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Inflammatory mediators of cognitive impairment in bipolar disorder

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Abstract

Objectives—Recent studies have pointed to neuroinflammation, oxidative stress and neurotrophic factors as key mediators in the pathophysiology of mood disorders. Little is however

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Isabelle Bauer managed and searched the literature and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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known about the cascade of biological episodes underlying the cognitive deficits observed during the acute and euthymic phases of bipolar disorder (BD). The aim of this review is to assess the potential association between cognitive impairment and biomarkers of inflammation, oxidative stress and neurotrophic activity in BD.

Methods—Scopus (all databases), Pubmed and Ovid Medline were systematically searched with no language or year restrictions, up to November 2013, for human studies that collected both inflammatory markers and cognitive data in BD. Selected search terms were bipolar disorder, depression, mania, psychosis, inflammatory, cognitive and neurotrophic.

Results—Ten human studies satisfied the criteria for consideration. The findings showed that high levels of peripheral inflammatory-cytokine, oxidative stress and reduced brain derived neurotrophic factor (BDNF) levels were associated with poor cognitive performance. The BDNF *val66met* polymorphism is a potential vulnerability factor for cognitive impairment in BD.

Conclusions—Current data provide preliminary evidence of a link between the cognitive decline observed in BD and mechanisms of neuroinflammation and neuroprotection. The identification of BD specific inflammatory markers and polymorphisms in inflammatory response genes may be of assistance for therapeutic intervention.

Keywords

neuroinflammation; oxidative stress; neurotrophin; cognitive functioning; bipolar disorder

Introduction

The mood symptoms of bipolar disorder (BD) are more often than not accompanied by verbal and working memory deficits (1, 2), poor sustained attention (3) and reduced executive functioning (4–6). Cognitive deficits persist during the euthymic phase of BD (7, 8) which suggests that cognitive dysfunction may not be attributable to mood disturbance. In the last decade an increasing number of papers have emphasized the roles of inflammation, oxidative stress and related cellular degeneration in the pathophysiology of mood disorders (9–11). It is however still unclear whether these mechanisms are associated with the risk of developing cognitive impairment in patients diagnosed with BD.

BD is characterized by high peripheral levels of pro-inflammatory agents, such as interleukins (in particular IL-6, IL-2R, IL-1beta), tumour necrosis factor (TNF-α) and cellular TNF-α receptors (TNFR1) (12), and elevated pro-oxidative C-reactive protein (CRP) concentrations (13–16). This increase in the peripheral inflammation is likely to be associated with elevated neuroinflammation. Indeed cytokines penetrate the brain via leaky regions (e.g. choroid plexus) and are associated with the increased expression of pro-inflammatory eicosanoids (prostaglandin 2 - PGE_2), nitric oxide (NO) (17), TNF-α, IL-1β, reactive oxygen species as well as monocytes and macrophages in the brain (17–19) (Figure 1). Alongside the increase in peripheral inflammation, BD has been associated with a decrease in brain-derived neurotrophic factor (BDNF) levels (20, 21). Neurotrophins, such as BDNF, are a group of secreted proteins that are essential for neuron survival and synaptic functioning (22–25).

Clinical and preclinical evidence suggest that multiple mood episodes disrupt the homeostasis between inflammatory mechanisms, oxidative processes, and neuroprotective mechanisms, such as BDNF, and lead to neuronal death (apoptosis) (26, 27). This cycle of events is defined as “neuroprogression” and has been linked to an increase in the individual’s vulnerability to psychological stress, brain atrophy and ultimately cognitive impairment (28, 29). The concept of “staging” has been applied to the pathophysiology of BD to explain the progressive decline in mental health, psychosocial functioning and cognitive performance over the course of the disease (30–32).

Accordingly, neuroimaging studies show that individuals diagnosed with BD exhibit a significant loss of gray matter volume and white matter integrity, which is likely related to inflammatory processes such as apoptosis, cellular shrinkage, alterations in neurogenesis and reduced gliogenesis (33). Recent neuroimaging studies have also identified a significant cortical atrophy and enlargement of the ventricles in individuals who experienced multiple mood episodes as compared to gender and age-matched healthy individuals (34, 35). Furthermore, an inverse relationship between gray matter volumes and length of illness has also been reported (36, 37).

In summary, chronic inflammation may lead to structural brain abnormalities and cognitive deficits in individuals diagnosed with BD. However, to date, this hypothesis has not been systematically reviewed. Thus, the purpose of this review is to assess the potential association between cognitive impairment and biomarkers of inflammation, oxidative stress and neurotrophic activity in individuals diagnosed with BD.

