have provided mixed findings. Although a systematic review in this field was published (Stuart and Baune, 2014), a quantitative synthesis of studies addressing peripheral blood levels of chemokines in BD has not been performed so far. Moreover, the majority of previous studies investigated chemokine levels at specific mood studies and thus it remains largely unknown whether chemokine alterations represent trait or state markers of BD. Generalization of findings in this field is also needed to compare chemokine alterations in BD to data from previous meta-analyses of studies addressing them in patients with major depression and schizophrenia. Therefore, in this study we aimed to perform a systematic review and meta-analysis of observational studies investigating peripheral blood levels of chemokines in BD.

2. Material and methods

2.1. Search strategy

Two reviewers (BS and MM) performed independent online search in accordance with the PRISMA guidelines (Moher et al., 2009) using the following combination of keywords: “bipolar” or “mania” or “manic” or “depress*” and “chemokine” or “ccl*” or “cxcl*” or “cxcr*” or “mcp*” or “IL-8” or “interleukin-8”. We considered publication records from 6 databases including MEDLINE, ERIC, CINAHL Complete, International Pharmaceutical Abstracts as well as the Academic Search Ultimate and the Health Source: Nursing/Academic Edition. Online search covered the publication period from database inception until 26th December 2019. In addition, reference lists from eligible publications were checked. All discrepancies were resolved by discussing results of initial searches with the third reviewer (BM).

2.2. Eligibility criteria

Studies were considered eligible if they met the following inclusion criteria: 1) reported the levels of chemokines determined in serum or plasma samples; 2) necessary data (mean and SD of chemokine levels and age as well as mood phase) were available in the article or upon request (if necessary corresponding authors of eligible publications were contacted); 3) compared the levels of chemokines between patients with BD and healthy controls and 4) articles were written in English language. The following publication records were excluded: 1) animal model studies; 2) studies without a group of healthy controls; 3) studies measuring mRNA levels of chemokines and 4) studies without necessary data to perform meta-analysis.

2.3. Data extraction

We extracted the following data from eligible publications (mean ± SD or the number of cases): 1) age; 2) sex; 3) body-mass index (BMI); 4) the levels of chemokines; 5) cigarette smoking rate; 6) symptomatic severity according to the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale (HDRS) and the Young Mania Rating Scale (YMRS); and 7) information about mood state on the day of assessment. In case of data provided as median and interquartile range, data were converted as reported previously (Hozo et al., 2005). We calculated SD by dividing interquartile range by 1.35. In turn, the median was used as an approximation of the mean (Higgins and Green, 2011). The GetData Graph Digitizer 2.26 was used in case of studies that presented chemokine levels using scatter plots. It is the software that enables to obtain raw data from graphs and plots. A basic quality assessment was performed by evaluating if patients with BD and controls were comparable in terms of age and sex (Bartoli et al., 2018). We defined relevant comparability as an absolute non-significant difference in age and sex ($p > 0.05$).

2.4. Data analysis

Data analysis was limited to chemokines that were determined by at least three independent studies. We used random-effects models due to expected heterogeneity. Effect size estimates were calculated as Hedges' g using random-effects models. Heterogeneity was assessed based on Cochran Q tests and I^2 statistics. A leave-one-out sensitivity analysis was conducted to verify if any single study accounted for heterogeneity. Subgroup analysis was performed to investigate the association between specific mood states and the levels of chemokines. Meta-regression analyses were performed for continuous moderators that were assessed by at least 6 studies and categorical moderators with each group represented by at least 4 studies (Fu et al., 2011). In this regard, the effects of age, sex, symptomatic manifestation (scores of HDRS, MADRS and YMRS), biological material (serum vs. plasma) and the method used for the measurement of chemokine levels were tested by meta-regression analysis. Results were considered statistically significant if the p-value was less than 0.05. Results of pooled analyses were presented using forest plots. All analyses were performed using the STATISTICA software, version 12.5. Our systematic review and meta-analysis was registered in the PROSPERO database (CRD42019134969).