Literature search

Scopus (all databases), Pubmed and Ovid Medline were systematically searched with no language or year restrictions, up to November 2013, for research articles addressing the relationship between bipolar disorder, inflammation and cognition. Selected search terms were ‘bipolar disorder’, ‘depression’, ‘mania’, ‘psychosis’, ‘inflammatory’, ‘cognitive’ and ‘neurotrophic’ as occurring either anywhere in the article (for Pubmed and Ovid Medline) or in the case of PUBMED, in the title, abstract or keywords only. The search engines listed above were chosen because of their well-established accuracy and exhaustive search across multidisciplinary fields such as psychology, nutrition, biochemistry and medicine (38). Inclusion was restricted to studies with clinical populations with a diagnosis of BD, studies were cognitive functioning was assessed using pen and paper or computerized cognitive batteries, and where inflammatory markers or polymorphisms of inflammatory genes using blood or other tissues were quantified. Excluded studies included those using animal models, clinical populations with neurological and cardiovascular diseases, children, adolescents, pregnant or lactating mothers,. Exclusion criteria was defined by the following considerations. Cognition is affected by a range of neurochemical mechanisms and cardiovascular parameters. During pregnancy and lactation, a number of physiological changes take place and this physiological state could affect cognitive performance. Finally, since the nervous system of children, and adolescents is still developing, the relationship between inflammation and cognition in children cannot be equated to that observed in a mature central nervous system. All data were extracted by a single, non-blinded, reviewer

(IB) to determine if studies met inclusion criteria and, in cases where this information was not provided in abstracts, full texts were obtained. All papers identified were published in English. No papers were identified prior to 2003. Duplicates, review articles and articles not fulfilling the search criteria were removed (Figure 2).

Quality evaluation

Since there is no official instrument for the evaluation of observational studies in psychiatry and inflammation we conducted a quality evaluation based on the Centre for Reviews and Dissemination (CRD) Hierarchy of evidence (39) and a revised version of Ibrahim and colleague's quality evaluation scale (40). The CRD Hierarchy of evidence ranks study designs in descending order of strength: 1. Experimental studies, 2. Quasi experimental studies, 3. Controlled observational studies, 3a. Cohort studies, 3b. Case control studies, 4. Observational studies without control groups, 5. Expert opinion based on theory, laboratory research or consensus. The quality evaluation scale was composed of 6 items: 1) The clinical sample was representative of the target population, 2) The control group was appropriately matched (e.g. by age, gender) to the clinical sample 3) The authors conducted sample size calculations and/or power analyses 4) The study used well-established measures of inflammation 5) The study used well-established measures of cognitive functioning 6) The authors reported confidence intervals and/or effect sizes of their findings. Each item was scored one point if the criterion was satisfied. The overall quality score was calculated by adding the scores of all items.

Study Characteristics

We identified ten published clinical studies exploring the association between peripheral pro-inflammatory cytokines, oxidative markers, neurotrophins and cognitive performance in individuals diagnosed with BD. Two studies collected peripheral measures of oxidative stress (CRP, RBANS) and peripheral pro-inflammatory cytokine measurements (IL-18, TNF). Eight studies examined the relationship between BDNF levels or polymorphism and cognitive functioning (see Table 1). All studies were observational in nature and did not involve any anti-inflammatory and/or antioxidant treatments. Cognitive performance in all studies comprised of traditional pen-and-paper tests and computerized cognitive batteries. Table 1 summarizes the study characteristics.

Results of identified Studies

Pro-inflammatory cytokines, markers of oxidative stress and cognitive functioning

Peripheral serum CRP expression was negatively correlated with performance scores of immediate memory, language, and attention, on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in a study involving 107 individuals diagnosed with BD. The authors interpreted these results as indicating that oxidative damage negatively affects cognitive functioning in BD patients. However, as this study did not include a control population it is unknown whether the relationship between CRP expression and cognitive performance is specific to individuals diagnosed with BD, or whether it may also be observed in healthy controls (41).

Peripheral serum expression of the pro-inflammatory cytokine, TNF-α, was found to be negatively correlated with accuracy on the delayed memory component on the Rey Auditory Verbal Learning Test (RAVLT), in a study consisting of 54 medicated individuals diagnosed with euthymic (absence of a depressive or manic cycle) BD type I. Furthermore, the expression of two soluble TNF receptors (sTNFr1 and sTNFr2) was higher in euthymic BD individuals as compared to healthy controls. (42). It is noteworthy that BD patients and healthy individuals did not differ in terms of TNF-α levels. The authors concluded that this result may have been related to the fast degradation of TNF-α in peripheral tissues (42). Further, the elevated production of sTNF receptors may explain why cognitive deficits persist during the euthymic phase of BD (43, 44). Given that previous research shows that the production of sTNF receptors is catalyzed by TNF-α (45), it is however unclear why the levels of sTNF receptors did not correlate with cognitive performance in Doganavsargil Baysal et al.'s study (42).

At present, research regarding the relationship between inflammatory response and cognitive performance in BD is extremely limited. The above studies however provide preliminary evidence of the negative effects of pro-inflammatory and oxidative processes on high-order cognitive abilities such as memory, attention and executive functioning.