3. Results

Initial online search identified 3753 records and 13 publications were finally included in systematic review and meta-analysis (Bai et al., 2014; Barbosa et al., 2013; Benedetti et al., 2017; Brietzke et al., 2011; Drexhage et al., 2011; Fiedorowicz et al., 2015; Jacoby et al., 2016; Jakobsson et al., 2015; Lu et al., 2019; O'Brien et al., 2006; Panizzutti et al., 2015; Poletti et al., 2019; Wang et al., 2016) (Fig. 1). These studies represented data from 1221 BD patients and 663 controls (for

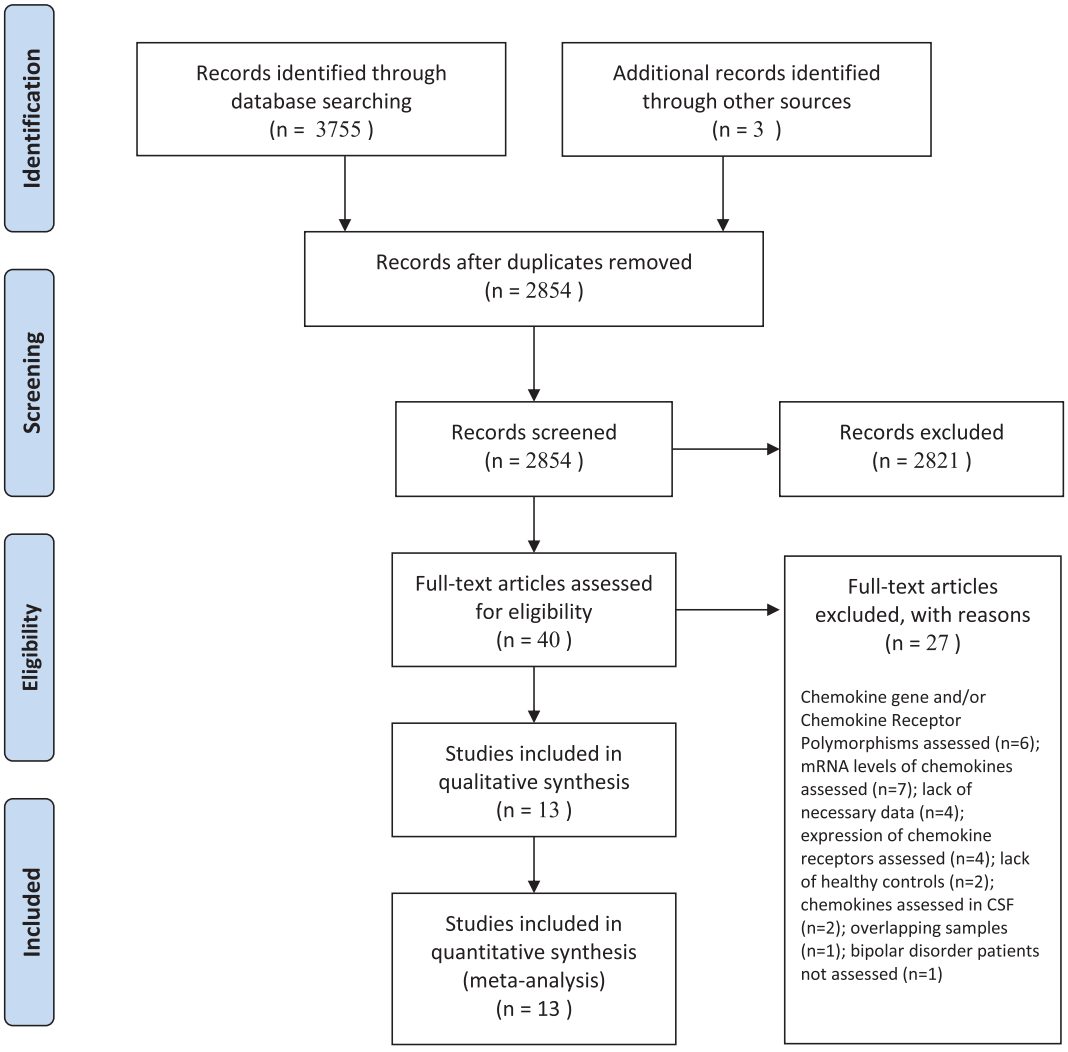

Fig. 1. Selection of studies (Moher et al., 2009).

summary see Table 1). Patients with BD and controls were matched for age except for three studies (Benedetti et al., 2017; Jacoby et al., 2016; Poletti et al., 2019), in which controls were significantly younger than BD patients. There were significantly more females among BD patients compared to controls in one study (Wang et al., 2016). Five studies (Bai et al., 2014; Benedetti et al., 2017; Fiedorowicz et al., 2015; Jacoby et al., 2016; Panizzutti et al., 2015), controlled for the effects of BMI. However, in three of them, all patients with BD or at least one subgroup of patients (at specific mood phase) had significantly higher BMI compared to controls (Bai et al., 2014; Jacoby et al., 2016; Panizzutti et al., 2015). In turn, six studies assessed cigarette smoking status (Bai et al., 2014; Fiedorowicz et al., 2015; Jacoby et al., 2016; Jakobsson et al., 2015; Lu et al., 2019; Wang et al., 2016). In two studies (Fiedorowicz et al., 2015; Lu et al., 2019), cigarette smoking status was similar among BD patients and controls. The GetData Graph Digitizer 2.26 was used to extract chemokine levels from two studies (Barbosa et al., 2013; Lu et al., 2019). Meta-analysis was performed for five chemokines: IL-8 (CXCL8), MCP-1 (CCL2), eotaxin-1 (CCL11), eotaxin-2 (CCL24) and interferon-γ-induced protein 10 (IP-10, CXCL10) (Table 2).

3.1. IL-8 (CXCL8)

Data for the analysis of IL-8 (CXCL8) levels were obtained from 9 studies (Barbosa et al., 2013; Benedetti et al., 2017; Brietzke et al., 2011; Drexhage et al., 2011; Jacoby et al., 2016; Lu et al., 2019; O'Brien et al., 2006; Poletti et al., 2019; Wang et al., 2016). The levels of IL-8 (CXCL8) were significantly higher in patients with BD compared to controls (Table 2, Supplementary Fig. 1). This difference remained significant ($g = 0.49$, 95%CI: 0.22–0.75, $p < 0.001$) after removing studies that did not meet the comparability criterion (Barbosa et al., 2013; Benedetti et al., 2017; Poletti et al., 2019). Subgroup analysis revealed that this association was limited to patients during depression, even after removing studies with significant between-group differences in age and/or sex (Benedetti et al., 2017; Jacoby et al., 2016; Poletti et al., 2019) ($g = 1.24$, 95%CI: 0.49–1.99, $p = 0.001$). Heterogeneity was significant in main analysis and subgroup analyses, except for the subgroup analysis of depressed patients. Meta-regression analysis revealed a significant negative correlation between illness duration and effect size estimates (Table 3).

3.2. MCP-1 (CCL2)

The analysis of MCP-1 (CCL2) was based on 8 studies (Bai et al., 2014; Barbosa et al., 2013; Benedetti et al., 2017; Brietzke et al., 2009; Drexhage et al., 2011; Fiedorowicz et al., 2015; Jakobsson et al., 2015; Poletti et al., 2019). The levels of MCP-1 (CCL2) were significantly higher in patients with BD compared to controls (Table 2, Supplementary Fig. 2). This difference remained significant ($g = 0.32$, 95%CI: 0.02–0.63, $p = 0.039$) after removing studies that did not meet

Table 1
General characteristics of studies included in systematic review and meta-analysis.