Neurotrophins and cognitive functioning

In one study, middle-aged euthymic BD patients were found to have higher peripheral BDNF expression than gender-matched healthy individuals. However, there was no significant correlation between BDNF expression and the Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) scores (46). This negative finding may be due to the type of tests used to measure cognitive functioning. Indeed the MMSE and the FAB provide a short and generic assessment of age-related cognitive decline (e.g. in Alzheimer's and fronto-temporal dementia) but are not sufficiently sensitive to detect mood-related cognitive changes (47, 48). Furthermore, since the participants of this study were relatively young (M±SD: 50.88±9.11 years), they likely exhibited a high level of accuracy on these tests.

Dias et al. (2009) found that serum BDNF levels positively correlated with accuracy on a verbal fluency task in individuals diagnosed with BD. It is important to emphasize that, contrary to the findings of Barbosa et al., Dias et al. found no difference in BDNF expression between euthymic BD and healthy individuals, in peripheral blood samples (49). Participants in this study were medicated, which may have influenced BDNF expression and confounded results. In particular, valproate-treated participants had higher BDNF levels, and lithium-treated participants lower BDNF levels, when compared with non-medicated healthy volunteers (49). Additionally, this study involved individuals with euthymic BD. While previous research shows that BDNF expression can fluctuate during manic and depressive episodes (20, 50), previous research demonstrated that, during the euthymic phase of BD, BDNF expression is comparable to that of healthy volunteers (51).

Consistent with Dias et al.'s study (2009), Chou et al. did not find any difference in plasma BDNF expression between euthymic BD and healthy controls. Furthermore, in the clinical sample there was no significant correlation between BDNF expression and cognitive

performance (52). Since the mean illness duration was shorter (6 years) than that in Dias et al.'s study (13 years) it could be hypothesized that illness duration counteracts the beneficial effects of BDNF on cognitive performance. In another study poor lithium responders were found to have lower BDNF levels compared to healthy controls. By contrast, excellent lithium responders (ELR) exhibited BDNF levels comparable to those of healthy controls, and performed better than non-ELR on all tasks of the Cambridge Neuropsychological Test Automated Battery (CANTAB), in particular the spatial working memory task (53). Thus, it could be hypothesized that high BDNF levels counteract the cognitive decline observed in BD.

Previous research has focused on the relationship between the genotype of BDNF and cognitive functioning. In particular, studies have associated the BDNF *val66met* polymorphism with BD symptomatology. In this BDNF gene variation the *valine (val)* allele is replaced by the methionine *(met)* allele at codon 66 (54). In the present review, we identified one study showing that *met* carriers diagnosed with BD have smaller hippocampi volumes and larger ventricles than *val/val* carriers. Moreover, *met* carriers were seen to encounter more difficulties in verbal fluency and working memory tasks than the *val/val* group (55).

Additionally, Rybakowski et al. found that individuals with a BDNF *val66met* polymorphism developed BD type 1 approximately 11 years earlier than *val/val* carriers and performed more poorly on a test of executive functioning (Wisconsin Card Sorting Test - WCST) (56). A few years later Rybakowski et al. found that the *val/val* genotype was associated with higher accuracy on the N-back and WCST tests when compared with *val/met* and *met/met* genotypes (57).

By contrast, another identified study, by Tramontina et al. found that *val/val* carriers diagnosed with BD type I made more perseverative errors than *val/met* and *met/met* participants. Thus the *met* allele was not seen to be associated with cognitive impairment in this study (58), possibly due to the heterogeneous ancestry of Tramontina et al.'s participants (European, Amerindian and African) as compared to the more homogenous European ancestry of participants involved in Rybakowski's study. Alternatively, other factors such as the age of onset of the disease and the severity of BD may have blunted the differences between *met* and *val* carriers, however the influence of these variables were not explored.

Overall, current findings provide initial evidence of an association between decreased BDNF levels and a high risk of cognitive decline in BD. Furthermore, the BDNF *val66met* polymorphism appears to be a potential risk factor for cognitive impairment in BD.

Quality evaluation: findings

The quality and reliability of the 10 studies included in this review are shown in Table 2. The CDR hierarchy of evidence was estimated to be 3–4, as the current studies are not randomized cross-sectional studies with and without a control group. Given the observational nature of the studies, the current findings provide little information on trends over time and do not investigate possible causality link between inflammation and cognitive

impairment in bipolar disorder. Further, investigators were not blinded to the case/control status of their participants. This raises the possibility that the knowledge of the diagnosis may have affected their testing style and cognitive evaluation. The clinical populations were recruited in hospital settings and their diagnosis was based on well-established clinical scales such as the SCID (59) and the Mini International Neuropsychiatric inventory, (60) which indicates that the clinical profile of the samples is a reliable representation of the bipolar illness. All studies used well-accepted techniques to estimate inflammatory markers (e.g. ELISA assays) and widely used measures of cognitive functioning (e.g. Repeatable Battery for the Assessment of Neuropsychological Status). It could therefore be concluded that the current results provide an accurate description of the cognitive functioning and inflammatory response in BD patients. While the average sample size was satisfactory as it ranged from medium to large (N > 30), only two studies reported estimating the sample size based on power analyses. As a result, some of the studies may be underpowered and report misleading findings. In addition, the lack of information on the effect sizes and the confidence intervals of the statistical analyses limit the evaluation of the size of the experimental effects of the findings. Other methodological flaws include the absence of a control population in three studies and inadequate matching of the control population to the clinical population in six studies. Moreover, given the current trend for overrepresentation of positive studies in medicine and hard sciences (11), it is possible that a number of unpublished studies did not find any link between inflammation and cognition in bipolar disorder.