Study	BD patients				Healthy controls			Chemokines included in meta-analysis	Assay	Serum/ plasma	Medications
	N	Age	%males	Mood state	N	Age	%males				
Bai et al. (2014)	130	44.5 ± 11.8	32.1	Mania/hypomania, depression and euthymia	130	41.8 ± 9.7	35.4	MCP-1	ELISA	Serum	Li, ACs and APs
Barbosa et al. (2013)	70	49.8 ± 11.8	28.0	Mania and euthymia	50	46.7 ± 9.1	35.7	IL-8, IP-10, MCP-1, eotaxin-1 and eotaxin-2	ELISA	Plasma	Li, ACs and APs
Benedetti et al. (2017)	37	45.9 ± 14.5	27.0	Depression	24	27.5 ± 10.0	37.5	IL-8, IP-10 and MCP-1	CBA	Serum	Li
Brietzke et al. (2009)	30	43.2 ± 11.9	27.6	Euthymia	30	43.2 ± 14.5	17.2	IL-8, MCP-1, eotaxin-1, eotaxin-2 and IP-10	ELISA	Serum	Medicated
Drexhage et al. (2011)	38	41.6 ± 9.6	24.0	Euthymia	22	41.3 ± 9.5	14.0	MCP-1	CBA	Serum	Li, ACs, ADs, APs and BDZ
Fiedorowicz et al. (2015)	37	39.7 ± 13.4	64.9	Mania, depression and euthymia	29	43.0 ± 13.0	66.0	MCP-1	ELISA	Plasma	Li, ACs, ADs, APs and sedatives/ hypnotics
Jacoby et al. (2016)	60	42.7 ± 11.7	61.7	Mania, depression, mixed state and euthymia	35	36.7 ± 11.6	57.1	IL-8	ELISA	Plasma	Li, ACs, ADs and APs
Jakobsson et al. (2015)	221	36 [28 – 47]	38.0	Euthymia	112	34 [27 – 44]	44.6	MCP-1	ELISA	Serum	Li, ACs, ADs, APs and BDZ
Lu et al., (2019)	26	32.5 ± 5.4	38.5	Mania/mixed state and depression	20	33.7 ± 3.8	40.0	IL-8	ELISA	Serum	Medicated
O'Brien et al. (2006)	21	39.3 ± 18.2	42.9	Mania and depression	21	36.5 ± 11.5	42.9	IL-8	ELISA	Plasma	Li, ACs, APs and ADs
Panizzutti et al.(2015)	31	45.8 ± 14.0	25.8	Euthymia	27	45.7 ± 9.9	29.6	Eotaxin-1 and eotaxin-2	ELISA	Serum	Li, ACs, APs, ADs and BZD
Poletti et al. (2019)	26	48.0 ± 13.0	30.8	Depression	23	27.5 ± 10.0	34.8	IL-8, IP-10 and MCP-1	CBA	Serum	Medicated
Wang et al. (2016)	494	32.5 ± 12.0	50.6	Mania/hypomania, depression and euthymia	140	31.9 ± 8.2	57.8	IL-8	ELISA	Plasma	Medicated

Abbreviations: ACs – anticonvulsants, ADs – antidepressants, APs – antipsychotics, BD – bipolar disorder, BDZ – benzodiazepines, CBA – cytometric bead array or similar multiplex assays, ELISA – enzyme-linked immunosorbent assay, IL-8 – interleukin-8, IP-10 – interferon-γ-induced protein 10, Li – lithium, MCP-1 – monocyte-chemoattractant protein-1, NOS – the Newcastle-Ottawa Scale

Table 2
Main and subgroup analyses of chemokine levels in bipolar disorder.

Chemokine	Analysis	k	Meta-analysis			Heterogeneity analysis		
			g	95%CI	p	I^2	Q	p(Q)
IL-8 (CXCL8)	Main analysis	14	0.26	0.11–0.41	< **0.001**	75.5%	53.1	< **0.001**
	Depression	5	0.75	0.42–1.07	< **0.001**	33.1%	6.0	0.200
	Euthymia	4	−0.06	−0.56 to 0.44	0.815	81.3%	16.1	**0.001**
	Mania	4	0.46	−0.08 to 1.00	0.092	76.3%	12.7	**0.005**
MCP-1 (CCL2)	Main analysis	13	0.40	0.18–0.63	< **0.001**	76.5%	51.2	< **0.001**
	Depression	4	0.57	0.28–0.86	< **0.001**	0%	1.0	0.809
	Euthymia	6	0.09	−0.33 to 0.51	0.667	84.3%	32.0	< **0.001**
	Mania	3	0.27	−0.43 to 0.98	0.445	86.0%	14.3	< **0.001**
Eotaxin-1 (CCL11)	Main analysis	5	0.55	0.21–0.89	**0.001**	47.8%	7.7	0.105
	Euthymia	4	0.46	0.06–0.87	**0.025**	48.6%	5.8	0.120
Eotaxin-2 (CCL24)	Main analysis	5	0.13	−0.10 to 0.36	0.269	0%	3.4	0.488
	Euthymia	4	0.07	−0.20 to 0.34	0.615	0%	2.8	0.425
IP-10 (CXCL10)	Main analysis	4	0.95	0.67–1.22	< **0.001**	83.2%	23.9	< **0.001**
	Euthymia	2	0.76	0.43–1.10	< **0.001**	0%	0.1	0.731
	Depression	2	1.81	−0.16 to 3.77	0.072	94.1%	17.1	< **0.001**

Significant results ($p < 0.05$) were marked with bold characters.
k refers to the number of comparisons.
Abbreviations: IL-8 – interleukin-8, IP-10 – interferon-γ-induced protein 10, MCP-1 – monocyte-chemoattractant protein-1.

the comparability criterion (Barbosa et al., 2013; Benedetti et al., 2017; Poletti et al., 2019). Subgroup analysis demonstrated that this association was limited to patients during depressive relapse, even after excluding studies with significant between-group differences in age and/or sex (Benedetti et al., 2017; Poletti et al., 2019) (g = 0.52, 95%CI: 0.07–0.96, p = 0.022). Heterogeneity was significant in main analysis and subgroup analyses, except for the subgroup analysis of patients with depressive episode. No significant correlates of effect size estimates were found in meta-regression analysis (Table 3).

3.3. Eotaxin-1 (CCL11)

Data for the analysis of eotaxin-1 (CCL11) levels were obtained from 3 studies (Barbosa et al., 2013; Brietzke et al., 2009; Panizzutti et al., 2015). Main analysis revealed that the levels of eotaxin-1 (CCL11) were significantly higher in patients with BD compared to controls (Table 2, Supplementary Fig. 3). Subgroup analysis demonstrated significantly higher levels of eotaxin-1 (CCL11) in patients during euthymia. After removing the study that did not meet the comparability criterion (Barbosa et al., 2013), the difference in eotaxin-1 (CCL11) was non-significant (g = 0.36, 95%CI: −0.17 to 0.90, p = 0.184). Heterogeneity was not significant in all analyses. Meta-regression analyses were not performed due to low number of studies.

3.4. Eotaxin-2 (CCL24)

The analysis of eotaxin-2 (CCL24) was based on 3 studies (Barbosa et al., 2013; Brietzke et al., 2009; Panizzutti et al., 2015). Main analysis and subgroup analysis of euthymic patients did not demonstrate any significant differences in eotaxin-2 (CCL24) levels between BD patients and controls (Table 2, Supplementary Fig. 4), even after removing the study that did not meet the comparability criterion (Barbosa et al., 2013) (g = −0.07, 95%CI: −0.42 to 0.29, p = 0.716). Heterogeneity was not significant across all analyses. Meta-regression analyses were not performed due to low number of studies.