Discussion

This review aimed to examine the literature exploring the relationship between the cognitive deficits seen among individuals diagnosed with bipolar disorder, and markers of inflammation, neurotrophins and oxidative damage. Thus, we conducted a systematic search of the human literature on inflammation and cognition in BD. It is important to emphasize that this is a novel approach as previous reviews have linked inflammation with mood symptoms, but have not explored the relationship between peripheral markers of inflammation and cognitive impairment. We identified 10 observational studies. Of these studies 2 investigated the relationship between pro-inflammatory cytokines (TNF-a) and markers of oxidative stress (CRP) and 8 investigated the relationship between the neurotrophin BDNF, and cognitive functioning. The results of these studies indicate that the cognitive deficits observed in individuals diagnosed with BD appear to be associated with an increased inflammatory state and a decrease in the neurotropic factor, BDNF. Despite the limited number of studies in this field and their heterogeneity in terms of cognitive outcome measures, these studies provide preliminary evidence that an elevated inflammatory state negatively affects frontotemporal cognitive abilities such as memory, attention and executive functions, and indicate a need for further investigation.

Consistent with previous research (28), we identified one study showing that individuals diagnosed with BD have reduced hippocampi volumes and larger ventricles. Importantly, this was associated with more difficulties in verbal fluency and working memory tasks (55). Previous authors have speculated that systemic toxicity and cognitive dysfunction are directly related to the number of episodes suffered by the patient (32) and that peripheral

cytokine and BDNF expression could be potential markers of illness progression, thus corroborating the “staging” hypothesis of BD (61). However, as all the studies identified in the present systematic review were observational in nature, there appears to be no research regarding the relationship between inflammatory markers and changes in cognitive measures over the course of the BD. A longitudinal design study could be a suitable approach to explore the relationship between peripheral biomarkers of inflammation, oxidative stress and neurotrophic activity. This type of design may also help clarify the relationship between biomarkers and cognitive impairment at different phases of the disease.

None of the reviewed studies investigate the relationship between oxidative stress, mitochondrial dysfunction and neuroprogression. However, a number of studies using animal models of mania have observed increased levels of reactive oxygen species (ROS), a marker of mitochondrial dysfunction (62). One study demonstrated increased lipid peroxidation, and a high number of free radical, superoxide in submitochondrial particles of the prefrontal cortex and hippocampus (2). A second study showed that repeated amphetamine exposure, which induces manic symptomatology in animal models, increases levels of anti-oxidant enzymes, superoxide dismutase (SOD) and catalase (CAT), in regional specific manner, in the prefrontal cortex, hippocampus and striatum (3). The authors interpreted these results to reflect an imbalance between SOD and CAT expression, potentially indicative of a predisposition to the generation of ROS (63, 64). Increased oxidative stress has been associated with abnormalities in the glutamatergic system and neuronal apoptosis. Neuronal apoptosis has been hypothesized to be a progressive process that begins at synaptic terminals and dendrites and continues to the cell body via apoptotic cascades (65, 66). The dynamic of neuronal cell death mechanisms may underlie the decline in neurocognitive function observed over the course of the bipolar illness. Additionally, clinical research indicates that BD is characterized by low levels of brain energy metabolites such as creatine and high lactate and glutamate-related metabolite concentrations, which are clinical markers of mitochondrial dysfunction (67), as assessed using magnetic resonance spectroscopy (MRS)(68). Lactate accumulation may indicate a shift to anaerobic glycolytic mechanisms, possibly due to inadequate energy production within the mitochondria (68, 69). Anaerobic glycolysis produces less adenosine triphosphate (ATP) molecules than aerobic glycosis, and reduced ATP production could lead to cerebral hypometabolism, brain dysfunction and eventually cognitive impairment (70).

A further limitation of the studies reviewed here is that they differ with respect to the estimation of the peripheral levels of inflammatory biomarkers. Indeed, as illustrated in Table 1, the majority of the studies measured the expression of cytokines, BDNF and antioxidants in serum, plasma, or whole blood cells (a combination of serum, plasma and erythrocytes). For instance, since plasma cells have a short turnover (71), they may be ideal to measure acute inflammation (e.g. infection), but may not reflect a state of chronic inflammation. Erythrocytes and whole blood cells (which have a turnover of approximately 12 weeks) (72) may therefore be better indices of inflammatory markers in cell membranes and possibly the brain tissue. Further, previous studies have shown that aminoacids and carbohydrate levels differ significantly between plasma and serum (8, 73). In particular, BDNF levels are higher in serum compared to plasma (40, 73, 74). The latter result is probably due to the release of BDNF from platelets to serum during the coagulation process

(40). Hence, finding of studies using serum BDNF levels may not be comparable to those of studies using plasma BDNF levels. Quality evaluation of the current studies reveals some methodological concerns in terms of research design and statistical analyses, as earlier discussed. Hence, caution should be taken in the interpretation of the data presented in this systematic review, regarding the relationship between inflammation and cognition in bipolar disorder.

Surprisingly, none of the studies identified investigated the relationship between the inflammatory response and the hypothalamic-pituitary-adrenal (HPA) axis activation. Indeed a number of mood disorders present with abnormalities in the HPA axis, such as increased levels of cortisol and corticotropin-releasing factor (CRF)(75). A potential explanation for the abnormal HPA axis activity is that pro-inflammatory cytokines disrupt the glucocorticoid function and lead to glucorticoid resistance, characterized by cortisol and CRF hypersecretion. In turn, glucocorticoid resistance initiates pro-inflammatory mechanisms and reduces peripheral BDNF levels (73, 76). Both glucocorticoid resistance and inflammation have been associated with depressed mood and cognitive difficulties (73). It is notable that in medicated BD patients the glucocorticoid receptor antagonist, mifepristone improves mood and spatial working memory, and to a lesser extent, verbal fluency and spatial recognition (74, 77). In particular, the improvement in spatial memory appear to be related to the cortisol response to mifiprestone, not mood changes (74). It could be speculated that mifiprestone inhibits the proinflammatory response by regulating the HPA-axis activity, however this remains unknown as these studies did not collect inflammatory markers. Taken together these findings provide a strong rationale for the development of trials investigating the synergistic role of the inflammatory response and the HPA-axis function in the pathophysiology of BD.

In conclusion, research in the field of cognition and inflammation in BD is still in its infancy and additional work is needed to understand how pro-inflammatory processes affect brain function and induce cognitive impairment. The identification of inflammatory markers and polymorphisms in inflammatory response genes underlying cognitive decline will have important implications for the development of new therapies targeting chronic inflammatory conditions such as BD.

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Glossary

ACC	Anterior cingulate cortex
AMPH	d-amphetamine
ATP	adenosine triphosphate
BBB	Brain blood barrier
BD	Bipolar disorder

CAT	Catalase
CANTAB	Cambridge Neuropsychological Test Automated Battery
CPT	Continuous performance test
CRF	Corticotropin-releasing factor
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
ELR	excellent lithium responders
ERK	Extracellular signal-regulated kinase
FAB	Frontal Assessment Battery
FEP	First episode psychosis
FTT	Finger tapping test
GABA	Gamma-Aminobutyric acid
GPx	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione (GSH)
HC	Healthy control
HPA	Hypothalamic-pituitary-adrenal
IL	Interleukin
INF-α	Interferon-α
LPS	Lipopolysaccharide
MDA	Malondialdehyde
MDD	Major Depression Disorder
MINI	Mini International Neuropsychiatric Interview
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
Na+K+ATPase	Sodium-potassium adenosine triphosphatase pump
NFkB	Nuclear factor-kappa B
NGF	Nerve growth factor
NO	Nitric oxide
NMDA	N-methyl-D-aspartic acid
NOS	Reactive nitrogen species

NPSH	Non-protein thiols
NT-3/NT-4	Neurotrophin 3 or 4
O&NS	Oxidative and nitrosative stress
PANSS	Positive and negative syndrome scale
PET	Positron emission tomography
PG	Prostaglandins
PhSe2	Diphenyldiselenide
RAVLT	Rey's Auditory Verbal Leaning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
ROS	Reactive oxygen species
sACC	Subgenual anterior cingulate cortex
SB	Sodium butyrate
fMRI	functional magnetic resonance imaging
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
sMRI	structural magnetic resonance imaging
SOD	Superoxide dismutase
SSRI	Selective serotonin reuptake inhibitors
TAS	Total anti-oxidant status
TBARS	Thiobarbituric acid reactive substances
TNF	Tumour necrosis factor
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test

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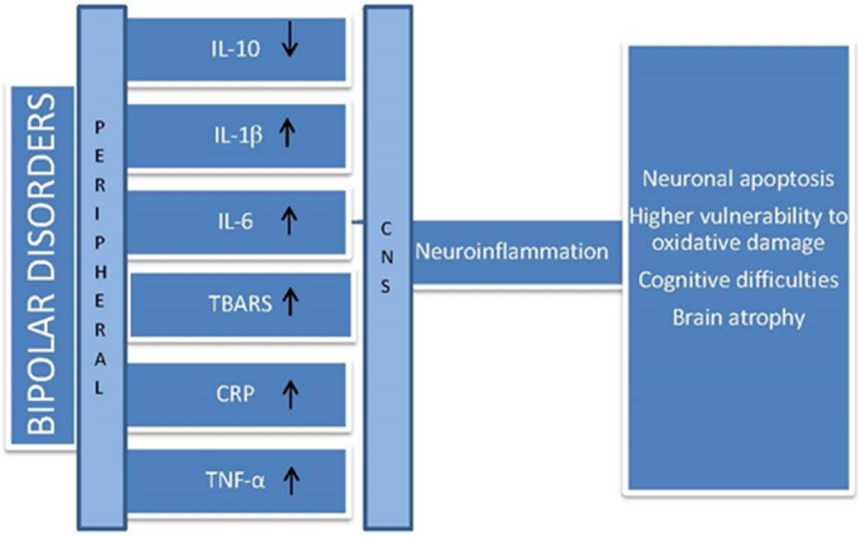

Figure 1.