3.5. IP-10 (CXCL10)

The levels of IP-10 (CXCL10) were determined by 4 studies (Barbosa et al., 2013; Benedetti et al., 2017; Brietzke et al., 2009; Poletti et al., 2019). The levels of IP-10 (CXCL10) were significantly higher in patients with BD compared to controls (Table 2, Supplementary Fig. 5). However, the majority of studies included in this analysis did not meet the comparability criterion (Barbosa et al., 2013; Benedetti et al., 2017; Poletti et al., 2019). Subgroup analysis demonstrated that this association appeared in patients during euthymia but not in those with depressive relapse. Heterogeneity was significant in main analysis and

Table 3
Meta-regression of chemokine levels.

Chemokine	Moderator	k	β	95%CI	p	Adj. R^2
IL-8 (CXCL8)	Mean difference in age	11	0.01	−0.03 to 0.05	0.600	
	Mean difference in %males	14	0.03	−0.79 to 0.85	0.939	
	HDRS	8	0.06	−0.0005 to 0.11	0.052	
	YMRS	8	0.01	−0.02 to 0.04	0.411	
	Illness duration	7	−0.07	−0.10 to −0.03	< **0.001**	97.4%
	Serum vs. plasma	14	0.02	−0.50 to 0.55	0.929	
MCP-1 (CCL2)	Mean difference in age	13	0.02	−0.01 to 0.06	0.215	4.7%
	Mean difference in %males	13	−2.26	−4.74 to 0.22	0.074	22.6%
	MADRS	7	0.01	−0.03 to 0.05	0.558	
	YMRS	7	0.01	−0.03 to 0.06	0.601	
	Illness duration	11	−0.06	−0.13 to −0.01	0.083	
	Serum vs. plasma	13	−0.65	−2.32 to 0.42	0.264	

k refers to the number of comparisons per analysis. Significant moderators were marked with bold characters ($p < 0.05$).
Abbreviations: HDRS – the Hamilton Depression Rating Scale, IL-8 – interleukin-8, MADRS – the Montgomery-Asberg Depression Rating Scale, MCP-1 – monocyte-chemoattractant protein-1, NOS – the Newcastle-Ottawa Scale, YMRS – the Young Mania Rating Scale.

subgroup analysis of patients during depressive episode. Meta-regression analyses were not performed due to low number of studies.

4. Discussion

Main findings from our meta-analysis imply that the levels of IL-8 (CXCL8) and MCP-1 (CCL2) are elevated in patients with BD during depressive episodes but not other mood states. Effect size estimates were small and medium in pooled analyses as well as medium and large in subgroup of analyses of depressive patients. Two recent meta-analyses revealed that MCP-1 (CCL2) levels are also elevated in patients with major depression (Eyre et al., 2016; Leighton et al., 2018). However, results of these meta-analysis with respect to IL-8 (CXCL8) levels are less consistent (Eyre et al., 2016; Köhler et al., 2017; Leighton et al., 2018). In this regard, it might be hypothesized that elevated levels of MCP-1 (CCL2) and IL-8 (CXCL8) are related to depressive relapse as a transdiagnostic phenomenon (Fusar-Poli et al., 2019).

There are several mechanisms that might explain the role of MCP-1 (CCL2) and IL-8 (CXCL8) in depression. MCP-1 (CCL2) and IL-8 (CXCL8) together with their receptors are constitutively expressed by the central nervous system (CNS) cells. These chemokines are involved in several processes within the CNS, including neuronal differentiation, migration and proliferation of microglia as well as regulation of the HPA axis response (Stuart et al., 2015). Importantly, both chemokines can also pass through the BBB. The study by Torres-Platas et al. (2014) demonstrated increased microglial priming and macrophage recruitment within the dorsal anterior cingulate white matter of depressed suicide completers that was accompanied by up-regulated expression of the *MCP-1* gene. Surprisingly, a recent transcriptomic study of dorsolateral prefrontal cortex showed significantly lower expression of *IL-8* (*CXCL8*) gene in major depression compared to controls (Pantazatos et al., 2017). One of studies included in our meta-analysis revealed that the levels of IL-8 (CXCL8) and MCP-1 (CCL2) positively correlated with cortical thickness in the anterior cingulate cortex (Poletti et al., 2019). These discrepancies might be explained by limited sample size, especially in case of post mortem studies, and the fact that subclinical inflammation does not occur in all patients with mood disorders. Although there is evidence that the levels of some pro-inflammatory markers are elevated in depression, the effects of variability and potential confounding factors should also be taken into consideration. For instance, a recent meta-analysis by Osimo et al. (2020) demonstrated elevated levels of IL-8 (CXCL8) in depression. However, discordant results were found in sensitivity analysis due to the effect of matching for BMI. Moreover, variability of IL-8 (CXCL8) levels was similar in patients with depression and healthy controls. Available evidence indicates that treatment-resistance and a history of childhood trauma are well-known correlates of subclinical inflammation in depression and thus they might account for variability of cytokine levels in this group of patients (Pariante, 2017).

Our meta-analysis also revealed that differences in the levels of MCP-1 (CCL2) and IL-8 (CXCL8) between BD patients and controls tend to decrease with illness duration. Several lines of evidence indicate that BD is a progressive illness and staging models with recommended personalized therapeutic approaches are in development (Berk et al., 2017). However, the exact mechanisms of biological neuroprogression remain unknown. At this point, it should be noted that chemokines exert pleiotropic activities that extend beyond the effects on immune-inflammatory processes. It has been reported that MCP-1 (CCL2) exerts neuroprotective activity against neurotoxicity and neuronal apoptosis related to overactivation of the NMDA receptors (Trettel et al., 2019). Similarly, IL-8 (CXCL8) has been shown to inhibit neuronal apoptosis induced by amyloid-β and increase the levels of brain-derived neurotrophic factor (Ashutosh et al., 2011). These findings might be relevant to neuroprogression observed in BD. Therefore, it cannot be excluded that the activation of chemokine signalling is a response to other processes underlying the pathophysiology of BD. To date, there are few studies looking at differences in subclinical inflammation at early and late stages of BD. For instance, it has been reported that attenuated inflammatory response of monocyte-derived macrophages is more pronounced in BD patients at late stages of illness compared to early-stage patients and controls (Ascoli et al., 2019). Kauer-Sant'Anna et al. (2009) also observed that IL-6 levels tend to decrease in late-stage BD patients. Similarly, a recent meta-analysis of inflammatory markers in depression demonstrated that illness duration is significantly positively correlated with variation of IL-8 (CXCL8) levels (Osimo et al., 2020).

This systematic review also indicates that BD is associated with elevated levels of eotaxin-1 (CCL11) and IP-10 (CXCL10) (medium and large effect size estimates). In turn, differences in the levels of eotaxin-2 (CCL24) between BD patients and controls were insignificant. However, due to low number of studies, insights from subgroup analyses are limited. Available evidence suggests that these alterations are more closely related to euthymic state. Analysis of data from two studies of depressed BD patients indicates that this mood state is related to unaltered IP-10 (CXCL10) levels. Eotaxin-1 (CCL11) is a potent stimulator of eosinophils that have been associated with a number of allergic conditions known to be prevalent in BD patients (Wu et al., 2016). Moreover, eotaxin-1 (CCL11) has been shown to shift immune processes into Th2 responses, the phenomenon reported in BD (Brambilla et al., 2014; Teixeira et al., 2018). Relevance of this chemokine to the pathophysiology of psychiatric disorders is also associated with the involvement of eotaxin-1 (CCL11) in aging and neurodegeneration processes, regulation of neural progenitor cells and microglia (Teixeira et al., 2018). Less is known about the potential mechanisms linking IP-10 (CXCL10) with BD. This chemokine is secreted by neurons, glia and stromal cells in response to IFN-γ, and acts as a chemoattractant of T cells and natural killer cells to the CNS (Michlmayr and McKimmie, 2014).