Bipolar disorders are characterized by elevated levels of peripheral pro-inflammatory cytokines such as interleukins (IL-6, IL-2R, IL-1beta), tumour necrosis factor (TNF-α) and oxidative stress (Thiobarbituric acid reactive substances -TBARS and C-reactive protein - CRP). Pro-inflammatory agents enter the central nervous system (CNS) via the blood brain barrier, activate the brain inflammatory signal and release inflammatory agents, monocytes and macrophages in the brain. Exposure to pro-inflammatory substances and reactive oxidative substances is associated with neuronal damage and loss of brain function.

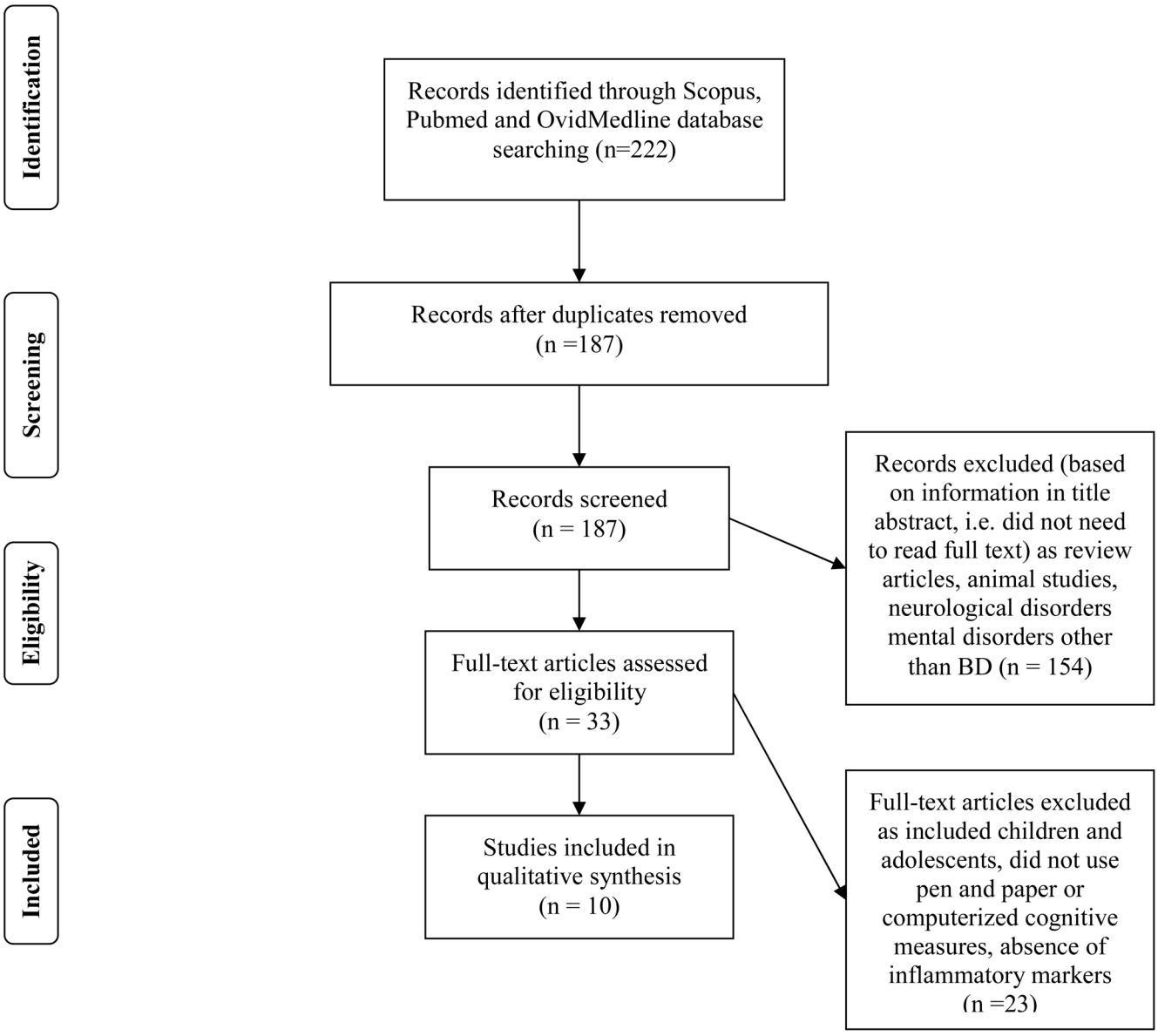

Figure 2.

PRISMA flowchart (38) showing the filtering process used to select the 10 studies included in the systematic review of studies investigating inflammatory markers and cognition in bipolar disorder

Table 1

Summary of studies that explored changes in inflammatory and oxidative stress biomarkers, and cognitive measures in individuals with bipolar disorder; BD = Bipolar disorder, HC = Healthy control

Citation	Subject description (diagnosis, gender (M/F)	Age (Years)	Design	Duration of illness (years)	Antipsychotic/mood stabilizer medication (Yes or No)	Cognitive measures	Inflammatory biomarker	Statistics	Outcome + Evidence of a link between inflammation and cognition −no evidence of a link between inflammation and cognition
Oxidative stress and cytokines									
Dickerson et al. (2013) *Journal of Affective Disorders*	107 BD (31/76)	36.3±13.4	Observational study	≈ 20 years	Yes	Repeatable Battery for the Assessment of Neuropsychological status (RBANS) Wechsler Adult Intelligence Scale (WAIS III), Trail Making Test	Serum CRP	Logistic regression	+Lower RBANS scores in the High CRP group compared to the Low CRP group
Doganavsargil-Baysal et al. (2013) *Human Psychopharmacology*	54 euthymic BDI (18/36) 18 HC (5/13)	BD: 39.46±11.62 HC 38.33±10.80	Observational study	≈ 13 years	Yes	Wisconsin Card Sorting Test (WCST), Rey's Auditory Verbal Leaning Test (RAVLT)	Serum TNF	Spearman's correlation, t-test	+BD have higher levels of sTNFr1 and sTNFr2 than HC +BD exhibit lower cognitive performance on WCST and RAVLT than HC +sTNFr2 levels correlate positively with illness duration
Neurotrophin									
Aas et al. (2013) *Progress in Neuropsychopharmacology*	249 BD (122/127) and 476 HC	BD: 20–40 HC: 34.79±10.25	Observational study	Not provided	Yes	California Verbal Learning test, letter number sequencing, digit span forwards/ backwards, Color Word Interference test, verbal fluency, block design, matrix reasoning, vocabulary	BDNF gene (not specified whether serum or plasma)	Regression model	+*val/met* BDNF gene carriers are more vulnerable to childhood trauma sequels, have smaller hippocampal volumes and larger ventricles
Barbosa et al. (2012) *Journal of Affective Disorders*	25 euthymic BD (8/17) vs 25 HC (11/14)	BD: 50.88±9.11 HC: 48.04±7.08	Observational study	27.88±11.8	Yes	Mini-Mental State Examination and Frontal Assessment Battery	Plasma BDNF	Mann-Whitney U test, Spearman's correlation	+Higher BDNF in the BD than HC −No correlation between BDNF and executive functioning
Chou et al. (2012) *Journal of affective disorders*	23 BD (6/17) and 33 HC (12/21)	HC: 37.6±7.8 BD: 36.5±8.9	Observational study	5.7±4.68	Yes	Go/No-Go task of the test for attentional performance, Memory (Wechsler Memory scale	Plasma BDNF	t-test, ANCOVA, correlation	−no difference in BDNF levels between BD and HC

Citation	Subject description (diagnosis, gender (M/F)	Age (Years)	Design	Duration of illness (years)	Antipsychotic/mood stabilizer medication (Yes or No)	Cognitive measures	Inflammatory biomarker	Statistics	Outcome + Evidence of a link between inflammation and cognition −no evidence of a link between inflammation and cognition
						– III), Word list, Face test, Color trail test, Wisconsin – III), Word list, Face test, Color trail test, Wisconsin – III), Word list, Face test, Color trail test, Wisconsin – III), Word list, Face test, Color trail test, Wisconsin	card sorting test card sorting test card sorting test card sorting test	+reduced face recognition and accuracy on the WCST in BD compared to HC
Dias et al. (2009) *Bipolar disorders*	65 euthymic BD (24/41), 50 HC	BD: 37.8±10.51 HC:33.6±9.66	Observational study	13.3±8.78	Yes	Wechsler Memory Scale, Wechsler Intelligence Scale for adults revised	Serum BDNF	*t*-test, ANOVA,	−No difference in BDNF levels between BD and HC +Positive correlation between BDNF levels and verbal fluency in BD and HC
Rybarkowski et al. (2003) *Bipolar disorder*	54 BD I (18/36)	BD: 18–72 (mean 46 years)	Observational study	16±12	Yes	Wisconsin Card Sorting Test	Whole blood BDNF gene	*t*-test	+the *val/val* BDNF polymorphism exhibits better cognitive functioning than the *val/met* genotype +the *val* allele was associated with an earlier onset of illness
Rybarkowski et al. (2006) *Psychiatry and Clinical Neurosciences*	111 BD (37/74) 160 HC (gender ratio N/A)	BD: 43.4±13.7 HC: 32.9±11.5	Observational study	N/A	N/A	Wisconsin Card Sorting Test, N-back test	Whole blood BDNF gene	*t*-test, ANOVA	+The percentage of correct reactions to the N-back test and accuracy on WCST was higher in the *val/val* group compared with *val/met* and *met/met*
Rybarkowski et al. (2010) *International Journal of Neuropsychopharmacology*	60 BD (25/35) 60 HC (25/35)	BD: 52.6±10.2 HC:52.1±13.6	Observational study	22.2±10.8	Yes	CANTAB	Plasma BDNF level	Mann-Whitney/Kruskal-Wallis ANOVA	+BD have lower BD have poorer cognitive performance and lower BDNF plasma levels than HC +No difference in plasma BDNF levels between ELR and HC
Tramontina et al. (2009) *Revista Brasileira de Psiquiatria*	64 BD I (14/50)	BD I: 42.3±11.1	Observational study	N/A	Yes	Wisconsin Card Sorting Test	BDNF gene (not specified whether serum or plasma)	Mann-Whitney's U analysis, ANCOVA	−The percentage of non-perseverative errors was higher in the *val/val* group −No association between *met* allele and cognitive functioning