Our study has some limitations that need to be acknowledged. Firstly, sample size in a number of studies was relatively low, especially when subgroup analyses of eotaxin-1 (CCL11), eotaxin-2 (CCL24) and IP-10 (CXCL10) are taken into account. For this reason, we were unable to perform meta-regression analysis for these chemokines. Moreover, the difference in eotaxin-1 (CCL11) between BD patients and controls was not significant after removing studies that did not meet the comparability criterion. In addition, the majority of studies included in the analysis of IP10 (CXCL10) levels were characterized by significant between-group differences in age and/or sex. It is also important to note that several studies included in our meta-analysis did not control for some potential confounding factors, including anthropometric parameters (e.g. BMI), medication effects, comorbid physical health impairments or cigarette smoking status. Indeed, some studies have demonstrated that obesity is associated with higher levels of chemokines (Borges et al., 2018). There is also evidence that pharmacological treatment may impact the levels of chemokines in BD. It has been shown that lithium may interact with signalling pathways mediated by some chemokines (CXCL4 and CXCL12) (Kast, 2008; Kim et al., 2007). Lithium treatment has also been associated with higher levels of IL-8 (CXCL8) in the cerebrospinal fluid of BD patients (Isgren et al., 2015). Similarly, it has been reported that valproic acid increases the production of IL-8 (CXCL8) in mice (Leu et al., 2017). However, recent meta-analyses have not revealed significant effects of antidepressants and antipsychotics on chemokine alterations in depression and psychosis (Capuzzi et al., 2017; Więdłocha et al., 2018). In turn, cigarette smoking has been associated with elevated levels of various chemokines, including IL-8 (CXCL8), IP-10 (CXCL10), MCP-1 (CCL2) and MIP-1α (CCL3) (Strzelak et al., 2018). Finally, insufficient representativeness may serve as another limitation since the majority of studies did not report initial sample of patients and controls approached for enrolment and reasons of non-participation were not provided.

In summary, results of this study indicate that several chemokine alterations may appear in BD and are related to mood state and illness progression. Specifically, elevated levels of IL-8 (CXCL8) and MCP-1

(CCL2) are likely to occur during depression; however, increase in the levels of IL-8 (CXCL8) tends to be less pronounced in patients with longer illness duration. In turn, elevated levels of eotaxin-1 (CCL11) and IP-10 (CXCL10) occur in euthymia. We found no evidence of altered chemokine levels in mania; however, studies of manic patients were underrepresented in our meta-analysis. More studies are needed to generalize conclusions on the levels of these chemokines in other mood states. Our findings can improve the concept of BD staging that offers personalization of treatment strategies. Results of this meta-analysis might also provide grounds for the development of novel treatment strategies since chemokine alterations are increasingly being recognised as potential treatment targets for non-psychiatric diseases (Poeta et al., 2019). The observation that chemokine alterations appear mainly in depressive BD patients suggests that the efficacy of potential interventions targeting chemokine signalling might depend on mood phase. However, it is of great importance to understand what is the role of enhanced chemokine signalling in BD before developing specific treatments. Indeed, it remains unknown whether activation of chemokine signalling is a downstream effector of other pathophysiological processes and whether it exerts deleterious effects on illness progression. Therefore, longitudinal studies investigating clinical correlates of chemokine alterations in BD are warranted. These studies need to take into consideration a number of confounding factors, including those that were not controlled by the majority of studies represented in our meta-analysis (e.g., the measures of visceral adiposity, comorbid physical health impairments, concomitant medications or substance use). Moreover, animal model studies might provide further insights into a cross-talk between chemokine signalling and neurobiological processes involved in the pathophysiology of BD.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.04.013.

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