Table 2

Quality assessment of the 10 studies included in the review. The Overall Quality Score was calculated by adding scores of items 1 to 6; CRD levels are: 1. Experimental studies, 2. Quasi-experimental studies, 3. Controlled observational studies, 3a. Cohort studies, 3b. Case control studies, 4. Observational studies without control groups, 5. Expert opinion based on theory, laboratory research or consensus; BD = Bipolar disorder, HC = healthy control

Citation	Overall Quality Score (1–6)	CRD Hierarchy of evidence (Levels 1–5)	Sample size N < 30 small N = 30–50 medium N > 50 large	Item 1 Representative sample	Item 2 Matched control groups	Item 3 Power analysis/ Sample size calculation	Item 4 Adequate assessment of inflammation	Item 5 Adequate measure of cognition	Item 6 Confidence intervals (CI) or or effect size (ES)
				Criterion is fulfilled = 1 Criterion is not fulfilled = 0					
Dickerson et al. (2013)	4	4	Large, 107 BD	1, patients were recruited in a psychiatric health care program, diagnosis was based on SCID	0, No HC	0	1	1	1, CI, no ES
Doganavsargil-Baysal et al. (2013)	6	3	Small/Medium 54 BDI 18 HC	1, patients were recruited in an outpatient psychiatric clinic, diagnosis was based on DSM-IV TR	1, HC matched by age, gender, educational level	1	1	1	0, No CI, Estimated ES = 1
Aas et al. (2013)	3	3	Large 249 BD 476 HC	1: Patients recruited in hospitals, diagnosis based on DSM-IV criteria.	0, HC not demographically matched	0	1	1	0, No CI/ES
Barbosa et al. (2012)	4	3	Small, 25 BD 25 HC	1, patients recruited in an out/ inpatient psychiatric clinic, diagnosis based on Mini International Psychiatric inventory	1, HC matched by age and gender	0	1	1	0, No CI/ES
Chou et al. (2012)	4	3	Small 23 BD 33 HC	1: patients were diagnosed based on DSM-IV criteria.	1, age-matched HC	0	1	1	0, No CI/ES
Dias et al. (2009)	3	3	Medium 65 BD 50 HC	1, patients diagnosed based on DSM-IV criteria and Mini International Psychiatric inventory	0, HC not demographically matched	0	1	1	0, No CI/ES
Rybakowski et al. (2003)	3	4	Medium 54 BD I	1: Outpatients recruited in hospitals, diagnosis based on DSM-IV criteria.	0, No HC	0	1	1	0, No CI/ES
Rybakowski et al. (2006)	3	3	Large 111 BD 160 HC	1: inpatients recruited in hospitals, diagnosis based on DSM-IV criteria.	0, Not matched	0	1	1	0, No CI/ES
Rybakowski et al. (2010)	4	3	Large 60 BD 60 HC	1: Patients attending an outpatient lithium clinic, diagnosis based on DSM-IV criteria - SCID	1, age and gender-matched HC	0	1	1	0, No CI/ES

Citation	Overall Quality Score (1–6)	CRD Hierarchy of evidence (Levels 1–5)	Sample size N < 30 small N = 30–50 medium N > 50 large	Item 1 Representative sample	Item 2 Matched control groups	Item 3 Power analysis/ Sample size calculation	Item 4 Adequate assessment of inflammation	Item 5 Adequate measure of cognition	Item 6 Confidence intervals (CI) or or effect size (ES)
				Criterion is fulfilled = 1 Criterion is not fulfilled = 0					
Tramontina et al. (2009)	4	4	Medium 64 BD I	1: outpatients recruited in a hospital setting, diagnosis based on DSM-IV criteria.	0, No HC	1	1	1	0, No CI/ES